CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 209190

Name: Lidocaine (patch), 5%

Sponsor: Institute Biochimique SA

Approval Date: April 30, 2020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA209190Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

APPROVAL LETTER

ANDA 209190

ANDA APPROVAL

Rhodes Pharmaceuticals L.P.
498 Washington Street
Coventry, RI 02816
Attention: Todd M. Delehant, Ph.D.
Director Regulatory Affairs

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on April 14, 2016, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Lidocaine Patch 5%.

Reference is also made to the complete response letter issued by this office on May 3, 2019, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your Lidocaine Patch 5% to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Lidoderm Patch 5%, of Teikoku Pharma USA, Inc.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the

date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts.

All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at https://www.fda.gov/media/71211/download. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, PharmD
CAPT, USPHS
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Catherine Poole

Digitally signed by Catherine Poole
Date: 4/30/2020 12:20:59PM
GUID: 5407887a000a1c0c26055eafb8e3258a

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

LABELING

Lidocaine Patch 5 % - Patch Label

100 mm

143mm

(b) (4)

cut along dotted line

Lidocaine
Patch 5%

Each adhesive patch contains:
Lidocaine . . . . . 700 mg (50 mg per gram adhesive)
in an aqueous base.
Methylparaben and propylparaben as preservatives.

USUAL DOSAGE: Apply up to 3 patches. See package insert for complete prescribing information.

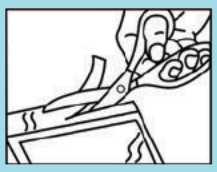
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

WARNING: Keep used and unused patches out of the reach of children, pets and others.

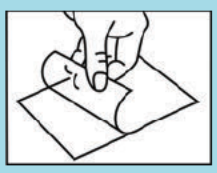
R_x Only
1 Patch (10 cm x 14 cm)

Marketed by:
Rhodes Pharmaceuticals L.P. Coventry, RI 02816
Manufactured by:
Altergon Italia Srl, Morra de Sanctis, Avellino 83040, Italy

DIRECTIONS FOR USE
Do not store patch outside the sealed envelope.

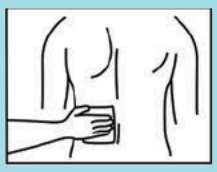


Cut the envelope along the dotted line. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Safely discard the remaining unused pieces of cut patches where children and pets cannot get to them.



Remove the transparent release liner (clear plastic backing) before application of patch to the skin.

Apply immediately after removal from the protective envelope.



Apply the prescribed number of patches, only once for up to 12 hours within a 24 hour period. Remove patches if irritation occurs.

Placement of external heat sources, such as heating pads or electric blankets, over Lidocaine patches is not recommended.

Lidocaine patch 5% may not stick if it gets wet. Avoid contact with water, such as bathing, swimming or showering.

Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get them.

303193-0A

2 03 4285-8118-30 3

LOT:

EXP:

143 mm

PDDIE-339 Rev 2
Lidocaine Carton

Rx Only

NDC 42858-118-30
Lidocaine
Patch 5%

Rhodes

NO VARNISH

NDC 42858-118-30
Lidocaine
Patch 5%

Each adhesive patch contains:
Lidocaine . . . . . 700 mg (50 mg per gram adhesive) in an aqueous base.
Methylparaben and propylparaben as preservatives.

USUAL DOSAGE:
Apply up to 3 patches. See package insert for complete prescribing information.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [see USP Controlled Room Temperature].

WARNING:
Keep used and unused patches out of the reach of children, pets and others.

30 Patches

30 Envelopes
Containing 1 Patch Each

Marketed by: Rhodes Pharmaceuticals L.P., Coventry, RI 02816
Manufactured by: Altergon Italia Srl, Morra de Sanctis, Avellino 83040, Italy

Rhodes

Rx Only

NO VARNISH

Rx Only

NDC 42858-118-30
Lidocaine
Patch 5%

Rhodes

NO VARNISH

NDC 42858-118-30
Lidocaine
Patch 5%

DIRECTIONS FOR USE
Do not store patch outside the sealed envelope.

Cut the envelope along the dotted line. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Safely discard the remaining unused pieces of cut patches where children and pets cannot get to them.

Remove the transparent release liner (clear plastic backing) before application of patch to the skin.

Apply immediately after removal from the protective envelope.

Apply the prescribed number of patches, only once for up to 12 hours within a 24 hour period. Remove patch if irritation occurs.

Placement of external heat sources, such as heating pads or electronic blankets, over Lidocaine patches is not recommended.

Lidocaine patch 5% may not stick if it gets wet. Avoid contact with water, such as bathing, swimming, or showering.

Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them.

N 3 42858-118-30 9

303192-0A

Rhodes

Rx Only

Lot

EXP

NO VARNISH

345 mm

441 mm

(b) (4)

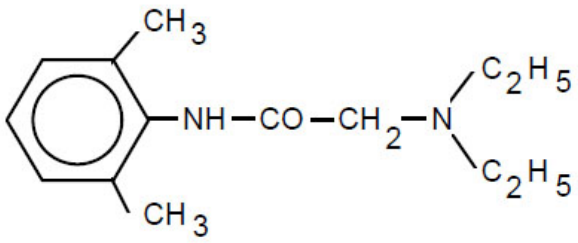
Lidocaine Patch 5%

Rx only

DESCRIPTION

Lidocaine patch 5% is comprised of an adhesive material containing 5% lidocaine, which is applied to a non-woven polyester felt backing and covered with a polyethylene terephthalate (PET) film release liner. The release liner is removed prior to application to the skin. The size of the patch is 10 cm x 14 cm.

Lidocaine is chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl), has an octanol:water partition ratio of 43 at pH 7.4, and has the following structure:



Each adhesive patch contains 700 mg of lidocaine (50 mg per gram adhesive) in an aqueous base. It also contains the following inactive ingredients: purified water, glycerin, sorbitol, polyacrylic acid, sodium carboxymethylcellulose, sodium polyacrylate, propylene glycol, urea, kaolin, tartaric acid, gelatin, polyvinyl alcohol, dihydroxyaluminum aminoacetate, edetate disodium, methylparaben, and propylparaben.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Lidocaine is an amide-type local anesthetic agent and is suggested to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses.

The penetration of lidocaine into intact skin after application of a lidocaine patch 5% is sufficient to produce an analgesic effect, but less than the amount necessary to produce a complete sensory block.

Pharmacokinetics

Absorption

The amount of lidocaine systemically absorbed from lidocaine patch 5% is directly related to both the duration of application and the surface area over which it is applied. In a pharmacokinetic study, three lidocaine patches were applied over an area of 420 cm^2 of intact skin on the back of normal volunteers for 12 hours. Blood samples were withdrawn for determination of lidocaine concentration during the application and for 12 hours after removal of patches. The results are summarized in Table 1.

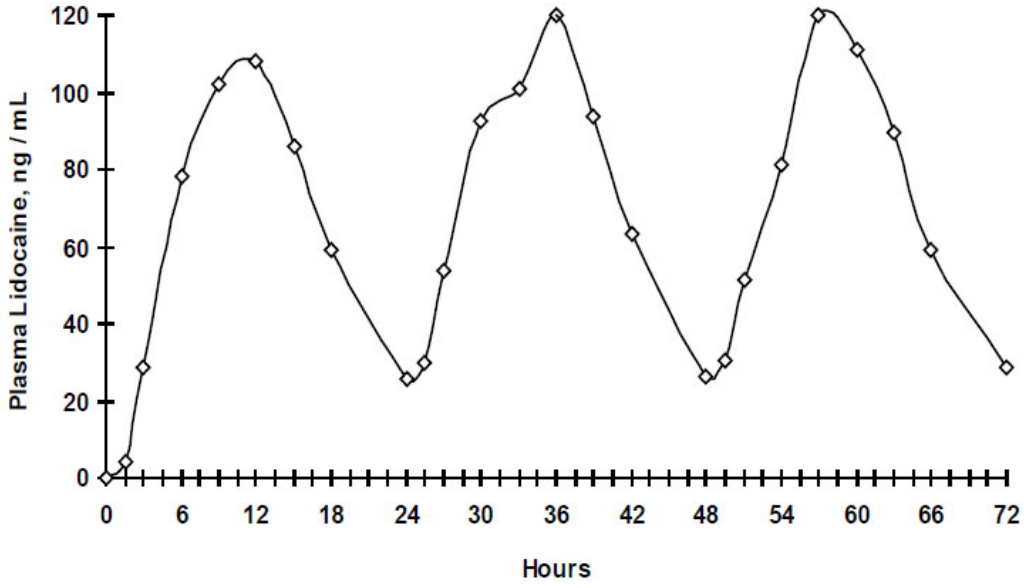
Table 1
Absorption of lidocaine from Lidocaine Patch 5%
Normal volunteers (n=15, 12-hour wearing time)

Lidocaine Patch 5%	Application Site	Area (cm^2)	Dose Absorbed (mg)	C_{max} (mcg/mL)	T_{max} (hr)
3 patches (2100 mg)	Back	420	64 ± 32	0.13 ± 0.06	11 hr

When lidocaine patch 5% is used according to the recommended dosing instructions, only 3 ± 2% of the dose applied is expected to be absorbed. At least 95% (665 mg) of lidocaine will remain in a used patch. Mean peak blood concentration of lidocaine is about 0.13 mcg/mL (about 1/10 of the therapeutic concentration required to treat cardiac arrhythmias). Repeated application of three patches simultaneously for 12 hours (recommended maximum daily dose), once per day for three days, indicated that the lidocaine concentration does not increase with daily use. The mean plasma pharmacokinetic profile for the 15 healthy volunteers is shown in Figure 1.

Figure 1

Mean lidocaine blood concentrations after three consecutive daily applications of three lidocaine patches simultaneously for 12 hours per day in healthy volunteers (n = 15).



Distribution

When lidocaine is administered intravenously to healthy volunteers, the volume of distribution is 0.7 to 2.7 L/kg (mean 1.5 ± 0.6 SD, n = 15). At concentrations produced by application of lidocaine patch 5%, lidocaine is approximately 70% bound to plasma proteins, primarily alpha-1-acid glycoprotein. At much higher plasma concentrations (1 to 4 mcg/mL of free base), the plasma protein binding of lidocaine is concentration dependent. Lidocaine crosses the placental and blood brain barriers, presumably by passive diffusion.

Metabolism

It is not known if lidocaine is metabolized in the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites, including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to, but less potent than that of lidocaine. A

minor metabolite, 2,6-xylidine, has unknown pharmacologic activity but is carcinogenic in rats. The blood concentration of this metabolite is negligible following application of lidocaine patch 5%. Following intravenous administration, MEGX and GX concentrations in serum range from 11 to 36% and from 5 to 11% of lidocaine concentrations, respectively.

Excretion

Lidocaine and its metabolites are excreted by the kidneys. Less than 10% of lidocaine is excreted unchanged. The half-life of lidocaine elimination from the plasma following IV administration is 81 to 149 minutes (mean 107 ± 22 SD, n = 15). The systemic clearance is 0.33 to 0.90 L/min (mean 0.64 ± 0.18 SD, n = 15).

CLINICAL STUDIES

Single-dose treatment with lidocaine patch 5% was compared to treatment with vehicle patch (without lidocaine), and to no treatment (observation only) in a double-blind, crossover clinical trial with 35 post-herpetic neuralgia patients. Pain intensity and pain relief scores were evaluated periodically for 12 hours. Lidocaine patch 5% performed statistically better than vehicle patch in terms of pain intensity from 4 to 12 hours.

Multiple-dose, two-week treatment with lidocaine patch 5%, was compared to vehicle patch (without lidocaine) in a double-blind, crossover clinical trial of withdrawal-type design conducted in 32 patients, who were considered as responders to the open-label use of lidocaine patch 5% prior to the study. The constant type of pain was evaluated but not the pain induced by sensory stimuli (dysesthesia). Statistically significant differences favoring lidocaine patch 5% were observed in terms of time to exit from the trial (14 versus 3.8 days at p-value <0.001), daily average pain relief, and patient's preference of treatment. About half of the patients also took oral medication commonly used in the treatment of post-herpetic neuralgia. The extent of use of concomitant medication was similar in the two treatment groups.

INDICATIONS AND USAGE

Lidocaine patch 5% is indicated for relief of pain associated with post-herpetic neuralgia. It should be applied only to **intact skin**.

CONTRAINDICATIONS

Lidocaine patch 5% is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type, or to any other component of the product.

WARNINGS

Risk of Methemoglobinemia

Cases of methemoglobinemia have been reported in association with local anesthetic use. Although all patients are at risk for methemoglobinemia, patients with glucose-6-phosphate dehydrogenase deficiency, congenital or idiopathic methemoglobinemia, cardiac or pulmonary compromise, infants under 6 months of age, and concurrent exposure to oxidizing agents or their metabolites are more susceptible to developing clinical manifestations of the condition. If local anesthetics must be used in these patients, close monitoring for symptoms and signs of methemoglobinemia is recommended.

Signs of methemoglobinemia may occur immediately or may be delayed some hours after exposure, and are characterized by a cyanotic skin discoloration and/or abnormal coloration of the blood. Methemoglobin levels may continue to rise; therefore, immediate treatment is required to avert

more serious central nervous system and cardiovascular adverse effects, including seizures, coma, arrhythmias, and death. Discontinue lidocaine patch 5% and any other oxidizing agents. Depending on the severity of the signs and symptoms, patients may respond to supportive care, i.e., oxygen therapy, hydration. A more severe clinical presentation may require treatment with methylene blue, exchange transfusion, or hyperbaric oxygen.

Accidental Exposure in Children

Even a *used* lidocaine patch 5% contains a large amount of lidocaine (at least 665 mg). The potential exists for a small child or a pet to suffer serious adverse effects from chewing or ingesting a new or used lidocaine patch 5%, although the risk with this formulation has not been evaluated. It is important for patients **to store and dispose of lidocaine patch 5% out of the reach of children, pets, and others** (see HANDLING AND DISPOSAL).

Excessive Dosing

Excessive dosing by applying lidocaine patch 5% to larger areas or for longer than the recommended wearing time could result in increased absorption of lidocaine and high blood concentrations, leading to serious adverse effects (see ADVERSE REACTIONS, Systemic Reactions). Lidocaine toxicity could be expected at lidocaine blood concentrations above 5 mcg/mL. The blood concentration of lidocaine is determined by the rate of systemic absorption and elimination. Longer duration of application, application of more than the recommended number of patches, smaller patients, or impaired elimination may all contribute to increasing the blood concentration of lidocaine. With recommended dosing of lidocaine patch 5%, the average peak blood concentration is about 0.13 mcg/mL, but concentrations higher than 0.25 mcg/mL have been observed in some individuals.

PRECAUTIONS

General

Hepatic Disease
Patients with severe hepatic disease are at greater risk of developing toxic blood concentrations of lidocaine, because of their inability to metabolize lidocaine normally.

Allergic Reactions
Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine. However, lidocaine patch 5% should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

Non-intact Skin
Application to broken or inflamed skin, although not tested, may result in higher blood concentrations of lidocaine from increased absorption. Lidocaine patch 5% is only recommended for use on intact skin.

External Heat Sources
Placement of external heat sources, such as heating pads or electric blankets, over lidocaine patch 5% is not recommended as this has not been evaluated and may increase plasma lidocaine levels.

Eye Exposure
The contact of lidocaine patch 5% with eyes, although not studied, should be avoided based on the findings of severe eye irritation with the use of similar products in animals. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

Information for Patients

Methemoglobinemia

Inform patients that use of local anesthetics may cause methemoglobinemia, a serious condition that must be treated promptly. Advise patients or caregivers to stop use and seek immediate medical attention if they or someone in their care experience the following signs or symptoms: pale, gray, or blue colored skin (cyanosis); headache; rapid heart rate; shortness of breath; lightheadedness; or fatigue.

Drug Interactions

Antiarrhythmic Drugs

Lidocaine patch 5% should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.

Local Anesthetics

When lidocaine patch 5% is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

Drugs That May Cause Methemoglobinemia When Used with Lidocaine Patch 5%

Patients who are administered local anesthetics are at increased risk of developing methemoglobinemia when concurrently exposed to the following drugs, which could include other local anesthetics:

Examples of Drugs Associated with Methemoglobinemia:

Class	Examples
Nitrates/Nitrites	nitric oxide, nitroglycerin, nitroprusside, nitrous oxide
Local anesthetics	articaine, benzocaine, bupivacaine, lidocaine, mepivacaine, prilocaine, procaine, ropivacaine, tetracaine
Antineoplastic agents	cyclophosphamide, flutamide, hydroxyurea, ifosfamide, rasburicase
Antibiotics	dapsone, nitrofurantoin, para-aminosalicylic acid, sulfonamides
Antimalarials	chloroquine, primaquine
Anticonvulsants	Phenobarbital, phenytoin, sodium valproate
Other drugs	acetaminophen, metoclopramide, quinine, sulfasalazine

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

A minor metabolite, 2,6-xylidine, has been found to be carcinogenic in rats. The blood concentration of this metabolite is negligible following application of lidocaine patch 5%.

Mutagenesis

Lidocaine HCl is not mutagenic in Salmonella/mammalian microsome test nor clastogenic in chromosome aberration assay with human lymphocytes and mouse micronucleus test.

Impairment of Fertility

The effect of lidocaine patch 5% on fertility has not been studied.

Pregnancy

Teratogenic Effects
Pregnancy Category B.

Lidocaine patch 5% has not been studied in pregnancy. Reproduction studies with lidocaine have been performed in rats at doses up to 30 mg/kg subcutaneously and have revealed no evidence of harm to the fetus due to lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, lidocaine patch 5% should be used during pregnancy only if clearly needed.

Labor and Delivery

Lidocaine patch 5% has not been studied in labor and delivery. Lidocaine is not contraindicated in labor and delivery. Should lidocaine patch 5% be used concomitantly with other products containing lidocaine, total doses contributed by all formulations must be considered.

Nursing Mothers

Lidocaine patch 5% has not been studied in nursing mothers. Lidocaine is excreted in human milk, and the milk:plasma ratio of lidocaine is 0.4. Caution should be exercised when lidocaine patch 5% is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Application Site Reactions

During or immediately after treatment with lidocaine patch 5%, the skin at the site of application may develop blisters, bruising, burning sensation, depigmentation, dermatitis, discoloration, edema, erythema, exfoliation, irritation, papules, petechia, pruritus, vesicles, or may be the locus of abnormal sensation. These reactions are generally mild and transient, resolving spontaneously within a few minutes to hours.

Allergic Reactions

Allergic and anaphylactoid reactions associated with lidocaine, although rare, can occur. They are characterized by angioedema, bronchospasm, dermatitis, dyspnea, hypersensitivity, laryngospasm, pruritus, shock, and urticaria. If they occur, they should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Other Adverse Events

Due to the nature and limitation of spontaneous reports in postmarketing surveillance, causality has not been established for additional reported adverse events including:

Asthenia, confusion, disorientation, dizziness, headache, hyperesthesia, hypoesthesia, lightheadedness, metallic taste, nausea, nervousness, pain exacerbated, paresthesia, somnolence, taste alteration, vomiting, visual disturbances such as blurred vision, flushing, tinnitus, and tremor.

Systemic (Dose-Related) Reactions

Systemic adverse reactions following appropriate use of lidocaine patch 5% are unlikely, due to the small dose absorbed (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Systemic adverse effects of lidocaine are similar in nature to those observed with other amide local anesthetic agents, including CNS excitation and/or depression (lightheadedness, nervousness, apprehension, euphoria,

confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold, or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest). Excitatory CNS reactions may be brief or not occur at all, in which case the first manifestation may be drowsiness merging into unconsciousness. Cardiovascular manifestations may include bradycardia, hypotension, and cardiovascular collapse leading to arrest.

OVERDOSAGE

Lidocaine overdose from cutaneous absorption is rare, but could occur. If there is any suspicion of lidocaine overdose (see ADVERSE REACTIONS, Systemic Reactions), drug blood concentration should be checked. The management of overdose includes close monitoring, supportive care, and symptomatic treatment. Dialysis is of negligible value in the treatment of acute overdose with lidocaine.

In the absence of massive topical overdose or oral ingestion, evaluation of symptoms of toxicity should include consideration of other etiologies for the clinical effects, or overdosage from other sources of lidocaine or other local anesthetics.

The oral LD_{50} of lidocaine HCl is 459 (346 to 773) mg/kg (as the salt) in non-fasted female rats and 214 (159 to 324) mg/kg (as the salt) in fasted female rats, which are equivalent to roughly 4000 mg and 2000 mg, respectively, in a 60 to 70 kg man based on the equivalent surface area dosage conversion factors between species.

DOSAGE AND ADMINISTRATION

Apply lidocaine patch 5% to intact skin to cover the most painful area. Apply the prescribed number of patches (maximum of 3), only once for up to 12 hours within a 24-hour period. Patches may be cut into smaller sizes with scissors prior to removal of the release liner (see HANDLING AND DISPOSAL). Clothing may be worn over the area of application. Smaller areas of treatment are recommended in a debilitated patient, or a patient with impaired elimination.

If irritation or a burning sensation occurs during application, remove the patch(es) and do not reapply until the irritation subsides.

When lidocaine patch 5% is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

Lidocaine patch 5% may not stick if it gets wet. Avoid contact with water, such as bathing, swimming, or showering.

HANDLING AND DISPOSAL

Hands should be washed after the handling of lidocaine patch 5%, and eye contact with lidocaine patch 5% should be avoided. Do not store patch outside the sealed envelope. Apply immediately after removal from the protective envelope. Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them. Lidocaine patch 5% should be kept out of the reach of children.

HOW SUPPLIED

Lidocaine patch 5% is available as the following:
Carton of 30 patches……. NDC 42858-118-30
(packaged in individual child-resistant envelopes)

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

For more information, call Rhodes Pharmaceuticals L.P. at 1-888-827-0616.
Marketed by:
Rhodes Pharmaceuticals L.P.
Coventry, RI 02816, USA

Manufactured by:
Altergon Italia Srl
Zona Industriale ASI, Morra de Sanctis
Avellino, 83040, Italy

303194-0A

Revised 01/2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

LABELING REVIEW(s)

L ABELING REVIEW A

Division of Labeling Review A
Office of Regulatory Operations A
Office of Generic Drugs (OGD) A
Center for Drug Evaluation and Research (CDER) A

A

Date of A Rev ew	3/16/2020 A
ND ANumber( )	209190 A
Rev ew Number	3 A
ppl cant Name	Rhodes Pharmaceuticals L.P. A
E Aabl Ae AName & Strengt ( ) A [Ad A "(OTC)" after strength if app Alicable]	Lidocaine Patch 5% A A
Propo e APropr etary Name	NA A
Subm i An Rece ve ADate	2/27/2020 A
Pr mary Label ng Rev ewer	Rita Lindie A
Secon Ary Label ng Rev ewer	Refer to signature page A

Rev ew Conclu An A

☐ ACCEPTABLE – No Comments A
☒ ACCEPTABLE – Include Post Ap Aroval Comments A
☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Ap Aplicant A
☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Ap Aplicant A

†Theme - Cho Ase an item. A

Justification for Major Deficiency - Cho Ase an item. A

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to A Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling A minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant. A

On Policy Alert List A A ☒ Yes A ☐ A No A
Combined Insert/Outsert A ☐ Yes A ☒ A No (If yes, indicate ANDA number) A

A

1 LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR ATTACHMENT TO APPLICATION

Labeling Deficiencies determined on (add date) based on your submission(s) received (add date):

1. GENERAL COMMENTS
   Comment
2. CONTAINER LABEL
   a. Comment
   b. Comment
3. CARTON LABELING
4. PRESCRIBING INFORMATION
   a. Comment
   b. Subheading
      i. Comment
      ii. Comment
5. MEDICATION GUIDE
6. STRUCTURED PRODUCT LABELING (SPL)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with Choose an item. all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR ATTACHMENT TO APPLICATION WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) received (add date)

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

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I . o your re pon .b . y o en ure your ANDA ddre . e . . ed exc u .v .e h . c . m he . pproved drug produc . P e . e en ure h . . exc u .v .e nd p .en . . ed n he e ec ron c OB re . ddre . ed nd upd . ed n your pp c . on En ure your be ng .gn w .h your p . en nd . exc u .v y . emen . .

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1.3 POST APPROVAL REVISIONS .

The e commen . w . be ddre . ed po . pprov . (n he f r be ng upp emen rev ew) .

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PRESCRIBING INFORMATION .

Remove the “Pregnancy Category B” per the Pregnancy and Lactation Labeling Rule (79 FR 72064). .

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2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments:

Labeling was found to be acceptable in C2 review (1/23/2017 submission). Applicant submitted the following amendment

Rhodes Pharmaceuticals L.P. (Rhodes) is herein submitting a Labeling Amendment to the pending application to update the proposed product labeling to align with changes to the RLD. These changes are being made in accordance with 21 CFR 314.60.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: Container and carton labeling were found to be acceptable in C2 review. Post approval comment from C2 (add the NDC number to the top third portion of the principal display panel per 21 CFR 207.35(b)(3) is no longer applicable per regulations.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

Click here to enter text.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? YES If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review SLC to add language for Methemoglobinemia associated with the use of local anesthetics.
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES If Yes, please explain.

(b) (4)

[redacted]

Is the drug product listed on the Susceptibility Test Interpretive Criteria web page**?** NO

3.2 MODEL LABELING

Table 1: Review Model Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** (*If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)* **NDA# /Supplement# (S-000 if original):** 020612/S-014 **Supplement Approval Date:** 11/2/2018 **Proprietary Name:** Lidoderm® **Established Name:** lidocaine patch **Description of Supplement:** This supplemental new drug application provides for revisions to the labeling for LIDODERM consistent with our May 21, 2018, Safety Labeling Change Notification letter.
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old), or 201.66 (OTC)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments: Applicant revised labeling to be in accordance with RLD, NDA 020612/S-014 approved 11/2/2018. Changes are acceptable.

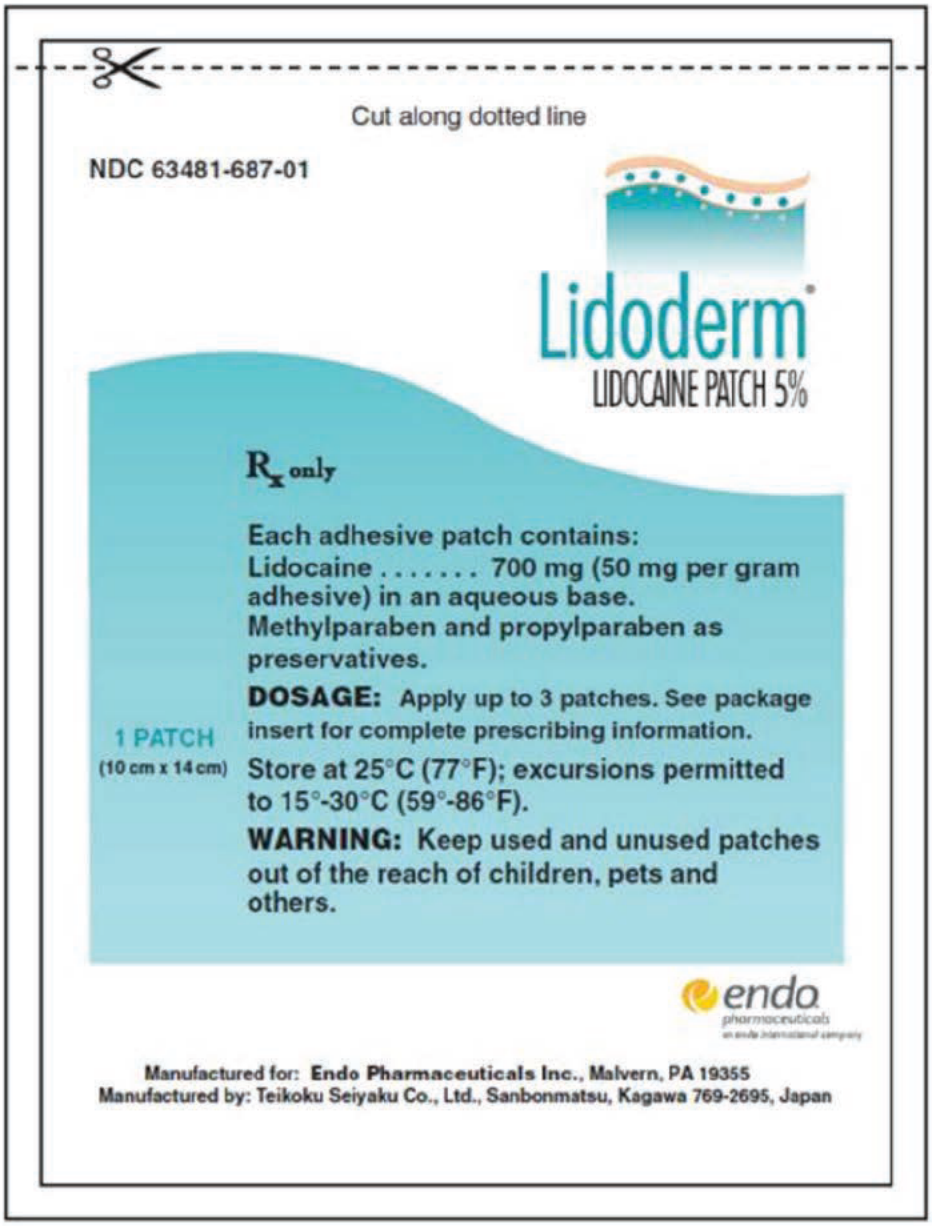
Post-approval comments (can be send out on 1st labeling revision if still applicable).

PRESCRIBING INFORMATION

Remove the "Pregnancy Category B" per the Pregnancy and Lactation Labeling Rule (79 FR 72064).

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: DARRTS S-012 approval letter]



DIRECTIONS FOR USE

Do not store patch outside the sealed envelope.

Cut the envelope along the dotted line. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Safely discard the remaining unused pieces of cut patches where children and pets cannot get to them.

Remove the transparent release liner (clear plastic backing) before application of patch to the skin.
Apply immediately after removal from the protective envelope.

Apply the prescribed number of patches, only once for up to 12 hours within a 24 hour period. Remove patches if irritation occurs.

Placement of external heat sources, such as heating pads or electric blankets, over LIDODERM patches is not recommended.

LIDODERM may not stick if it gets wet. Avoid contact with water, such as bathing, swimming or showering.

Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them.

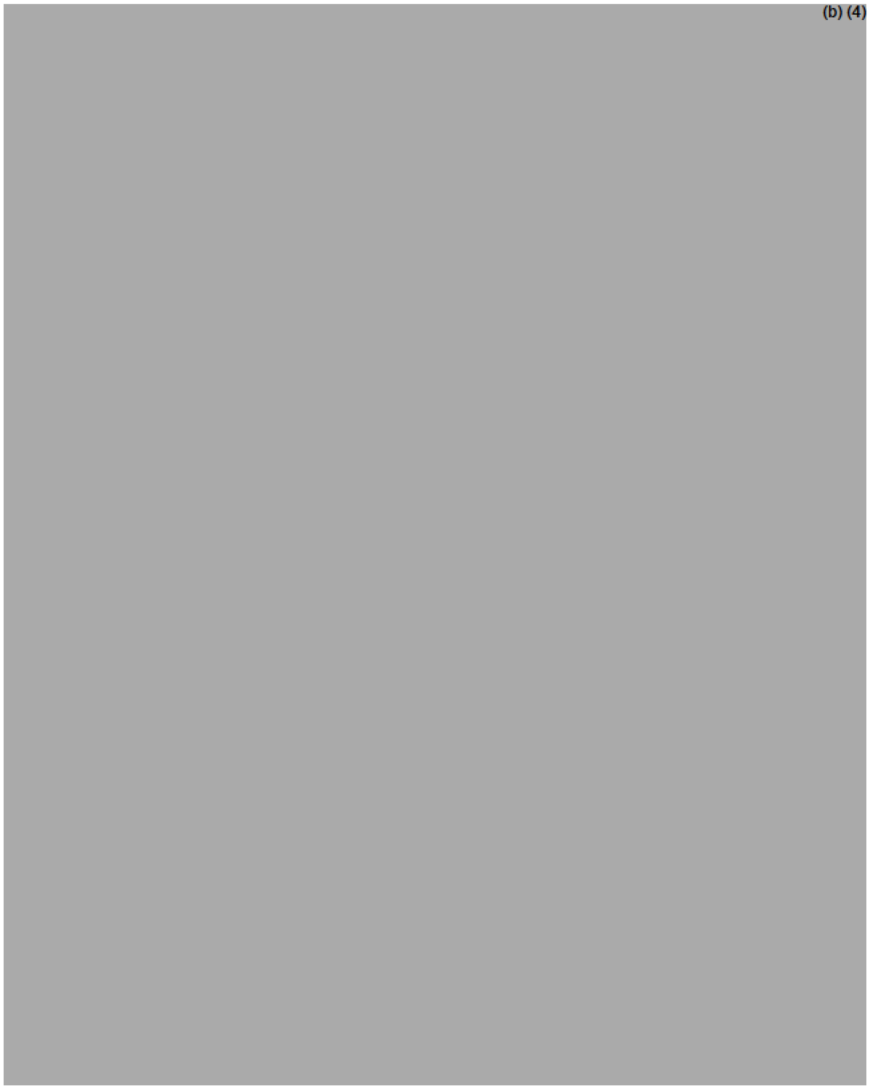
[redacted]

LOT:

EXP:

211374

1 Page has been withheld in full as b4 draft labeling immediately following this page



3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 3/16/2020.

Table 2: United States Pharmacopeia (USP)				
	YES or NO	**Date**	**Monograph Title (NA if no monograph)**	**Packaging and Storage/Labeling Statements (NA if no monograph)**
Currently Official	No		Click here to enter text.	Click here to enter text.
Not Yet Official	Click here to enter text.	Click here to enter the date when the monograph becomes official.	Click here to enter text.	Click here to enter text.

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

Click here to enter text.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 3/16/2020.

Table 3 provides Orange Book patents for the Model Labeling **Click here to enter NDA number** and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
Click here to enter text.						

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

Click here to enter text.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
Click here to enter text.					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

Click here to enter text.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	Currently Proposed	Assessment

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
inactive ingredients: purified water, glycerin, sorbitol, polyacrylic acid, sodium carboxymethylcellulose, sodium polyacrylate, propylene glycol, urea, kaolin, tartaric acid, gelatin, polyvinyl alcohol, dihydroxyaluminum aminoacetate, disodium edetate, methylparaben and propylparaben.	inactive ingredients: purified water, glycerin, sorbitol, polyacrylic acid, sodium carboxymethylcellulose, sodium polyacrylate, propylene glycol, urea, kaolin, tartaric acid, gelatin, polyvinyl alcohol, dihydroxyaluminum aminoacetate, edetate disodium, methylparaben, and propylparaben.	No changes

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Lidocaine patch 5% is available as the following: **Carton of 30 patches…… NDC 42858-118-30** (packaged in individual child-resistant envelopes)	Lidocaine patch 5% is available as the following: **Carton of 30 patches…….. NDC 42858-118-30** (packaged in individual child-resistant envelopes)	No changes

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Marketed by: Rhodes Pharmaceuticals L.P Coventry, RI 02816 Manufactured by: Altergon Italia Srl, Morra de Sanctis Avellino 83040, Italy	Marketed by: Rhodes Pharmaceuticals L.P. Coventry, RI 02816, USA Manufactured by: Altergon Italia Srl Zona Industriale ASI, Morra de Sanctis Avellino, 83040, Italy	No changes

5. COMMENTS/CONSULTS FOR OTHER DISCIPLINES

Describe questions, issues and consults sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

Refer to the Consult Screening flow chart to determine any necessary consults.

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

From CMC review finalized 3/3/2020

LABELING

{For ANDA only}

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☐ N/A

If "No," explain.

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

None

List of Deficiencies:

N/A

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container (patch)	Final	1 patch	1/23/2017	Satisfactory
Patch envelope	Final	1 envelope containing 1 patch	1/23/2017	Satisfactory
Carton	Final	30 patches (1 patch per envelope)	1/23/2017	Satisfactory
(Other – specify)	Choose an item.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	1/2019	2/27/2020	Satisfactory
Medication Guide	Choose an item.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Patient Information	Choose an item.	Click here to enter text.	Click here to enter text.	Click here to enter text.
SPL Data Elements		Click here to enter text.	Click here to enter text.	Click here to enter text.

Rita 9
Lindie 9

i ita 9 si ned b 9Rita Lindie 9
ate: 3/16/2020 02:52:38PM 9
GUI : 53c57083000163 fca7572eedfad43b0 9

Theresa 9
Liu 9

i ita 9 si ned b 9Theresa Liu 9
ate: 3/18/2020 11:56:07AM
GUI : 508da70a00028d58 11de18a5 8cda6f 9

L ABELING REVIEWA

Division of Labeling Review A
Office of Regulatory Operations A
Office of Generic Drugs (OGD) A
Center for Drug Evaluation and Research (CDER) A

Date of A Rev ew	2/27/2017 A
ND ANumber( )	209190 A
Rev ew Number	2 A
ppl cant Name	ARhodes Pharmaceuticals L.P. A
E abl Ae Name & Strengt ( )	Lidocaine Patch 5% A
Propo e Propr etary Name	NA A
Subm i An Rece ve Date	1/23/2017 A
Label ng Rev ewer	Rita Lindie A
Label ng eam Lea Ar	Theresa Liu A

Rev ew Conclu An A

☐ ACCEPTABLE – No Comments. A

☒ ACCEPTABLE – Include Post Ap Aroval Comments A

☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Ap Alicant. A

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily A Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included A in the Complete Response (CR) letter to the applicant. A

☐ On Policy Alert List A

1 g ING COMMENgTS g

1 1 L g ING D gFICI NCI S ND COMMENgTS FOR gTT gR TO PP gIC gNT g

abelin Deficiencies determined on (add date) based on your submission(s) dated (add date): g

1. GENERAL COMMENTS g
   Comment g

2. CONTAINER LABEL g
   a. Comment g
   b. Comment g
3. CARTON LABELING g
4. PRESCRIBING INFORMATION g
   a. Comment g
   b. Subheading g
      i. Comment g
      ii. Comment g
5. MEDICATION GUIDE g
6. STRUCTURED PRODUCT LABELING (SPL) g

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect g the full content of the labeling as well as the planned ordering of the content of the labeling. The container label g and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text g size, and style. g

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed g labeling with Choose an item. all differences annotated and explained. We also advise that you only address the g deficiencies noted in this communication. g

However, prior to the submission of your amendment, please check labeling resources, including g DRUGS@FDA, the electronic Orange Bogk and the NF-USP online, for recent updates and make any g necessary revisions to your labels and labeling. g

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new g documents posted on the CDER web site at the following address – g

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17 g

1 2 COMMENgTS FOR gTT gR TO PP gIC gNT WH gN g ING IS CC gPT g

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) g dated (add date) g

1 3 POST PPROVg R gVISIONS g

These comments will NOT be sent to the applicants at this time. g
These comments will be addressed post approval (in the first labeling supplement review). g

1 P i ENVELOPE i

Please add the ND i number to the top th rd port on of the pr nc pal d splay panel per 21 FR i 207 35(b)(3) i

2. PRIOR LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments:

The below comments are from the labeling review C1 based on the submission dated 4/14/16.

1. GENERAL COMMENTS
   Include the country of origin on all your labeling pieces.

2. PATCH LABEL
   We note that final printed labeling (FPL) for the patch was not submitted for this application. Please ensure to include the established name and strength of the drug product, Lidocaine Patch 5%, on the patch when submitting FPL of the patch.

3. PATCH ENVELOPE
   a. Please ensure that the dotted line for cutting is only present on the top (as one single straight line), as opposed to along all four sides.
   b. We recommend revising the presentation of the established name from all upper case letters to title case (i.e., Established Name) to improve its readability.
   c. Relocate "Rx Only" symbol and net quantity statement to the lower portion of principal display panel and remove the bold facetype.
   d. Revise "DOSAGE" to read as (b) (4)
   e. Add the following statement to appear in conjunction with the storage statement: "[see USP Controlled Room Temperature]".

4. CARTON LABELING
   See applicable patch envelope comments.

5. PRESCRIBING INFORMATION
   Please replace the abbreviation (b) (4) with "mcg" for clarity.

6. STRUCTURED PRODUCT LABELING (SPL)
   Revise the list of the inactive ingredients to reflect the list of the inactive ingredients in your package insert and consistent with your submission.

Applicant responded to all of the above comments. Per applicant, "please note that the dotted line for cutting will only be present on the top as one single straight line per FDA Easily Correctable Deficiency comment, Labeling: (3) (a) Patch Envelope. The light dotted lines, shown on the label, are for die line purposes to show the layout of the envelope heat seal to the back panel."

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

3 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

Comments to applicant:

- Please add the NDC number to the top third portion of the principal display panel per 21 CFR 207.35(b)(3).

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

NA to enter text.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.

DEL PRESCRIBING INFRe e A TINee

Tabl 1: R evi w Mod e Lab eling for Pr scribing Information and Pati nt Lab eling e (Ch eck th ebox us ed as th eMod e Lab eling) e
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** e *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling* e *information.)* e **NDA# /Suppl ment# (S-000 if original):** 020612/S-012 e **Suppl ment Approval Dat :** 1/7/2015 e **Propri tary Name:** Lidoderm® e **Establish ed Name:** lidocaine patch e **D escription of Suppl ment:** e This supplemental application, submitted as a “Changes Being Effected in 30 days” supplement, e provides for the addition of the statements “Lidoderm may not stick if it is wet. Avoid contact with water e such as bathing, swimming or showering.” to the DOSAGE AND ADMINISTRATION section of the e Package Insert, Overwrap Envelope, and Carton labeling. e
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** e **ANDA#/Suppl ment# (S-000 if original):** NA to enter text. e **Suppl ment Approval Dat :** NA to enter text. e **Propri tary Name:** NA to enter text. e **Establish ed Name:** NA to enter text. e **D escription of Suppl ment:** e
☐ **TEMPLATE (.g., BPCA, PREA, Carv eout):** NA to enter text. e
☐ **OTHER (D escrib e):** eNA to enter text. e

Reviewer Assessment: e

Is the Prescribing Information same as the model labeling, except for differences allowed under e 21 CFR 314.94(a)(8)? **YES** e
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES** e
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO** e

Reviewer Comments: Aceeptable e

NA to enter text. e

DEL CNe TAINER LABELS e

o **del container/carton/blister labels** [Source: DARRTS S-012 approval letter e

Cut along dotted line

NDC 63481-687-01

R_x only

Each adhesive patch contains:
Lidocaine . . . . . 700 mg (50 mg per gram adhesive) in an aqueous base.
Methylparaben and propylparaben as preservatives.

DOSAGE: Apply up to 3 patches. See package insert for complete prescribing information.

1 PATCH
(10 cm x 14 cm)

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

WARNING: Keep used and unused patches out of the reach of children, pets and others.

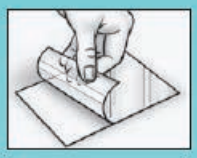
endo pharmaceuticals
an endo international company

Manufactured for: **Endo Pharmaceuticals Inc.**, Malvern, PA 19355
Manufactured by: Teikoku Seiyaku Co., Ltd., Sanbonmatsu, Kagawa 769-2695, Japan

DIRECTIONS FOR USE

Do not store patch outside the sealed envelope.

Cut the envelope along the dotted line. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Safely discard the remaining unused pieces of cut patches where children and pets cannot get to them.



Remove the transparent release liner (clear plastic backing) before application of patch to the skin.
Apply immediately after removal from the protective envelope.

Apply the prescribed number of patches, only once for up to 12 hours within a 24 hour period. Remove patches if irritation occurs.

Placement of external heat sources, such as heating pads or electric blankets, over LIDODERM patches is not recommended.

LIDODERM may not stick if it gets wet. Avoid contact with water, such as bathing, swimming or showering.

3 63481-687-017

Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them.

211374

[redacted]

LOT:

EXP:

(b) (4)

3 c TED STATES PHARMACOPE A (SP) & PHARMACOPE A FORc M (PF) c

We sear hed the USP and PF to determine if the drug produ t under review is the subje t of a USP monograph c or proposed USP monograph. c

Table 2: USP and PF Search Results c				
	Date c Searched c	Monograph c ? YES or c NO c	Monograph Title c (NA if no monograph) c	Packaging and Storage/Labeling c Statements c (NA if no monograph) c
US c P c	3/8/2017 c	No c	NA to enter text. c	NA to enter text. c
PF c	3/1/2017 c	No c	NA to enter text. c	NA to enter text. c

Reviewer Comments: c

NA to enter text. c

3 5 PATE cTS A cD EXCL cS V T ES c

The Orange Bcok was sear hed on 3/1/2017. c

Table 3 provides Orange Bcok patents for the Model Labeling NDA 020612 and ANDA patent ertifi ations. c

(For appli ations that have no patents, N/A is entered in the patent number olumn) c

Table 3: Impact of Model Labeling Patents on ANDA Labeling c						
Patent c Number c	Patent c Expiration c	Patent c Use Code c	Patent Use Code Definition c	Patent c Certificatio n c	Date of c Patent c Cert c Submissio n c	Labeling c Impact c (enter c “Carve- c out” or c “None”) c
NA to enter text. c	c					

r Ass ssm ant: r

Is the applicant's "patent ca ve out" acceptable? **NA** r

Reviewer Comments: r

NA to ente text. r

Table 4 p ovides O ange Book exclusivities fo the Model Labeling and ANDA exclusivity statements. r

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling r					
Exclusivity Code r	**Exclusivity Expiration** r	**Exclusivity Code Definition** r	**Exclusivity Statement** r	**Date of Exclusivity Submissio n** r	**Labeling Impact** r **(enter "Carve-out" or "None")** r
NA to enter text. r	r				

r Ass ssm ant: r

Is the applicant's "exclusivity ca ve out" acceptable? **NA** r

Reviewer Comments: r

NA to ente text. r

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT r

Tables 5, 6, and 7 desc ibe any changes in the inactive ing edients, dosage fo m desc iption, package sizes, and r manufactu e /dist ibuto /packe statements of the P esc ibing Info mation o D ug Facts fo OTC p oducts r when compa ed to the p evious labeling eview. r

r Ass ssm ant: r

A e the e changes to the inactives in the DESCRIPTION section o Inactive Ing edients (OTC)? **NO** r
A e the e changes to the dosage fo m desc iption(s) o package size(s) in HOW SUPPLIED o package size(s) r fo OTC? **NO** r
A e the e changes to the manufactu e /dist ibuto /packe statements? **YES** r
If yes, then comment below in Tables 5, 6, and 7. r

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC) r		
Previous Labeling Review r	**Currently Proposed** r	**Assessment** r
Each adhesive patch contains 700 mg of lidocaine (50 mg per gram adhesive) in an aqueous base. It also contains the following inactive ingredients: purified r water, sorbitol, glycerin, polyacrylic acid, sodium carboxymethylcellulose, r propylene glycol, sodium polyacrylate, urea, kaolin, tartaric acid, gelatin, r polyvinyl alcohol, dihydroxyaluminum r aminoacetate, disodium edetate, r methylparaben and propylparaben. r	Each adhesive patch contains 700 mg of lidocaine (50 mg per gram adhesive) in an aqueous base. It also contains the following inactive ingredients: purified r water, glycerin, sorbitol, polyacrylic acid, sodium carboxymethylcellulose, sodium polyacrylate, propylene glycol, urea, r kaolin, tartaric acid, gelatin, polyvinyl r alcohol, dihydroxyaluminum r aminoacetate, disodium edetate, r methylparaben and propylparaben. r	r r r r r No changes r

6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Lidocaine patch 5% is available as the following: Carton of 30 patches…… …… NDC 42858-118-30 (packaged in individual child-resistant envelopes)	Lidocaine patch 5% is available as the following: Carton of 30 patches…… … NDC 42858-118-30 (packaged in individual child-resistant envelopes)	No changes

7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Marketed by: Rhodes Pharmaceuticals L.P Coventry, RI 02816	Marketed by: Rhodes Pharmaceuticals L.P Coventry, RI 02816 Manufactured by: Altergon Italia Srl, Morra de Sanctis Avellino 83040, Italy	Updated to include "manufactured by" information as requested by Agency.

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:

NA to enter text.

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments:

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container (patch)	Final	1 patch	1/23/2017	Satisfactory
Patch Envelope	Final	1 envelope containing 1 patch	1/23/2017	Satisfactory
Blister	Choose an item.	NA to enter text.	NA to enter text.	NA to enter text.
Carton	Final	30 patches (1 patch per envelope)	1/23/2017	Satisfactory

r – sp ncify) m	Choose an itemm . m	NA to enter text. m	NA to enter m text. m	NA to enter text. m
Tabl 9 R wi w Summary of Pr scribing Informa ion and Pa i n Lab ling m				
	Final or Draf or NA m	m **R vision Da mand/or Cod** m	m **Submission R o iv d Da** m	m **R commenda i on** m
Pr scribing Informa ion m	Final m	1/2017 m	1/23/2017 m	Satisfactory m
Medica ion Guid m m	Choose an itemm . m	NA to enter text. m	NA to enter m text. m	NA to enter text. m
Pa i n Informa ion m m	Choose an itemm . m	NA to enter text. m	NA to enter m text. m	NA to enter text. m
SPL Da a El m nts m		1/2017 m	1/23/2017 m	Satisfactory m

Theresa I
Li I

i i a y si ned by Theresa Li I
a e: 3/02/2017 10:33:58AM I
GUI : 508da70a00028d58911de18a598cda6f I

Ri a I
Lindie I

i i a y si ned by Ri a Lindie
a e: 3/01/2017 11:16:48AM I
GUI : 53c570830001639fca7572eedfad43b0 I

L ABELING REVIEWA

Division of Labeling Review A
Office of Regulatory Operations A
Office of Generic Drugs (OGD) A
Center for Drug Evaluation and Research (CDER) A

Date of A Rev ew	1/4/2017 **A**
ND ANumber( )	209190 **A**
Rev ew Number	1 **A**
ppl cant Name A	Rhodes Pharmaceuticals L.P. **A**
E tabl Ae Name & Strengt ( )	Lidocaine Patch 5% **A**
Propo e Propr etary Name	NA **A**
Subm i An Rece ve Date	4/14/2016 **A**
Label ng Rev ewer	Rita Lindie **A**
Label ng eam Lea Ar	Theresa Liu **A**

Rev ew Conclu An A

☐ ACCEPTABLE – No Comments **A**

☐ ACCEPTABLE – Include Post Approval Comments **A**

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant. **A**

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily A Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included A in the Complete Response (CR) letter to the applicant. **A**

☐ On Policy Alert List **A**

TABLE OF CONTENTS

1 f ING COMMENTS f

1 1 L f ING D fFICI NCI S ND COMMENTS FOR f TT fR TO PP fIC fNT f

Labeling De iciencies determined on January 5, 2017 based on your submission dated April 14, 2016: f

1. GENERAL COMMENTS f
   Include the country o origin on all your labeling pieces. f

2. PATCH LABEL f
   We note that inal printed labeling (FPL) or the patch was not submitted or this application. f
   Please ensure to include the established name and strength o the drug product, Lidocaine Patch f
   5%, on the patch when submitting FPL o the patch. f

3. PATCH ENVELOPE f
   a. Please ensure that the dotted line or cutting is only present on the top (as one single straight f
      line), as opposed to along all our sides. f
   b. We recommend revising the presentation o the established name rom all upper case letters to f
      title case (i.e., Established Name) to improve its readability. f
   c. Relocate "Rx Only" symbol and net quantity statement to the lower portion o principal display f
      panel and remove the bold acetype. f
   d. Revise "DOSAGE" to read a f" (b) (4) " f
   e. Add the ollowing statement fo appear in conjunction with the storage statement: "[see USP f
      Controlled Roo om Temperature]". f

4. CARTON LABELING f
   See applicable patch envelope comments. f

5. PRESCRIBING INFORMATION f
   Please replace the abbreviations (b) (4) with "mcg" or clarity. f

6. STRUCTURED PRODUCT LABELING (SPL) f
   Revise the list o the inactive ingredients to re lect the list o the inactive ingredients in your f
   package insert and consistent with your submission. f

Submit your revised labeling electronically. The prescribing in ormation and any patient labeling should re lect f
the ull content o the labeling as well as the planned ordering o the content o the labeling. The container label f
and any outer packaging should re lect the content as well as an accurate representation o the layout, color, text f
size, and style. f

To acilitate review o your next submission, please provide a side-by-side comparison o your proposed f
labeling with your last submitted labeling with all di erences annotated and explained. We also advise that you f
only address the de iciencies noted in this communication. f

However, prior to the submission o your amendment, please check labeling resources, including f
DRUGS@FDA, the electronic Orange Boo k and the NF-USP online, or recent updates and make any f
necessary revisions to your labels and labeling. f

I Ee keep ANDA labeli g cu e E, we sugges ha y u subsc ibe he aily weekly up a es f ew E cume Es p s e E he CD ER web si e a he f ll wi g a E ess – E

h p://se vice.g v elive y.c m/se vice/subsc ibe.h ml?c Ee=USFDA_17 E

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE E

The Divisi E f Labeli g has Efu he ques i Es/c mme Es a his ime base Ey u labeli g submissi E(s) E a e (a E a e). E

1.3 POST APPROVAL REVISIONS E

These c mme Es will NOT be se E he applica Es a his ime. E
These c mme Es will be a E esse p s app Eval (i he fi s labeli g suppleme E eview). E
NA e Ee ex . E

2. LABELING REVIEW INFORMATIONE

2.1 REGULATORY INFORMATIONE

Has the ANDA beEn accepted for filing? YES E
Are there any pending issues in DLR's SharePoint Drug Facts? NO E If Yes, please explai . E
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO E If Yes, please explai . E

2.2 MODEL LABELING E

2.2.1 MODEL PRESCRIBING INFORMATION E

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling E (Check the box used as the Model Labeling) E
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** E *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA RLD information.)* E **NDA#/Supplement# (S-000 if original):** 020612/S-012 E **Supplement Approval Date:** 1/7/2015 E **Proprietary Name:** Lidoderm®E **Established Name:** lidocaine patch E **Description of Supplement:** E This supplemental application, submitted as a "Changes Being Effected in 30 days" supplement, E provides for the addition of the statements "Lidoderm may not stick if it is wet. Avoid contact with water E such as bathing, swimming or showering." to the DOSAGE AND ADMINISTRATION section of the E Package Insert, Overwrap Envelope, and Carton labeling. E

T t : R tvi w Mod t L t ing for Pr scri ing Inform a ibn nd P ti n L t ing t (Ch tck h t ox us td s h t Mod t L t ing) t
☐ **MOST RECENTLY APPROVED ANDA RLD LABELING t** **ANDA#/Supp tment# (S-000 if origin t):** NA to enter text. t **Supp tment Approv t D t :** NA to enter text. t **Propri t ry N tme: t** NA to enter text. t **Es t ish td N tme: t** NA to enter text. t **D tscrip ion of Supp tment:** NA to enter text. t
☐ **TEMPLATE (.g., BPCA, PREA, C trv t-ou):** NA to enter text. t
☐ **OTHER (D tscri t):** NA to enter text. t

2.2.2 MODEL CONTAINER LABELS t

Model container/carton/blister labels (Source: DARRTS S-012 approval letter) t

Cut along dotted line

NDC 63481-687-01

R_x only

Each adhesive patch contains:
Lidocaine . . . . . 700 mg (50 mg per gram adhesive) in an aqueous base.
Methylparaben and propylparaben as preservatives.

DOSAGE: Apply up to 3 patches. See package insert for complete prescribing information.

1 PATCH
(10 cm x 14 cm)

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

WARNING: Keep used and unused patches out of the reach of children, pets and others.

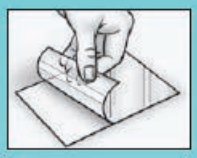
endo pharmaceuticals
an endo international company

Manufactured for: **Endo Pharmaceuticals Inc.**, Malvern, PA 19355
Manufactured by: Teikoku Seiyaku Co., Ltd., Sanbonmatsu, Kagawa 769-2695, Japan

DIRECTIONS FOR USE

Do not store patch outside the sealed envelope.

Cut the envelope along the dotted line. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Safely discard the remaining unused pieces of cut patches where children and pets cannot get to them.



Remove the transparent release liner (clear plastic backing) before application of patch to the skin.
Apply immediately after removal from the protective envelope.

Apply the prescribed number of patches, only once for up to 12 hours within a 24 hour period. Remove patches if irritation occurs.

Placement of external heat sources, such as heating pads or electric blankets, over LIDODERM patches is not recommended.

LIDODERM may not stick if it gets wet. Avoid contact with water, such as bathing, swimming or showering.

3 63481-687-01 7

Fold used patches so that the adhesive side sticks to itself and safely discard used patches or pieces of cut patches where children and pets cannot get to them.

211374

[redacted]

LOT:

EXP:

2 c TED STATES PHARMACOPE A (SP) & PHARMACOPE A FORc M (PF) c

We sear hed the USP and PF to determine if the drug produ t under review is the subje t of a USP monograph c or proposed USP monograph. c

Table 2: USP and PF Search Results c				
	Date c Searched c	Monograph c ? YES or c NO c	Monograph Title c (NA if no monograph) c	Packaging and Storage/Labeling c Statements c (NA if no monograph) c
USP c	1/6/2017 c	NO c	NA to enter text. c	NA to enter text. c
PF c	1/5/2017 c	NO c	NA to enter text. c	NA to enter text. c

2 4 PATE cTS A cD EXCL cS V T ES c

The Orange Bcok was sear hed on 1/5/2017. c

Table 3 provides Orange Bcok patents for the Model Labeling (NDA 020612) and ANDA patent ertifi ations. c (For appli ations that have no patents, N/A is entered in the patent number olumn.) c

Table 3: Impact of Model Labeling Patents on ANDA Labeling c						
Patent c Number c	Patent c Expiration c	Patent c Use Code c	Patent Use Code Definition c	Patent c Certification c	Date of c Patent Cert c Submission c	Labeling c Impact c (enter Carve- c out c or None) c
NA to enter text. c	c					

Table 4 provides Orange Bcok ex lusivities for the Model Labeling and ANDA ex lusivity statements. c

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
NA to enter text.					

2.5 MANUFACTURING FACILITY

Table 5 provides a description of the drug product manufacturing facility.

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	Name and Address on ANDA Container/Carton	Name and Address on ANDA Prescribing Information
3.2.P.3 Altergon Italia S.r.l. (Altergon), Zona Industriale A.S.L. Morra De Sanctis Avellino 83040 Ital (b) (4)	Container (envelope) Marketed by: Rhodes Pharmaceuticals L.P Coventry, RI 02816 Carton Marketed by: Rhodes Pharmaceuticals L.P Coventry, RI 02816	Marketed by: Rhodes Pharmaceuticals L.P Coventry, RI 02816

3. ASSESSMENT OF ANDA LABELING AND LABELS

The results for each material reviewed in this section provide the basis for the labeling comments to the applicant.

Is this product Rx or OTC? Please check one.

☒ Rx Product (If Rx, skip 3.2 OTC DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE.)
☐ OTC Product (If OTC, skip 3.1 RX DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE)

3.1 RX (PRESCRIPTION) DRUG PRODUCT

3.1.1 RX: PRESCRIBING INFORMATION

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Is the established name for this ANDA acceptable? **YES**
Does the Model Labeling have combined insert labeling for multiple NDAs or dosage forms? **NO**
Are the required USP recommendations reflected in the labeling? **NA**
Is the applicant's "patent carve out" acceptable? **NA**

Is the applicant's "exclusivity carve out" acceptable? **NA**
Is the Manufacturer statement acceptable? **NO**

Reviewer Comments:
Comments to applicant:
-Please replace the abbreviations "µg" with "mcg" for clarity.
- Include the country of origin on all your labeling pieces.

3.1.1.1 RX: DESCRIPTION

We reviewed the DESCRIPTION section for accuracy (with input from the chemistry review, if appropriate) and acceptability from Labeling perspective. We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling Inactive Ingredients	ANDA Labeling Inactive Ingredients
inactive ingredients: dihydroxyaluminum aminoacetate, disodium edetate, gelatin, glycerin, kaolin, methylparaben, polyacrylic acid, polyvinyl alcohol, propylene glycol, propylparaben, sodium carboxymethylcellulose, sodium polyacrylate, Dsorbitol, tartaric acid, and urea.	inactive ingredients: purified water, sorbitol, glycerin, polyacrylic acid, sodium carboxymethylcellulose, propylene glycol, sodium polyacrylate, urea, kaolin, tartaric acid, gelatin, polyvinyl alcohol, dihydroxyaluminum aminoacetate, disodium edetate, methylparaben and propylparaben.

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling Memorandum of Understanding (MOU)?
YES, chemistry review pending
(Note: The MOU became effective on November 1, 2014. MOU does not apply to amendment reviews for ANDAs originally reviewed before November 1, 2014.)

If the chemistry review follows the MOU, labeling reviewer is not responsible for reviewing for accuracy of the DESCRIPTION section for chemical properties, system components of the drug product, etc. Please refer to the MOU, Appendix A, DESCRIPTION section for delineation of responsibilities. If chemistry review does NOT follow the MOU, labeling reviewer will follow the traditional review approach of reviewing the entire DESCRIPTION section.)

Are the inactive ingredients information consistent with "Components and Composition" information as provided in Module 3.2.P.1? (If Chemistry follows the MOU, refer to the Labeling section of Chemistry review.) **YES**
For products required to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **NA**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO (See comment under Section 4)**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **NA** Has the statement been verified by chemistry? **NA**

Reviewer Comments: Acceptable
NA to enter text.

3.1.1.2 RX: HOW SUPPLIED/STORAGE AND HANDLING

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 7 and will be referred to the appropriate review discipline for evaluation.

Table 7: Comparison of Model Labeling to ANDA Labeling f	
Model f Labeling f	LIDODERM (lidocaine patch 5%) is available as the following: f Carton of 30 patches, packaged into individual child-resistant envelopes NDC 63481- f 687-06 Store at 25ºC (77ºF); excursions permitted to 15o-30oC (59o-86oF). [See USP f Controlled Room f Temperature]. f
ANDA f Labeling f	Lidocaine patch 5% is available as the following: f Carton of 30 patches…… ……NDC f 42858-118-30 f (packaged in individual child-resistant envelopes) f Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP f Controlled Room Temperature]. f

R f ***Ass ssm ntf*** f

Does the chemistry review ollow the Chemistry/Labeling MOU? **YES, chemistry review pending** f
I the chemistry review does NOT ollow the MOU, is the description (scoring, color and imprint) o the f
inished product in the HOW SUPPLIED section consistent with the in ormation in Module 3.2.P.5.1 or Drug f
Product Speci ication? **NA** f
Does the ANDA require the same color coding as the Model Labeling? **NO** f
Is there any di erence in scoring con iguration betwe en the ANDA and the Model Labeling? **NA** f
Are the packaging sizes and con igurations acceptable as compared to the Model Labeling? **YES**
I the packaging con iguration is di erent than the Model Labeling, does it require addition or deletion o f
labeling statements? **NA** f
Is the storage or dispensing statement acceptable as compared to the Model Labeling? **YES**
Is the storage or dispensing statement acceptable as compared to the USP? **NA** f

Reviewer Comments: Ac ceptable f

3.1.2 RX: MEDICATION GUIDE f

Is Medication Guide required? **NO** f
I YES go to Reviewer Assessment below, i NO go to section 3.1.3. f

R f ***Ass ssm ntf*** f

Was Medication Guide submitted? **NA** f
Is the Medication Guide same as the model labeling, except or allowable di erences? **NA** f
Does the Medication Guide meet the requirements o 21 CFR 208.20? **NA** f
Has the Appplicant committed to provide a su ficient number o medication guides? **NA** f
Is the phonetic spelling o the proprietary or established name present? **NA** f
Is FDA 1-800-FDA-1088 phone number included? **NA** f

Reviewer Comments: f
NA to enter text. f

3.1.3 RX: OTHER PATIENT LABELING f

Are other patient labeling required? **NO** f
I YES go to Reviewer Assessment below, i NO go to section 3.1.4. f

R f ***Ass ssm ntf*** f

Was other patient labeling submitted? **NA** f
Is the patient labeling the same as the model labeling, except or allowable di erences? **NA** f

Reviewer Comments: f
NA to enter text. f

3.1.4 RX: CONTAINER LABEL

Was container label (other than Blisters) submitted? **YES**
(For BLISTER labels go to section 3.1.5.)

We evaluated the container labels for the inclusion of all required statements and safety considerations.

Reviewer Assessment:

Is the established name acceptable? **YES**
Is title case used in expressing the established name? **NO**
Does labeling comply with Tall Man lettering recommendations found on FDA webpage? **NA**
Is container label too small to contain all required information? **NO** If yes, does the container meet the "too small" exemption found in 21 CFR 201.10(i)? **NA**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **YES**
Is the following information properly displayed?

- Net quantity statement: **YES**
- Route(s) of administration (other than oral): **YES**
- Warnings (if any) or cautionary statements (if any): **NA**
- Medication Guide Pharmacist instructions per 21 CFR 208.24(d): **NA**
- Controlled substance symbol: **NA**
- Usual Dosage statement: **YES**
- Product strength equivalency statement: **NA**
- NDC: **YES**
- Bar code per 21 CFR 201.25(c)(2): **YES**

Is the Manufacturer/Distributor/Packager statement acceptable? **YES**
For foreign manufacturers, does the labeling have the country of origin? **NO**
Are the required USP recommendations reflected on the label(s)? **NA**
Is the storage or dispensing statement consistent with the How Supplied section of the insert? **YES**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**
Are multiple strengths differentiated by use of different color or other acceptable means? **NA**
Are the labels of related products differentiated to avoid selection errors? **NA**
Does the ANDA require the same color coding as the Model Labeling? **NO**
Are the requirements of 21 CFR 201.15 met for all required label statements? **YES**
Are the requirements of 21 CFR 201.100 met for all required label statements? **YES**

Reviewer Comments:
Comments to applicant:
-We note that final printed labeling (FPL) for the patch was not submitted for this application. Please ensure to include the established name and strength of the drug product, Lidocaine Patch 5%, on the patch when submitting FPL of the patch.
- Please ensure that the dotted line for cutting is only present on the top (as one single straight line), as opposed to along all four sides.
-We recommend revising the presentation of the established name from all upper case letters to title case (i.e., Established Name) to improve its readability.
-Relocate "Rx Only" symbol and net quantity statement to the lower portion of principal display panel and remove the bold facetype.
-Revise "DOSAGE" to read as [redacted] (b) (4)
- Add the following statement to appear in conjunction with the storage statement: "[see USP Controlled Room Temperature]".
-Include the country of origin.

3.1.4.1 RX: CONTAINER LABEL FOR PARENTERAL SOLUTIONS

b tai er f r pare teral luti b? **NO** b
f YES g t Reviewer A be bme t el w, if NO g t e ti b3.1.4.2. b

Reviewer Assessment: b

the pr du t tre gth expre ed a t tal qua tity per t tal v lume f ll wed y the b e trati per milliliter b (mL), a de bri ed i the USP, Ge eral Chapter <1> je ti b? **NA** b f v lume i le btha 1 mL, i tre gth per fra ti b f a milliliter the bly expre bi b f tre gth? **NA** b the qua tity r pr p rti b f all i a tive i gredie t li ted bla el a required u der 21 CFR b 201.100( )(5)(iii)? **NA** b

Reviewer Comments: b
NA t e ter text. b

3.1.4.2 RX: CONTAINER LABEL FOR SOLID INJECTABLE b

b tai er f r lid i je ta le (ther tha Pharma y Bulk Pa kage)? **NO** b
f YES g t Reviewer A be bme t el w, if NO g t e ti b3.1.4.3. b

Reviewer Assessment: b

the tre gth i term s fbthe t tal am ou bt f drug per vial? **NA** b Are i bru ti b f r re b tituti ba d re ulta t b e trati bpr vided, if pa e permit ? **NA** b the qua tity r pr p rti b f all i a tive i gredie t li ted bla el a required u der 21 CFR b 201.100( )(5)(iii)? **NA** b

Reviewer Comments: b
NA t e ter text. b

3.1.4.3 RX: CONTAINER LABEL FOR PHARMACY BULK PACKAGE b

b tai er a Pharma y Bulk Pa kage (pare teral preparati b f r admixture)? **NO** b
f YES g t Reviewer A be bme t el w, if NO g t e ti b3.1.5. b

Reviewer Assessment: b

the tre gth i term s fbthe t tal am ou bt f drug per vial? **NA** b there a pr mi e t, bxed de larati breadi g "Pharma y Bulk Pa kage – N t f r Dire t fu i b" bthe b pri ipal di play pa el f ll wi g the expre bi b f tre gth? **NA** b D be the b tai er la el i bude graduati bmark ? **NA** b Are i bru ti b f r re b tituti ba d re ulta t b e trati bpr vided, if pa e permit ? **NA** b D be la el b tai the required i f rmati b bpr per a epti te h ique i budi g time frame i whi h the b tai er may e u ed b e it ha de e tered? **NA** b the qua tity r pr p rti b f all i a tive i gredie t li ted bla el a required u der 21 CFR b 201.100( )(5)(iii)? **NA** b

Reviewer Comments: b
NA t e ter text. b

3.1.5 RX: UNIT DOSE BLISTER LABEL b

b tai er a U bit D be Bli ter Pa k? **NO** b
f YES g t Reviewer A be bme t el w, if NO g t e ti b3.1.6. b

Reviewer Assessment: b

D be ea h li ter i bude bly be d bage u it (e.g., be ta let, be ap ule)? **NA** b D bpr prietary ame, e ta li hed ame, tre gth, ar bde, a d ma ufa turer appear a burately bea h li ter b ell? **NA** b

Reviewer Comments: b

NA to enter text.

3.1.6 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Was carton labeling submitted? **YES**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Are the answers to the Container Label questions the same for the Carton Labeling? **YES** If no, please explain the differences in the Reviewer Comments section.
If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **NA**
If country of origin is not on Container, does it appear on outer packaging labeling? **NO**

Reviewer Comments:
Comments to applicant:
-See container label comments.

3.2 OTC (OVER THE COUNTER) DRUG PRODUCT

3.2.1 OTC: LABELING THAT INCLUDES DRUGS FACTS INFORMATION

Reviewer Assessment:

Is Drug Facts Labeling format acceptable per 21 CFR 201.66? **NA**
Does "Questions?" have a toll-free number no less than 6 pt. font size per 21 CFR 201.66(c)(9) or "1-800-FDA-1088" per 21 CFR 201.66 (c)(5)(vii)? **NA**
Did firm submit a Labeling Format Information Table to evaluate the font size? **NA**
Is the applicant's "patent carve out" acceptable? **NA**
Is the applicant's "exclusivity carve out" acceptable? **NA**
Is the established name for this ANDA acceptable? **NA**
Is title case used in expressing the established name? **NA**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **NA**
Is the following information properly displayed?
- Pharmacological category: **NA**
- Net quantity statement: **NA**
- Route(s) of administration (other than oral): **NA**
- Warnings (if any) or cautionary statements (if any): **NA**
- NDC: **NA**
- Bar code per 21 CFR 201.25(c)(2): **NA**

Is the Manufacturer/Distributor/Packager statement acceptable? **NA**
For foreign manufacturers, does the labeling have the country of origin? **NA**
Are the required USP recommendations reflected in the labeling? **NA**
Is the storage statement acceptable? **NA**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**
Are multiple strengths differentiated by use of different color or other acceptable means? **NA**
Are the labels of related products differentiated to avoid selection errors? **NA**

Reviewer Comments:
NA to enter text.

3.2.1.1 OTC: INACTIVE INGREDIENTS COMPARISON

We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

8: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section P	
Model PLP ing Inactive Ingredients P	**ANDA Inactive Ingredients P**
NA to enter text. P	NA to enter text. P

Reviewer Assessment: **P**

Are the inactive ingredients information consistent with "Components and Composition" information as provided in Module 3.2.P.1? **NA P** **P**
Are the inactive ingredients listed in alphabetical order? **NO P**
For products required/recommended to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **NA P** **P**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA P**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **NA** Has the statement been verified by chemistry? **NA P** **P**

Reviewer Comments: **P**
NA to enter text. P

3.2.1.2 OTC: HOW SUPPLIED AND STORAGE INFORMATION P

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 9 and will be referred to the appropriate review discipline for evaluation. **P** **P**

9: Comparison of Model PLP ing to ANDA finished product P	
Model PLP ing P	**Description of Finished Product** (Source: NA to enter text.) P NA to enter text. P **Packaging Configurations** (Source: NA to enter text.) P NA to enter text. P **Storing Conditions** (Source: NA to enter text.) P NA to enter text. P
ANDA P	**Description of Finished Product** (Source: NA to enter text.) P NA to enter text. P **Packaging Configurations** (Source: NA to enter text.) P NA to enter text. P **Storing Conditions** (Source: NA to enter text.) P NA to enter text. P

Reviewer Assessment: **P**

Is the description (scoring, color and imprint) of the finished product consistent with the Drug Product Quality submission? **NA P** **P**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NA P**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **NA P**

e ackaging con igura ion is di eren an e Model Labeling, does i require addi ion or dele ion o labeling s a emen s? **N A**

s e s orage s a emen acce able as com ared o e Model Labeling? **N A**

s e s orage s a emen acce able as com ared o USP? **N A**

Reviewer Comments:

NA o en er ex .

3.2.2 OTC: PATIENT LABELING

s a ien labeling required? **N**

YES go o Reviewer Assessmen below, i NO go o sec ion 3.3.

Reviewer Assessment:

Was a ien labeling submi ed? **N A**

s e a ien labeling e same as e model labeling, exce or allowable di erences? **N A**

Reviewer Comments:

NA o en er ex .

3.3 CONTAINER/CLOSURE

We evalua ed e con ainer/closure sys em o is roduc o de ermine i s ecial c ild-resis an ackaging is required based on ackaging con igura ion. Ad i ionally, we evalua ed o r as ec s o e con ainer closure a rela e o e dosage orm, roduc ormula ion, and roduc class. Below is a descri ion o e con ainer/closure or e ANDA roduc .

Reviewer Assessment:

Describe con ainer closure (e.g., 30s CRC, 100s non-CRC) and ci e source o in orma ion in **Reviewer Comments** ex box.

Does e con ainer require a c ild-resis an closure (CRC) as described in e Poison Preven ion Ac and regula ions? **YES**

Are e am er viden requiremen s me or OTC and Con rolled Subs ances? (quali y review ollows e c emis ry-labeling MOU, ob ain answer rom A endix D o c emis ry review; i quali y review does no ollow e MOU, labeling reviewer is res onsible or assessing or am er vidence) **N A**

For ophthalmic products:

Does is o almic roduc ca color ma c American Academy o O almology (AAO) ackaging color-coding sc eme? **N A**

For parenteral products:

s ere ex on e ca / errul overseal o is inje able roduc ? **N A**

YES, does ex com ly vi e recommenda ions in USP General C r <1>? **N A**

Wha s e ca color? **NA to enter text.**

NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments:

From 3.2.P.7 QOS:

1 Page has been withheld in full as b4 (CCI/TS) immediately following this page

3.4 CALCULATIONS FOR CONTENTS IN LABELING

Is calculation of ingredient(s) required? **NO**
If YES, go to Table 10 and Reviewer Assessment below, if NO go to section 3.5.

We verified the calculation on the following content.

Table 10: Ingredients		
Ingredient	**Stated Content**	**Location of the Information**
NA to enter text.	NA to enter text.	NA to enter text.

(Note: For Rx products, if chemistry review follows the MOU, chemistry reviewer will verify the accuracy of the active and inactive ingredient amount(s) if information is in the DESCRIPTION and HOW SUPPLIED sections for all products, and additionally, DOSAGE AND ADMINISTRATION section for parenteral products. See Chemistry-Labeling MOU, Appendix A, Miscellaneous section for discussion on calculations.)

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling MOU? **NA**
Are the stated contents in the table above acceptable? **NA**
Aluminum content in small volume parenterals, large volume parenterals, and pharmacy bulk packages, which are used in TPNs, need to be in the labeling per 21 CFR 201.323.
Did the chemistry reviewer verify the aluminum content? **NA**
Are the labeling requirements met per 21 CFR 201.323? **NA**

Reviewer Comments:
NA to enter text.

3.5 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

Was SPL submitted? **YES**

We evaluated the SPL data elements to ensure they are consistent with the information submitted in the ANDA.

Table 11: ANDA Tablet/Capsule Size and Imprint		
Tablet/Capsule Strength	**ANDA Tablet/Capsule Size (mm) and imprint code from SPL**	**ANDA Tablet/Capsule Size (mm) and imprint code (Cite source of information such as the chemistry review that follows the MOU, Product Specification in 3.2.P.5.1, Commercial Batch Record in 3.2.P.3.3. etc.)**
NA to enter text.	NA to enter text.	NA to enter text.

Reviewer Assessment:

For solid oral dosage forms: Do size and imprint code from the SPL data elements match the information provided in the quality submission? **NA**
Are all the other data elements (strength, inactive ingredients, product characteristics, packaging etc.) consistent with the information submitted in the ANDA labeling? **NO**

Reviewer Comments:
Comments to applicant:
-Revise the list of the inactive ingredients to reflect the list of the inactive ingredients in your package insert and consistent with your submission.

ME NTS FR HE (I STRY REVIEWER (

Describe issue s) sent to and/or received from the chemistry also known as drug product quality) reviewer: (

(b) (4)

5 (E NTS FR T(HER REVIEW DIS (IPLINES (

Describe questions/issue s) sent to and/or received from other review discipline reviewer s): (

Reviewer omments: (

6 $ PE (IAL N SIDERATIN S (

NA to enter text. (

RALL ASS dSSMEN dT F MAT dRIALS R d I WED d

Tables 12 an 13 provi e a summary of recommen ations for each labeling piece analyze in this review. d

Table 12: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA d	**Packaging Sizes** d	**Submission Received Date** d	**Recommendation** d
Container (Patch envelope) d	Draft d	1 envelope containing 1 patch d	4/14/2016 d	Revise d
Blister d	NA to enter text.	NA to enter text. d	NA to enter text. d	NA to enter text. d
Carton d d	Draft d	30 patches (1 patch per envelope) d	4/14/2016 d	Revise d
(Other – Patch) d	NA to enter text.	NA to enter text. d	NA to enter text. d	NA to enter text. d
Table 13 Review Summary of Prescribing Information and Patient Labeling d				
	Final or Draft or NA d	**Revision Date and/or Code** d	**Submission Received Date** d	**Recommendation** d
Prescribing Information d	Draft d	3/2016 d	4/14/2016 d	Satisfactory d
Medication Guide d d	NA to enter text.	NA to enter text. d	NA to enter text. d	NA to enter text. d
Patient Information d	dNA to enter text.	NA to enter text. d	NA to enter text. d	NA to enter text. d
SPL Data Elements d	NA to enter text. d	3/2016 d	4/14/2016 d	Revise

Theresa 5
Li 5

i i a y si ned by Theresa Li 5
a e: 1/09/2017 09:18:02AM 5
GUI : 08da70a00028d 8911de18a 98cda6f 5

Ri a 5
Lindie 5

i i a y si ned by Ri a Lindie 5
a e: 1/09/2017 07:40:32AM 5
GUI : 3c 7083000165 9fca7 72eedfad43b0 5

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

MEDICAL REVIEW(s)

Clinical Review of Comparative (Threshold) Analyses for Drug-Device Combination Products

Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

ANDA#	209190
Drug Product	Lidocaine Patch
Strength(s)	5%
ANDA Applicant	Rhodes Pharmaceuticals LP
Reference Listed Drug (RLD)	Lidoderm (lidocaine) Patch, 5%
RLD#	020612
RLD Approval Date	3/19/1999
RLD Sponsor	Teikoku Pharma USA, Inc.
Primary Reviewer	Sunny Tse, PhD Clinical Reviewer, DCR/OB/OGD
Secondary Reviewer	Ying Fan, PhD Team Leader, ANDA Team, DCR/OB/OGD
Submission Date	4/14/2016
Materials Reviewed	• Draft Guidance "Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA" (01/2017) • RLD labeling dated 1/2019 • Proposed generic product (ANDA) labeling dated 1/2019 • Test product and RLD samples provided by the Applicant: 9/4/2019
Date of Review	10/23/2019
GDUFA Goal Date	3/29/2020
Comparative Threshold Analyses Conclusion	☐ No Design Differences - Acceptable ☒ Minor Design Differences ☒ Acceptable ☐ Not acceptable ☐ Other Design Differences ☐ Acceptable ☐ Not acceptable

Deficiency Classification	☐ Major ☐ Minor ☒ **N/A (Review is Adequate)** ☐Comments to the Office of Pharmaceutical Quality (OPQ) ☐Comments to the Division of Labeling Review (DLR)

1 INTRODUCTION AND BACKGROUND

1.1 Summary of Drug Product Information Pertinent to Review

Th s s a comparat ve analys s f Rh es Pharma eut als P's ("Applicant") proposed generic a ne Pat h (5%) subm itted under ANDA 209190 an the Referen e ste Drug (RLD), erm (l a ne) Pat h, 5%. The RLD was appr ve un er NDA 020612 f r rel ef f pa n ass ate with post-herpet neuralgia. The RLD s nten e f r a m n strat n by the user. The pr p se an RLD rug pr ducts are el vere t the user v a pat h ta n ng a ne, (5%) an theref re, t s s ere a mplex rug- ev e mb nat n pr duct. There are urrently 2 gener vers ns f the a ne Pat h (ANDAs 200675 an 202346).

Th s rev ew evaluates the el very ev e nst tuent part f the mb nat n pr duct nten e t a m n ster the rug pr duct an any ass ate pr duct label ng an pa kag ng. Th s rev ew f uses n the analys s f the user nterfa e[1] f r the rug- ev e mb nat n pr duct mpar ng the pr p se gener an the RLD.

1.2 Other Relevant Information

All mparat ve thresh l analyses rev ews that have been mplete f r the pr p se gener pr duct (subm itted by ther appl ants un er separate ANDAs) have been rev ewed. There are n pre-ANDA meet ng pa kages r ntr lled resp n en es f r th s rug pr duct, referr ng t NDA 020612 as an RLD, that relate t rug- ev e es gn evaluat n r mparat ve thresh l analyses rev ew.

2 COMPARATIVE (THRESHOLD) ANALYSES REVIEW AND DISCUSSION

DCR ute a mparat ve analys s f the user nterfa e f the pr p se gener mb nat n pr duct an ts RLD, a ne Pat h (NDA 020612).

2.1 Labeling Comparison: RLD vs. Proposed Generic Product

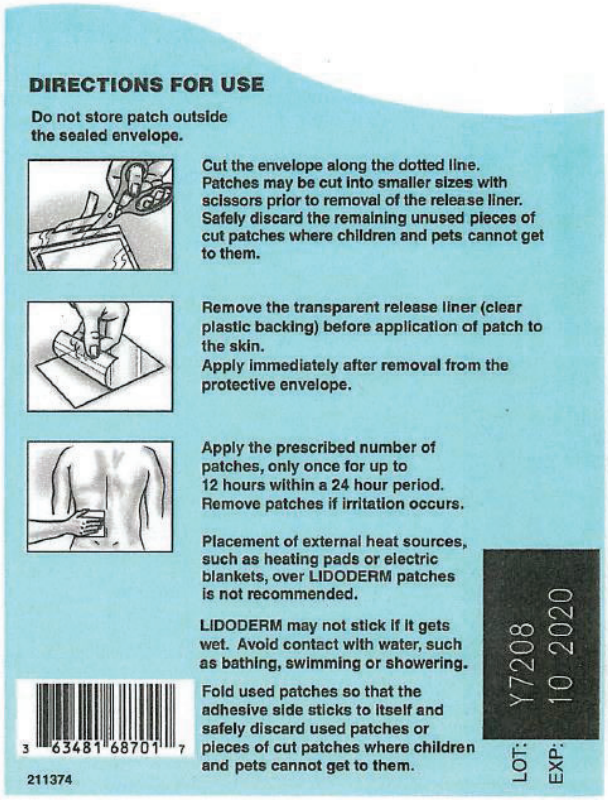
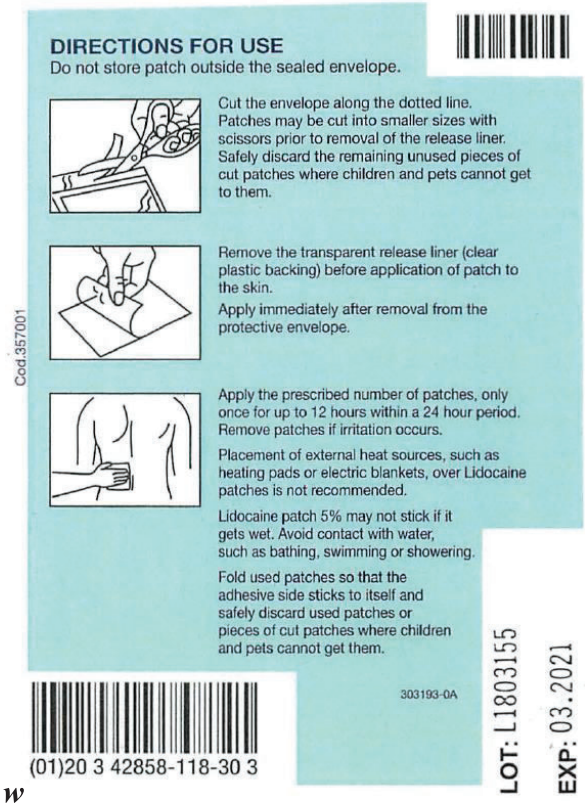
S e-by-s e, l ne-by-l ne label ng mpar s n f the *Directions For Use* was u te between the RLD an the pr p se gener pr duct. Ex ept f r the el very ev e nst tuent part label ng, the rev ew f the rema n er f the label s eferre t the D v s n f abel ng Rev ew (D R). The RLD label was r g nally appr ve n 3/19/1999. The m st urrent RLD label was rev se 1/2019.[2] The RLD label ng n lu es Pres r b ng Inf rmat n (PI) an D re t ns f r Use.

[1] User nterfa e refers t all mp nents f the mb nat n pr duct w th wh h a user ntera ts.
[2] NDA 020612 erm (l a ne) Pat h, 5% abel, rev se 1/2019. https://el st.f a.g v/prpllr/publ /spl/7 6 8ee-72e5-4f a-9966-2975a96 9465/7 6 8ee-72e5-4f a-9966-2975a96 9465.v ew

Table 1: **Labeling Comparison: RLD vs. Proposed Generic Product**

Delivery device constituent part labeling: RLD vs. Proposed Generic Product	**Yes/No/NA**
(1) Any difference in the **description/design**?	**No**
(2) Any difference in the **administration**?	**No**
(3) Any difference in the **illustration(s)/figure(s)**?	**Yes-Minor**
(4) Any differences in the end-user Directions for Use?	**Yes-Minor**

Table 2: w a is n f RLD and P w sed Gene ic P wduct Di ecti ns f wUse w

RLD w	P w sed Gene ic P wduct w
	

w w

w

***Revie er's Comments**: There were acceptable minor design differences identified in the w Directions for Use between the proposed generic product and RLD. Text in the Directions for w Use is the same for the RLD and proposed generic products. The figures in the IFU are similar. w However, RLD figures have shading, whereas the proposed generic product figures do not. This w difference is minor and acceptable. w*

w

Overall, the labeling comparison supports that the proposed generic product can be substituted w for the RLD without the intervention of a health care provider and/or without additional w training prior to use of the proposed generic product. w

w

2.2 C w a ative task analysis: RLD vs. P w sed Gene ic P wduct w

DCR examined the dosing delivery tasks of the proposed generic product compared to the RLD. w

w

***Revie er's Comments**: There were no design differences identified in the tasks of w administering/using the proposed drug product compared to the RLD product. The steps for w using the generic product are the same as the steps for using RLD. w*

w

Overall, the task analysis comparison supports that the proposed generic product can be w substituted for the RLD without the intervention of a health care provider and/or without w additional training prior to use of the proposed generic product. w

ANDA 209190
a ne Pat h, 5%

2.3 Ph sical comparison of the deliver device constituent part: RLD vs. Proposed Generic Product

DCR exam ine the el very ev ye nst tuent part f the R yD an pr p se gener pr yu t us ng samples pr v ye by the Appl ant. Representat ve ph t s are presente n Table 3bel w.

Table 3: Comparison of Actual Samples – Photos of RLD and Proposed Generic Product

(b) (4)

Ph t s taken by Rev ewer n 9/12/2019

***Reviewer's Comments**: The brand name Lidoderm® is printed on the RLD patch, and the generic name, Lidocaine Patch 5%, is printed on the proposed generic product. This is an acceptable minor design difference.*

Overall, the physical comparison of the delivery device constituent part supports that the proposed generic product can be substituted for the RLD without the intervention of a health care provider and/or without additional training prior to use of the proposed generic product.

3 APPLICANT'S THRESHOLD ANALYSES

ANDA 209190 s a GDUFA I ANDA. Theref re, the appl ant n t subm t thresh l analyses n urrent subm ss yyn.

4 CONCLUSION

Fr m a l n yal safety perspe t ve, there are a yeptable m n r es gn yfferen es betweyen the R yD an pr p se rug el very ev ye. Theref re, DCR yn lu es th s gener ymb nat n pr yu t an be subst tute f r the R yD w th ut the ntervent n f a health are pr v yer an / r w th ut a y t nal tra n ng pr r t use f the gener mb nat n pr yu t an that the es gn fferen es f r th s ymb nat n ev ye yes n t alter the safety r eff a y pr f le f th s pr p se ANDA pr yu t un er the yn yt ns f use as spe yf e n the label ng. In summary, DCR f n s the pr p se rug el very ev ye user nterfa e f r the pr p se gener y a ne Pat h **acceptable.**

5 RECOMMENDATION

The Cl n al D s pl ne has mplete ts rev ew f the mparat ve (thresh l) analyses an has:

No comments at this time.

Sunny f
Tse f

D f y s fned by Sunny Tse f
D f e: 10/23/2019 06:36:36PM f
GUID: 508d 6 0002855c7d 84880bd716ed2 f

Y n f
F n f

D f y s fned by Y n fF fn f
D f e: 10/24/2019 08:22:10AM f
GUID: 507d9e07000062 f73c410 f 19b793c f

Clinic l Review of Skin Irrit tion, Sensitiz tion nd Adhesion Studies

Division of Clinic l Review (DCR) a
Office of Bioequiv lence (OB), Office of Generic Drugs (OGD) a
Center for Drug Ev lu tion & Rese rch (CDER) a

ANDA number a	209190 a
Drug Product L a	ca ne T p cal Patch, 5% a
Strength(s) a	5% a
Applic nt N me a	Rh es Pharmaceut cals .P. a
Tre tment Indic tion a	Rel ef f pa n ass c ate w th p st-herpet c neuralg a a
Reference Listed Drug (RLD)	L a erm® (l a ca ne) T p cal Patch, 5% a
Reference St nd rd (RS) L a	erm® (l a ca ne) T p cal Patch, 5% a
NDA number for RLD a	020612 a
RLD Applic nt N me a	Te k ku Pharma USA, Inc. a
Origin l Submission D te a	04/14/2016 a
Materi ls Reviewed a	FDA Stat st cal rev ew by S nesh Chatt pa hyay, PhD a c mplete a n 06/06/2017 a FDA Stat st cal A a en m by Stella Gr sser, PhD a c mplete a n 06/15/2017 a OSIS nspect a rep rt: 12/08/2016 a Draft Pr uct Spec f c Gu ance f r a ca ne Patch, a 5%, rec mmen a n 12/2016; Rev se 05/2017, a 07/2014, 01/2016 a
Prim ry Reviewer a	Sun y Tse, PhD a Cl n cal Rev ewer, ANDA Team a
Second ry Reviewer a	Car l Y. K n, PharmD a Act ng Team ea er, ANDA Team a
Terti ry Reviewer a	Sarah Y n, MD a D s n D ect r a
D te of Completion a	06/19/2017 a
GDUFA DATE a	07/02/2017 a

DCR Con lusion c	The appl cat n s rec mmen e f r appr val fr m c D v s n f Cl n cal Rev ew (DCR) perspect ve. The c a hes n ata fr m PK/a hes n stu y RP- ID-PK001 c are acceptable. The sk n rr tat n an sens t zat n stu y c RP- ID-SSI ha mult ple screpanc es n atasets wh ch c ma e t ff cult t have c nf ence n the stu y results. c H wever verall, the m n c fferences n test c f rmulat n c mpare t the reference pr uct were n t c expecte t p se any greater safety c ncern f r rr tat n c r sens t zat n p tent als f the test pr uct; n c were c fferences n rr tat n r sens t zat n sugeste n RP- c ID-PK001. Theref re DCR c nclu es the t tal ty f the c nf rmat n n the appl cat n supp rts appr val. OSIS c nspect n f n ng f r the appl cat n s acceptable. c

Tabl of Cont nts e

Clinic l Review of Skin Irrit tion, Sensitiz tion nd Adhesion Studies for a ANDA 209190 a

1 EXECUTIVE SUMMARY a

1.1 Approv l Recommend tion a

The D v s an f Cl n cal Rev ew (DCR) rec mmen s appr val f th s appl cat n, c nt ngent n a appr val rec mmen at ns fr m the ther sc pl nes n the rev ew team. OSIS nspect n a f n ang s acceptable. a

1.2 Summary of Clinic l Findings

1.2.1 Brief Overview of Clinic l Progr m a

Th s rev ew f cuses n tw a stu æs subm itte a t ensure that the sk n rr tat n an sens t zat n a p tent als f the appl cant's a ca ne T p cal Patch, 5% (test pr auct) are n greater than th se a f the reference l ste rug (R aD) a erm T p cal Patch, 5%, an that the test pr auct a heres a t the sk n as well as the R aD ver the nten e urat n f wear. Tw a stu æs are sk n rr tat n a an sens t zat n stu y (RP- ID-SSI) an pharmac k net c/a hes a n stu y (RP- ID-PK01). a The pharmac k net c ata an f rmulat n are æme a equate by the D v s an f a B aequ valence II (DBII). a

1.2.2 Comp a r tive Irrit tion a

The appl cant c n ucte ne c mb ne sk n rr tat n an sens t zat n stu y (RP- ID-SSI). a Stu y RP- ID-SSI was a ran am ize , s ngle-center, c ntr lle , evaluat r-bl n e , repeat nsult a patch test stu y t evaluate the p tent al f r sk n rr tat n an sens t zat n f a test a ca ne a Patch, 5% c mpare t the reference a erm® (a ca ne Patch, 5%) the Reference ste a Drug (R aD), n 248 healthy a ult subjects. B ath treatments (1/4 patch f test an reference a pr aucts) were place s multane usly f r a 2-3 ay wear cycle per appl cat n ver a t tal f 9 a appl cat ns (21 ays f In uct n Phase), f ll we by a 12-14 ay Rest Phase an subsequent a 48-hr Challenge phase, f ll we by a 3- ay bservat n an rr tat n evaluat n. Dermal a rr tat n was assesse 0.5, 24, 48, an 72 h urs after patch rem oval ur ng the Challenge Phase. a N asubjects part c pate n a re-challenge phase. a

Acc r ng t the FDA analys s, the stu y RP- ID-SSI (test pr auct, n=182, reference, n=180) a em onstrates that the rr tat n p tent al f the test pr auct s n n- nfer r t the reference. Us ng a the least ava lable number f stu y p pulat n number ava lable base n further exclus an f a subjects ue t nappr pr ate stu y es gn by the FDA stat st cal rev ewer, the FDA's upper a b un f the ne-s a 95% c nf ence nterval f the test mean-1.25 reference mean s -0.041, a w th n the n n- nfer r ty marg n f ≤=0. H awever, the FDA stat st cal rev ewer c nclu e that a the stu y ata are n t rel able t ensure a equate nterpretat n f the stu y results. The pr mary a cl n cal rev ewer als agree that ata ntegr ty s n quest n. As a result, FDA stat st c ans an a DCR cl n cal rev ewers ha a meet ng n June 8, 2017. At th s meet ng, DCR sec n ary an a tert ary rev ewers scusse the rat nale f r DCR rec mmen ang appr val f th s appl cat n a base n a we ght f ev æence appr ach, supp rte by ther nf rmat n ava lable w th n a subm iss aan; .e., the æfference n f rmulat n (see Sect n 2.7) s n t expecte t be ass c ate a

w th a change n rr tat n r sens t zat n p tent a , an the bserve safety pr f e has n t ra se l unexpecte c ncerns (see Sect n 2.5 be lw). l

1.2.3 Comparative Sensitization l

Of 227 subjects eva uate fr m the same rr tat n/sens t zat n stu y RP- ID-SSI, n patch ha l ev lence f p tent a sens t zat n react n t e ther the test r the reference pr luct. A s refer l t Sect n 1.2.2 ab ve. l

1.2.4 Comparative Adhesion l

The a hes ve pr pert es f Rh l es Pharmaceut ca s .P.'s l ca ne T p ca Patch, 5% an the l reference were assesse n the pharmac k net c/a hes ln stu y (RP- ID-PK0101) wh ch was l c ns stent w th the raft pr luct spec f c gu lance. Stu y RP- ID-PK0101 was a ran l m ze , l pen- abe , tw l-per l , cr ss ver, s ng e lse b lequ va ence an patch a hes ln stu y enr l ng l 48 subjects. Dur ng each per l , each subject rece ve a s ng e 12 h ur app cat n f 3 test l pr lucts r reference pr lucts. After a rest per l f 7 ays, each subject rece ve a s ng e 12 l h ur app cat n f the ther treatment arm. C lns stent w th the raft pr luct spec f c gu lance, l patch a hes ln f r each patch was assesse ur ng each per l at 6 h urs (± 30 m in) f l w ng l patch app cat n an pr r t patch rem ov l . l

Acc r ng t the FDA's ana yses f a hes n perf rmance between test pr luct an the l reference, the a hes n ata fr m stu y RP- ID-PK0101 em onstrate n n- nfer r ty f the test l pr luct c mpare t the reference us ng the current FDA stat st ca meth l (Test-Reference ≤ l 0.15). The upper b un f ne-s le 95% c nf ence nterva f Test mean m inus Reference l mean s -0.4075, wh ch s w th n n- nfer r ty marg n f ≤ 0.15. The stu y utc me s the l same us ng the tra lt na FDA meth l (Test-1.25 Reference ≤0). l

1.2.5 Comparative Safety l

In rr tat n an sens t zat n stu y RP- ID-SSI (n=248), 129 (52.0%) subjects rep rte at east l ne a verse event. M ostl a verse events were m i l r m o drate n ntens ty. Three subjects l exper ence ser us a verse events unre ate t the stu y rug an sc nt nue the stu y. Three l subjects rep rt ng a ser us a verse event (SAE) ha asthmat c br nch t s an acute upper l resp rat ry nfect l (b) (6) my car a nfarct l (b) (6) an eft s e ra cu lpath l (b) (6) l One subjec (b) (6) ha a papu ar rash n the back an ab l men pr r t patch app cat n f r the l cha enge phase. N l eath was rep rte . The m ostlfrequent y rep rte a verse events were l app cat n s te prur tus (42.3%), hea ache (6.9%), app cat n s te pa n (5.2%), an back pa n l (3.6%). Because the app cant c l ecte app cat n s te react ns w th ut spec fy ng treatment l arm, t was n t p ss b e t c mpare the nc lence f app cat n s te a verse events betwe en test l an reference pr lucts. l

In pharmac k net c/sk n a hes ln stu y RP- ID-PK0101 (n=48), 2 subjects wh app e the test l pr luct ha treatment emergent a verse events (TEAEs). Subjec (b) (6) rep rte trans ent l zz ness. Subjec (b) (6) rep rte hea ache, nausea, an v m t ng. N l TEAEs were rep rte l f l w ng a m n strat n f the reference. N l subject sc nt nue the stu y ue t an a verse l event. There were n SAEs rep rte . Th s stu y sh we n c n ca y s gn f cant f fference n l safety pr f es betwe en the test an reference pr lucts. l

2 CLI ICAL REVIEW N

2.1 Introduction and Background N

2.1.1 Summary of Drug Information N

Reference Listed Drug L NIDODERM® N	
RLD Applicant ame N	Te k ku Pharma USA, Inc. N
RLD DA umber N	020612 N
Date of RLD Approval	03/19/1999 N
Current Label[1]	01/2015 N
Approved Indication N	rel ef f pa n ass c ate w th p st-herpet c neuralg a N
Recommended N **Dose/Administration** N	• Apply the prescr be number f patches (max mum f 3), N nly nce f r up t 12 h urs w th n a 24 h ur per N. N Patches may be cut nt smaller s zes w th sc ss rs pr Nt N rem ov N f the release l ner. N • L NIDODERM may n t st ck f t gets wet. Av N c ntact w th N water, such as bath ng, sw mming r sh wer ng. N
Application site N	Apply IDODERM t ntact sk n t c ver the m st a nful area. N
Boxed Warnings N	N Ne N
Commonly reported N **Adverse Events** N	**Application Site Reactions:** bl sters, bru s ng, burn ng N sensat n, ep gmentat n, ermat t s, sc l rat n, e ema, N erythema, exf l at n, rr tat n, papules, petech a, prur tus, N ves cles, r may be the l cus f abn rmal sensat n. These N react ns are generally m l n trans ent, res lv ng N sp ntane usly w th n a few m nutes t h urs N **Allergic Reactions:** Allerg c an anaphylact N react ns N ass c ate w th l ca ne, alth ugh rare, can cur. They are N character ze by ang e ema, br nch spasm, ermat t s, N yspnea, hypersens t v ty, laryng spasm, prur tus, sh ck, an N urt car a. N
Contraindications L N	IDODERM s c ntra n ate n pat ents w th a kn wn h st ry N f sens t v ty t l cal anesthet cs f the am i e type, r t any N ther c mp nent f the pr duct. N
Prominent Warnings/ Precautions N	**Accidental Exposure in Children** N Even a use IDODERM patch c nta ns a large am unt f N l ca ne (at least 665 mg). The p tent al ex sts f r a small ch l N r a pet t suffer ser us a verse effects fr m chew ng r N ngest ng a new r use IDODERM patch, alth ugh the r sk N

[1] http://www.access ata.f a.g v/ rugsatf a_ cs/label/2015/020612s012lbl.p f N

	w th th s f rm ulat n has n tbeen eval ate . It s mp urtant f r u pat ents t st re an u sp se f IDODERM ut f the reach f u ch l ren, pets an u thers. u **Excessive Dosing** u Excess ve us ng by apply ng IDODERM t larger areas r f r u l nger than the rec mmen u wear ng t me c ul res lt n u ncrease abs rpt n f l uca ne an th gh bl u c ncentrat ns, u lea ng t ser us a verse effects. System c a verse effects f u l uca ne are s m lar n nat re t th se bserve w th ther u am i eu cal anesthet c agents, ncl ung CNS exc tat n an r u epress n (l ght-hea e ness, nerv usness, apprehens n, u e ph na, c nf s n, z ness, r ws ness, t n t s, bl rre r u ble v s n, v m t ng, sensat ns f heat, c l r n mbness, u tw tch ng, trem rs,c nv ls ns, nc nsc u sness, resp rat ry u epress n an arrest). Exc tat ry CNS react ns may be br ef u r n t c c nat all, n wh ch case the f rst man festat n may be u r ws ness merg ng nt nc nsc u sness. Car uvasc lar u man festat ns may ncl e bra ycar a, hyp tens n an u u car uvasc lar c llapse lea ng t arrest. u ca ne t x c ty u c ul be expecte at l uca ne bl u c ncentrat ns ab ve 5 u µg/mL. The bl u c ncentrat n f l uca ne s eterm neu by u the rate f system c abs rpt n an el m nat n. nger urat n u f appl cat n, appl cat n f m re than the rec mmen u n mber f patches, smaller pat ents, r mpa re el m nat n u may all c ntr b te t ncreas ng the bl u c ncentrat n f u l uca ne. Withurec mmen u u s ng f IDODERM, the u average peak bl u c ncentrat n s ab ut 0.13 µg/mL, b t u c ncentrat ns h gher than 0.25 µg/mL have been bserve n u s me n w u als. u
Mechanism of Action L u ca ne s an am i e-type l cal anesthet c agent an us u s ggeste t stab l ze ne n nal membranes by nh b t ng the u n c fl xes req re f r the n t at n an c n uct n f u mp ses. u	
Absorption u	When IDODERM s se acc n ng t the rec mmen u s ng nstr ct ns, nly 3 ± 2% f the se appl e s expecte u t be abs rbe . u

2.1.2 R gulatory Background

2.1.2.1 Guidanc on Drug Product e

A raft pr uct spec f c gu ance f r e ca ne T p cal Patch, 5% s ava lable. Table 2.1 e pr v es a br ef verv ew f the raft pr uct spec f c gu ance rec mmen at ns. e

Tabl 2.1: Drug Product Guidanc e

Draft Product e Sp eific Guidanc e	Draft Gu ance n e ca ne[2]
Dat Post d	Rec mmen e d 2/2006; Rev se 05/2007, 07/2014, 10/2016 e
R commend d e Studi s e	1. Fast ng B equ valence (BE) Stu y e 2. A hes on Stu y e 3. Sk n Irr tat on an Sens t zat on Stu y e
Fasting BE Study e	**D sign:** S ngle- se, n v v eus ng three t p cal patches e **Subj ct population**: N rmal healthy males an females, general e p pulat on e **Tr atm nt dosing**: Apply three t p cal patches s multane usly ver a e 12-h ur per e **P rtin nt additional comments**: e • Use fewer patches, pr v e the plasma c ncentrat ons f l eca ne e are measurable t a equately character ze the pharmac k net c e pr f le f l eca ne f r b equ valence (BE) assessment base n the e 90% c nf ence nterval cr ter a. e • Inclu e a 24-h ur p st- se sampl ng t me n the BE stu y. e • In a e t on t pharmac k net c ata, rep t the "apparent se" e el vere . The apparent se can be eterm ine by subtract ng the e rema n ng am ount f l eca ne n each patch (use patch) fr m the e manufacture am ount. Analyze an enclu e n the calculat on the e am ount f a hes ve res ue fr m each patch left n the sk n. e
Adh sion Study e	**D sign**: Ran em ize e, s ngle- se, tw e-treatment n v v e **Subj ct population**: Healthy males an females, general p pulat on e **Tr atm nt dosing**: A hes on perf rmance f the ntact test an R D e patches must be f rmally evaluate an may be c mpare n the e pharmac k net c (PK) BE stu y r n a separate parallel r cr ss ver e a hes on stu y f s ngle 12-h ur patch appl cat ons f the act ve test e pr uct versus the R D. e **P rtin nt additional comments**: e • N patch re nf rcement s all we when the stu y s be ng use t e establ sh a equate a hes on perf rmance t supp rt pr uct e appr val. A hes on sc r ng s t be perf rme eat least a ly, n th s e case just pr r t rem val at the en e f a 12-h ur appl cat on. F e e patches that c mpletely etach, a sc re f 4 sh ul be carr e e f rwar n the a hes on analys s f r all rema n ng bservat ons n the e

[2] http://www.f a.g v/ucm/gr ups/f ag v-publ c/@f ag v- rugs-gen/ cuments/ cument/ucm086293.p f e

	appl cat n per k. k
S kin Irritation and Sensitization Study	k**Design**: Ran km ize , evaluat r-bl n e , n v v w th n-subject repeat k test k **Strength:** 5% (a m in stere as ne-f urth f the test an ne-f urth f k the reference) k **Subject population**: Healthy males an females, general p pulat n k **Treatment dosing**: k In uct n Phase - Dur ng the n uct n phase, all test art cles (.e., ne- k f urth f test pr kuct, ne-f urth f the R kD, ne-f urth f the pt nal k veh cle patch, an pt nal negat ve c ntr l) are t be appl e k s multane usly t each subject at kferent s tes. The test art cles t be k use are as f ll ws: k 1. One-f urth f test pr kuct (the test pr kuct evaluate sh ul be k the actual patches t be markete .) k 2. One-f urth f the R kD k 3. One-f urth f the pt nal veh cle patch (the pt nal veh cle k patch sh ul have all f the nact ve ngre kents an be ent cal k t the test pr kuct n every manner except f r the absence f k l kca ne.) k 4. Opt nal negat ve c ntr l (an example f the pt nal negat ve k c ntr l s an dkclus kn type ev ce w th n rmal sal ne appl e n k a p lyester pa w th n the ev ce chamber.) k Sequent al patch appl cat ns are t be appl e t the same sk n s tes k every 48-72 h urs an t have each f them rema n n place f r 48-72 k h urs, f r a t tal f 21 ays alt gether. k Rest per k – n patch appl cat n f r 14-17 ays k Challenge phase – a s ngle 48-h ur appl cat n f ne-f urth f the test k pr kuct, ne-f urth f the R kD, ne-f urth f the pt nal veh cle patch, k an the pt nal negat ve c ntr l t a naïve s te k **Pertinent additional comments**: k • A hes n sh ul be evaluate pr r t patch rem ovdk thr ugh ut the k ent re stu y per k t ensure a equate sk n c ntact f r max mal k n uct n f rr tat n an sens t zat n. k • Irr tat n evaluat n: In uct n phase – at the t me f each patch k change; Challenge phase – 30 m inutes an at 24, 48, an 72 h urs k after challenge patch rem ovdk. k • F r subjects wh exper ence rr tat n c ns stent w th a c mb ne k sc re f ≥ 3, r wh exper ence sympt mat c nt lerable rr tat n, k the patch may be m ovdk t a new s te n r er t c mplete the 21- ay k In uct n Phase an c nt nue w th the sens t zat n part f the stu y. k • If a patch c mpletely etaches, t sh ul be replace w th n 24 h urs k an the subject sh ul c nt nue n the stu y. Dur ng the 21- ay k In uct n Phase, f a patch s c mpletely etache f r m orekthan 24 k

	h urs (unless the atch was rem ovep f r an unacce table egree f p rr tat n), the subject sh ul be exclu e fr m b th the rr tat n an p sens t zat n analyses f r that r puct. Dur ng the 48-hr Challenge p Phase, f a atch s c m pletely etache f r m orepthan 24 h urs, the p subject sh ul be exclu e fr m the sens t zat n analys s. p • Due t safety c ncerns, t s n t rec mmen e t s multane usly p a ply tw pwh le, act ve, p ca ne Patch 5% atches n the same p subject ur ng the 21- ay sk n rr tat n an sens t zat n stu y. The p t mum es gn f th s stu y w pl e en n the es gn f the test p r puct atch. S nce the R pD has a matr x es gn that can be safely p cut, ne-f urth f the atch can be use f r these stu pes. If the test p r puct atch als has a es gn that can be cut t a smaller s ze, t p sh ul als be cut n ne-f urth an ne-f urth f the test r puct p atch a pl e s multane usly w th ne-f urth f a R pD atch (t p se arate sk n s tes). It w pul n t be acce table t manufacture a p se arate batch f r puct n r er t use a smaller atch n th s stu y. p

Guidance for Industry p

On 6/1/2016, the FDA pste a raft gu pance f r n ustry ent tle *Assessing Adhesion with* p *Transdermal Delivery Systems and Topical Patches for ANDAs (June 2016)*[3] ("A phes pn p Gu pance"). Th s A phes pn Gu pance r v pes u pate rec mmen at ns f r the es gn an p c n uct f a hes pn stu pes. The A phes pn Gu pance als nclu es u pate stat st cal analys s p meth p t evaluate a hes pn erf rmance. p

2.1.2.2 Generic Product Development p

The a pl cant p n t subm i c ntr lle c pres pn ences an r t c l f r th s a pl cat n. p

2.1.2.3 Relevant Communications with Other Generic Applicants p

Merca p searches y el e 25 results, n ne f wh ch were relevant t the sk n rr tat n, p sens t zat n, an a hes pn stu pes evaluate f r th s current a pl cat n. p

2.1.2.4 Other ANDA submissions for same or related product p

ANDA p	Applicant p	Current Status p	Status Date p
200675 p	ACTAVIS ABORATORIES UT INC p	A p r ve p	8 /23/2012 p
202346 p	MY pAN TECHNO pOGIES INC p	A p r ve p	8 /7/2015 p
[redacted]			(b) (4)
203265 p	NOVEN PHARMACEUTICA pS INC p	C pm plete Res pnse p ssue – p A pequate DCR rev ew p	09/13/2016 p
[redacted]			(b) (4)

[3] htt ://www.f a.g v/ pwnl a s/Drugs/Gu panceC pm pl anceRegulat ryInf rmat n/Gu pances/UCM504157. pf p

ANDA i	Appl cant i	Current Status i	Status Date i
205882	KREMERS URBAN MANUFACTURING INC i	Pen ing - DCR i rec mmen e i appr val i	10/26/2016 i
206463 i	AMNEA i PHARMACEUTICA iS i	Pen ing - DCR i rec mmen e i appr val i	07/20/2016 i
[redacted]			(b) (4)

2.1.3 Other Relevant Informat on i

n ne i

2.2 Descr pt on of Cl n cal Data and Sources i

The appl cant c n ucte ne c mb ne sk n rr tat n an sens t zat n stu y (RP- ID-SSI) an i pharmac k net c/sk n a hes in stu y (RP- ID-PK001). i

Table 2.2: Source of Cl n cal Data i

Study # i	RP-LID-SSI i	RP-LID-PK001 i
Study Type i	sk n rr tat in an sens t zat in i	pharmac k net c/a hes in i
CRO i	Fr ntage Cl n cal Serv ces Inc.	Fr ntage Cl n cal Serv ces Inc. i
Study Per od i	08/12/2013 t 12/16/2013 i	08/22/2013 t 09/18/2013 i
Study Center	Fr ntage Cl n cal Serv ces Inc. i 241 Ma n Street i Hackensack, New Jersey 07601 i	Fr ntage Cl n cal Serv ces Inc. i 241 Ma n Street i Hackensack, New Jersey 07601 i
Enrollment i	248 i	48 i

2.3 Cl n cal Rev ew Methods i

2.3.1 Overv ew of Mater als Consulted n Rev ew i

ANDA Subm ss on(s) i	**04/14/2016 (eCTD Sequence 0000):** Or g nal i Subm ss i n i **05/23/2016 (eCTD Sequence 0001):** Resp nse t i Inf rmat n Request fr m D v s n f F l ng i Rev ew – atasets i **08/15/2016 (eCTD Sequence 0003):** Resp nse t i ECD fr m Stat st cs ate 08/30/2016 f r rr tat n i an sens t zat n stu y RP- ID-SSI – quest ns i regar ng sk pe v s ts, patch a hes n, make-up i patches i **09/06/2016 (eCTD Sequence 0004):** Resp nse t i ECD fr m DCR ate 08/23/2016 f r rr tat n an i sens t zat n stu y RP- ID-SSI – quest ns i

	regar 0ng patch re nf rcement an 0a verse events 0 **9/29/2 0 06 (eCTD Sequence 0 5):** Resp 0nse t 0 ECD fr m DCR ate 0 09/16/2016 f r rr tat 0a an 0 0 sens t zat 0a stu 0 RP- ID-SSI – quest 0as 0 regar 0ng rr tat 0a assessment, patch a hes 0n, an 0 0 appl cat 0a s te a 0erse events 0 **1 0 21/2 0 06 (eCTD Sequence 0 6):** Resp 0nse t 0 ECD fr m Stat st cs ate 10/03/2016 f r rr tat 0a 0 an 0sens t zat 0a stu 0 RP- ID-SSI – quest 0as 0 regar 0ng ataset 0crepanc es 0 **12/ 9/2 0 06 (eCTD Sequence 0 7):** Resp 0nse t 0 ECD fr m Stat st cs ate 11/18/2016 f r rr tat 0a 0 an 0sens t zat 0a stu 0 RP- ID-SSI – ssues 0 regar 0ng atasets an 0stu 0 pr ce ure 0 Th s ANDA s subm itte0 0n eCTD f rmat an 0 0 ent rely electr n c. The ANDA subm iss 00n s 0 arch ve at the f l0 w 0ng l cat 0a: 0 \\c sesub1\evspr 0\ANDA209190\209190.enx 0
FDA Statistical Review	ANDA 209190 Stat st cal Pr mary Rev ew 0 ("A209190_stat st cal. 0c") by S 0nesh 0 Chatt pa hyay, PhD, C 0mplete n 06/06/2017 0

2.3.2 Overview of Methods Used to Evaluate Data Quality and Integrity 0

Study # 0	RP-LID-SSI 0	RP-LID-PK 0 1 0
Office of Study 0 Integrity and 0 Surveillance 0	Establ shment Inspect 0a Rep 0t 0 rev ew subm itte0 12/08/2016. 0 Please see sect 0a 2.6.1 f r 0 eta ls. 0	Decl ne t Inspect Mem os0bm itte0 0 05/19/2016. Please see sect 0a 2.6.1 f r 0 eta ls. 0
Blinding 0	Irr tat 0a an 0sens t zat 0a 0 evaluat r bl n 0 0	Evaluat 0a f ermal react 0as at the 0 appl cat 0a s tes was cl n cally assesse 0 0 n a bl n 0 fash 0n 30 m nu0es an 0 2 0 h 0rs after patch rem ova0 0
Randomization 0	s te f patch app0l cat 0a: ne s 0e f the nfrascapular area f the 0 back; 2-l cat 0a (upp0er/l wer) 0 ran 0m iza0 0a 0	0w 0treatment sequences (T-R, R-T) 0
Retention of 0 Reserve Samples 0	n/a 0	Retent 0a (reserve) samples f the 0 reference an 0est f rmulat 0a were 0 selecte an 0eta ne by the Pr nc pal 0 Invest gat r (r es gne0) n a l cke , 0 secure pharmacy cab net n c mpl ance 0 w 0 0 (b) (4) Stan 0r Operat ng Pr ce ures. 0

Revie er's comments: w

- *The irritation/sensitization evaluator was blinded for study RP-LID-SSI. The applicant's* w *method of blinding is acceptable.* w
- *Randomization is acceptable for both studies RP-LID-SSI and RP-LID-PK0001.* w
- *OSIS indicated the study data for study RP-LID-SSI were acceptable.* w
- *OSIS declined to inspect study RP-LID-PK0001 clinical site due to acceptable inspection* w *history.* w

2.3.3 Were Trials Conducted in Accordance with Accepted Ethical Standards w

Stu ies RP- ID-SSI an RP- ID-PK0001 appear t have been c n uct n acc r ance w th w accepte eth cal stan ar s. The IRB appr ve the r g nal pr t c l an the Inf rme C nsent w F rm pr r t the start f the stu y f r b th stu ies. w

2.3.4 Evaluation of Financial Disclosure w

F r stu ies RP- ID-SSI an RP- ID-PK0001, a F rm FDA 3454 (ate 03/04/2016) s subm itte w w f r all nvest gat rs. The appl cant ha n f nanc al arrangements w th the nvest gat rs t w scl se. w

2.4 Review of Skin Irritation, Sensitization, and Adhesion w

2.4.1 General Approach to Review of Skin Irritation, Sensitization and Adhesion w

Stu y RP- ID-SSI was rev ewe t ver fy that test pr uct s n m re rr tat ng an sens t z ng w than the reference. RP- ID-PK0001 was rev ewe t ver fy that the a hes n perf rmance f the w test pr uct s n w rse than that f the reference. w

2.4.2 Detailed Review of Skin Irritation, Sensitization and Adhesion Studies w

2.4.2.1 Skin Irritation and Sensitization Study (RP-LID-SSI) w

Applicant's Study #:	RP- ID-SSI w
Title w	A Ran m ze , C ntr lle Stu y t Evaluate the Sk n Irr tat n w an Sens t zat n P tent al f a Test w ca ne 5% T p cal Patch w C mpare t w erm 5% T p cal Patch Us ng a Repeat Insult w Patch Test Des gn n Healthy A ults w

Objec ives t	The pr mary bject ves f th s stu y were: t • T tvaluate the sk n rr tat tn n tice tby t p cal t appl cat tn f the test l t ca ne 5% patch c tmpare t t erm 5% l t ca ne patch f ltl w tng 21 ays f t exp sure n healthy a tlt male an tfemale subjects. t • T tvaluate the sk n sens t zat tn n tice tby t p cal t appl cat tn f the test l t ca ne 5% patch c tmpare t t erm 5% l t ca ne patch after a 21- ay In tct tn t Phase, f ltl we by a 48-h tr Challenge Phase n healthy t a tlt male an tfemale subjects. t The sec n tary bject ve f th s stu y was: t • T assess the safety an tt lerab l ty f a test l t ca ne 5% t t p cal patch c mpare t t erm 5% l t ca ne patch n t healthy a ult male an tfemale subjects. t

2.4.2.1.1 Pro ocol Review t

Pro ocol Version t	Pro ocol Da e t	IRB Approval Da e t
1.0 t	07/25/2013 t	07/31/2013 t

Reviewer's comments: t

The protocol was approved prior to study initiation (study period: 08/12/2013 to 12/16/2013). t

2.4.2.1.2 S udy Design t

Overall S udy Design t

Stu y RP- ID-SSI was a tw t treatment, s ngle s te, mult ple-appl cat n, evaluat r-bl n e , t three-phase, ran t m ze stu y n 248 healthy a ults. Cumulat ve sk n rr tat n an sens t zat n t p tent als f the test pr tuct were c mpare t reference by repet t ve placement f each t treatment t the same sk n s te. B tth treatments (1/4 test pr tuct patch an 1/4 reference t pr tuct) were place s multane tusly an replace 3 t mes wetkly at the stu y s te f r a t tal f 9 t appl cat ns (21 ays f In uct n Phase). If patch a hes tn was assesse as <50% a here but t n t etache (m oretthan half the system l ft ng ff f the sk n w th ut fall ng ff), the subject t was sche ule f r a make-up patch appl cat n. The sk n rr tat n assessment f r the patch t a here <50% was n t nclu e n the rr tat n analyses. Subjects wh t n t return f r ne t v s t t the stu y s te ur ng the In uct n Phase were nstructe t keep the patches n place. t They were sche ule t rece ve a make-up patch appl cat n at the last v s t ur ng the In uct n t Phase. The make-up patches were rem ovet 48 h urs later an the patch s tes were assesse . t There was a 12-14- ay rest phase. Then f ll we a subsequent 48-hr Challenge phase, w th a 3- t ay bservat n an rr tat n evaluat n. Dermal rr tat n was assesse 0.5, 24, 48, an 72 t h urs after patch rem ovatl ur ng the Challenge Phase. There were 2 c h rts. The C th rt 1 t treatment start ate was 08/20/2013. The last C th rt 1 treatment exp sure ate was 09/26/2013. t The C th rt 2 treatment start ate was 11/05/2013. The last C th rt 2 treatment exp sure ate was t 12/13/2013. t

Table .3: Overall Study Design 2

Study/Protocol Number 2	RP- ID-SSI 2		
Subject Population 2	Healthy, a ult subjects wh met the nclus 2n/exclus 2n cr ter a f r th s stu y 2		
Blinding 2	Th s stu y was bl n e t the stu y staff perf rm ing2he rr tat 2n an 2 sens t zat 2n assessments. 2		
Randomization 2	Appl cat 2n s tes were es gnate as "upper" an "l wer" n the 2 ran 2m iza2 2n sche ule, wh ch perta ne t the relat ve p s t 2n ng f 2 the test an reference stu y pr 2ucts t each ther. 2		
Treatment arms	**Test 2**		**Reference 2**
Reinforced 2	Yes 2		Yes 2
Number of period/phase 2	**Induction 2**	**Rest 2**	**Challenge 2**
Duration 2	21 ays 2	12-14 2 ays 2	5 ays 2
Dose administered 2	1/4 test patch 2 1/4 reference patch 2	n ne 2	1/4 test patch 2 1/4 reference patch 2
Dosing regimen 2	1/4 test patch 2 1/4 reference patch 2	n ne 2	1/4 test patch 2 1/4 reference patch 2
Number of applications	3 t mes/we2k appl cat 2ns; 2 t tal f 9 f r test an 2 reference 2	n ne 2	1 f r test an reference 2
Application site 2	Stu y patches were appl e 2 s multane usly t the same 2 s tes n ne s 2e f the 2 nfrascapular area f the 2 back. Subjects returne t 2 the stu y s te at 48-h ur 2 ntervals t have the 1/4 2 patches rem ove2 an 2 replace by stu y s te 2 pers 2nnel. 1/4 patches 2 appl e n Fr 2y rema ne 2 n place f r 72 h urs unt l 2 M on2ay. 1/4 patches appl e 2 n Satur ay rema ne n 2 place f r 72 h urs unt l 2 Tues ay. 2	n ne 2	The test an reference stu y 2 patches were appl e t 2 naïve s tes n the p2p s te 2 s 2e f the sp ne n Day 36 2 f r 48 h urs r unt l rem oval 2 ue t excess ve l cal 2 rr tat 2n. The respect ve s te 2 f appl cat 2n ("upper" r 2 "l wer") was the same as 2 that use ur ng the 2 In uct 2n Phase. 2
Adhesion assessment times	pr 2t rem oval f each 1/4 2 patch 2	n ne 2	pr 2t rem oval f each 1/4 2 patch 2
Irritation assessment times	f ll2 w ng rem oval f each 2 1/4 patch an pr 2t 1/4 2 patch replacement 2	n ne 2	0.5, 24, 48, an 72 h urs 2 after 1/4 patch rem oval 2

Reviewer's comments: 2

The applicant's study design is different from the draft product specific guidance. The applicant 2 allowed an additional "make-up" patch if patch adhesion was less than 50%. In addition, the 2 applicant's Other Effects scale for skin reactions included one additional "no other 2 observations", which is not present in the product specific guidance. For Other Effects scale, the 2 applicant used continuous numerical scores of 0 to 6 whereas the drug specific guidance 2

reco m ends nu neric equivalent scores of 0 to 3 only. The FDA statistical analyses relied on m the FDA-reco m ended scale and study design for the analyses of irritation and sensitization. m

Treatment Arms *m*

Table 2.4: Treatment Arms (Study # RP-LID-SSI) *m*

Treatment arms *m*	**Test** *m*	**Reference** *m*
Pr mct Name *m*	ca ne T p cal Patch, 5% L *m*	erm® (l mca ne) T p cal Patch, 5% *m* *m*
Strength *m*	5% *m*	
Patch s ze L *m*	ength: 14 cm, Wi th 10 cm *m* (¼ patch f the test pr mct was appl e) *m* *m*	ength: 14 cm, Wi th 10 cm *m* (¼ patch f the reference pr mct was appl e) *m* *m*
Manufacturer *m*	Alterg n, Ital a *m*	[redacted](b) (4) f r En *m* Pharmaceut cals *m* *m*
Batch/ m N m L *m*	1304191 *m*	Y2282 *m*
Manufacture Date *m*	04/2013 *m*	n/a *m*
Exp rat m Date *m*	n/a *m*	10/2015 *m*
D sage F m *m*	t p cal patch *m*	
R te f a m n strat m *m*	t p cal *m*	
Re nf rce w th tape *m*	Yes *m*	

Study Population Selection *m*

Th s stu y enr lle male an female subjects at least 18 years l . See appl cant's stu y rep rt, *m* Sect n 9.6 (pages 29-30 f 149) f r the full l st f the appl cant's nclus m an exclus m *m* cr ter a. *m*

Reviewer's comments: *m*

The applicant's inclusion/exclusion criteria incorporated all the inclusion and exclusion criteria m fro m the draft product specific guidance. All of the applicant's additional inclusion and m exclusion criteria are acceptable. A key applicant inclusion criterion was that a subject was to m be free of any syste c or der atologic disorder, which, in the opinion of the investigator, would m interfere with the study results or increase the risk of adverse event. Two of these key applicant m exclusion criteria were: Not willing to refrain fro m swi ming or bathing such that the patch will m be sub merged for the duration of the study and not willing to refrain fro m excessive exercise or m physical activity for the duration of the study. m

Restrictions during the study *m*	Subjects c ul n t use system c/t p cal analges cs (e.g. asp r n, *m* Aleve, M otrm, A v l, Nupr n) f r at least 72 h urs pr mt an *m* ur ng the stu y. Subjects c ul take oc as mal acetam n ph en as *m* nee e f r hea ache r ther pa n. Subjects c ul n t use *m* system c/t p cal c rt c ster ms f r at least 3 weeks pr mt r ur ng *m* the stu y. Subjects c ul n t use system c/t p cal ant h stam nes f r *m* at least 72 h urs pr mt r ur ng the stu y. Other ver-the-c unter *m* r prescr pt m me cat ns were pr h b te ur ng the stu y, *m* nclu ng ur ng the Rest Phase, unless appr ve by the Sp ns r an *m* nvest gat r n a case-by-case bas s. Female subjects us ng h rm onal *m*

	c ntracept ves c nt n e therapy ur ng the st uy. Whereas bath ng u was all we (l w t b bath/fr ntal sh wers), the patche area was n t u t be s ake an was t be kept as ry as p ss ble, per the u nstr ct ns g ven t each s bject. u
Treatment compliance	All patches were appl e an rem ove u by cl n cal st uy staff. u Rec r s f patch appl cat ns an v s t sche ule c mpl ance were u rec r e n the s bjects' s urce uc ments an CRFs. u

Reviewer comments u

- *The restrictions on medication use during the study reflect the applicant's exclusion criteria* u *and are acceptable. The RLD labeling recommended avoidance of patch contact with water,* u *such as showering. The applicant's allowance of frontal showers was an acceptable* u *compromise to maintain subject hygiene as the patch application site was on the back and* u *the induction phase was 21 days.* u
- *The applicant's measures to ensure treatment compliance are acceptable.* u

Assessme ts n

The appl cant use the f ll w ng scales an sens t zat n ef n t n ur ng stu y RP- ID-SSI: n

Table 2.5: Dermal Respo se n

Score	Descriptio n
0 n	N nev nence f rr tat n n
1 n	M m mal erythema, barely percept ble n
2 n	Def n te erythema, rea ily v s ble, m in mal e ema r m in mal papular n resp nse n
3 n	Erythema an papules n
4 n	Def n te e ema n
5 n	Erythema w th e ema an papules n
6 n	Ves cular erupt n n
7 n	Str ng react n sprea ng bey n appl cat n s te n

Table 2.6: Other Effects n

Score n	Descriptio n
0 n	n ther bservat ns n
1 n	sl ghtly glaze appearance n
2 n	marke glaze appearance n
3 n	glaz ng w th peel ng an crack ng n
4 n	glaz ng w th f sures n
5 n	f lm f r e ser us exu ates c ver ng all r part f the n patch s te n
6 n	small petech al er s ms an /r scabs n

Sens t zat n Def n t n n

A sk n sens t zat n react n was ef ne as the evel pment, at the s te f re-exp sure t the n patch, f ef n te erythema c mb ne w th the presence f any f the f ll w ng s gns: papules, n e ema, ves cles, bullae, crack ng, f ssur ng, crust ng, peel ng, r sprea bey n the c nf nes f n patch appl cat n s te. Such react ns were requ re t have a t me c urse c mpat ble w th a n sens t zat n react n; that s, such a react n curr ng at the beg nn ng f the In uct n Phase n was eme a s gn f pr r sens t zat n, an react ns wh ch marke ly mpr ve w th n a 72-96 n h ur t meframe were n t character st c f an allerg c resp nse, an were class f e as an rr tant n resp nse. Sk n sens t zat n react ns m ost kely cur n the Challenge Phase, alth ugh they n c ul cur later n the In uct n Phase, an w ul have a t me c urse character st c f Type IV n elaye hypersens t v ty react ns. n

Reviewer's comments: n

- *The applicant's Dermal Response scale is the same as recommended by the draft product specific guidance.* n
- *The applicant's Other Effects scale for skin reactions had an additional observation, "no other observations", which was not present in the product specific guidance. Also, the applicant's Other Effects scale numeric scoring was different than what is recommended in the product specific guidance. The FDA statistical reviewer followed the draft product specific guidance's numerical scale.* n

- *The F D1 statistician followed the draft product specific guidance sensitization criteria D for the F D1 analysis. D*

Endpoints D

Primary D **Endpoints** D	Dermal resp nse sc res an Dsc res f r ther effects D • Dermal response scores and scores for other effects collected during the Induction Phase to evaluate the skin irritation potential of the study product. • Dermal response scores and scores for other effects collected during the Challenge Phase to evaluate the skin sensitization potential of the study product. • The number of patches removed due to an unacceptable degree of irritation. • The number of days until sufficient irritation occurs to preclude patch application.

Reviewer's comments: D
The applicant's primary endpoints are acceptable. D

Statistical Analysis Plan D
See appl cant's stu y rep rt, Sect n 9.10 (page 37) an FDA Stat st cal Rev ew, Sect n 3.2.7.2 D – 3.2.7.4 (pages 34 - 38) f r eta ls f the stat st cal analys s plan. The appl cant's analys s D p pulat ns ef n t ns are pr v Do bel w. D

Appl cant's Irr tat n Analys s P pulat n D
Irritation: D
The appl cant's rr tat n analys s p pulat n nclu e all subjects wh rece ve test/reference D pr Dducts such that sequent al test/reference pr Dduct appl cat ns were n t etache fr m the sk n D f r l nger than 24 h urs ur ng the 21- ay In uct n Phase (unless the patch was rem ovD f r an D unacceptable egree f rr tat n). If a test/reference pr Dduct etache an c ul n t be replace D w th n 24 h urs, r a subject Dn t kn w when a test/reference pr Dduct etache , the subject's D patch was exclu e fr m the test/reference rr tat n analys s p pulat n. D

Sensitization: D
All subjects wh rece ve test/reference pr Dducts (Challenge Phase) an wh have c mplete the D In uct n Phase, wear ng the test/reference pr Dducts f r the ent re 21 ays an c mplete the D Rest Phase. A D t nally the challenge test/reference pr Dducts must be attache f r 48 h urs D (unless the challenge test/reference pr Dduct was rem ovD ue t a sens t zat n react n) w th the D subject return ng f r evaluat n at least 24 h urs after rem ovaD f the challenge test/reference D pr Dduct. D

Reviewer's comments: D
The applicant's irritation analysis population definition is consistent with the draft product D specific guidance per-protocol population for irritation. D

The applicant's sensitization analysis population definition is different than the draft product D specific guidance sensitization analysis population definition. The draft product specific D guidance recommends the subject to return for at least one of the scheduled evaluations at 48 D

and 72 ours after removal of t e c allenge patc . However, t e applicant's sensitization h analysis population includes subjects w ho return for evaluation at least 24 ours after removal h of t e c allenge patc . T e FDA statistician used t e definition specified in t e drug specific h guidance for t e FDA analysis. h

2.4.2.1.3 Study Subjects h

Subject Disposition h

Tw hhun re f rty-e ght (248) healthy a ult subjects were entere nt th s stu y an rece ve at h least ne appl cat n f patches. A t tal f 227 subjects c mplete the stu y. h

Subjects Analyzed h

Of the 248 subjects ran hm ize nt the stu y, 228 test subjects an 228 reference subjects were h nclu e n the appl cant's rr tat n PP p pulat n an 227 test subjects an 227 reference h subjects were nclu e n the appl cant's sens t zat n PP p pulat n. h

Reviewer's comments: h

T e FDA clinical reviewer did not recommend any c anges to t e applicant's irritation and h sensitization PP populations for t e FDA analysis.[4] h

Demographics h

The em ogrhaph cs f the rr tat n an sens t zat n stu y RP- ID-SSI are as f ll ws. h

Table 2.7: Demographic and Baseline Characteristics for Irritation and Sensitization h Study: Gender, Race and Age h

		All Enrolled h (N=248) h
Gender h	Female h	184 (74.19%) h
	Male	64 (25.81%) h
Race h	As an	3 (1.21%) h h
	Black h	135 (54.44%) h
	Wh te h	110 (44.35%) h
Age Group in Years h h	18-40 h	111 (44.76%) h
	41-64 h	129 (52.02%) h
	65-75 h	8 h (3.23%) h
Age in Years h	Mean, SD h	41.39, 12.22 h
	Min, Max h	18, 69 h
	Q1, Me han, Q3	33, 43, 49 h

S urce: FDA Stat st cal Rep rt Table 18 h

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[4] h http://pan rama.f a.g v/ hcument/prev ew?vers hnID=5775b58a0093c7eb4704e2b302f4bb00&ID=5775b58a0093c h 7ea3a9a373c525c3883 h

Reviewe 's comments: r
There was a higher percentage of females in the study. Enrolled subjects consist mainly of black r
and white subjects. The age range of subjects is consistent with the applicant's inclusion criteria r
of ≥ 18 years of age. These demographics are acceptable and have no impact on the study r
outcome because both test and reference patches were applied simultaneously to the same r
subject. r

2.4.2.1.4 Results r

Irritation Results r
The appl cant's rr tat n analys s results are as f ll ws. r

Table 2.8: Applicant Irritation Analysis Results (Study RP-LID-SSI) r

Variable r	Hypotheses r	LSmean r Test r	LSmean r Reference	Estimate of r $\mu_A - 1.25*\mu_B$ r	One-Sided r 95% Upper r Confidence r Bound r
Mean Irritation r Score ("dermal r response" + "other effects" scores r from induction r phase assessments) r	H_0: $\mu_A - 1.25*\mu_B \geq 0$ r H_1: $\mu_A - 1.25*\mu_B < 0$ r r	0.21r r	0.212 r	-0.001 r	-0.015 r

S urce: Appl cant Stu y Rep rt Table 9 r

Because the appl cant's stu y es gn s s gn f cantly fferent fr m the rec mmen at n r
pr v re n the rug spec f c gu rance f r th s pr ruct ue t a r t nal make-up patch use, r
FDA stat st cal rev ewer perf rme 6 fferent stu y p pulat ns p st-h c t evaluate whether r
th se pr t c l v rlat ns ent f e by the FDA stat st cal rev ewer change the stu y utc me. r
FDA stat st cal rev ewer ent f e mult ple ata nc ns stenc es n rr tat n sc res fr m the r
r g nal ataset t subsequent atasets n resp nse t the r ECD requests. r

The 6 var ants f the PP p pulat n c ns rere f r the FDA rr tat n analys s (PPPI1 – PPPI6) r
nclu e a justments wh ch rem ov r subjects ue t a s gn f cant pr t c l ev at ns r r
v rlat ns. The ef n t n f r each stu y p pulat n an the summary results are l ste bel w. r

The patches exclu e fr m PPPI1 are: r

- A patch type that r n t have all n ne patch appl cat ns r r n t have all n ne r rr tat n assessments f r arsubject. r
- All patches fr m Subject [redacted] (b) (6) Th s s base n the OSIS r nspect n rep rt. r

The patches exclu e fr m PPPI2 are: r

- All patches exclu e fr m PPPI1. r
- All patches fr m the subjects wh sk ppe a v s t ur ng the n uct n phase. r

The patches excl ue fr m PPPI3 are: u

- All patches excl ue fr m PPPI1. u
- All patches that were etache ur ng the n uct n phase base n the patch etachment u flag b t n t kn wn t be replace w th n 24 h urs after etachment. The atasets u s bm itteu n December 9, 2016 were se f r th s eterm inat n. u

The patches excl ue fr m PPPI4 are: u

- All patches excl ue fr m PPPI3. u
- All patches fr m the s bjects wh sk ppe a v s t ur ng the n uct n phase. u

The patches excl ue fr m PPPI5 are: u

- All patches excl ue fr m PPPI1. u
- All patches that were etache ur ng the n uct n phase base n the a hes un sc res u b t n t kn wn t be replace w th n 24 h urs after etachment. The atasets s bm itteu u n December 9, 2016 were se f r th s eterm inat n. u

The patches excl ue fr m PPPI6 are: u

- All patches excl ue fr m PPPI5. u
- All patches fr m the s bjects wh sk ppe a v s t ur ng the n uct n phase. u

Tabl 2.9: Irritation Analysis R sults (Study RP-LID-SSI) e

	Appl cant e		FDA e											
	Test[1]	Refer ence[2]	e Test[1]	Refer ence[2]	e Test[1]	Refer ence[2]	e Test[1]	Refer ence[2]	e Test[1]	Refer ence[2]	e Test[1]	Refer ence[2]	e Test[1]	Refer ence[2] e
Irr tat n Analys s e PP P pulat n e	Appl cant's FIAP e		e PPPI1 e		PPPI2 e		PPPI3 e		PPPI4 e		PPPI5 e		PPPI5 e	
Var able e	CII[3]		MIS[4]		MIS[4]		MIS[4]		MIS[4]		MIS[4]		MIS[4]	
Number f Patches e	228 e	228 e	222 e	222 e	196 e	196 e	193 e	192 e	176 e	175 e	199 e	199 e	182 e	180 e
Mean e	0.211	0.212	0.206	0.210	0.209	0.214	0.220	0.224	0.223	0.227	0.216	0.226	0.218	0.227 e
SD e	0.354	0.344	0.323	0.345	0.341	0.354	0.336	0.350	0.345	0.360	0.333	0.354	0.341	0.362 e
Upper 95% UCB[5] e f r Test –Reference[6]	0.015 e													
Upper 95% UCB[5] e f r Test - e 1.25*Reference[7]	-0.034 e		-0.038 e		-0.038 e		-0.039 e		-0.041 e		-0.039 e		-0.039 e	
C nclus n: Is Test e N n-Infer r t e Reference? e	Yes e		Yes e		Yes e		Yes e		Yes e		Yes e		Yes e	
Sens t zat n e Analys s e PP P pulat n e	Appl cant's FSAP e		e PPPS1 e		PPPS2 e		PPPS3 e		PPPS4 e		PPPS5 e		PPPS5 e	
Number f Patches e	225 e	225 e	217 e	215 e	191 e	189 e	187 e	186 e	170 e	169 e	192 e	193 e	175 e	174 e
Number f e Sens t zat n e	0 e	0 e	0 e	0 e	0 e	0 e	0 e	0 e	0 e	0 e	0 e	0 e	0 e	0 e

[1]Test: e ca ne 5% t p cal patch (D str bute by Rh ees Pharmaceut cals .P. an manufacture by Alterg n, Ital a) e
[2]Reference: e erm® (l e ca ne patch 5%) (manufacture by Te k ku Se yaku C e, t . f r En e Pharmaceut cals, Inc.) e
[3]CII: Cumulat ve Irr tancy In ex ef ne by the appl cant as the mean f the rr tat n sc res (ermal resp nse + ther effects) ur ng the n uct n phase. e Appl cant's ther effects scale s fferent fr m FDA's. e
[4]MIS: Mean rr tat n sc re s the mean f the 9 rr tat n sc res (ermal resp nse + ther effects) ur ng the n uct n phase. e
[5]UCB=Upper C nf ence B un e
[6]Appl cant's n n- nfer r ty cr ter n: 95% UCB f r Test – Reference <0.11; [7]FDA's n n- nfer r ty cr ter n: 95% UCB f r Test – 1.25*Reference <0. e
S urce: FDA Stat st cal Rep rt Table 74 e

Reviewe 's comments: r
The results of all six above-mentioned FDA irritation analyses demonstrate non-inferiority of the r test product to the reference product. However, due to inconsistency in irritation scores reported r in multiple datasets, DCR primary reviewer cannot make adequate conclusion of irritation r assessment from the irritation and sensitization study RP-LID-SSI. Please see FDA statistical r report for further details. r

Sensitization Results r

Table 2.10: Patche Rh Rtat on Sco e ≥ 2 at 48 o 72 Hou Evaluat on n Challenge R Pha e R

Subject D	T eat ment*	R tat on Sco e at R Challenge Pha e emoval R				R Max tat o n Sco e Du Rng R nduct R on R Pha e R	Appl cant' R Dete m nat on R of Potent al R Sen R zat on n the Challenge Pha e R (Ye , No) R	FDA R Dete m nat on of R R Potent al R Sen R zat on (Ye , No) R Ba ed on R tat on Sco e R
		D Re ent T me afte Pha e Patch r						
		30 Min R	24 RH r	48 RH r	72 RH r			
(b) (6)	A R	1 R	2 R	2 R	1 R	2 R	No R	No R
	B R	1 R	2 R	2 R	1 R	3 R	No R	No R

*: A=Test, B=Reference. R
Source: FDA Statistical Report Table 60 R

Reviewer's comments: R
No subjects demonstrated a sensitization response during this study. However, due to same R *reason as stated above, DCR primary reviewer cannot make adequate conclusion regarding* R *sensitization potential. Please see FDA statistical report for further details.* R

2.4.2.2 Ph rm acokinetic/Skin Adhesion Study (RP-LID-PK001) a

Applic nt's Study #:	RP- ID-PK001 a
Title a	A Ran am ized, Open- abel, Tw a-Per a, Cr ss ver, S ngle D se a B aequ valence Stu y f a ca ne 5% T p cal Patch an a erm® n Healthy A ults un ar Faste C n at as a
Objectives a	The pr mary bject ves f th s stu y were: a • T assess the b aequ valence f a s ngle 2100 mg se (3 a patches) f a test f rmulat a f l aca ne 5% t p cal patch a versus a erm® after a 12-h ar appl cat a n healthy a a ult male an afemale subjects un ar faste ac n at as. a • T assess the apparent se el vere f lla w ag a appl cat a f a s ngle 2100 mg se f a test f rmulat a a f l aca ne 5% t p cal patch versus a erm® after a 12- a h ar appl cat a n healthy a ult male an afemale subjects a un ar faste ac n at as. a • T assess patch a hes ve perf rmance f a test f rmulat a a f l aca ne 5% t p cal patch versus a erm® after a 12- a h ar appl cat a n healthy a ult male an afemale subjects. a The sec n ary bject ve f th s stu y was: a • T assess the safety an at lerab l ty f a s ngle 2100 mg a se f a test f rmulat a f l aca ne 5% t p cal patch a versus a erm® after a 12-h ar appl cat a n healthy a a ult male an afemale subjects un ar faste ac n at as. a

Reviewer's comments: a
Only the adhesion data were evaluated in this clinical review. Per DBII, the pharmacokinetic a study is acceptable. a

2.4.2.2.1 Protocol Review a

Protocol Version a	Protocol D ate a	IRB Approv hD ate a
1 a	08/08/2013 a	08/16/2013 a

Reviewer's comments: a
The study began on 09/04/2013, after the approval of the protocol on 08/16/2013. a

2.4.2.2.2 Study Design a

Over ll Study Design nd Pl n a
Th s s a ran am ze , pen-label, tw a-per a, cr ss ver, s ngle- se faste b aequ valence stu y a an patch a hes an stu y. The a hes ve pr perty f Rh aes Pharmaceut cals .P.'s l aca ne a t p cal patches (test pr auct) was c mpare t a erm® (reference). Dur ng each per a, three a t p cal patches f an ass gne treatment were appl e s multane usly (2100 mg) t the a nfrascapular area f the back n e ther s a f the sp ne, w th ut cclus an, w th appr x mately a

2.5 cm betwe n each atch f r a t tal f 12 h urs. F l w ng a wash ut er p f 7 ays, p subjects cr sse ver t the alternate reference (R) r test (T) f rmulat n an the same p r ce ures were erf rme at the same t me pnts as n te f r Per p 1. p

Table 2.11: Overall Study Design p

Study/Protocol Number p	RP- D-PK 1 p		
Subject Population p	healthy a ult male an female subjects p		
Blinding o p	en-label stu y p		
Randomization p	treatment sequence p		
Treatment arms p	**Test** p		**Reference** p
Reinforced p	n p		
Number of period/phase p	**Period 1** p	**Rest** p	**Period 2** p
Duration p	12 h prs p	7 ays p	12 h prs p
Dose administered p	3 x 70 mg t pcal test r p n pe p reference r ucts a pl e p s multane sly (210 mg)		3 x 70 mg t pcal test r p reference r ucts a pl e p s multane usly (210 mg)
Dosing regimen p	12 hrs p	n/a p	12 hrs p
Number of applications p	1 p	n/a p	1 p
Application site p	the nfrasca lar area f p the back n e ther s e f p the s me, w th t p cclus m, w th p a pr x mately 2.5 cm p betwe n each atch p	n/a p	the nfrasca lar area f p the back n e ther s e f p the s me, w th t p cclus m, w th p a pr x mately 2.5 cm p betwe n each atch p
Adhesion assessment times	6 h prs (± 30 m in) p p f l w pg atch p a pl cat n an p r t p atch rem val p	n/a p	6 h prs (± 30 m in) p p f l w pg atch p a pl cat n an p r t p atch rem val p

Reviewer's comments: p

- *The applicant's study design is consistent with the draft product specific guidance. The* p *draft product specific guidance recommends that adhesion scoring is to be done at least* p *daily.* p
- *The FDA's primary endpoint is the mean of adhesion scores at 6 hours (± 30 min)* p *following patch application and prior to patch removal.* p
- *The treatment administrations are consistent with the draft product specific guidance.* p *Per RLD label, up to maximum of 3 patches can be applied at once up to 12 hours within* p *a 24 hour period.* p

Trea men Arms t
Deta ls f each treatment are pr v te n the table bel w.

Table 2.12: Trea men Arms (S udy # RP-LID-PK001) t

Trea men arms t	Tes	t Reference t
Pr tuct Name t	ca ne T tp cal Patch, 5% L t	erm® (l t ca ne) t T tp cal Patch, 5% t
Strength t	5% t	
Patch s ze t	Wh le patch: ength: 14 cm, t Wi th: 10 cm t	Wh te patch: ength: 14 cm, t Wi th: 10 cm t
Manufacturer t	Alterg n t	(b) (4), f r t En t Pharmaceut cals t
Batch/ tt N t L	1304191 t	Y2282 t
Manufacture Date t	04/2013 t	n/a t
Exp rat tn Date t	n/a t	10/2015 t
D tsage F tm t	t p cal patch t	
R tute f a m n strat tn t	t p cal t	

Reviewer's comments: t

- *Test product lot # L1304191 is also used in irritation/sensitization study RP-LID-SSI.* t
- *The composition and size of test product lot # L1304191 is the same as the to-be-* t *marketed product.* t

S udy Popula ion Selec ion t
Stu y RP- ID-PK0101 enr lle healthy v lunteers age 18 t 45 years f age. See appl cant's t stu y rep rt, Sect n 9.2 (pages 23-25 f 143) f r the full l st f the appl cant's nclus tn an t exclus tn cr ter a.

Reviewer's comments: t

- *The draft product specific guidance does not specify inclusion/exclusion criteria for the* t *adhesion study. The applicant's inclusion/exclusion criteria are acceptable.* t

Res ric ions during he s udy t	tSubjects were n t t apply t p cal pr tucts t r wash the back, r t engage n strenu us act v ty ur ng the 12- h ur patch appl cat n t per t . On the ay f ts ng, subjects were n t t c nsume any water w th n t 1 h ur bef re an 1 h ur after patch appl cat n an were t rema n t faste f r at least 4 h urs f ll w ng patch appl cat n. Water was t ffere *ad libitum* after the 1-h ur p st- tse bl t sample was t c llecte . Water, s ft r nks (s tas) w th ut caffe ne r n n-c trus t fru t ju ces were ffere w th meals an *ad libitum* beg nn ng 4 h urs t p st- tse. Subjects were t refra n fr m ngest ng alc h l r caffe ne w th n 24 t h urs pr t t each tse. Subjects were t refra n fr m ngest ng t grapefru t pr tucts an grapefru t-c nta n ng ju ces w th n 72 h urs t pr t t each tse.

Trea men compliance	Alt patches were appl e by cl n c pers nnel. The ate an tt me stu ty t rug was a m n stere t each subject were tcumente . t

Reviewer comments t

- *The applicant's restrictions during the study and treatment compliance assurance are* t *acceptable.* t

Assessmen s t

The f ll w ng a hes n scale was use ur ng the stu y RP- ID-PK0tt01: t

Table 2.13: Pa ch Adhesion Scoring Sys em t

0 = ≥ 90% a here (essent ally n l ft ff f the sk n) t 1 = ≥ 75% t < 90% a here (s me e ges nly l ft ng ff f the sk n) t 2 = ≥ 50% t < 75% a here (less than half f the system l ft ng ff f the sk n) t 3 = < 50% a here by n t etache (m ore than half the system l ft ng ff f the sk n w th ut t fall ng ff) t 4 = patch etache (patch c mpletely ff the sk n) t

Reviewer's comments: t

The applicant's adhesion scale is consistent with the draft product specific guidance. t

Endpoin s t

Primary Endpoint	mean a hes tn sc res t

Reviewer's comments: t

The FDA statistical analysis used adhesion scores at 6 hours (± 30 min) following patch t *application and prior to patch removal for assessment of the cumulative adhesion score during* t *the 12 hour application period. This is acceptable as the draft product specific guidance* t *recommends adhesion scoring to be performed at least daily and in this case, the applicant* t *evaluated at 6 hours and just prior to removal at the end of a 12-hour application.* t

S a is ical Analysis Plan t

See appl cant's pr t c l, Sect n 13.1 (page 36-37 f 45) an FDA Stat st cal Rev ew, Sect n t 3.3.6.2 (pages 88 - 89) f r eta ls f the stat st cal analys s plan f r eta ls f the stat st cal t analys s plan. t

Reviewer's comments: t

All 48 enrolled subjects completed the study and were included in the applicant and FDA t *adhesion analyses.* t

This clinical reviewer did not recommend any changes to the applicant's adhesion population t *for the FDA analysis.* t

2.4.2.2.3 S udy Subjec s t

Subjec Disposi ion t
F rty-e ght (48) subjects, age 18-45 years, were enr lle n RP- ID-PK001. F rty-e ght (48) t subjects c mplete the stu y. t

Subjec s Analyzed t
The a hes tn analys s c h rt s the 48 subjects enr lle . t

Demographics t
The em ogrtaph cs f the PK BE/a hes n stu y RP- ID-PK001 are as f ll ws. t

		All Enrolled t (N=48) t
Gender t	Female t	23 t (47.92%) t
	Male t	25 t (52.08%) t
Race t	Black t	19 t (39.58%) t
	Wh te t	29 t (60.42%) t
Age Group t in Years t	18-40 t	35 t (72.92%) t
	41-64 t	13 t (27.08%) t
Age in t Years t	Mean, SD t	31.96, 9.22 t
	M in, tMax t	18, 45 t
	Q1, Me tan, Q3 t	22, 31.5, 45 t

S urce: FDA Stat st cal Rep rt Table 63 t

Reviewer's comments: t
The demographic distributions for gender, race, and age should have no impact on the adhesion t of the test and reference products. t

2.4.2.2.4 Resul s t

Adhesion Resul s t
The a hes tn sc res f r each patch sh ul be m on tt ne ver t me. It s bserve that ut f a t t tal f 288 patches n the PP p pulat n, 1 patch t n t sat sfy m on tt n c ty f the a hes tn t sc res. The FDA stat st cal rev ewer perf rme the analyses by m on tt n z ng the a hes tn t sc res where at each t me p tnt the a hes tn sc re f a patch s replace by the h ghest a hes tn t sc re f the prev tus assessments f the current a hes tn sc re s bserve t be less than the t a hes tn sc re at any f the prev tus t me p tnts. Th s meth t s als kn wn as the w trst t bservat n carr e f rwar (WOCF). t

Table 2.14: Primary Non-inferiori y Analysis of Mean Adhesion Score (Mono onized) for t Tes vs. Reference Pa ches per FDA (RP-LID-PK001) t

Variable t	Hypo heses t	LSmean Tes t (SE) t	LSmean Reference t (SE) t	Es ima e t of t $\mu_T - \mu_R$ t	One-Sided 95% t Upper Confidence t Bound t
Mean Adhesion t Score t	H_0: $\mu_T - \mu_R > \delta$ t H_1: $\mu_T - \mu_R \leq \delta$ t	0.5278 t (0.1257) t	1.1632 t (0.1257) t	-0.6354 t	-0.4075 t

S urce: DA Stat st cal Rep rt Table 68 F

Table 2.15: Number and Percent of Test and Reference Patches with Each Monotonized F Adhesion Score at Each Assessment (RP-LID-PK001) F

Assessment Time	Treatment	Adhesion Score									
		0		1		2		3		4	
6 Hours	Test	109	(75.69%)	24	(16.67%)	9	(6.25%)	2	(1.39%)	0	(0.00%)
	Reference	79	(54.86%)	38	(26.39%)	9	(6.25%)	12	(8.33%)	6	(4.17%)
12 Hours	Test	86	(59.72%)	32	(22.22%)	11	(7.64%)	10	(6.94%)	5	(3.47%)
	Reference	44	(30.56%)	40	(27.78%)	22	(15.28%)	17	(11.81%)	21	(14.58%)

S urce: DA Stat st cal Rep rt Table 66 F

Reviewer's comments: F
According to the FDA statistical review, the adhesion study RP-LID-PK001 demonstrates non-inferior adhesion performance of the test product to the reference product. F

2.4.3 Brief Statements of Skin Irritation, Sensitization and Adhesion Conclusions F

2.4.3.1 Irritation Conclusion F

The ata subm itte f r stu y RP- ID-SSI em nstrate that the sk n rr tat n p tent al f Rh Fes F Pharmaceut cals .P.'s. F ca ne T p cal Patch, 5% s n w rse than that f the R D. Results F fr m RP- ID-SSI are supp rte by ther ev Fence fr m the appl cat n that supp rts the F c nclus n that the sk n rr tat n p tent al f the Rh Fes F ca ne T p cal Patch, 5% s n F w Frse than that f the R HD; .e., the Fference n f rmulat n (see Sect n 2.7 bel w) s n t F expecte t be ass c ate w th a change n rr tat n r sens t zat n p tent al, an the bserve F safety pr f le has n t ra se unexpecte c ncerns (see Sect n 2.5 bel w). F

2.4.3.2 Sensitization Conclusion F

N Fsubject ha p tent al sens t zat n react n t e ther the test r the reference pr Fuct n stu y F RP- ID-SSI. Als refer t Sect n 2.4.3.1. F

2.4.3.3 Adhesion Conclusion F

The ata em nstrate that the a hes ve perf rmance f Rh Fes Pharmaceut cals .P.'s. F ca ne T Fp cal Patch, 5% s at least as g F as that f the R HD. F

2.5 C mparative Review f Safety

2.5.1 Descripti n f Adverse Events o

2.5.1.1 Skin Irritati n and Sensitizati n Study (RP-LID-SSI) o

Of 248 subjects enr lle n the rr tat n an sens t zat n stu y RP- ID-SSI, 129 (52.0%) o subjects rep rte at least ne a verse event. M stca verse events were m l r m o crate n o ntens ty. Three subjects exper ence ser us a verse events unrelate t the stu y rug an o sc nt nue the stu y. Three subjects rep rt ng a ser us a verse event (SAE) ha asthmat c o br nch t s an acute upper resp rat ry nfect o (b) (6) my car al nfarct o (b) (6) an left o s e ra ccul pathy (b) (6) One subjec (b) (6) ha a papular rash n the back an o en pr r o t patch appl cat n f r the challenge p o . N o eath was rep rte . The m stfrequently o ccurr ng a verse events were appl cat n s te prur tus (42.3%), hea ache (6.9%), appl cat n o s te pa n (5.2%), an back pa n (3.6%). Because the appl cant c llecte appl cat n s te react ns o w th ut spec fy ng treatment arm, t was n t p ssble t c mpare the nc cence f appl cat n s te o a verse events betwccn test an reference pr ccts. o

Please see Table 2.16 bel w f r the appl cant's safety p pulat n nc cence f a verse events. o

Tabl 2.16: Incid nc of Adv rs Ev nts – Applicant Saf ty Population e

Body System / Adverse Event	Reported Incidence by Cohort and Overall Study No. RP-LID-SSI		
	Cohort 1 N= 123 n (%)	Cohort 2 N= 125 n (%)	Overall N= 248 n (%)
Cardiac disorders	0	1 (0.8)	1 (0.4)
Myocardial infarction	0	1 (0.8)	1 (0.4)
Gastrointestinal disorders	3 (2.4)	3 (2.4)	6 (2.4)
Abdominal pain	2 (1.6)	0	2 (0.8)
Constipation	1 (0.8)	0	1 (0.4)
Diarrhoea	1 (0.8)	0	1 (0.4)
Dry mouth	1 (0.8)	0	1 (0.4)
Flatulence	1 (0.8)	0	1 (0.4)
Toothache	1 (0.8)	1 (0.8)	2 (0.8)
Vomiting	0	2 (1.6)	2 (0.8)
General disorders and administration site conditions	45 (36.6)	64 (51.2)	109 (44.0)
Application site pain	7 (5.7)	6 (4.8)	13 (5.2)
Application site pruritus	43 (35.0)	62 (49.6)	105 (42.3)
Fatigue	0	3 (2.4)	3 (1.2)
Immune system disorders	1 (0.8)	0	1 (0.4)
Hypersensitivity	1 (0.8)	0	1 (0.4)
Infections and infestations	1 (0.8)	8 (6.4)	9 (3.6)
Bronchitis	1 (0.8)	0	1 (0.4)
Upper respiratory tract infection	0	1 (0.8)	1 (0.4)
Viral infection	0	7 (5.6)	7 (2.8)
Musculoskeletal and connective tissue disorders	5 (4.1)	10 (8.0)	15 (6.0)
Arthralgia	0	1 (0.8)	1 (0.4)
Back pain	3 (2.4)	6 (4.8)	9 (3.6)
Muscle spasms	1 (0.8)	0	1 (0.4)
Musculoskeletal discomfort	1 (0.8)	0	1 (0.4)
Neck pain	0	1 (0.8)	1 (0.4)
Pain in extremity	0	3 (2.4)	3 (1.2)
Nervous system disorders	9 (7.3)	10 (8.0)	19 (7.7)
Dizziness	2 (1.6)	1 (0.8)	3 (1.2)
Headache	8 (6.5)	9 (7.2)	17 (6.9)
Radiculopathy	0	1 (0.8)	1 (0.4)

Psychiatric disorders	3 (2.4)	0	3 (1.2)
Dysphoria	1 (0.8)	0	1 (0.4)
Euphoric mood	1 (0.8)	0	1 (0.4)
Insomnia	1 (0.8)	0	1 (0.4)
Mood swings	1 (0.8)	0	1 (0.4)
Renal and urinary disorders	0	1 (0.8)	1 (0.4)
Nephrolithiasis	0	1 (0.8)	1 (0.4)
Reproductive system and breast disorders	1 (0.8)	1 (0.8)	2 (0.8)
Dysmenorrhoea	1 (0.8)	1 (0.8)	2 (0.8)
Respiratory, thoracic and mediastinal disorders	2 (1.6)	3 (2.4)	5 (2.0)
Asthma	1 (0.8)	0	1 (0.4)
Oropharyngeal pain	1 (0.8)	3 (2.4)	4 (1.6)
Skin and subcutaneous tissue disorders	2 (1.6)	2 (1.6)	4 (1.6)
Pruritus	1 (0.8)	1 (0.8)	2 (0.8)
Pruritus generalised	0	1 (0.8)	1 (0.4)
Rash papular	1 (0.8)	0	1 (0.4)
Vascular disorders	1 (0.8)	0	1 (0.4)
Hot flush	1 (0.8)	0	1 (0.4)
Total	**53 (43.1)**	**76 (60.8)**	**129 (52.0)**

Source: Applicant Study Report Table 13

Reviewer's comments:
Application site related events occurred in 44% of enrolled subjects. Forty two percent of enrolled subjects had application site pruritus, which is expected from this type of study design. Because the applicant did not collect treatment arm information related to application site adverse events, this reviewer could not compare between products. Other systemic adverse events reported in this study have been reported similar to those in the RLD labeling.

SAEs, Including Death
No subjects died during this study. SAEs are listed below.

Table 2.17: Subjects Reporting an SAE

Subject	Cohort	Phase	SAE Reported	SAE Onset	SAE Resolution
(b) (6)	1	Induction	Asthmatic bronchitis and acute upper respiratory infection	(b) (6)	(b) (6)
	2	Challenge	Myocardial infarction		
	2	Induction	Left side radiculopathy		Not yet recovered[1]

Note: Cohort 1 was initiated in August and completed in September.
Cohort 2 was initiated in November and completed in December.
[1]Clinic attempted to follow up after discharge from the hospital for 30 days with no success.

S urce: A p l cant Stu y Re prt Table 14 p

Reviewer's comments: p

- *Due to SAEs, three subjects were discontinued from the study. This reviewer agrees with the investigator's assessment that those 3 SAE are not related to the study drug.* p

Pregnancy p
N psubject became regnant ur ng th s stu y. p

2.5.1.2 Pharmacokinetic/Skin Adhesion Study (RP-LID-PK001) p

Of 48 subjects enr lle n harmac k net c a hes n stu y, tw (4.2%) subjects re prte at least p ne TEAE f ll w ng a m in strat n f test r puct an n subject re prte any TEAE f ll w ng p a m in strat n f the reference r puct. p

Subjec (b) (6) re prte pz ness an subjec (b) (6) re prte hea ache, nausea an v m it ng. These p AEs were c ns pere m l n ntens ty, pss bly relate t stu y rug, an were res lve w th ut p res pual effects r any act n taken. p

There were n a pl cat n s te relate AEs re prte n th s stu y. p

S gn f cant A pverse Events, Inclu ping Death p
n ne p

TEAEs that le t stu y rug sc nt nuat n p
n ne p

Pregnancy p
There were n regnanc es re prte f r Stu y RP- ID-PK0p01. p

Table 2.18: Incidence of Adverse Events – Applicant's Safety Population p

Body System / Adverse Event	Reported Incidence by Treatment Group Fasted Bioequivalence Study No. RP-LID-PK001	
	Test N=48 n (%)	Reference N=48 n (%)
Gastrointestinal disorders	**2 (4.2)**	**0**
Nausea	1 (2.1)	0
Vomiting	1 (2.1)	0
Nervous system disorders	**2 (4.2)**	**0**
Dizziness	1 (2.1)	0
Headache	1 (2.1)	0
Total	**2 (4.2)**	**0**

Source: Applicant Study Report Table 12-1

Reviewer's comment: *The incidence of adverse events reported in the test group is low and consistent with the RLD labeling. No application site related adverse events were observed from a single application 3 patches for 12 hours in both test and reference groups.*

2.5.2 Brief Statement of Safety Conclusions

The systemic AE profile for the test product is acceptable.

2.6 Relevant Findings From Other Consultant Reviews

2.6.1 Office of Study Integrity and Surveillance

A routine inspection was requested by OSIS on 04/20/2016 for irritation/sensitization study RP-LID-SSI. The OSIS inspection occurred from 10/17/2016 through 10/22/2016. Per OSIS memo dated 05/19/2016, OSIS declined to inspect the in vivo PK BE study with adhesion component based on acceptable inspection history. OSIS EIR dated 12/08/2016 observation #2 pertained to irritation and sensitization study RP-LID-SSI noted the following:

"An investigation was not conducted in accordance with the investigational plan. Specifically, in clinical study number RP-LID-SSI, 12 study subjects with patches that had completely fallen off (Class 4) were given Make-up Visits at the end of the study, when the study protocol only required study subjects that had greater that 50% of the patch fallen off, but not completely fallen off (Class 3), to have a make-up visit."

OSIS recommended that clinical study data be accepted for further Agency review, except for subjec(b) (6) OSIS recommended data from subject (b) (6) (b) (6) be excluded from per protocol analysis due to a protocol deviation. The inspection outcome was acceptable.

Due to applicant's protocol deviation related to "make-up" patches, FDA statistical reviewer performed subgroup analysis excluding all subjects who had the same issue as identified by the OSIS. Based on the FDA statistical result, the study outcome remained the same.

Reviewer's comments:
Although OSIS recommended accepting data for the review for study RP-LID-SSI, the FDA statistical reviewer identified numerous inconsistent irritation scores from the original dataset compared to subsequent datasets submitted in response to their ECD requests. Thus, DCR primary reviewer is concerned with data quality.

2.6.2 Office of Biostatistics

See FDA Statistical Review[5]

Reviewer's comments:

[5] http://panorama.fda.gov/task/view?ID=570ff5950007410d7a1b29ccd88d6ecc

The CR primary reviewer agrees with the Office of Biostatistics conclusion. D

2.7 Formulation D

2.7.1 Product Design D

	Generic Drug Product D	RLD Product D
Polymeric adhesive	S ngle p lymer a hes ve D	S ngle p lymer a hes ve D
Composition of D Unit per area D	Each a hes ve patch c nta ns 700 mg f l Dca ne (50 mg per gram D a hes ve) n an aque us base. It als c nta ns ther nact ve ngre Dents. D	
Type D	a (b) (4)	Ma (b) (4)
Size D	10 cm x 14 cm D	10 cm x 14 cm D
Shape D	rectangle D	rectangle D
Layers D	3 layers D	3 layers D
Figure D	N Df gure was f un n the D appl cant's subm ss Dn D	N Df gure was f un n the appr ve D label ng f D erm® D
Dose delivered D	700 Dmg f l Dca ne D	700 mg f l Dca ne D

2.7.2 Generic and RLD Components and Composition[6] D

2.7.2.1 Test Formulation D

Ingredient D	Function D	% Formula D	Milligrams Per Patch D
ca ne D	Act ve ngre Dent D	5.00 D	700 D
Pur f e Wate D	(b) (4)		
Glycer n D			
S rb t l S lut D			
P lyacryl c Ac D			
S Dum P lyacrylate D			
S Dum Carb xymethylcellul se D			
Pr pylene Glyc D			
Urea D			
Ka l n D			
Tartar c Ac D			
Gelat n D			
P lyv nyl Alc h l (PVA) D			

[6] OGD DBII rev ew ate 05/11/2017 pages 35-37 f 43 D

	[redacted] (b) (4)		
Dihydroxyaluminium Aminoacetat			
Edetate Disodiu			
Methylparaben			
Propylparaben			
Total		**100.0**	

2.7.2.2 NDA 020612 Formulation

Ingredient	mg/g adhesive	mg/patch	[redacted] (b) (4)	Purpose
Lidocaine	50	700		active
[redacted] (b) (4)				[redacted] (b) (4)
Glycerin				
Sorbitol, 70%				
Polyacrylic acid 20% w/w				
Sodium polyacrylate				
Sodium carboxymethyl cellulose				
Propylene glycol				
Urea				
Kaolin				
Tartaric acid				
Gelatin				
Polyvinyl alcohol				
Dihydroxyaluminum aminoacetate				
Disodium edetate				
Methylparaben				
Propylparaben				
Total				

Reviewer's comments:
The test product and the RLD are qualitatively the same but quantitatively different. Except for sodium carboxymethyl cellulose and dihydroxyaluminum aminoacetate, all other inactive ingredients present in the test product were the same o [redacted] (b) (4) than those present in the RLD. According to DBII review dated 04/24/2017, a slight increase o [redacted] (b) (4) for sodium carboxymethyl cellulose in the test formulation compared to that in the RLD is not a safety concern and is acceptable based on the pharmacology/toxicology consult response. Sodium carboxymethylcellulose i [redacted] (b) (4) for example. In addition, for dihydroxy aluminum amino acetate, another ANDA 200675 (Lidocaine patch) approved on 08/23/2012 include [redacted] (b) (4) amount than the level proposed in the test formulation

[redacted](b) (4)). *Thus, the DBII x deems the test product acceptable. See DBII review for details.* x

2.8 Relevant findings from Secondary and Tertiary Reviewers x

Base n ata screpanc es bserve by the FDA pr mary stat st cal rev ewer f r rr tat n x sc res n stu y RP- ID-SSI, DCR pr mary rev ewer c nclu e that n a equate x c nclus xn can be ma e fr m th s stu y. As a result, DCR sec n ary an tert ary rev ewers x c ns xere all relevant f n xngs an base n we ght f ev xence appr ach, supp rte by x ther nf rmat n ava lable w th n subm iss x n as f ll ws, DCR rec mmen s appr val f x th s appl cat n: x

1. The appl cant's test pr xuct s nly quant tat vely xfferent fr m the R xD. Except f r x tw x nact ve ngre xents, s x um carb xymethylcellul se an hy r xyalum inum x am in acetate, all ther nact ve ngre xents present n the test f rmulat n are x qual tat vely the same an are at levels same r [redacted](b) (4) th se f the R xD. DBII x eterm ine that the am ount f hy r xyalum inum pr p se n the test pr xuct s x w th n the level f an appr ve x ca ne patch f r an ther gener c appl cant (ANDA x 200675). A x t nally, wh le hy r xyalum inum am in acetate s c ns xere a x p tent al sk n rr tant, the xfference between the test an R xD patch am ounts s small x [redacted](b) (4) an s n t expecte t be cl n cally s gn f cant. Regar ng th [redacted](b) (4) am ount x [redacted](b) (4) f s x um carb xymethylcellul se present n the test pr xuct c mpare t the x R xD, DCR eterm ine that t s unl kely that th x [redacted](b) (4) w xul affect the safety x pr f le, as s x um carb xymethylcellul se s c ns xere a n n- rr tat ng an n n- x sens t z ng substance that s even use as a [redacted](b) (4) Theref re, verall, DCR x sec n ary an tert ary rev ewers c nclu e that the m in r xfferences n test x f rmulat n c mpare t the reference pr xuct xn t p se any greater safety c ncern x f r rr tat n r sens t zat n p tent als f the test pr xuct. x
2. Per DBII, the test pr xuct s eeme t be b xequ valent t the R xD base n a x pharmac k net c stu y. In th s same stu y, a hes xn perf rmance f the test pr xuct x was sh wn t be acceptable. x
3. Per FDA stat st cal rev ewers, the appl cant's atasets ha nc ns stent rr tat n x sc res that ra se c ncerns regar ng ata ntegr ty. Per OSIS, there were n x s gn f cant f n xngs bserve f r the rr tat n/sens t zat n stu y an ata were x c ns xere acceptable f r FDA rev ew. Theref re, wh le DCR ackn wle ges the x stat st cal rev ew team's c ncerns w th the ata fr m stu y RP- ID-SSI, the lack f x c rr b xrat ng c ncerns fr m OSIS nspect n makes t m orex xff cult t just fy x c mpletely sregar ng stu y results. x
4. Because the appl cant's stu y es gn s s gn f cantly xfferent fr m the x rec mmen at n pr v xe n the rug spec f c gu xance f r th s pr xuct ue t x nc ns stent make-up patch use, FDA stat st cal rev ewer perf rme 6 xfferent stu y x p pulat ns p st-h c t evaluate whether th se pr t c l v xlat ns ent f e by the x FDA stat st cal rev ewer c ul change the stu y utc me. Base n FDA stat st cal x rev ewer's 6 xfferent stu y p pulat ns analyze , the stu y utc me rema ne the x same, meet ng n n- nfer r ty cr ter a. Alth ugh the atasets may appear t be x unrel able n s me cases, verall assessment f atasets x n't present any b as r x better rr tat n resp nse t war the test pr xuct c mpare t the reference pr xuct. x

The ata screpanc es ere ma nly ue t p wr qual ty c ntr l. Tak ng nt w c ns wsrat n that there s a l wpre-test c ncern f r rr tat n/sens t zat n, an n w ser us rr tat n/sens t zat n events n the evel pment pr gram, DCR sec n ary w an tert ary rev e wsrs c nclu e that th s s a equate t supp rtw appr val. w

2.9 Conclusion and Recommendation w

2.9.1 Conclusion w

There s a equate nf rmat n n ANDA 209190 t c nclu e that the m in w ffferences n test w f rmulat n f Rh wes Pharmaceut cals .P.'s w ca ne T p cal Patch 5% c mpare t the w reference pr wuct, w erm T p cal Patch, 5%, wes n t p se any greater safety c ncern f r w rr tat n r sens t zat n p tent als f the test pr wuct. The cl n cal ata fr m Stu y RP- ID- w PK0w01 em onstwrate that the a hes ve perf rmance f Rh wes Pharmaceut cals .P.'s w ca ne w T pw cal Patch, 5% s at least as g w as that f the R wD, w erm® (l wca ne) T pw cal Patch, w 5%. w

2.9.2 Recommendations w

DCR rec mmen s appr val f th s appl cat n, c nt ngent n appr val rec mmen at ns fr m w the ther sc pl nes n the rev e wteam. w

N n A n OMMENTS TO BE PROV DED TO THE APP n ANT n

The Cli ical Discipli e has completed its review o ANDA 209190 a d has o comme ts at this n time. n

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Division o ini h Review onsu t tion h

Lidocaine Topical Patc , 5% h

Drug Produ t:	Lidocaine Topical Patc , 5 % h
ANDA:	209190 h
ANDA App i nt:	R bdes P armaceuticals, L.P. h
Re eren e Listed Drug (RLD) h NDA, Approv h D te RLD Sponsor:	Lidoderm® (lidocaine) patc 5% h NDA 020612, Approved on 03/19/1999 Teikoku P arma, USA Inc. h
Ph rm a dogy-Toxi o ogy h Prim ary h Reviewer:	Mi Young Yang, P D h P armacologist, Division Of Clinical Review (DCR) h Office of Bioequivalence (OB) h Office of Generic Drugs (OGD) h
Medi h O fi er h Prim ary h Reviewer:	Mónica L. Fiszman, MD, P D h Clinical Reviewer h DCR,OB,OGD h
Medi h O fi er h Se ond ry Reviewer:	Lolita Lopez, MD h Clinical Team Leader h DCR,OB,OGD h
Terti ry Reviewer	Daiva S tty, MD h Deputy Director h DCR,OB,OGD h
To:	Beena Mat ew, P arm.D. h Division of Filing Review (DFR) h Office of Regulatory Operations (ORO) h
Re son or onsu t:	Assess t e safety of t e excipient carboxymet ylcellulose (CMC) sodium h in t e drug product at t e levels proposed. h
D te o Submission:	04/13/2016 h
D te o onsu t:	04/28/2016 h
D te Assigned:	06/07/2016 h
D te o omp etion:	05/10/2017 h
on lusion:	DCR concludes t at t h [redacted] (b) (4) CMC sodium [redacted] (b) (4) h in t e proposed lidocain h d to t e RLD d h additional safety concerns, and is acceptable from Clinical and P arm/Tox h perspectives. h

1 Exe utive Summ ry: h

T is review addresses a consult from t e Division of Filing Review (DFR) to evaluate t e h applicant's justification regarding t e safety of t e ig er level of carboxymet ylcellulose h (CMC) sodium in t e proposed generic lidocaine 5% patc compared to t e RLD, submitted h under ANDA 209190 by R bdes P armaceuticals L.P. T e RLD, Lidoderm® Topical Patc 5% h was approved for t e relief of pain associated wit post- erpetic neuralgia on 03/19/1999 (NDA h 020612, sponsor: Teikoku P arma USA Inc.) Eac patc contains 700 mg of lidocaine. h

According to the RLD's label, patients may apply up to four packets in a 24-hour period. The proposed packet contains CMC sodium [redacted] (b) (4) [redacted]. The RLD contains [redacted] (b) (4) [redacted]. The range for amount of CMC sodium in the proposed formulation is [redacted] (b) (4) compared to the RLD. The MDE for the proposed product is also [redacted] (b) (4) than any product listed in the FDA IID Database with similar conditions of use.

DCR evaluated the CMC sodium in the proposed lidocaine topical patch from clinical safety and pharm/toxicology perspectives. The applicant's justification, FDA database and other sources were reviewed for information relevant to this consult.

CMC sodium is the sodium salt of a polycarboxymethyl ether of cellulose. It is generally recognized as safe (GRAS) as a miscellaneous and general purpose food additive without limitations when used in accordance with good manufacturing practice (21CFR 182.1745). Applied locally, CMC sodium is considered as a non-irritating and non-sensitizing substance. There are no published clinical studies reporting adverse events with CMC sodium applied topically to skin. The World Health Organization (WHO) determined as "no specified" Acceptable Daily Intake (ADI) for oral cellulose derivatives because WHO considered that no toxicity may be expected after ingestion.

The Applicant submitted two clinical studies to support approval of the ANDA; a skin irritation/sensitization study (Study RP-LID-SSI) was conducted and reviewed by the ANDA review team in DCR, and a bioequivalence study (Study RP-LID-PK001) is under review by the Division of Bioequivalence. The adequacy and acceptability of the study conducted and results are pending review.

From a pharm/tox perspective, the non-clinical data indicate that the proposed level of sodium CMC in the new version of lidocaine patch was safe when compared to the RLD.

Based on available information, it is unlikely that a [redacted] (b) (4) in the amount of CMC sodium in the proposed formulation compared to the RLD would affect the safety profile of the proposed formulation.

2 Recommendation:

From a clinical safety and Pharm/Tox perspectives, DCR concludes that the amount of carboxymethylcellulose (CMC) sodium in the proposed new lidocaine patch 5% is acceptable. The amount of CMC sodium [redacted] (b) (4) [redacted] in the proposed patch is unlikely to pose an increased safety risk to the patient when the new drug product is used as a therapeutic equivalent of the RLD.

DCR has no recommendations to convey from a clinical safety and Pharm/Tox perspectives.

3 Regulatory Background:

The RLD, Lidoderm (lidocaine patch 5%) was given orphan drug designation on 10/24/1995 for the indication of the relief of allodynia (painful hypersensitivity) and chronic pain associated with post-herpetic neuralgia[1]. It was subsequently approved by FDA for marketing for the relief of pain associated with post-herpetic neuralgia on 03/19/1999 (per Orange Book and DARRTS) under NDA 020612 (sponsor: Teikoku Pharma USA).

On 04/14/2016, Rhodes Pharmaceuticals L.P. (Rhodes), the applicant, submitted ANDA 209190 for a generic lidocaine patch 5%, the RLD is Lidoderm®. The applicantion included two studies to support approval of the ANDA: a skin irritation/sensitization study (Study RP-LID-SSI) which is reviewed by the ANDA review team in DCR, and a pharmacokinetic (PK) bioequivalence (BE) study (Study RP-LID-PK001) is reviewed by the Division of Bioequivalence II (DB II). Both studies are currently under review.

The proposed patch contains the excipient carboxymethylcellulose (CMC) sodium that i (b) (4) than the amount present in the RLD. DFR sent a consult to DCR stating the amount of excipient in the proposed product could not be justified by the IIG database, MDD, or RLD formulation, and requested evaluation of the Pharm/Tox data submitted by the applicant.

3.1 Current Draft Guidance

There is product specific bioequivalence guidance for lidocaine topical patch, 5% at the "Bioequivalence Recommendations for Specific Products" website:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm086293.pdf (last revision, January 2016)

Active Ingredient: Lidocaine
Dosage Form: Route: Patch; topical
Recommended Studies: ***Three*** studies

1. Type of study: Fasting
   Design: Single-dose, in vivo, using three topical patches
   Strength: 5%
   Subjects: Normal healthy males and females, general population.
   Additional Comments:
   - Apply three topical patches simultaneously over a 12-hour period.
   - You may use fewer patches, provided the plasma concentrations of lidocaine are measurable to adequately characterize the pharmacokinetic profile of lidocaine for bioequivalence (BE) assessment based on the 90% confidence interval criteria.
   - Please include a 24-hour post-dose sampling time in the BE study.
   - In addition to pharmacokinetic data, please report the "apparent dose" delivered. The apparent dose can be determined by subtracting the remaining amount of lidocaine in each patch (used patch) from the manufactured amount. Analyze and include in the calculation the amount of adhesive residue from each patch left on the skin.

[1] FDA Intranet-Search Orphan Drug Designations and Approvals- Accessed on 08/ 08/2016
http://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=92395

2. Type Sdy: Adhe i n Sdy S
De ign: Rand mized, ingle-d Se, w S rea men in viv S
reng h: 5% S
bjec : Heal hy male and emale , general p p la i n. S
Ad Sli i nal c mmen S peci ic rec mmenda i n are pr vided bel w. S

3. Type Sdy: kin irri a i n and en i iza i n Sdy S
De ign: Rand mized, eval a S-blinded, in viv wi hin- Sbjec repea e S
reng h: 5% (admini ered a ne- Sr h he e and ne- Sr h he re erence) S
bjec : Heal hy male and emale , general p p la i n. S

Reviewer's comments*: The product specific guidance for lidocaine 5% patch recommends three* S *studies as listed above. As mentioned earlier, the firm conducted two (instead of three) studies as* S *recommended by the guidance, a PK/BE study and an irritation and sensitization study. Instead of* S *conducting a separate adhesion study (see item 2 above), the applicant included an adhesion* S *assessment in their BE study RP-LIDPK081 study.* S

3.2 Orange Bo Sk Information S

There are hree marke ed pre crip i n en rie in he Orange B Sk S Lid caine, T pical Pa ch S 5% (es Table 1 bel w). Lid derm Pa ch 5%, NDA 020612 ha RLD de igna i n. S

Table 1: Orange Bo Sk Currently Approved Applications for Lidocaine, Topical Patch 5% (n= 3) S

Appl S N S	TE S C Sle S	RLD	Ac ive S Ingredien S	D Sage F Sm; R S e S	S reng h S	Pr prie ary Name S	Applican S
N020612	AB S	Ye S	L id caine	Pa ch; T Spical	5% S	Lid derm S	TEIKOKU PHARMA U SA S
A202346	AB S	N S	L id caine	Pa ch; T Spical	5% S	Lid caine	MYLAN S TECHNOLOGIE S
A200675	AB S	N S	L id caine	Pa ch; T Spical	5% S	Lid caine	ACTAVI LAB SUT S INC S

rce: earch n 08/02/16 by hi reviewer She n-line Orange B Sk S
TE=Therape Sc Eq ivalence S
RLD=Re erence Li ed Dr g S

3.3 RLD Formulation S

The RLD, Lid derm® pa ch (NDA 020612), rm ula S n i pre en ed in Table 2. S

Table 2 y u lati n f Lid de y T ypical Patch 5%y[2,3] y

Ing edients y	uncti n y	P tenc y(%) y	Lid de y® y Weight (gy)/Patch y
Lidocaine, USP y	Active	5.00 % y	700 y
Gelatin, NF y	(b) (4)		
Edetate Disodium, USP y			
Glycerin, NF y			
D-Sorbitol, NF y			
Kaolin, NF y			
Sodium Polyacrylate			
Carboxymethylcellulose Sodium, NF y			
Polyacrylic Acid y			
Dihydroxyaluminum y Aminoacetate, USP y			
Propylene Glycol, NF y			
Polyvinyl Alcohol, NF y			
Tartaric Acid, NF y			
Methylparaben, NF y			
Propylparaben, NF y			
Urea y			
(b) (4)			

3.4 P y sed Gene ic y u lati n y

The proposed generic formulation was obtained from Section 3.2.P.1 in the application y submission dated 04/13/2016[4]. y

Table 3 C yp siti n f Lid caine d ug P yduct (ANDA 209190) y

Ing edients y	uncti n y	P tenc (%) y	LIDODERM® y Weight(gy)/Patch
Lidocaine, USP y	Active	5.00 %	700 y
Glycerin, NF y	(b) (4)		
D-Sorbitol, NF y			

[2] NDA 020612/ S10-DARRTS, 12/28/2006, CMC Review (Table 1) y
[3] ANDA 203265, DARRTS, 8/8/2012, CONSULT REV-NONCLINICAL-01- Emami, Armaghan y
[4]ANDA 209190 \\cdsesub1\evsprod\anda209190\0000\m3\32-body-data\32p-drug-prod\lidocaine\32p1-desc- y comp\description-and-composition.pdf y

Polyacrylic Acid	(b) (4)
Carboxymethylcellulose Sodium, NF	
Sodium Polyacrylate Starch	
Propylene Glycol, NF	
Urea, USP	
Kaolin, NF	
Tartaric Acid, NF	
Gelatin, NF	
Polyvinyl Alcohol, NF	
Dihydroxyaluminum Aminoacetate, USP	
Edetate Disodium, USP	
Methylparaben, NF	
Propylparaben, NF	

Reviewer's comments: *The proposed formulation is qualitatively the same, only the amounts for few ingredients differ in minor percentages; polyvinyl alcohol amount is slightl* (b) (4) *in the RLD* (b) (4) *) compared t* (b) (4) *(proposed); dihydroxyaluminum aminoacetate is slightl* (b) (4) *in the propose* (b) (4) *versu* (b) (4) *in the RLD. DCR is consulted for CMC sodium in the proposed formulatio* (b) (4) *the amount i* (b) (4) (b) (4) *than in the RLD Lidoderm 5% (700 mg patch).*

4 Labeling:

The current product label for Lidoderm® (lidocaine) patch 5% was approved on 01/07/2015. See the full label for additional details[5]. There is no black box warning.

4.1 Indications

Relief of pain associated with post-herpetic neuralgia.

4.2 Off-Label Uses

A search of the NIH Clinical Trial Website[6] retrieved the following off-label uses for lidocaine topical patch 5%: Neuropathic pain, low back pain, myofascial pain, osteoarthritis [OA], diabetic neuropathy, fractures, and carpal tunnel syndrome.

[5] Lidoderm Patch , Label – S012, 01/07/2015
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020612s012lbl.pdf
[6] https://clinicaltrials.gov/ct2/results?term=lidocaine+patch&Search=Search

Reviewer's comment : *In the majority of clinical trials the dose of lidocaine topical patch 5% was up to 4 patches applied topically once daily although the Lidoderm label recommends only up to 3 patches within 24 hours.*

4.3 Dosage and Administration

Apply Lidoderm to intact skin to cover the most painful area. **Apply the prescribed number of patches (maximum of 3)**, only once for up to 12 hours within a 24 hour period. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Clothing may be worn over the area of application. Smaller areas of treatment are recommended in a debilitated patient, or a patient with impaired elimination.

If irritation or a burning sensation occurs during application, remove the patch (es) and do not reapply until the irritation subsides.

When Lidoderm is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.
Lidoderm may not stick if it gets wet. Avoid contact with water, such as bathing, swimming or showering.

(b) (4)

4.4 Contraindications

Lidoderm is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type, or to any other component of the product.

4.5 Adverse Reactions

Application Site Reactions
During or immediately after treatment with Lidoderm (lidocaine patch 5%), the skin at the Site of application may develop blisters, bruising, burning sensation, depigmentation, dermatitis, discoloration, edema, erythema, exfoliation, irritation, papules, petechia, pruritus, vesicles, or may be the locus of abnormal sensation. These reactions are generally mild and transient, resolving spontaneously within a few minutes to hours.

Reviewer's comment : *Per label, application site reactions are generally mild to moderate and resolve spontaneously.*

Allergic Reactions
Allergic and anaphylactoid reactions associated with lidocaine, although rare, can occur. They are characterized by angioedema, bronchospasm, dermatitis, dyspnea, hypersensitivity, laryngospasm, pruritus, shock, and urticaria. If they occur, they should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Other Adverse Events
Due to the nature and limitation of spontaneous reports in postmarketing surveillance, causality has not been established for additional reported adverse events including:
Asthenia, confusion, disorientation, dizziness, headache, hyperesthesia, hypoesthesia,

lighthea e ne n metallic ta te nau ea nervou ne n pai exacerbate npare the ia nom nolna ce n ta te alteratio nvomiti g vi ual i turba ce nuch a blurre vi io nflu hi g ti itu na n tremor. n

4.6 Use i Specific Populatio s n

Preg a cy Labor a n Delivery: The label tate that Li o erm ha not bee ntu ie i n preg a cy a n it houl be u e n uri g preg a cy o ly if clearly nee e . Li o erm ® ha not n bee ntu ie ni labor a n elivery. Li ocai e i not co trai ricate ni labor a n elivery. Shoul n Li o erm be u e nco comita tly with other pro uct co tai i g li ocai e total o e n co tribute nby all formulatio n mu t be co ni ere . n
Pe iatric U e: Safety a n effective e ni pe iatric patie t have ot bee e tabli he . n
Geriatric U e: The label make no comme t about geriatric u e. n

5 Discussio : n

DCR wa co nulte by DFR regar i g the level of the excipie t carboxymethylcellulo e (CMC) n i the propo e nge eric li ocai e topical patch 5%. The propo e npatch co tai nCMC no ium n (b) (4) per patch while the RLD co tai n (b) (4) per patch or a nMDE Therefore the amou t n of CMC no ium i the propo e nformulatio ni (b) (4) tha nthe amou t pre e t i the RLD. n

DFR' co nult reque t tate *in-verbatim*: n

> *"The above excipient(s) could not be justified by the IIG database, MDD, or RLD* n *formulation.* n
> *Please evaluate the Pharm/Tox data submitted in section 2.6.6: "Toxicology Written* n *Summary" to determine if these inactive ingredient(s) are safe for use in this drug* n *product at the levels proposed."* n

5.1 Applica n's Justificatio n

The Safety A ne me t for CMC no ium ubmitte by Rho e i clu e precli ical ata from the n publi he literature o nPK a n toxicity after local a mi i tratio na n y temic expo ure. The n a imal ata are reviewe ni Sectio n5.6 of thi review. n

For the cli ical afety a ne me t Rho e referre to re ult of the two cli ical tu ie nubmitte n u ner ANDA 209190[7]. n

5.2 Brief Descriptio nof Excipie t n

Carboxymethylcellulo e (CMC) o ium i the o ium alt n of a polycarboxymethyl ether of n cellulo e. It co tai nNLT 6.5% a n NMT 9.5% of o ium (Na n) calculate o the nie ba i . n CMC no ium i al o k ow na cellulo e gum (Cn G). n

[7] ANDA 209190-Sectio n2.6.6. CMC Safety Review-Page 10-11. \\c ne ub1\ev pro \a na209190\0000\m2\26- n o cli - um\ o nemc- af-rev.p f n

Cosmeti - se -The ellulose derivatives are used in a wide variety of osmeti s and toiletries as - thi keners, suspending agents, film formers, stabilizers, emulsifiers, emollients, binders, or - water retention agents. Generally, the majority of uses are in hair produ ts, eye and fa ial - makeups, and skin -are preparations. The on entration of use an range up to 10%. However, - the elluloses are most frequently used in -on entrations of >0.1 1 %. In 19 1, CG was used in - a total of -12 formulations, most of whi h were eye and skin makeup and skin -are preparations. - Of these -12, 11 % in orporated CG at unreported -on entrations; 73% at on entrations of - >0.1 1 %; 13% at on entrations <0.1 %; and 3% at on entrations of > 1 5%. -
Non -osmeti - se CG is used in the pharma euti al industry as a tablet ex ipient, suspending - and vis osity in reasing agent, bulk laxative, demul ent, dental adhesive, and as an absorption - medium. -

Synonyms[9] -Aku ell; Aqualon CMC; Blanose; Carbose D; armellosum natri um; **cellulose** - **gum**; **CMC sodium**; Dyna el; E466; Finnfix; Ki -olateNym œl-ZSB; SCMC; **sodium** - **carboxymethylcellulose**; sodium e-ulose gly olate; Sunrose; Tylose CB; Tylose MGA; Walo el C; Walo el CRT; Xylo Mu ine. -

5.3 Maximal Daily Dose (MDD) and Maximal Daily Exposure (MDE) Calculations -

MDD: A - ording to the label, patients may apply up to **three patches** in a 24 hour period. - The proposed pat h -ontains 700 mg of lido aine, whi h results in an MDD of 700 mg x 3 - pat hes = 2100 mg. -

(b) (4)

5.4 Excipient in FDA Approved Drug Products -

Excipient CMC Sodium as Active Ingredient -

CMC sodium is an a tive ingredient listed under 21 CFR 349.12 for as ophthalmi demul ent - for over the -ounter (OTC) human use at on entrations between 0.2 to 2.5 % [10].-CMC sodium - ophthalmi solution is indi ated [11]*for the temporary relief of burning, irritation, and discomfort* - *due to dryness of the eye or exposure to wind or sun. For use as a protectant against further* - *irritation or to relieve dryness of the eye, for use as a lubricant to prevent further irritation or to* -

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Ameri an College of Toxi ology, Final Report on the Safety Assessment of Hydroxyethyl ellulose, - Hydroxypropyl ellulose, Methyl ellulose, Hydroxypropyl Methyl ellulose, and Cellulose Gum, *International* - *Journal of Toxicology*, 5, 1 59 (19 6) -

[9] Carboxymethyl ellulose Sodium :Handbook of Ina tive Ingredients, a -essed on -/9/2016 - https //www.medi ines omplete. om/m d/ex ipients/ urrent/1001935347.htm?q= arbomellose&t=advan ed&ss=mn - &tot=23&p=3#_hit -

[10] 21 CFR §349.12 (Ophthalmi demul ents) http //www.e fr.gov/ gi - bin/retrieveECFR?gp=1&SID=3609b77b5 4ae7a9125 3b 759e0 a -&h=L&mc=true&n=pt21.5.349&r=PART&ty - =HTML#se21.5.349_112 -

[11] 21 CFR §349.60 Labeling of ophthalmi demul ent drug produ ts http //www.e fr.gov/ gi - bin/retrieveECFR?gp=1&SID=3609b77b5 4ae7a9125 3b 759e0 a -&h=L&mc=true&n=pt21.5.349&r=PART&ty - =HTML#se21.5.349_112 -

relieve dryness of the eye[12]. The dose and administration is to*: Instill 1 or 2 drops in the affected eye(s) as needed and discard container.* OTC labels do not list adverse events.

Reviewer's Comments: *Conditions of use of this product (ophthalmic drops) differs from the proposed product (topical). In addition, the concentration of CMC sodium in this produc* (b) (4) *i* (b) (4) *than the CMC sodium concentration in the proposed formulation* (b) (4)

Excipient CMC Sodium as Inactive Ingredient

CMC sodium is an inactive ingredient used in FDA approved prescription drug products; the MDE in the proposed formulation for CMC sodium i (b) (4) An inactive ingredient search for CMC sodium was performed using the Inactive Ing atabase (IID). There are three approved transdermal systems, including the RLD (Lidoderm®, NDA 20612), that contain CMC sodium. The MDE of CMC sodium in the proposed formulatio (b) (4) the MDE for CMC sodium in the RLD and in FDA approved drug products as shown in Table 4. The proposed formulation ha (b) (4) CMC sodium compared to the RLD, Lidoderm.

Table 4: Search Results from the FDA Internal IID for Carboxymethylcellulose Sodium

Product (Application No)	Maximum Daily Dose	Indication	CMC sodium in drug product	Maximum Daily Exposure (MDE)
Proposed Formulation (Lidocaine 5%; ANDA 209190)	3 patches	Pain in post-herpetic neuralgia	(b) (4)	
RLD Lidoderm® (Lidocaine 5%; NDA 20612) -	3 patches	Pain in post-herpetic neuralgia		
Lidocaine (Lidocaine 5%; ANDA 200675)	3 patches	Pain associated with post-herpetic neuralgia		
Flector® (Diclofenac epolamine; NDA 21234)	2 patches	(b) (4)		

5.5 Clinical Evaluation

DCR reviewed the applicant's submission, FDA's Inactive Ingredient Database (IIG), Handbook of Inactive Ingredients, MERCADO, Code of Federal regulation (21 CFR), DARRTS, the Orange Book, the medical literature (Pubmed), RLD label and other databases for information relevant to this consult.

[12] Sodium CMC search in Dailymed (accessed on 8/9/2016)
https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b32ed9e8-d091-4f16-b416-5a62cdfee49a

The Appl S subm i ed wo l S l s ud es o suppor pSprov l of he ANDA: sk S S rr S o /se s Sz So s udy (Sudy RP-LID- Sl) urre Sly u der rev ew by he ANDA rev ew S e m DCR, Sl ph rm a oSk Se S/b oequ v le Se s udy (Sudy RP-LID-PK0Sl) urre Sly S u der rev ew by he D v s o of B oequ v le Se II (DB II). S

5.5.1 Clinical Evaluation of the Applicant's Justification S

Rhodes l S l jus f S o [13] w Sl b sed o he use of CMC sod um s Ge er lly Re og Szed S s Sfe (GRA S) food dSl Sve, Sl Sed FAO/WHO Sl EU s fe y form a oS. Rhodes lso S refers o he s fe y resul s from he BE s udy Sl he rr S o Sl se s Sz So s ud es hey S subm i ed Su der ANDA 209190. S

Rhodes s Ses h SCMC s ommo ly used s v s os y e h S er of he drug-m ar Sx solu o S op Sl (derm al) pSh rm a eSl S l formul So s Sl s lso l s ed s S S ve gred e S S L doderm® (L do S e P Sh 5%). por d S ses of se s Sz So sso S ed w h exposure o S sod um CMC produ Sh ve bee repor ed he l er ure. od um CMC s lso l s ed s GRA S S (Ge er lly Re og Szed s Sfe) d re Sfood dSl Sve (21 CFR 182.1745) w Shou l m i So s o her S h S good m a uSf Sur g pro esses. The Jo S FAO/WHO Exper Commi Se o Food Add Sves S (JECFA, 1990) d he EU Se Sf Commi Se for Food (CF, 1992) h d es bl shed S ep Sble d Sly S ke (ADI) for o Sl ellulose des v Sves for hum a So sump o s " o S spe Sf ed" CMC s prese S e Sh proposed p Sh [redacted](b) (4) A he m ax Sm d SS re omme ded d Sly dose of 3 p Sh es, p Se Sexposure o CMC he p Sh ould ppro Sh S [redacted](b) (4) d y f ll he CMC w Sl rele sed. For S ver ge p Se S(body we gh of 60 kg), o Sl S osure o CMC ould pSro S [redacted](b) (4) d y. S

***Reviewer's comments**: The applicant's justification based on WHO and GRAS information are reasonable.* S

The ppl S m akeSl refere Se o he r o Slus o of he wo l S l s ud es hey omple ed Sl S subm i eSl o he ANDA: S

Irritation and Sensitization Study (RP-LID-SSI). Th s s Sev lu So of sk S rr S o Sl S se s Sz So po e S l of he 5% L doderm p Sh formul So p Sel of hum a Solu Seers S follow Sg 21 d ys of exposure omp red o he proposed produ S repe - sul p Sh es s udy S 248 subje Sl, 227 (91.5%) omple ed he s udy s des g ed. All subje Sl re e ved es Sl S RLD produ Ss mul Seously, w h ppl S o s es r domly ss g ed. All ppl S o s of es S d RLD produ S o s s ed of o e-four h of he p Sh. Rhodes o Sluded "There w Sl o S d ffere Se sk S rr S y d Ses, Sl sk Sse s Sz So Slys s be weSl L do S e 5% op Sl S p Sh (Rhodes) Sl L doderm op Sl p Sh (RLD). I deed, S Slys s of d v du l umul Sve S rr S y Sl d v du l umul Sve derm al rSspo se d Sts y elded de S l s ores for S L do S e 5% op Sl p Sh Sl he L doderm op Sl p Sh. No p Sh w Sl removed for e her S u S ep Sble sk S rr S y or s ro g sk Sse s Sz So . Three (1.2%) subje Sl repor ed o e S ser ous dverse eve S; he op So of he Pr S p l I ves g Sor, hese AEs were u rel ed o S

[13] ANDA 209191 \\ dsesub1\evsprod\ Sl 209190\0008\m2\26- o Sl -sum\sod- m e-sSf-rev.pdf . p.4 S

study t st ot o l. Th study conclud d th t, L doc m 5% top c l p tch s w o s f nd o g n o lly w ll tol ot d n th s no o l, h olthy dult ol nd f o l popul t on." o

Bi equivalence Study Study RP-LID-PK001. Th b o qu v l nc of s ngl 2,100 g dos of o th p opos d p oduct w s copo o d to th RLD p oduct ft 12-hou ppl c t on n h olthy o dult ol nd f o l subj cts und of st d cond t ons (n=48). A s cond y obj ct v of th s o study w s to v lu t th s f ty nd tol ob l ty of th t st fo w l t on of l doc m 5% top c l o p tch v s us th RLD. Th s f ty nd tol ob l ty of th l doc m 5% top c l p tch w o o v lu t d by th nc d nc of t ot ont- o g nt dv s v nts, study d scont nu t on o nfo o t on, cl n c l l bo to y t st sults, v t l s gns, sk n ot t on ss ss onts, nd phys c l o x o n t on f nd ngs. Th o w o no s oous dv s v nts po t d du ng th study nd no t st o subj ct d scont nu d t ot ont du to n dv s v nt. "It w s conclud d th t, th t st p tch s o w o g n o lly s f nd w ll-tol ot d n th s t st popul t on". o

Ov o ll, Rhod s conclud d "Cl n c l nfo o t on on th top c l us of sod u oCMC s o copo on nt of fo w l t ons nd c t s th t th o s l ttl f ny sk fo ot t on o s ns t z t on. o Spo d c c s s of s ns t z t on ssoc t d w th xposu to sod u oCMC p oducts h v b on o po t d n th l t otu a Cl n c l nfo o t on on th Rhod s l doc m (5%) p tch h s o d t o n d th pot nt l fo dv s loc l (nd syst o c) ff cts s no d ff ont f o oth RLD o sugg st ng th t th nclus on of sod u oCMC t th st t d o unts do not p s nt cl n c l sk. o (Rhod s, 2013; 2014)." o

Reviewer's comments: *As menti ned earlier, these studies are presently under review by OGD. o The adequacy and acceptability f the study c nduct and results will be determined by the o review divisi ns in OGD.* o

5.5.2 Safety Information in Humans from Published Medical Literature o

No s f ty nfo o t on w s t v d f o oth publ sh d l t otu (PubMed) fo c llulos gum o o c boxy o thylc lulos (CMC) sod u oppl d top c ly to th sk n. Th o t cl s w o o t ov d f o oPub o d fo CMC sod u ous d s y -d ops. R po ts st t th t CMC sod u oo ophth l c solut on s v y w ll tol ot d nd ff ct v fo d y y nd postsu g c l y o c o[14,15,16]. Conc nt t ons of CMC sod u ot st d n two po ts w o 0.5 nd 1%. o

Reviewer's comments: *The use f CMC s dium as eye dr ps cann t be used t supp rt the o safety f CMC s dium when applied t the skin t pically because c nditi ns f use differ fr m o the pr p sed drug pr duct. In additi n, the c ncentrati n f CMC s dium f r phthalmic use is o l wer than in the pr p sed drug pr duct.* o

5.5.3 Safety Information in Humans from Other Sources o

WHO[17,18] o

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[14] http://www.ncb .nl. n h.gov/pub o d/27422973 o
[15] http://www.sc mc d oct.co/osc mc / t cl /p /S0886335015008494 o
[16] http://www.ncb .nl. n h.gov/pub o d/25880685 o
[17]WHO- Sod u oC oboxyt ohylc lulos - http://www. nch o o g/docu o nts/j cf /j coo no/v26j 08.ht o

Humans . n . substantial body of human data . as availabl inv stigating th .laxativ . ff cts . of modifi d c llulos s . hich occurs in som esubj cts at l v ls as lo . as 5 g/p rson/day . t . high r dos s diarrh a has b . n r port d in som esubj cts, but in oth rs constipation d v lop d . Studi s in humans did not xc . d th .addition of 30 g/p rson/day . n intak .of 30 g/day has . b . n r commend d as th .upp r saf l v l of di tary fib r in g n ral .

cc ptabl Daily Intak .(DI) Th .WHO committ . initially .stablish d a group . DI of 25 . mg/kg b . Information on th .ch mical structur , absorption, tissu .distribution, xcr tion, . m tabolism and human .xposur tog th r . ith appropriat clinical obs rvations sugg st d, that . no tru .toxic .ff cts could b . xp ct d .v n aft r high intak s, and th n a num rical limitation of . th . DI b com s unn c ssary JECF . in 1990 th r for allocat d CMC, on th .basis of th s . argum nts, a group . DI of "not sp cifi d"[19], as had b . n don . ith oth r bulking food additiv s, . to th .s v n modifi d c llulos s valuat d in its 35th s ssion .

Th .committ . mad , a g n ral comment on th .n . d to consid r th .possibl laxativ . ff ct of . an .xc ssiv .total di tary consumption of all bulking ag nts, particularly in vi . of th .additivity . of this .ff ct It th r for sugg st d that som econtrols to limit consumption should b . introduc d **The ability to produce laxation should be taken into account when using these . substances as food additives.** .

Reviewer's comment: *The concern for possible laxative effect described with CMC sodium . administered orally will not impact the safety of the proposed formulation intended for topical . use.* .

Cosmetic Ingredient Review .

Th . m nd d Saf ty . ss ssm nt of c llulos and r lat d polym rs.as us d in cosm tics . (Cosm tic Ingr di nt R vi . [20] (CIR)) for CMC sodium (s .arch t rm c llulos gum) stat s in . tabl 7 and pag .31 stat s that r p at d insult patch t sts (RIPTs), singl insult patch t sts . (SIPTs), cumulativ .irritancy t sts, and maximization t st hav .b . n conduct d in clinics using . C llulos Gum, ov rall, .as non-irritating and no s nsitizing Four hundr d subj cts . r t st d . and th .conc ntration . as 100% .

FDA .

ccording to th .Cod .of F d ral R gulations (CFR), 21CFR 182 1745, CMC sodium is . G n rally R cogniz d as Saf (GR . S) .h n us d in accordanc . ith good manufacturing . practic [21] as a misc llan ous and g n ral purpos food additiv . Th s l ct Committ . on GR . S . Substanc s (SCOGS) stat d *there is no evidence in the available information on sodium . carboxymethyl cellulose that demonstrates, or suggests reasonable grounds to suspect, a hazard* .

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[18]Summary of Evaluations P rform d by th .Joint F .O/WHO Exp rt Committ . on Food . dditiv s (1989) . http // . inch m org/docum nts/j cfa/j c val/j c_1662 htm .

[19] D .finition of "not sp cifi d" http //apps .ho int/iris/bitstr am/10665/37651/1/WHO_TRS_789 pdf pag .45 . DI **"not specified"** m ans that, on th .basis of th .availabl data (ch mical, bioch mical, toxicological, and oth r), . th total daily intak .of th substanc , arising from its us at th l v ls n c ssary to achi v th d sir d .ff ct and . from its acc ptabl background in food, do s not, in th .opinion of th .Committ ., r pr s nt a hazard to h alth For . that r ason, and for th .r asons stat d in th .individual valuations, th . stablishm nt.of an . DI xpr ss d in . num rical form is not d . m d n c ssary .

[20] Cosm tic Ingr di nt R vi . (s arch t rm C llulos Gum) http // . cir-saf ty org/ingr di nts .

[21] CFR Titl 21 - Chapt r I -Subchapt r B - Part 182 -Subpart B-§182 1745 http // . cfr gov/cgi- . bin/r tri v ECFR?gp=1&SID=6c47aa 6cfff9271719814b805891815&ty=HTML&h=L&mc=tru &r=SECTION&n . =s 21 3 182_11745 .

to the p u when t s sed at eve s that are now urrent or that m ght reasona y e expe ted u n f t re[22] u

5.5.4 S mmary Comments and Clinical Eval ation u

- uThe content of CMC sodium in the proposed formulatio u [redacted] than the amount in the RLD [redacted] It is als [redacted] than any product listed in the u FDA IIG Database with similar conditions of use. u
- CMC sodium is generally recognized as safe (GRAS) as a miscellaneous and general u purpose food additive when used in accordance with good manufacturing practice u (21CFR 182.1745). Applied locally, CMC sodium is considered as a non-irritating and no u sensitizing substance. No publication from the literature reports safety issues for CMC u sodium applied topically to the skin. u
- The WHO determined as "not specified" the ADI for CMC sodium because no true toxic u effects maybe are expected even after high intakes. u
- The Applicant submitted two studies to support approval of the ANDA: a skin u irritation/sensitization study (Study RP-LID-SSI) and a pharmacokinetic bioequivalence u study (Study RP-LIDPK001). Both studies are currently under review. u
- DCR considers that th [redacted] difference in the amount of CMC sodium between the RLD u and the proposed formulation is small. It is unlikely that a sligh [redacted] in the u amount of CMC sodium in the proposed formulation compared to the RLD may affect u the safety profile of the proposed formulation. u
- The irritation and sensitization study results submitted under ANDA 209190 is still under u review in OGD and should be considered when making a final safety determination about u the proposed lidocaine patch. u

5.6 Toxicology u

The available FDA guidance, published information, and two safety review and assessment of u carboxymethylcelluose (CMC) sodium reports provided by the applicant were reviewed from a u Pharm/Tox perspective to assess the safety o u [redacted] of CMC sodium in the proposed u generic lidocaine patch 5% (10 x 14 cm). CMC sodium is also known as cellulose gum (CG). u This review evaluated the safety of CMC sodium based on the route of exposure. The u nonclinical repeated dose toxicity studies using the oral route as well as dermal route were u reviewed for system toxicity in the current review. u

5.6.1 *Acute Toxicology* u

Several studies have been performed in rats, guinea pigs and rabbits to assess the acute toxicity u of CMC sodium with dermal and oral exposures[23]. The acute LD_{50} of CMC sodium by dermal u application in rabbits was > 2000 mg/kg body weight. The acute oral LD_{50} values of CMC u

[22] FDA GRAS Substances Database (Carboxymethylcellulose) accessed 08/08/2016 u
http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm261244.htm u
[23] TOXNET at http://chem.sis.nlm.nih.gov/chemidplus/rn/9004-32-4 u

sodium i mi . rats gui .a pigs a d rabbits w .r > 27000 mg/kg > 27000 mg/kg 16000 . mg/kg a d > 27000 mg/kg body w .ight r sp .tiv ly .

5.6.2 *Skin Sensitization* .

CMC sodium was ot s .sitizi g i th gui .a pig[24].

5.6.3 *Absorption, Distribution, Metabolism and Excretion* .

Du .to th .la k of th .d rmal absorptio .studi s of CMC sodium ,th. .studi s of orally . admi ist r d CMC sodium a d its d rivativ s w .r . valuat d to addr ss th .absorptio . distributio . m tabolisms a d .x r tio .prop rti s of CMC sodium . Th .publish d lit ratur . i di at s that . llulos d rivativ s pass u . ha g d through th gastroi t sti al tra t followi g . oral admi istratio i rats dogs a d ma .[8] · Approximat ly 90% of f d CMC sodium was . r ov r d i th rat f . s[25]. I a oth r xp rim e t. radio-lab ll d 14C-CMC sodium was . admi ist r d by oral gavag .i rats followi g 2 w . ks of pr tr atm e t.with u lab ll d CMC . sodium (500 mg/kg/day) admix d i th .di t Approximat ly 97% of th .radioa tivity was . x r t d (> 94% i to th f . s a d <1 83% i to th uri) a d < 1% of th radioa tivity was . r tai .d i th body of rats[26]. How .v r o ly 50% of CMC sodium was r .ov r d i th rabbit . f . s wh . rabbits w r f d o .di ts o tai i g CMC sodium[25] ·

5.6.4 *Genetic Toxicology* .

S v ral studi s i .ludi g Am s a d .hromosom ab rratio .t sts hav .b . o du t d to . addr ss th mutag . i pot .tial of CMC sodium a d all data i di at that CMC sodium is ot . mutag . i [25]. Sp .ifi ally a .Am s t. st with CMC sodium upto 5000 µg/plat was . gativ .i . Salmo . lla typhimurium ith r i th .pr s . or abs . of a liv r m taboli a tivatio .syst m . I th . hromosom ab rratio .assay with Chi .s hamst r fibroblasts CMC sodium was ot . g . otoxi .

No .vid . of ar i og . i ity was obs rv d aft r oral CMC sodium xposur for 2 y ars i . s v ral studi s i mi . a d rats This is dis uss d i mor d tail i th followi g s .tio .

5.6.5 *Dermal Irritation* .

A primary ski irritatio t st a d a uta . ous tol ra . t st of CG w r . o du t d o .mal . albi o rabbits[8] . For a primary ski irritatio t st 1 2 a d 10% aqu ous solutio s of CG w r . appli d o .th both fla ks i ta t a d abrad d ski s a d th d gr .s of irritatio .w r r ad aft r . 23 hour o . lusio . Th primary irritatio i di s ra g d from 0 (1% a d 10% CG) to 0 08 (4% . CG) (max = 8) w r . o irritati g .For a uta . ous tol ra . t st 1 2 a d 10% aqu ous . solutio s of CG w r appli d o .th . lipp d right a d l ft fla ks Ea h group had 3 rabbits .

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[24] Avi l® RC-501 (mi ro rystalli . llulos a d sodium arboxym thyl .llulos) Mat rial Saf ty Data Sh .t . 2010 .

[25] WHO Food Additiv s S ri s 26 at http://www i .h m org/do um e ts/j .fa/j .mo o/v26j 08 htm .

[26] Bar t al M taboli dispositio .i rats of r gular a d . zymati ally d polym riz d sodium . arboxym thyl .llulos , *Fd Chem. Toxic* .**33**(11) 901-907 (1995) .

Each sa R as s Rard unifor Ry by hand and giv n a ight 30 s c-a ssag . A R ications R R a d fiv ti Rs R R k for 6 R ks. Rcov ry as obs rv d for 7 days aft r th ast R a Rication. T Ro bio si s tak n fro R ach rabbit at 6 R ks R xai Rn d i crosco ica y. R Th Ran maximum cuta 4 u i itati 4i dic 4w 4 1 (1% CG, lightly i itati g a d lativ ly 4 w 4l t l at d), 0.67 (% CG, lightly i iati g a d lativ ly w 4l t l at d) a d 0.3 (10% CG, 4 i itati g a d w 4l t l at d) (max = 8), i dicati g th 4 ampl w 4 w 4l t l at d. 4

I a -w 4k ki i itati 4 tudy, applicati 4 f CG (u k 4w 4c 4c 4t ati 4) 4th hav d 4 abd mi al a 4a f abbit fiv tim s p4 4w 4k f 4 w 4k did 4t p 4duc ki i itati 4[8]. 4

5.6.6 *Repeated Dose Toxicology* 4

Du t th lack f th p at d d mal t xicity tudy f CMC dium, tw 13-w 4k p at d 4 d mal t xicity tudi f p 4duct f mati 4 c 4tai i g CMC dium a d th p at d al 4 t xicity tudi f CMC dium w 4 valuat d t add 4 th y t mic t xicity f CMC dium. 4

I a 13-w 4k p at d d 4mal t xicity tudy, 886 mg/kg f a w i kl m o th 4p 4duct 4 c 4tai i g 3% CMC dium wa appli d 4a a t i d 4 al hav d it f ach at 5 day p 4 4 w 4k f 13 w 4k by ubbi g. Tw 4c 4t l g 4up , u t at d a d tha 4l t at d g 4up , w 4 4 c mpa 4l t th t at d g 4up. Th p 4duct wa wip d ff l h u aft applicati b cau 4th 4 activ ag 4t, dium ilicat , wa a k 4w i ita t. N ig ifica t adv 4 ff ct w 4 t d 4 ba 4l 4m o tality, b dy w ight , ga w ight , h mat l gical a aly i , a d g 4 a d 4 mic 4c pic xami iati 4[8]. 4

I a 4th 413-w 4k p at d d 4mal t xicity tudy, 2900 mg/kg f a l ti 4c 4tai i g 1.1% 4 CMC dium wa appli d 4a a t i d 4 al hav d it f ach at 5 day p w 4k f 13 4 w 4k by ubbi g. C 4t l at w 4 t at d with di till d wat . N 4 ig ifica t adv 4 ff ct 4 w 4 b 4v d ba 4l 4m o tality, b dyw 4ght , h mat l gical valu 4, a d g 4 a d 4 mic 4c pic xami iati 4[8]. 4

S v 4al p at d al t xicity tudi with CMC dium hav b 4 p f m d i4 at , gui 4a 4 pig , abbit a d d g with du ati 4 a gi g f 4m 21 day t l y a [25]. F 4 xampl , at 4 c iv d a di t c 4tai i g 5% CMC dium f 8 m o th a d 4t xic ff ct w 4 b 4v d. 4 Rabbit w 4 f d with th di t c 4tai i g .8% a d 9% f CMC dium f tw p i d f 15 4 day with ut a y 4abl t xic ff ct . 4

I a p at d al t xicity tudy, 500 mg/kg a d 10000 mg/kg f CMC dium w 4 admi i t 4d 4 t b th whit at a d d g f 6 m o th whil th am ean4m ou 4t f CMC dium w 4 giv 4 t 4 gui 4a pig f 6 m o th a d l y a . Th 4 wa 4t t ub ta c - lat d adv 4 ff ct i at 4 a d gui 4a pig which w 4 t at d f 46 m o th ba 4l 4b dy w 4ght , h mat l gical a aly i , 4 a d g 4 a d mic 4c pic xami ati 4. N 4 ig ifica t adv 4 ff ct w 4 b 4v d i gui 4a 4 pig xp 4 d f 41 y a a d d g xp 4 d f 46 m o th ba 4l 4b dy w 4ght cha g 4, a d g 4 4 a d mic 4c pic xami ati 4[27]. 4

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[27] Sh la ki a d Cla k, Phy i l gical acti f dium ca b xym thy4lc llul 4 lab 4at y a imal a d huma 4. 4 *Food Res*., **13**, 29-35 (19 8). 4

In a 90 W p at W o al toxicit stu W, CMC so ium was giv n to Albino W ista ats in th i t W (0, 2.5, 5 an 10% b w W ght) fo 90 a s. Th W w W statisticall significant inc W s of W plasma alkalin phosphatas an alanin aminot ansf as l v ls in 10% osing g oup animals W without histopathological h patic chang s. W at intak an u in p o uction inc W s W with W inc W sing os s of CMC so ium u to th so ium cont nt of CMC so ium. Som eu W na W W pa am et W w W alt W. Fo xampl , chang s in uni a W H an 24 hou u ina W xc W on of W so ium of 5% an 10% osing g oup animals w W statisticall significant compa W to cont ol W g oups an th s chang s w W os W p n W t. Statisticall significant u ina W cit at xc W on W was not W n 10% osing g oup compa W to cont ol g oup. Th inc W s W occu W nc of W n ph ocalcinosis an h p W plasia of th u oth lial pith lium in som eo W h t at W g oups was W obs W W although th s inc W s s w W not os W p n W t no obs W W n both s x s. It coul W b an in i ct cons qu nc of an inc W s in u in alkalinit coupl W with an inc W s W calcium W xc W on. How W W, h p W plasia of u ina W bla W not W n 10% osing g oup animals was t st W substanc att ibut W T W atm ent W at W ff cts of ia h a an c cal nla g m ent W n 5% an W 10% osing g oups w W also obs W W Th s chang s a W g n W ll associat W with th W ing stion of non o low W g stabl compoun s[28]. Th W fo W, th No Obs W W A W W W Eff ct W L v l (NOAEL) fo 90 W a o al subch onic toxicit is 2.5% b w W ght of i t in ats. W

In a 2 W a p at W o al toxicit , CMC so ium was giv n to ats (100, 500 an 1000 mg/kg W bo W w W ght/ a) in th i t fo 2 W s[27]. Th bo W w W ghts an ha matological pa am et W W w W monito W monthl an histopathological anal sis w W con uct W at th n of t atm ent. W W Monthl w W ght co W in icat W o mal w W ght cu v s. Th W w W no iff W nc s in W ha matological an mic oscopic xaminations b tw W n t at W an cont ol animals. No W n oplasms w W foun in xp W m ent W animals. Th W fo W, th NOAEL fo 2 W a o al ch onic W toxicit is 1000 mg/kg bo W w W ght in ats. W

In anoth W 2 W a p at W o al toxicit , F344 ats c iv W 5 mg/kg bo W w W ght of CMC W so ium b gavag fiv a s p W w W k fo 2 W s[25]. Cont ols w W unt at W Exp W m ent W W animals w W xamin W w W kl fo clinical signs an th p W nc of palpabl l sions. M ean W W bo W w W ghts w W also monito W. G oss an mic oscopic xaminations w W p W o m e on W majo o gans an all g oss l sions. Su vival at s of CMC so ium t at W animals w W simila W to thos of cont ols. CMC t at W animals ha app oximat l th sam eo W f w W n oplasms than W cont ol animals. Th W fo W, th NOAEL fo 2 W a o al W ch onic toxicit is 5 mg/kg bo W w W ght W in F344 ats. W

In a 2 W a p at W o al toxicit , CMC so ium was giv n to mic in th i ts containing 0, 0.1 W an 1% of CMC so ium fo 100 w W ks. Th W was no ov bious iff W nc in mo talit an W tumou inci W c b tw W n t at W an cont ol g oups[25]. Th W fo W, th NOAEL fo 2 W a o al W ch onic toxicit is 1% b w W ght of i t in mic . W

In anoth W 2 W a p at W o al toxicit , B6C3F1 mic c iv W 50 mg/kg bo W w W ght of CMC W so ium b gavag fiv a s p W w W k fo 103 w W ks[25]. Unt at W mic s W W as cont ols. W Exp W m ent W animals w W xamin W w W kl fo clinical signs an th p W nc of palpabl W l sions. M ean W bo W w W ghts w W also monito W. G oss an mic oscopic xaminations w W W

[28] Ba t al., Subch onic O al Toxicit Stu W with R gula an Enz matically D pol m e iz W W So ium W Ca box m eth W c W olos in Rats, *Fd. Chem. Toxic.*, **33**, 909 – 917 (1995). W

performe , o ,m aor org , s , ll gross lesio s. Surviv l r tes of CMC so ium tre te , im ds, , were simil r those of co trols. CMC-tre te , im ds,h , pproxim tely the s me or fewer , eopl sms th , co trol , im ds,. Therefore the NOAEL for 2-ye r or l chro ic toxicity is 50 , mg/kg bo y weight i B6C3F1 mice. ,

5.6.7 *Reproductive Toxicology* ,

There w s o repro uctive toxicology stu y of CMC so ium by erm l , mi istr tio . I ste , sever l repro uctive toxicology stu ies by or l route of , mi istr tio ,were ev lu te ,to , ress , repro uctive toxicity of CMC so ium. ,

I , repro uctive stu y 20 m le,Spr gue-D ,wley r ts receive ,200 mg/kg of CMC so ium for t , le st 60 , ys , 40 fem le,r ts receive ,200 mg/kg of CMC so ium for t le st 14 , ys before , m ti ,g , uri g , 6- , y m ti ,g perio ,by g v ge. O ,e h lf of tre te ,fem le, , im ds,w ,s , co ti uously , mi istere ,with 200 mg/kg CMC so ium u til s crifice o , y 14 of gest tio , (tot l of 34 , y-tre tme t). The rem i i g h lf of the fem les w ,s co ti uously tre te ,u til , we ,i g of the proge y ,t , y 28 ,fter birth (tot l of 62 , y-tre tme t)[29]. Aver ge bo y weights , of p re ts (F0) were comp r ble for both tre te , co trol groups lthough the bo y weight , g i of CMC so ium-tre te ,m les w ,s ge er lly lower th , th t of co trols. The bo y weight , g i of offspri gs (F1) w ,s comp r ble for both tre te , co trol groups. No tre tme t- , rel te ,effects were observe ,i F0 b se ,o ,the preg , cy r tio the me , umbers of corpor , lute , impl ,t tio ,sites , the r tios corpor lute /impl ,t tio ,sites. The ,ur tio ,of , preg , cy , p rturitio w s orm l i the CMC so ium-tre te group. The r te of , resorptio s litter size , sex r tio i F1 were ,ot sig ific , tly ch , ge ,i the CMC so ium- , tre te , im ds,. Nesti g beh vior (ursi g suckli g , creepi g) eye ope i g , pi , et chme t were ,orm l i, CMC so ium-tre te ,F1 , im ds,. Beh vior l test results of F1 , i clu i g ,eg tive geot xis photophobot xis , explor tory locomotio p tter i , cyli ric l , c ge were comp r ble for both the CMC so ium-tre te , co trol groups. Therefore the , NOAEL w ,s 200 mg/kg for fertility repro uctive perform a ce , f t l evelopme t i r ts. ,

I , ter toge icity stu y preg , t Albi o CD-1 outbre ,mice from ys 6-15 of gest tio , receive ,CMC so ium (0 16 74 345 1600 mg/kg/ ,y) s ,cor oil solutio by g v ge[25], A , positive co trol group of 24 preg , t mice receive ,150 mg , spiri /kg bo y weight/ ,y. All , preg , t fem les survive , o effects were observe ,o , i ,tio ,or o ,m ter ,l or fet l , surviv l i CMC so ium-tre te ,groups. The ,umber of b orm lities see ,i either soft or , skelet l tissues of CMC so ium-tre te groups i , ot iffer from the umber occurri g , spo t ,eously i sh m-tre te ,co trols. ,

I , other ter toge icity stu y CMC so ium (0 16 74 345 1600 mg/kg/ ,y) w ,s give ,to , preg , t Wist r- erive ,r ts from ys 6-15 of gest tio , s cor oil solutio by g v ge[25], 250 , mg spiri /kg bo y weight/ y w s , mi istere to preg , t r ts s ,positive co trol. All , preg , t fem les survive ,u til the e , of the stu y. No effects were observe ,o , i ,tio ,or o , m ter ,l or fet l surviv l. The ,umber of b orm lities see ,i either soft or skelet l tissues of ,

[29] Fritz , Becker The suit bility of c rboxymethylcellulose s ,vehicle i repro uctive stu ies *Arzneimitteln* , *Forschung,* **31** 813-815 (1981). ,

CMC sod i rea ed gro ps d d no d ffer fro i he n b er occ ir ng spon aneo sly n sha i rea ed con rols. i

5.6.8 *R sk Assessment i*

The proposed ao i n of CMC sod i n he gener c l doca ne 5% pa ch s 754 g n each i pa ch (5.39%). Therefore, he appl can 's proposed a x i da ly expos re (MDE) wo ld i res l n expos re o 2262 g /day of CMC sod i based on he MDD n he RLD label (p o 3 i pa ches w ih n a 24 ho r per od) f all were released. i

CMC sod i s l s ed as GRAS (Generally Recogn zed as Safe) d rec food add ive i (21CFR 182.1745) when sed n accordance w ih good a n fac ir ng prac ce. CMC sod i s i also sed n cose i c for i la ons, o s of wh ch were eye and sk n a ke p and sk n care i prepara ons. CMC sod i s cons dered ner for op cal for i la ons and s no cons dered a i h ia n rr an or sens izer[8]. i

CMC sod i s an nac ve ngred en sed n FDA approved dr g prod c s. An nac ve i ngred en search for CMC sod i was perfom ed s ng he Inac ve Ingred en Da abase (IID) i and he res l s are presen ed n Table 4 (Sec on 5.4). There are hree approved dr g prod c s, i wh ch are ransdera i l sys es i ncl d ng he RLD (L doder® i , NDA 20612). However, he i levels of CMC sod i n he dr g prod c s are lower han he c iren proposed l i . The i c iren proposed l i for sod i CMC (.e. 754 g /pa ch) s 7.7% h gher han he ao i n n i he RLD (.e. 700 g /pa ch). i

For he safe y eval ion of CMC sod i n he proposed gener c prod c , he noncl n cal da a i from he p bl shed l era re were rev ewed. D e o a l i ed ava lab l y of dem al ox c y i s id es of CMC sod i, several oral chron c ox c y s id es were eval a ed o address he i sys e i c ox c y concern of CMC sod i. i

CMC sod i was no i agen c based on A i s es s. The absorp on of orally ad i n s ered i CMC sod i s very l i ed and he a jor y of orally ad i n s ered s excre ed n o feces. i Dem al expos re of CMC sod i s also no expec ed o be b oava lable beca se CMC sod i i s a h gh o lec lar we gh polye i r, wh ch canno pene ra e he sk n even fall CMC sod i s i released fro i he pa ch. i

For local ox c y, dem al ox c y s d es n rabb s nd ca e ha CMC sod i p o 10% was no i rr a ng for 4 wei k repea ed expos re. i

For sys e i c ox c y, 1000 g /kg/day of CMC sod i was no assoc a ed w ih any over i ox c y based on body we gh , cl n cal pa hology and h s opa hology n a wo year oral chron c i ox c y s id y. Therefore, he NOAEL of CMC sod i for 2 year repea ed dose ox c y n ra s i s 1000 g /kg/day (h ia n eq ivalen dose of 6000 g / ^{2}/day w ih a body s rface area i convers on fac or 6 for ra) wh ch s 4.3 fold h gher han he proposed MDE of 2262 g /day i (eq ivalen o 1394.9 g i/ ^{2}, ass i ng an average h ia n we gh ng 60 kg and s ng a body i s rface area convers on fac or 37 for h ia ns). i

In the e e te . l .se t xicity stu ies, 1000 mg/kg/ .y f CMC s . ium t e tment f guine . igs f . ne ye . n .gs f . six m onths i n t in uce ny etect ble t xicity b se n b . y . weight, n g .ss n mic .sc . ic ex min ti n The ef .e, the NOAEL f CMC s . ium in . guine igs n .gs is 1000 mg/kg/ .y (hum an equiv lent .se f 8000 mg/m^2/ .y in guine . igs n 20000 mg/m^2/ y in .gs with b . y su f ce e c nve si n f ct 8 n 20, . es ectively) The s fety m a gins between the hum an ex . su e n the n n-clinic l ex . su e . b se n the ne-ye . ch .nic t xicity stu y in guine igs n six-m onth ch .nic t xicity stu y . in .gs e 5 7 (8000/1394 9) n 14 3 (20000/1394 9) es ectively .

The s fety m a gins seem e s n ble en ugh n the . se limit f CMC s . ium is nl (b) (4) (b) (4) th n the m ount in the RLD . The ef .e, the . se m ount f CMC s . ium t the . MDD f . the . se gene ic f .mul ti n f li .c ine .tch is within the s fe nge .

Table 5: Toxicology Data Summary Table for CMC Sodium .

C .nt min nt N .me .	CMC S . ium .		
D ug .	Li .c ine .		
D .s ge F . m .	P tch .		
R .ute .	T .ns e m d ..		
St engths Av il ble .	5%.		
M aximum D .ily D .se .	3 .tches .		
D .s ge St engh .	C .nt min nt (mg) / Unit D .se .	D .s ge Units t MDD .	Exci ient (mg) t MDD .
5%.	(b) (4)		
Stu y (efe ence)	**Shelanski and Clark, *Food Res.*, 13, 29-35 (1948)** .	Shel nski n .Cl k, *Food Res.*, **13**, 29-35 (1948) .	Shel nski n .Cl k, *Food Res.*, **13**, 29-35 (1948) .
R .ute f A .min .	**oral (in the diet)** o .	l (in the iet) o .	l (in the iet) .
Du .ti n(.ys) .	**2 years** .	1 ye .	6 m onths .
S ecies .	**Rats** .	Guine ig .	D .gs .
Effect Level .	**NOAEL = 1000 mg/kg/day** .	NOALE = 1000 mg/kg/ .y .	NOAEL = 1000 mg/kg/ .y .
BSA C .nv .	**6000 mg/m^2/day** .	8000 mg/m^2/ .y .	20000 mg/m^2/ .y .
S fety F ct (s) .	**4.3 fold** .	5 7 f l .	l 4 3 f l .

6 Conclusion: .

F .m b th clinic l n h .m/t x e s ectives, DCR c nclu es th . (b) (4) iffe ence in the . m ount f CMC s . ium in the . se gene ic li .c ine t .ic l .tch 5% (b) (4) .es . n t . e . t .se ny . iti n l s fety c nce ns when c m p e t the RLD, Li . e m® (2100 . mg/ .y) .

7 Referen e

7 C lini al

See footnotes

7 2 Toxi ology

See footnotes

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

CHEMISTRY REVIEW(s)

U.S. FOOD & DRUG ADMINISTRATION

RE OMMENDATION

☒ Appro al
☐ Complete Resp o Mi nse- nor
☐ Complete Resp a Ma nse- jor
☐ Complete Resp a Ma nse- jor-Facilities Only C

ANDA 209190
Assessment #4

Drug Product Name	Lidocaine Patch 5%
Dosage Form	Patch
Strength	5%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Rhodes Pharmaceuticals L.P.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
SD 1 Original	04/14/2016	Drug Product, Facilities
SD 3 Quality/Response to Information Request	05/23/2016	Drug Product, Facilities
SD 4 Response to IR	08/05/16	Facilities
SD 5 Response to ECD Bioequivalence	08/15/16	Facilities
SD 6 Response to ECD Clinical Bioequivalence	09/06/16	Facilities
SD 7 Response to ECD/Quality	09/29/2016	Drug Product, Process, Facilities
SD 10 Response to ECD/Quality	01/23/2017	Drug Product, Facilities
SD 12 Response to CR	09/26/2017	Drug Product, Microbiology, Biopharmaceutics,
SD 13 Response to CR	09/12/2018	Drug Product
SD 14 Response to CR	07/30/2019	Drug Product
SD 15 Response to Labeling	09/04/2019	Drug Product
SD 16 Response to IR	02/04/2020	Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	N/A	N/A
Drug Product	Adchara Pongpeerapat	Brock Roughton
Manufacturing	Cassandra Abellard	Derek Smith
Microbiology	Yuansha Chen	Neal Sweeney
Biopharmaceutics	Kelly Nolen	Tapash Ghosh
Regulatory Business Process Manager	Fred Echoles	
Application Technical Lead	Brock Roughton	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

FDA U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

MFs:

	Type		Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	Type II	(b) (4)		Adequate	July 5, 2018	Assessed by Xinghua Wu
	Type III		(b) (4)	N/A		
	Type II			N/A		
	Type II			N/A		
	Type IV			Adequate	December 11, 2017	Assessed by Adchara Pongpeerapat
	Type IV			Adequate	February 4, 2020	Assessed by Adchara Pongpeerapat

THER D S *proved ANDA*

Documen	Application Number	Description
RLD	NDA 20612	Lidoderm (Lidocaine Patch 5%)

2. CONSULTS

Discipline	Status		Date	Assessor
Biostatistics	N/A			
Pharmacology/ Toxicology	Complete	(b) (4)	April 29, 2019	Narendranath Reddy Chintagari

Pharmacology/ Toxicology	Complete	[redacted] (b) (4)	No. 7, 9	Narendranath Reddy Chintagari
Pharmacology/ Toxicology	Complete	[redacted] (b) (4) (b) (4)	Sept. 3, 9	Wei Ding
CDRH-ODE	N/A			
CDRH-OC	Complete	**Adequate:** Applicant's response to a design controls deficiency submitted on December 9, 7 is adequate	No. 5, 8	Isabel Tejero del Rio
Clinical	N/A			
Other	N/A			

EXECUTIVE SUMMARY (APPROVALS ONLY)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the drug product:

- The applicant has provided acceptable raw material, in-process, and finished product controls
- The applicant has accepted the in vitro drug release acceptance criteria recommended by Biopharmaceutics
- The Office of Pharmaceutical Manufacturing Assessment overall recommendation on all the manufacturing facilities is "Approve"
- The proposed expiry date of 36 months is acceptable
- The labeling has adequate quality information

Therefore, from a quality perspective, ANDA 209190 is recommended for approval.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The basis for the applicant's ANDA is the approved reference listed drug (RLD), Lidoderm (NDA 20612), listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Electronic Orange Book). The drug product is topical patch available in 5% strength containing 700 mg of lidocaine per patch. The drug product is packaged in individual child-resistant pouches.

Final recommended dissolution method/specification acknowledged by Firm?	☒ Yes ☐ No ☐ N/A
Are there comparability protocols provided? If yes, how many?	☐ Yes How many:_____ ☒ No
If USP monograph exists, do the specifications conform to the current USP?	☒ Yes ☐ No *(see comments) ☐ N/A
Is the application compliant with USP <232/233> requirements or ICH Q3D (regarding elemental impurities)?	☒ Yes ☐ No *(see comments) ☐ N/A

**Only the drug substance has a USP monograph.*

Proposed Indication(s) including Intended Patient Population	Relief of pain associated with post-herpetic neuralgia

Duration of Treatment	Up to 3 patches worn for maximum of 12 hours per 24 hours
Maximum Daily Dose	2100 mg (cumulative drug content of 3 systems)
Alternative Methods of Administration	Patches may be cut into smaller sizes with scissors prior to removal of the release liner.

B. Quality Assessment Overview (Please note: ATLs should check the most recent policy alert list)

Drug Substance

Lidocaine is official in USP and EP. The drug substance specification agrees with the USP monograph. The applicant references DMF (b) (4) held by (b) (4)

(b) (4)

The labeling contains acceptable quality information.

outcome of the inspection, the firm's acceptable compliance history, and (b) (4) experience with transdermal product manufacturing. In addition, use of (b) (4) for testing of the drug product is acceptable.

Per the CDRH consult review memo, the drug product manufacturing facility (Altergon) was found acceptable. In addition, CDRH determined that the applicant has provided acceptable documentation of the facility's quality management system and design controls.

Biopharmaceutics
The applicant developed and validated an adequate in vitro drug release method. In addition, the firm's proposed drug release acceptance criteria are adequate based on the submitted drug release data.

The following drug release method and acceptance criteria are recommended for the test product and have been accepted by the applicant:

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criteria
USP apparatus 5 (paddle over disk)	50	Acetic acid/sodium acetate buffer, pH 4.0 at 32ºC	500	10 minutes: NMT (b) (4) 30 minutes: (b) (4) 180 minutes: NLT (b) (4)

Microbiology

The product is non-sterile. The drug product specification (microbial limits testing) and test method validation/suitability complies with USP <61>, <62> and <1111>. The applicant commits to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life (36 months).

Shelf Life Considerations

The applicant has provided 36 months of long-term stability results for batch manufactured on the (b) (4) intended to be used for commercial production. (b) (4) (b) (4) The proposed expiry date of 36 months is acceptable.

Policy Alert

(b) (4)

C. Risk Assessment

Drug Product CQAs	Initial Risk Ranking		Updated Risk Ranking After Assessment Cycle #4	
Physical stability (polymorphism and recrystallization)	Medium	(b) (4)	Low	(b) (4)
Physical stability (cohesive)	High		Low	
Physical stability (adhesive)	High		Low	

Drug Product CQAs	Initial Risk Ranking		Updated Risk Ranking After Assessment Cycle #4	
		(b) (4)		(b) (4)
Chemical stability	High		Low	
Assay	Medium		Low	
Content uniformity	High		Low	

Drug Product CQAs	Initial Risk Ranking		Updated Risk Ranking After Assessment Cycle #4	
		(b) (4)		(b) (4)
Drug release	Medium		Low	
Microbial limits	Low		Low	

App ication Technica Lead Name and Date: Brock Roughton; March 2, 2020 I

219 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

i

E ING

{For ANDA only}

i

R Reg onal Informat on i

1.14 Label ng

Labe ling i & i Packag ng i nformat on i

***DESCRIPTION* sect on i**

Is the i nformat on i nc uded i n the ☒ Yes i ☐ No i
If "No," exp a n. i
i
Is the d rug product subject to a USP mono graph? i ☐ Yes i ☒ No i
If "Yes," state if labe ling is d ssa sfactor y to USP stat ement n the Descr pt on (e g., USP tests
per od c ng Meets USP ass ay tests 2. Meets USP ng an c mpur t es tests 3). i
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Descr pt on, a ert the labe ling rev ewer. i
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***HOW SUPPLIED* sect on i**

i) i Is the i nformat on i nc uded ☒ Yes i ☐ No i

If "No," exp a n. i

ii) i Are the stor age cond t ons ass gned acceptable? i ☒ Yes i ☐ No i

If "No," exp a n. i

i

***DOSAGE AND ADMINISTRATION* sect on, for n jectables, and d wh ere applicable:** i

Did the applicant prov de qual ty data to support n t a cond t ons (e g. d luent compat b l ty
stud es)? i ☐ Yes i ☐ No i ☐ N/A i

If "No," exp a n. i

***For OTC Drug s and Cont ra nd cat ons* sect on i**

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

None

List of Deficiencies:

N/A

Primary Drug Product Reviewer Name and Date: Adchara Pongpeerapat, PhD, 1/24/17; 6/1/17

Secondary Drug Product Reviewer Name and Date: I concur with the above assessment.

Brock Roughton, PhD, 2/22/2017, 01-JUNE-2017

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PROCESS

Product Background:

ANDA:	209190
RLD:	NDA 20612 (Lidoderm®)
Drug Product Name / Strength:	Lidocaine topical patch, 5%
Route of Administration:	Topical
Applicant Name:	Rhodes Pharmaceutical L.P.

Product characteristics:

(b) (4)

(b) (4)

P.3 Manufacture

Batch Formula

Batch formula from P.3.2

Table 1 Batch Formula of Lidocaine Patch 5%

Ingredient	Function	(b) (4)
Lidocaine, USP	Active	
Purified water, USP	(b) (4)	
Glycerin, USP		
Sorbitol, USP (b) (4)		
Polyacrylic acid[1] (b) (4)		
Carboxymethylcellulose Sodium, USP		
Sodium polyacrylate[1]		
Propylene glycol, USP		
Urea, USP		
Kaolin, USP		

Table 1 Batch Formula of Lidocaine Patch 5%

Ingredient	Function	(b) (4)
Tartaric acid, NF		
Gelatin, NF		
Polyvinyl alcohol, USP		
Dihydroxyaluminum aminoacetate, USP[2]		
Edetate disodium, USP		
Methylparaben, NF[3]		
Propylparaben, NF[4]		
Total Patch Weight		
Total Batch Size		

(b) (4)

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Review cycle #1: James J. Norman 02/06/2017; 03/05/2017; 05/15/2017
Review cycle #2: James J. Norman 10/24/2017
Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Review cycle #1: Yubing Tang 03/04/2017, 03/05/2017 and 06/06/2017
Review cycle #2: Yubing Tang, 10/24/2017, 11/ 08/ 2017

James Norma

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(b) (4)

perform testing as outlined in the application.

CDRH CONSULT OUTCOME:

Per the CDRH consult review memo, the only manufacturing facility (Altergon) requiring review was found acceptable based on the 2016 PAI discussed above. However, the application is deficient from a documentation perspective. The CDRH deficiencies will be communicated in the Complete Response letter. Please see consult memo uploaded with the Facility IQA Chapter for details.

Comparability Protocols

Reviewer's Assessment: N/A

Post-Approval Commitments

Reviewer's Assessment: N/A

Lifecycle Management Considerations

N/A

QUALITY ASSESSMENT

List of Deficiencies:

CDRH deficiencies documented in IR#2 were not responded to by applicant in adequate time per RBPM. See CDRH consult.

Amend-12: All responses were acceptable with exception of a CDRH inadequate response on Design Review. As the application is being CR'd due to multiple disciplines, this one item will be included in the CR. Facilities remain acceptable from CDER; No changes made from original review.

Primary Facilities Reviewer Name and Date:

C. Abellard 06/12/2017 Consumer Safety Officer- OPF/ DIA-BII

Amend 12: C. Abellard 11/13/2017

Secondary Reviewer Name and Date:

D. Smith 06/26/2017

Cassandra Ab ard

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at 11/29/2017 08:16:21AM
GUI : 508da7 80002bf 5d5f 1 a12da3599d 4

MICROBIOLOGY

Product Background:

ANDA: 209190

Drug Product Name / Strength:
Proprietary: N/A
Non-proprietary: Lidocaine Patch 5%

Route of Administration: Topical patch

Applicant:
Name: Rhodes Pharmaceuticals L.P.
Address: 498 Washington Street, Coventry, Rhode Island 02816, USA

US Agent:
(b) (4)

Manufacturing Site:
Zona Industriale A.S.L.
Morra De Sanctis
Avellino 83040, Italy

Method of Sterilization: N/A. Drug product is non-sterile.

Review Summary:
The submission is recommended for approval from the Product Quality Microbiology review perspective.

List Submissions being reviewed (table):

Submitted	Received	Date assigned to reviewer
9/26/2017	9/26/2017	10/10/2017

Submission History (for 2nd Reviews or higher) N/A

Submit	Received	Reviewed
4/14/2016	4/14/2016	2/22/2017

Highlight Key Outstanding Issues from Last Cycle: Commitment to perform preservative effectiveness test at the end of the shelf life was not stated.

Concise Description Outstanding Issues Remaining: N/A

Product Quality Microbiology Assessment

This amendment responded to The Agency's complete response letter dated 7/7/2017.

Microbiological deficiencies from the last review cycle were conveyed to the applicant via a complete response letter dated 7/7/2017. Applicant's response was received on 9/26/2017. The original comment (in italics) and the applicant's response are included below.

Provide a commitment to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life (reference: Guidance for Industry ANDAs: Stability Testing of Drug Substances and Products - Questions and Answers).

Response: Rhodes commits to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life (36 months).

The applicant also provided the 36-month data for AET testing of the registration batch, Lot L1304191.

Log reductions w

Microorganisms			
S. aureus	(b) (4)		
P. aeruginosa			
E. coli			
C. albicans			
A. brasiliensis			

(b) (4)

Reviewer's Assessment: Preservativ
topical products.

Adequate

Primary Microbiology Reviewer Name and Date:

Yuansha Chen, Ph.D.

CDER/OPQ/OPF/DMA

10/26/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Neal J. Sweeney, Ph.D.

CDER/OPQ/OPF/DMA

11/4/2017

Yuansha Chen

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Nea Sweeney4

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U.S. FOOD & DRUG ADMINISTRATION

RE OMMENDATION

☐ Appro al
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☒ Complete Respo nse- Ma jor
☐ Complete Respo nse- Ma jor-Facilities Only

ANDA 209190
Assessment #3

Drug Product Name	Lidocaine Patch 5%
Dosage Form	Patch
Strength	5%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Rhodes Pharmaceuticals L.P.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
(1) Original	*04/14/2016*	*All*
(3) Quality/Response to IR	*05/23/2016*	*DP, Process, Facility*
(7) Response to ECD/Quality	*09/29/2016*	*DP*
(10) Response to ECD/Quality	*01/23/2017*	*DP, Process, Facility*
(12) Response to CR	*26-SEPT-2017*	*All*
(13) Response to CR	*12-SEPT-2018*	*All*

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance		
Drug Product	Adchara Pongpeerapat	Brock Roughton
Manufacturing	Cassandra Abellard	N/A
Microbiology	N/A	N/A
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Fred Echoles	
Application Technical Lead	Brock Roughton	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

FDA U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

MFs:

	Type		Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	Type II	(b) (4)		Adequate	July 5, 2018	Assessed by Xinghua Wu
	Type III		(b) (4)	N/A		
	Type III			N/A		
	Type III			N/A		
	Type IV			Adequate	Dec. 11, 2017	Assessed by Adchara Pongpeerapat
	Type IV			Inadequate	April 9, 2019	Assessed by Adchara Pongpeerapat

THER DO S ***proved ANDA***

Document	Application Number	Description
NDA	20612	RLD

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/ Toxicology	Complete	**Inadequate-Maior** (link to consult response): the (b) (4) pose safety concern and thus, are not acceptable from a Pharmacology/Toxicology perspective.	April 29, 2019	Narendranath Reddy Chintagari
CDRH-ODE	N/A			
CDRH-OC	Complete	**Adequate:** applicant's response to a design controls deficiency submitted on December 19, 2017 is adequate	Nov 5, 2018	M. Isabel Tejero del Rio
Clinical	N/A			
Other	N/A			

U.S. FOOD & DRUG ADMINISTRATION

ABBREVIATED EXECUTIVE SUMMARY (CR ONLY)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Major

The application is not recommended for approval due to quality related deficiencies summarized in Section II.E. OPQ recommends issuing a Complete Response Letter – **Major.**

II. QUALITY ASSESSMENT OVERVIEW

A. Drug Substance: Adequate

Lidocaine is official in USP and EP. The drug substance specification agrees with the USP monograph. The referenced (b) (4) held by (b) (4) (b) (4) is adequate. Lidocaine exhibits one polymorphic form. The analytical methods are acceptable.

Drug Product: Inadequate-Major

1. Primary Justification:

Theme 1: Product safety
Justification 1: The drug product deficiencies have been classified as MAJOR because there is need for safety assessment of extractables and leachables, inadequate assessment of extractables and leachables, or submission of that assessment in an unsolicited amendment as noted in Appendix A, Section A(2)(o) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). This information is required for establishing safety of the drug product. Upon receipt, in FDA's judgement, the review of this information will require substantial expenditure of FDA resources.

2. Secondary Justification:

Theme 2: Unqualified impurities
Justification 2: The drug product deficiencies have been classified as MAJOR because new toxicology studies are requested for the unqualified impurity as noted in Appendix A, Section A(2)(a) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). The review of these studies requires, in FDA's judgement, a substantial expenditure of FDA resources.

Lidocaine patch 5% is non-compendial. The drug product is topical patch with a (b) (4) similar to the RLD formulation. The formulation uses (b) (4) (b) (4)

The applicant has adequately mitigated the high risks identified in the initial quality risk assessment: chemical stability, physical stability (cohesive and adhesive), content uniformity, and solubility. The applicant has tightened the level of (b) (4) to an acceptable level. The proposed controls for (b) (4) are acceptable. The 36-month stability results show the (b) (4) trending in (b) (4) reaching the specification limit. The applicant should clarify the proposed expiration dating period. The applicant should demonstrate compliance with ICH Q3D.

The applicant has proposed control of adhesive impurities in the adhesive raw material. In addition, the applicant has adequately performed leachable studies and detected three leachables at toxicologically-relevant levels. To evaluate the safety and acceptability of (b) (4) (b) (4) do not pose any safety concern and are acceptable. However, the (b) (4) (b) (4) pose safety concern and are unacceptable from a pharm/tox perspective. DCR requests major deficiency for safety assessment of these impurities in the CR letter, placed below under the Pharmacology/Toxicology Deficiencies.

Labeling: Adequate

The labeling has acceptable quality information.

B. Manufacturing: Adequate

The applicant uses a standard process for producing (b) (4) topical patches. The main process steps are (b) (4) (b) (4) (b) (4) (b) (4)

(b) (4) manufactures and tests the drug substance. The last inspection of the facility was July 2016 and was classified VAI. The facility is acceptable because of the manufacturing history of this marketed API (over 10 years), the acceptable review of the DMF, and acceptable inspectional history. In addition, use of (b) (4) for testing of the drug substance is acceptable.

Altergon Italia S.r.l. (FEI# 3007086839) manufactures the drug product. The last inspection of the facility was performed November 2015 and was classified NAI. This facility is acceptable to manufacture this product because of the outcome of the inspection, the firm's acceptable compliance history, and experience with transdermal product manufacturing. In addition, use of (b) (4) (b) (4) for testing of the drug product is acceptable.

Per the CDRH consult review memo, the only manufacturing facility (Altergon) requiring review was found acceptable. In addition, CDRH determined that the applicant has provided acceptable documentation of the facility's quality management system and design controls.

C. Biopharmaceutics: Adequate

The applicant developed and validated an adequate in vitro drug release method. In addition, the firm's proposed drug release acceptance criteria are adequate based on the submitted drug release data.

The following drug release method and acceptance criteria are recommended for the test product and have been accepted by the applicant:

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criteria
USP apparatus 5 (paddle over disk)	50	Acetic acid/sodium acetate buffer, pH 4.0 at 32°C	500	10 minutes: (b) (4) 30 minutes: (b) (4) 180 minutes: (b) (4)

D. Microbiology: Adequate

The product is non-sterile. The drug product specification (microbial limits testing) and test method validation/suitability complies with USP <61>, <62> and <1111>. The applicant commits to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life (36 months).

E List of Deficiencies for Complete Response

. O verall Quality Deficiencies – N/A

. Drug Substance Deficiencies – N/A

3. Drug Product Deficiencies

1. We note that you have included elemental impurities in drug product specification. Please submit risk assessment and control of elemental impurities to demonstrate compliance with ICH Q3D. The information should include potential sources from raw materials, manufacturing equipment, container closure, water, etc.; identification of potential elemental impurities, and evaluation of the presence of elemental impurities in the drug product. The analytical methods should be able to detect potential elemental impurities and suitable for their . intended purposes.

2. The Drug Master File (DMF) [redacted] (b) (4) has been reviewed and found inadequate. The DMF holder, [redacted] (b) (4) was notified of the deficiencies on . April 10, 2019. Please consult with your DMF holder, and provide the updated relevant P.4 sections. Do not respond to this ANDA CR letter until you have confirmed that the DMF holder has responded to the DMF deficiency letter cited above or your amendment will not be considered a complete response.

3. In the September 26, 2017 submission, you established adhesive performance tests, [redacted] (b) (4)
You have included these tests in all stability time points. However, in the September 12, 2018 submission, we cannot locate the stability results for adhesive . performance test for 3 batches made with [redacted] (b) (4) [redacted] (b) (4) and for 3 batches made with [redacted] (b) (4) [redacted] (b) (4) up to 6-month time point. To compare the adhesive performance results between batches made with [redacted] (b) (4) provide all available adhesive performance test results on stability.

4. In the September 12, 2018 CR #9 response, you state that you are requesting 24-month shelf life for the drug product. However, the current document in section 3.2.P.8.1 submitted on April 14, 2016 indicates that the currently proposed expiration dating for the marketing packaging is 36 months. Clarify this discrepancy. In addition, discuss the cause for the increasing trend on the impurity at [redacted] (b) (4) at the end of shelf life and whether any changes to the control strategy are necessary to minimize formation of [redacted] (b) (4) during shelf life.

4. Labeling Deficiencies – N/A

M a 5. nufacturing Deficiencies – N/A

6 Biopharmaceutics Deficiencies – N/A

Mi 7 crobiology Deficiencies – N/A

8 Pharmacology/Toxicology Deficiencies

Theme 1: Product safety
Justification 1: The drug product deficiencies have been classified as MAJOR because there is need for safety assessment of extractables and leachables, inadequate assessment of extractables and leachables, or submission of that assessment in an unsolicited amendment as noted in Appendix A, Section A(2)(o) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). This information is required for establishing safety of the drug product. Upon receipt, in FDA's judgement, the review of this information will require substantial expenditure of FDA resources.

Theme 2: Unqualified impurities
Justification 2: The drug product deficiencies have been classified as MAJOR because new toxicology studies are requested for the unqualified impurity as noted in Appendix A, Section A(2)(a) of the Guidance for Industry, ANDA Submissions — Amendments to . Abbreviated New Drug Applications Under GDUFA (July 2018). The review of these studies requires, in FDA's judgement, a substantial expenditure of FDA resources.

We completed Pharmacology/Toxicology review of your information submitted in support of safety of leachables and impurities in your proposed generic lidocaine patch (5%) (dated 09/13/2018). We determined that the maximum daily exposures . (b) (4) (b) (4) raise safety concern and thus, are not acceptable from a Pharmacology/Toxicology perspective. For (b) (4) you justified its general and dermal toxicity concerns using (b) (4) Such an approach is not acceptable. For (b) (4) you did not address local toxicity concern for these compounds in the context of use of your proposed product, which has dermal route of administration and can be used chronically. Therefore, your safety assessment for these compounds is inadequate and not acceptable. To address these deficiencies, we recommend the following: .

- For (b) (4) address the systemic and local toxicity at its MDE level, for (b) (4) (b) (4) address the local toxicity concern at their respective MDE . levels from your proposed generic product. You may provide the justification

in ormation rom published literature. The adequacy o the data rom such a justi ication report will be a review issue upon submission.

- Alternatively, you may conduct a 90-day repeated-dose toxicity study with your inal, to-be marketed ormulation to quali y the sa ety o the above listed compounds at their potential MDE levels. Consider an appropriate animal model, clinically relevant route o administration and context o use o your generic drug product in the design o the nonclinical studies. You may provide scienti ic rationale or the chosen animal model and the study design. In addition, the doses used or each compound in the repeated-dose toxicity study should provide adequate margins o sa ety or its proposed clinical exposure rom your drug product. The adequacy o the data rom such nonclinical studies will be a review issue upon submission. I you have clari ying questions on the design o the nonclinical studies, you may submit your study design via General Correspondence route or our review.

Application Technical Lead Name and Date: *Brock Roughton, 01-MAY-2019* f

Recommendation: Complete Response - Major

ANDA 209190
Review #2

Drug Name/Dosage Form	Lidocaine Patch
Strength	5%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Rhodes Pharmaceuticals L.P.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
(12)	*26-SEPT-2017*	*All*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance		
Drug Product	Adchara Pongpeerapat	Brock Roughton
Process	James Norman	Yubing Tang
Microbiology	Yuansha Chen	Neal Sweeney
Facility	Cassandra Abellard	Derek Smith
Biopharmaceutics	Kelly Kitchens	Tapash Ghosh
Regulatory Business Process Manager	Camille Smith	
Application Technical Lead	Brock Roughton	
Laboratory (OTR)		
ORA Lead		
Environmental		

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

MFs:

	Type			Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)		Adequate	3/24/2016	Reviewed by Zhengfu Wang
	Type III		(b) (4)	N/A		
	Type II			N/A		
	Type II			N/A		
	Type IV			Adequate	11/29/2017	Reviewed by Adchara Pongpeerapat (pending upload into Panorama)
	Type IV			Inadequate	5/11/2016	Reviewed by Shalini Anand

ther Docu , *plications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20612	RLD

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	Complete	Inadequate (link to consult response)	11/13/2017	Bella Pelina
Clinical	N/A			
Other	N/A			

Abbreviated Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

The application is not recommended for approval due to quality related deficiencies summarized in Section II. OPQ recommends issuing a Complete Response Letter – **Major**.

II. Quality Assessment Overview

A. Drug Substance, Drug Product, and Labeling: Inadequate-Major

Lidocaine is official in USP and EP. The drug substance specification agrees with the USP monograph. The referenced DMF (b) (4) is adequate. Lidocaine exhibits one polymorphic form. The analytical methods are acceptable. The applicant should provide qualification for impurity reference standards.

Lidocaine patch 5% is non-compendial. The drug product is topical patch with a (b) (4) similar to the RLD formulation. The formulation uses (b) (4) (b) (4) (b) (4) is inadequate for (b) (4) In addition, control of adhesive impurities in the drug product is inadequate. The applicant has not adequately identified the extractables and has not adequately performed leachable studies. *This is a major deficiency. Leachables assessment is required for establishing safety of the drug product. Upon receipt, the review of this information will require substantial expenditure of FDA resources.*

The applicant has adequately mitigated the high risks identified in the initial quality risk assessment: chemical stability, physical stability (cohesive and adhesive), content uniformity and solubility. The applicant has tightened the level of (b) (4) (carcinogenic impurity) to a safe level. The proposed controls for impurities from (b) (4) are acceptable. The 36-month stability results show the increase trending in one of the unknown degradation compounds, reaching the specification limit. The applicant should justify the difference in dissolution during stability for the registration batches to assure strength, purity, and quality of the drug product during the proposed expiration dating period of 36 months.

The labeling has acceptable quality information.

B. Process: Adequate

The applicant uses a standard process for producing (b) (4) topical patches. The main process steps are (b) (4) (b) (4) The in-process controls are acceptable.

(b) (4)

C. Facility: Adequate with CDRH Deficiency

(b) (4) The last inspection of the facility was July 2016 and was classified VAI. The facility is acceptable to manufacture lidocaine for this application because of the amount of time the firm has been producing this marketed API (over 10 years), the acceptable review of the DMF, the recent inspection, and acceptable inspectional history. In addition, use of (b) (4) for testing of the drug substance is acceptable.

Altergon Italia S.r.l. (FEI# 3007086839) manufactures the drug product. The last inspection of the facility was performed November 2015 and was classified NAI. This facility is acceptable to manufacture this product because of the outcome of the inspection, the firm's acceptable compliance history, and experience with transdermal product manufacturing. In addition, use of (b) (4) (b) (4) for testing of the drug product is acceptable.

Per the CDRH consult review memo, the only manufacturing facility (Altergon) requiring review was found acceptable based on the 2016 PAI discussed above. However, the application is deficient from a documentation perspective. The CDRH deficiency will be communicated in the Complete Response letter.

D. Biopharmaceutics: Adequate

The applicant developed and validated an adequate drug release method to measure the release of lidocaine from the drug product. In addition, the firm's proposed drug release acceptance criteria are adequate based on the submitted drug release data.

The following drug release method and acceptance criteria are recommended for the test product and have been accepted by the applicant:

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criteria
USP apparatus 5 (paddle over disk)	50	Acetic acid/sodium acetate buffer, pH 4.0 at 32°C	500	10 minutes: NMT (b) (4) 30 minutes: (b) (4) 180 minutes: NLT (b) (4)

E. Microbiology (if applicable): Adequate

The product is non-sterile. The drug product specification (microbial limits testing) and test method validation/suitability complies with USP <61>, <62> and <1111>. The applicant commits to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life (36 months).

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None.

VIII. Microbiology Deficiencies

None.

IX. Combination Product Deficiencies

The following deficiency has been identified while conducting the documentation review of application ANDA 209190 for the Lidocaine Patch 5%, in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product:

1. Your response indicates that Altergon implemented an internal procedure for design control covering requirements for design and development planning, design input, design output, design review, design verification, design validation and design changes; however, reference of this procedure is not included in the response, nor is a description of Altergon's design control system provided. Further, the response did not include a summary of the plan used to design the combination product. Please provide the missing documentation.

Application Technical Lead Name and Date: I concur with the above deficiencies.

Brock Roughton, PhD, 04-DEC-2017

QUALITY ASSESSMENT

ANDA 209190
Review 1

Drug Name/Dosage Form	Lidocaine Patch
Strength	5%
Route of Administration	Topical
Rx/OTC Dispensed	Rx
Applicant	Rhodes Pharmaceuticals LP
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD 1 Original	*04/14/2016*	*All*
SD 3 Quality/Response to IR	*05/23/2016*	*DP, Process, Facility*
SD 7 Response to ECD/Quality	*09/29/2016*	*DP*
SD 10 Response to ECD/Quality	*01/23/2017*	*DP, Process, Facility*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance		
Drug Product	Adchara Pongpeerapat	Brock Roughton
Process	James Norman	Yubing Tang
Microbiology	Yuansha Chen	Neal Sweeney
Facility	Cassandra Abellard	Derek Smith
Biopharmaceutics	Kelly Kitchens	Haritha Mandula
Regulatory Business Process Manager	Camille Smith	
Application Technical Lead	Brock Roughton	
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental	N/A	

Abbreviated Executive Summary

I. Recommendations and Conclusion on Approvability

The application is not recommended for approval due to quality related deficiencies summarized in Section II. OPQ recommends issuing a Complete Response Letter – Inadequate-Minor

II. Quality Assessment Overview

A. Drug Substance, Drug Product, and Labeling: Inadequate-Minor

Lidocaine is official in USP and EP. Lidocaine exhibits one polymorphic form. The referenced DMF #011339 held by Delta Synthetic Co., Ltd. is adequate. To ensure the identity, strength, purity, and quality of the drug substance, the applicant should provide revised drug substance specification, analytical method validation, and reference standards information.

Lidocaine patch 5% is non-compendial. The drug product is topical patch with a hydrogel formulation, similar to the RLD formulation. The firm has not adequately mitigated the risks identified in the initial risk assessment (high risks: impurities, chemical stability, physical stability (cohesive and adhesive), content uniformity and solubility). The proposed specification has no control for release liner peel, cold flow, and absence of crystal. The stability results show the decrease trending in assay, but no trending in degradation compounds. The firm has not provided adequate information to demonstrate that the proposed analytical methods for drug product are fit for use.

The labeling has acceptable quality information.

B. Process: Inadequate-Minor

The applicant uses a standard process for producing hydrogel-based topical patches. The main process steps are mixing, kneading, spreading, curing, converting, and packaging. The batch size is 720-2880 kg, and no scale-up is proposed. The applicant introduced a new process line. The primary features of the new line are a faster spreading speed (10 m/min instead of 3 m/min) and faster packaging speed (300 pieces/ minute instead of 60-80 pieces/min). Microscopic patch appearance varies from batch to batch, suggesting variability in the process lines. The applicant should address the variability. The applicant should provide hold time studies for the Stage A and Stage B solutions. The applicant should define kneading and curing processes in P.3.3 or P.3.4.

C. Facility: Adequate

There are no significant outstanding issues with the firms involved in the manufacturing of the product. The CDRH consult identified several deficiencies captured in the Combination Product Deficiencies below.

D. Biopharmaceutics: Inadequate-Minor

The firm proposes to use the FDA-recommend drug release method for Lidocaine patch 5%. The drug release validation and proposed acceptance criteria are inadequate.

E. Microbiology: Inadequate-Minor

The product is non-sterile. The drug product specification (microbial limits testing) and test method validation/suitability complies with USP <61>, <62> and <1111>. The applicant should provide a commitment to perform preservative effectiveness test at the end of the shelf life.

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18 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

(b) (4)

perform testing as outlined in the application.

CDRH CONSULT OUTCOME:

Per the CDRH consult review memo, the only manufacturing facility (Altergon) requiring review was found acceptable based on the 2016 PAI discussed above. However, the application is deficient from a documentation perspective. The CDRH deficiencies will be communicated in the Complete Response letter. Please see consult memo uploaded with the Facility IQA Chapter for details.

Comparability Protocols

Reviewer's Assessment: N/A

Post-Approval Commitments

Reviewer's Assessment: N/A

Lifecycle Management Considerations

N/A

QUALITY ASSESSMENT

List of Deficiencies:

CDRH deficiencies documented in IR#2 were not responded to by applicant in adequate time per RBPM. See CDRH consult.

Primary Facilities Reviewer Name and Date:

C. Abellard 06/12/2017 Consumer Safety Officer- OPF/ DIA-BII

Secondary Reviewer Name and Date:

D. Smith 06/26/2017

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MICROBIOLOGY

Product Background:

ANDA: 209190

Drug Product Name / Strength:
Proprietary: N/A
Non-proprietary: Lidocaine Patch 5%

Route of Administration: Topical patch

Applicant:
Name: Rhodes Pharmaceuticals L.P.
Address: 498 Washington Street, Coventry, Rhode Island 02816, USA

US Agent:
(b) (4)

Manufacturing Site:
Zona Industriale A.S.L.
Morra De Sanctis
Avellino 83040, Italy

Method of Sterilization: N/A. Drug product is non-sterile.

Review Summary:
The submission is **NOT** recommended for approvable on the basis of sterility assurance.

List Submissions being reviewed (table):

Submitted	Received	Date assigned to reviewer
4/14/2016	4/14/2016	2/22/2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: Commitment to perform preservative effectiveness test at the end of the shelf life is not stated.

Product Quality Microbiology Assessment

All of the information in this review relates to patient risk associated with a non-sterile topical patch.

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – Lidocaine Patch 5% consists of a (b) (4) (b) (4) adhesive material, (b) (4) non-woven (b) (4) and covered with a (b) (4) film.

- **Drug product composition** – Each adhesive patch contains 700 mg of lidocaine (50 mg per gram adhesive) in an aqueous base. It also contains the following inactive ingredients: purified water, sorbitol, glycerin, polyacrylic acid, carboxymethylcellulose sodium, propylene glycol, sodium polyacrylate, urea, kaolin, tartaric acid, gelatin, polyvinyl alcohol, dihydroxyaluminum aminoacetate, edetate disodium, methylparaben and propylparaben. (b) (4)

- **Description of container closure system** – N/A

Reviewer's Assessment: The drug product composition and packaging are adequately described.

ADEQUATE

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

- **Preservative Effectiveness** – (P.5.6. (b) (4) eng.pdf)

Preservative content acceptance criteria for the drug product: 90%-110%

At the developmental phase, preservative effectiveness test was performed with (b) (4) of the labeled content of preservatives. Only test with the (b) (4) preservative content passed the acceptance criteria. Test was performed as per USP <51>. The drug product was mixed with the testing microorganisms and diluted 10X with (b) (4) resulting in 10^5-10^6 cfu/mL of inoculum. Samples were incubated 20-25°C and microorganisms were enumerated by membrane filtration method.

Acceptance criteria:
Bacteria: NLT 2 log reduction from the initial count at 14 days, and no increase from the 14 days' count at 28 days.
Yeast and Molds: No increase from the initial calculated count at 14 and 28 days.

Log reductions w (b) (4)

Microorganisms			
S. aureus	(b) (4)		
P. aeruginosa			
E. coli			
C. albicans			
A. brasiliensis			

Reviewer's Assessment: Preservativ
topical products.

ADEQUATE

P.3 Manufacture

P.3.1 Manufacturer

Zona Industriale A.S.L.
Morra De Sanctis
Avellino 83040, Italy

This site is responsible for manufacturing, release and stability testing of the drug product.

P.3.3 Description of the Manufacturing Process and Process Controls

- **Environmental monitoring including product bioburden –**

The applicant has not provided a description of environmental monitoring or the area classifications for the commercial production of the subject drug product. However, the subject drug product is a non-sterile topical patch with a preservative and acceptable microbial limits release specification. Therefore, patient risk is low from environmental contamination.

Reviewer's Assessment: The drug product, drug product manufacturing, and process controls were sufficiently described for the reviewer to determine which data are needed for sections P.5 (Specifications) and P.8 (Stability) below.

ADEQUATE

P.5 Control of Drug Product

P.5.1 Specifications

Test	Acceptance Criteria	Method
Total Aerobic Microbial Count	(b) (4)	USP <61>
Total Yeast & Mold Count		USP <61>

S. aureus *P. aeruginosa*	(b) (4)	USP <62>

Reviewer's Assessment: The drug product specification (microbial limits testing) and test method validation/suitability complies with USP <61>, <62> and <1111>.

ADEQUATE

P.7 Container Closure System See section P.1.

P.8 Stability

P.8.1 Stability Summary and Conclusion

Proposed expiry: 36 months.

P.8.2 Post-Approval Stability Protocol and Stability Commitment

Storage condition is 25°C/60% RH. Microbial limits tests, including TAMC, TYMC, absence of *S. aureus*, and absence of *P. aeruginosa*, will be performed at initial, 6, 12, 24 and 36 month.

The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the stability program.

Comment: Provide a statement to perform preservative effectiveness testing at the end of the drug product shelf life on at least one stability batch.

Reviewer's Assessment: The submitted post approval stability protocol and commitment does not comply with the Guidance for Industry: (1) Q1A(R2) Stability Testing of New Drug Substances and Products. A commitment to perform preservative effectiveness test at the end of the shelf life is requested.

INADEQUATE

P.8.3 Stability Data – See Section P.8.1.

Twenty-four months stability data were provided for lot # L1304151, L1304191 and L1304201. All microbial limits test results complied with the specification. No AET stability data was provided for the exhibit batches.

Reviewer's Assessment: ADEQUATE

R REGIONAL INFORMATION

R.1 Executed Batch Record

The batch records for exhibit batch lot # L1304151, L1304191 and L1304201 are provided.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

Store at 25°C; excursions permitted 15°C to 30°C. Apply lidocaine patch once up to 12 hours within a 24 hour period.

Reviewer's Assessment: There are no product quality microbiology issues related to drug product administration instructions described in the package insert.

ADEQUATE

List of deficiencies:

The following deficiencies listed below are: ☐ **Major** ☒ **Minor**
Major deficiencies - A CR is recommended ☐
Minor deficiencies - ☒ **10 day ECD** ☐ **30 day IR**

Provide a commitment to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life (reference: *Guidance for Industry ANDAs: Stability Testing of Drug Substances and Products - Questions and Answers*).

Primary Microbiology Reviewer Name and Date:

Yuansha Chen, Ph.D.

CDER/OPQ/OPF/DMA

4/21/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Neal J. Sweeney, Ph.D.

CDER/OPQ/OPF/DMA

4/21/2017

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

BIO PHARM /TOX REVIEW(s)

PHARMACOLOGY-TOXICOLOGY CONSULTATION REVIEW
Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation & Research (CDER)

Drug Product:	Lidocaine patch (5%)
ANDA#: **Applicant:**	209190 Rhodes Pharmaceuticals LP.
RLD#/Approval Date: **Sponsor:**	NDA 20612 (Lidoderm®; Lidocaine Patch, 5%); Approved on 03/19/1999 Teikoku Pharma USA Inc.
Pharmacology-Toxicology Primary Reviewer:	Narendranath Reddy Chintagari, BVSc & AH, MVSc, PhD Pharmacologist, DCR
Pharmacology-Toxicology Secondary Reviewer:	Sree Rayavarapu, DVM, PhD Staff Fellow (Toxicologist), DCR
Tertiary Reviewer:	Daiva Shetty, MD Acting Division Director, DCR
To:	Adchara Pongpeerapat, PhD Chemist, Division of Modified Release Products (DMRP), Office of Pharmaceutical Quality (OPQ)
Reason for Consult:	To evaluate the applicant's response (Amendment-14; submitted on 07/30/2019) to FDA-Complete Response Letter (CRL; dated 05/03/2019). Specifically, to review the safety of (b) (4)
Date of FDA-Complete Response:	05/03/2019
Date Response to FDA-Complete Response:	07/30/2019
Date of Completion:	11/07/2019
Conclusion:	• Fo (b) (4) the applicant provided comparative analytical data which demonstrated that (b) (4) from the proposed generic lidocaine when compared to Reference Listed Drug (RLD). DCR-Pharmacology/Toxicology defers the review and acceptability of comparative analytical data to Quality discipline. DCR-Pharmacology/Toxicology does not have any further deficiencies related to TMS. • Fo (b) (4) the proposed maximum daily exposure (MDE) levels are not likely to be different than that of RLD. Thus, the proposed do not raise any safety concern from a Pharmacology/Toxicology perspective. See Section 2 for Internal Recommendations. There is nothing to be conveyed to the ANDA applicant.
Deficiency Classification:	☐ Major ☐ Minor ☒ N/A (Review is Adequate)

1 Executive Summary:

This DCR Pharmacology/Toxicology (DCR-P/T) review evaluates ANDA 209190 applicant's response to FDA-Complete Response letter (CRL; Dated 05/03/2019). Specifically, this review [redacted]

The reference listed drug (RLD) is Lidoderm® (Lidocaine patch 5%; NDA 020612). The RLD is indicated for relief of pain associated with post-herpetic neuralgia. The maximum daily dose of lidocaine patch (5%) is 3 patches/day.

In the previous review cycle (review dated 04/29/2019), DCR-P/T reviewed the safety o [redacted] leachables [redacted] and [redacted] impurities [redacted] DCR- P/T concluded that the maximum daily exposures (MDEs) to [redacted] were determined not acceptable as there are inadequate data to justify their local and systemic toxicity concerns. P/T recommendations were conveyed to the ANDA applicant in a Complete Response (CR) letter dated 05/03/2019. The applicant responded to the CR on 07/30/2019 (Amendment-14).

Fo [redacted] the applicant provided comparative analytical data and demonstrated tha [redacted] leaches at [redacted] level from the proposed generic lidocaine when compared to RLD. The amount of [redacted] varied from [redacted] in RLD an [redacted] in the proposed generic lidocaine. The review and acceptability of analytical data is deferred to the Quality discipline. Nevertheless, based on the levels o [redacted] reported, its MDE is likely to be lower from the generic lidocaine when compared to RLD. Thus, the MDE o [redacted] from the proposed generic does not raise any safety concern when compared to RLD. Thus, DCR-P/T does not have any further deficiencies related t [redacted]

[redacted] Thus, it is likely that human subjects will be exposed to same levels of [redacted] and [redacted] if proposed generic is taken in place of RLD. Furthermore, DCR Clinical team reviewed Clinical trial data and did not identify any sensitization and irritation risk potential for the proposed generic lidocaine drug product. Thus, DCR-P/T determined that the proposed level [redacted] are not likely to alter the safety profile of generic lidocaine when compared to the RLD.

In summary, there are no further deficiencies related to [redacted] and the proposed levels o [redacted] do not raise any safety concerns from a P/T perspective.

2 Internal Recommendation:

Fo [redacted] the applicant did not provide any new nonclinical data. However, the applicant provided comparative analytical data which demonstrated tha [redacted] leaches at [redacted] level from

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Fo (b) (4) th fp opos d m axifmum d ily fxposu f (MDE) l v ls f ot f lik ly to b fdi f t th f th t o fRLD. Thus, th fp opos d l v ls do fot fis f y s f ty co c f om ff/T p fsp ctiv . f

3 fE xternal Recommendation: f

Th f o f commf d tio s to th f pplic ft. f

4 fR egulatory Background: f

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I fthis fg fd, OPQ fco fsult d (d t d 10/25/2018) DCR-P/T to fv lu ff fth fs f ty o fth f l fch bl s f d impu iti s id fti i d i th fp opos d g f ic lidoc i fp tch.[5] fDCR-P/T f compl t d i st cycl f vi w f(d t d 04/29/2019) f d d t mi fd th t th l v ls o (b) (4) (b) (4) w f cc pt bl but th fl v ls o (b) (4) w f d t mi fd to b f ot fcc pt bl .[6] fP/T d fici fci s w f commu ic t d to th f pplic ft i f CR f l tt f(d t d 05/03/20119).[7] Th f pplic ft fspo d d to th fCR f d submitt d fjusti ic tio f o f

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[1] ANDA 209190; Lidoc i fp tch (5%); DARRTS; Applic tio fhisto y f https://d f ts. d .gov/d f ts/ c s/Applic tio Histo yCo t ft/vi wApfplic tio Histo yCo t ft?_ f R di ct=530583 f 705199957&_ f P g =3 f

[2] ANDA 209190; Lidoc i fp tch; EDR S qu fc f0011(13); D ft d 09/12/2018; Modul 1.11.1. Qu lity f I o m atiof Am e dfm e tf f \\cds sub1\ vsp od\ fd 209190\0011\m1\us\111-i o m atiof - m e dfm e tfqu lity-i o m atiof - m e dfm e tf d -c l- f d t d-19-d c-2017.pd f

[3] ANDA 209190; Lidoc i fp tch; EDR S qu fc f0011(13); D ft d 09/12/2018; Modul 1.11.1. Qu lity f I o m atiof Am e dfm e tf f \\cds sub1\ vsp od\ fd 209190\0011\m1\us\111-i o m atiof - m e dfm e tfqu lity-i o m atiof - f m e dfm e tf spo s -to-c l-9-11-2018.pd f

[4] ANDA f209190; Lidoc i fp tch; EDR S qu fc f0011(13); D ft d 09/12/2018; Modul 3.2. P.7. Co t i f Closu f Syst m f \\cds sub1\ vsp od\ fd 209190\0011\m3\32-body-d t \32p-d ug-p od\lidoc i f-p tch-topic l- lt go \32p7-co t- f closu f-sys\co t i f-closu f-syst m-13.pd f

[5] ANDA 209190; Lidoc i fp tch; P fo fm a, Afpplic tio fLi cycl ; S d co sult fqu st (D ft d 10/25/2018) f http://p fo fm a df .gov/docum e tfvi w?ID=5bd1 4c900b1 b b 3b d14d5c1090 3 f

[6] ANDA 209190; Lidoc i fp tch; P fo fm a, Afpplic tio fLi cycl ; R spo d to co sult fqu st (d t d 04/19/2019) f http://p fo fm a df .gov/docum e tfp fvi w?v fsio ID=5cdfc37d100243 f 7139 d 7d12d7b&ID=5cc725720042 3 f 633 9 780c0763cb f

[7] ANDA 209190; Lidoc i fp tch; P fo m a, Applic tio Li cycl ; Uplo d i fl d cisio (d t d 05/03/2019) f http://p fo fm a df .gov/docum e tfp fvi w?v fsio ID=5cdfc2 fc0022 41 9 0588b9d0 fcd65&ID=5cc d 870f00758 f 794 38398399c08309 f

the safety o [redacted] (Amendment-14, dated 07/30/2019).[8] The applicant submitted justification related to P/T deficiencies is the subject of this review.

5 Discussion

In current post-CR Amendment-14 (dated 07/30/2019), the applicant submitted information to justify the safety of [redacted] in the generic lidocaine patch. The safety of proposed levels of [redacted] are discussed below.

Evaluation of safety o [redacted]

During the first cycle review, DCR-P/T evaluated the safety o [redacted] at a daily exposure level of [redacted] in the proposed generic lidocaine patch. DCR-P/T determined that the exposure [redacted] raises safety concern due to inadequate systemic and local toxicity data.

In the current post-CR submission (Amendment-14), the applicant provided nonclinical data from published literature to justify the safety o [redacted] In addition, the applicant also provided comparative analytical data to show the levels o [redacted] that can potentially leach from RLD vs proposed generic lidocaine.

DCR-P/T reviewed majority of the nonclinical submitted by the applicant in the previous review cycle. Applicant's current submission did not provide any additional nonclinical data that can alter previous P/T determination. Nevertheless, the applicant provided comparative analytical data to show the level o [redacted] that can potentially leach from RLD vs proposed generic lidocaine. Th [redacted] levels were measured at 32°C and 42°C a [redacted] different p [redacted] conditions. Comparative analytical data indicate tha [redacted] leached a [redacted] level from proposed generic (in the range o [redacted] compared to RLD (in the range of [redacted] The amounts o [redacted] leached from RLD and proposed generic under different tested conditions are shown in Table 1 below.

[redacted]

The review and acceptability of analytical data is deferred to the Quality discipline. Based on the levels o [redacted] observed in RLD vs proposed generic, the MDE o [redacted] is likely to b [redacted] from the proposed generic lidocaine when compared to RLD. Thus, the level o [redacted] from the proposed generic does not raise any safety concern. DCR-P/T does not have any further deficiencies related t [redacted]

[8] ANDA 209190; Lidocaine patch; GS Review; Sequence 0012(14); Dated 07/30/2019; Module; 1.11.4. Multiple Module Information Amendment (dated 07/30/2019) \\cdsesub1\evsprod\anda209190\0012\m1\us\111-information-amendment\multiple-module-information-amendments\response-crl-0012.pdf

Evaluation of safety of (b) (4):

In the previous cycle, DCR-P/T concluded that proposed levels o (b) (4) raises local toxicity concern. Therefore, DCR-P/T recommended that the applicant to justify the local toxicity of (b) (4) at their proposed levels.

In the current post-CR Amendment-14, the applicant did not provide any new toxicology information fo (b) (4); however, applicant provided summary of results a dermal exposure study (exposure dose-1%; duration-3 times/week; lifetime) conducted in mice to justify the levels o (b) (4) DCR-P/T reviewed this dermal toxicity study in the previous cycle and concluded that this study does not adequately justify the local toxicity of proposed level of (b) (4)

Fo (b) (4) the applicant did not provide any new toxicology information to justify the proposed levels. However, the applicant tried to justify the levels by indicating that polyacrylic acid constitutes only (b) (4) of formulation weight of lidocaine patch and thus, the level of (b) (4) is (b) (4) which does not raise safety concern based on existing data. We have previously reviewed available local and systemic toxicity data fo (b) (4) and concluded that MDE of (b) (4) from proposed generic are not justified.

(b) (4) Based on this information, it is likely that human subjects will be exposed to same levels of (b) (4) (b) (4) if proposed generic lidocaine is taken in place of RLD.

The applicant claimed that amounts of (b) (4) are likely to be (b) (4) in the final drug product as these compounds wer (b) (4) analytical evaluation threshold (AET) o (b) (4) in the leachable studies. Generally, leachable studies are not used to qualify exposures to impurities from the excipients; however, these data suggest that the levels of (b) (4) are likely to be (b) (4) in the final drug product.

Furthermore, DCR Clinical team reviewed Clinical trial data and did not identify any sensitization and irritation risk potential for the proposed generic lidocaine drug product.[10]

Thus, DCR-P/T determined that the proposed level (b) (4) are not likely to alter the safety profile of generic lidocaine when compared to the RLD.

[9] ANDA 209190; Lidocaine Patch; Mercado; Drug Product Primary Review; Dated 06/01/2017 http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f88128bf9f

[10] ANDA 209190; Lidocaine patch; Panorama; Application Lifecycle; Clinical Primary Review; Dated 06/19/2017 http://panorama.fda.gov/document/preview?versionID=59481e4600986e05dca721a57963dd8a&ID=59480aac0096c6f4ae1f00967866a170

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Fo (b) (4) th G p opos d MDE l v ls G ot lik ly to b G iff G t th G th t of G RLD. Thus, th G p opos d do G t G s G y s f ty co c G f om PG T p G p ctiv . G

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[11] ANDA 209190; GS R vi w; S qu G c G 011(13); D t d 09/12/2018; Modul 3.2. P.4.1. Sp cific tio s; G Poly c ylic cid G \\cds_sub1_vsp od_G 209190\0011\m3\32-body-d t \32p-d ug-p od\lidoc i G p tch-topic l- lt go \32p4-co t - G xcip\poly c ylic- cid\sp cific tio s-1.pdf G

[12] ANDA 209190; GS R vi w; S qu G c G 011(13); D t d 09/12/2018; Modul 3.2. P.4.1. Sp cific tio s; Sodium G Poly c yl t G \\cds_sub1_vsp od_G 209190\0011\m3\32-body-d t \32p-d ug-p od\lidoc i G p tch-topic l- lt go \32p4-co t - G xcip\sodium-poly c yl t \sp cific tio s-1.pdf G

[13] NDA 20612; Lidod G n® (Lidoc i G ; GS R vi w; S qu G c G 009(670); D t d 05/03/2019; Modul 1.13.5. G SummG y of m a uG ctu i g ch G g s G \\cds_sub1_vsp od_d_020612\0009\m1\us\113- G - p\sum-m a uG ch G pdf (P g #12) G

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PHARMACOLOGY-TOXICOLOGY CONSULTATION REVIEW
Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation & Research (CDER)
Lidocaine Patch 5%

Drug Product:	Lidocaine Patch 5%
DMF#/ANDA#: **Applicant:**	ANDA 209190 Rhodes Pharmaceuticals LP
RLD#/Approval Date: **Sponsor:**	NDA 20612, Approved 03/19/1999 Teikoku Pharma USA Inc
Pharmacology-Toxicology Primary Reviewer:	Wei Ding, PhD, DABT Toxicology reviewer, DCR
Pharmacology-Toxicology Secondary Reviewer:	Victoria Keck, MS, VMD Toxicologist, DCR
Tertiary Reviewer:	Daiva Shetty, MD Acting Director, DCR
To:	Adchara Pongpeerapat, Ph.D. Division of Modified Release Products (DMRP) Office of Lifecycle Drug Products (OLDP) Office of Pharmaceutical Quality (OPQ)
Reason for Consult:	To review Ames assay results o [redacted] (b) (4)
Date of Submission:	08/08/2019
Date Consult Received:	08/20/2019
Date of Completion:	09/18/2019
Conclusion:	Under the conditions of the valid Ames assay, the impurit [redacted] (b) (4) did not exhibit bacterial mutagenicity potential and can be controlled as a non-mutagenic impurity.
Deficiency Classification:	☐ Major ☐ Minor ☒ N/A (Review is Adequate)

1. Executive Summary:

This Pharmacology/Toxicology review addresses a consult request from the Division of Modified Release Products (DMRP), in the Office of Pharmaceutical Quality (OPQ) to review Ames test for the impurity [redacted] (b) (4) in Lidocaine Patch 5% under ANDA 209190.

The reference listed drug (RLD) for Lidocaine Patch 5% is Lidoderm® (Lidocaine Patch 5%) under NDA 20612. The RLD was approved on 03/19/1999 and it is sponsored by Teikoku Pharma USA Inc. Lidoderm (Lidocaine Patch 5%) is comprised of an adhesive material containing 5% lidocaine. The size of the patch is 10 cm x 14 cm. Lidoderm® is indicated for relief of pain associated with post-herpetic neuralgia, which should be applied only to intact skin.[1] The maximum daily dose (MDD) is 2100 mg of lidocaine or 3 patches/day. If controlled the impurity level as not more than (NMT [redacted] (b) (4) the limit of impurity is NMT [redacted] (b) (4) or [redacted] (b) (4)

Based on computational mutagenicity analysis (report # TSI-18-001), Rhodes Pharmaceuticals LP, the ANDA applicant, states that the impurit [redacted] (b) (4) is potentially mutagenic. To justify the proposed limit of NMT [redacted] (b) (4), the applicant submitted an Ames test of the impurity and concluded that the impurity is non-mutagenic. OPQ consulted DCR to evaluate the Ames test result and assess the mutagenicity potential of [redacted] (b) (4)

Upon review, DCR Pharm/Tox determined that under the conditions of the conducted Ames test, [redacted] (b) (4) is not mutagenic in any of the tested four *Salmonella* strains (TA98, TA100, TA1535, TA1537) and *Escherichia coli* strain WP2 uvrA both in the presence and absence of metabolic activation (S9).

2. Recommendation (Internal)

Under the conditions of this valid Ames assay [redacted] (b) (4) is not mutagenic and may be controlled as a non-m

3. Comments to be conveyed by the RPM to the ANDA applicant:

N/A.

4. Regulatory Background:

Rhodes Pharmaceuticals LP submitted ANDA 209190 for Lidocaine Patch 5%. The RLD for Lidocaine Patch 5% is Lidoderm® (Lidocaine Patch 5%) under NDA 20612. The RLD was approved on 03/19/1999 and it is sponsored by Teikoku Pharma USA Inc.

[1] RLD (NDA 020612, Lidoderm®) Drug Label Information obtained at Drugs@fda: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020612s014lbl.pdf Accessed at: 08/26/2019

Th (Q)SAR study of th m pur t m (b) (4) d cat d that m t s pot nally u ta m c. To just fy a l mt that xc nds th Thr shold of Tox colo nal m Co c r (TTC), th ANDA appl ca t sub mtt d th A m s t st r port to just f (b) (4) (b) (4) as o - motox c m pur ty.[2] DMRP/OLDP co sult d DCR (dat d m 08/08/2019) to valuat th A m s assay r sults a d ass ss th u ta m c ty pot nal of th (b) (4) (b) (4) m pur ty. m

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5. Genetic Toxicology: m
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Study t tl : Bact r al R v rs Mutat o Assay m
Study um b r: (b) (4) m
Study r port locat o : (b) (4)
Sub mss o t m: 7/11/2019 m
Study Spo sor: (b) (4)
Co duct m laboratory:
Dat of study t at o : 2/11/2019 m
GLP com pl a c : Y s m
QA stat m t: Y s m
T st art cl : (b) (4)
T st art cl m d scr pt o : m
Batch #:
Pur ty: m

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5.1. Key Findings: m
m

(b) (4) d d ot duc a dos -d p nd nt cr as of th m r v rta t colo ms *Salmonella typhimurium* stra ns TA98, TA100, TA1535 a d TA1537 a d m *Escherichia coli* stra m Pm2*uvr*A, both pr s n a d abs n of mtabol c act vat o (S9). m U nd r th co d t o s of th s val d A m s assa (b) (4) s m ot u ta m c. m

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[2] ANDA 209190, A m s r port 3.3.P.2, at \\cds_sub1_vsprod\a_da209190\0012\3_\32-body-data\32p-dru - m prod\l doca m-patch-top cal-alt r o \32p2-pharm -d v\pharm ac ut cal-d v lop m t-3.pdf Acc ss d 08/26/2019 m

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5.5. Study Validity: u

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Th s bm tt d Am s assay s val d b ca s of th follow u r aso s: u

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- Th s l ct o of fo r stra us of *Salmonella typhimurium* a d o u stra uof *E. coli* s u ad q at a d s accorda c w th OECD 471 ud l u. u
- Th sp c f cat o a d co c utrat o of S u (b) (4) s w th uacc ptabl ra u . u
- Th dos s l ct o s ad q at bas d o th u h l m t dos (b) (4) a d u dos s l ct o s w ur w th uhalf lo t rvals. u
- At l ast thr o tox c dos s ar t st d s u ach stra uboth pr s uc a d abs uc of u S9. u
- Back mo ud m uta ts p r plat ar w th uth h stor cal ra u for ach bact r al stra uboth u pr s uc a d abs uc of S9. u
- Pos t v co trols prod c d cl ar cr as th m a u umb r of r v rta t colo u s p r u plat wh u compar d to v h cl co trol. u
- Us o (b) (4) as th sol pos t v co trol th pr s uc of S9 s acc ptabl u b ca s th ff cacy of S9 m x was charact r z d s u a add t o al m uta u , u (b) (4) wh ch r q ur s m tabol c act vat o u

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6. Discussion: u

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(b) (4) d d ot prod c a dos -d p ud ut cr as th u m a u umb r of r v rta ts, ua y of th f v t st r stra us, at th top dos s t st d both th u abs uc a d th pr s uc of S9. Th u at v co trol a d pos t v co trol val us all fall to th u h stor cal co trol val ura u . Th pos t v co trols s d th c rr t st dy prod c d mor u tha 3-fold cr as th m a u umb r of r v rta ts all th f v t st r stra us, th abs uc u as w ll as pr s c of S9. H c , d r th co d t o s of th s val d Am s assa u (b) (4) (b) (4) s ot m uta u c. u

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7. Conclusion: u

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U ud r th co d t o s of th val d Am s assay, mp ur ty (b) (4) d d ot xh b t bact r al m uta u c ty pot t al. u

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PHARMACOLOGY-TOXICOLOGY CONSULTATION REVIEW
Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation & Research (CDER)

Lidocaine patch (5%)

Drug Product:	Lidocaine patch (5%)
ANDA#: **Applicant:**	209190 Rhodes Pharmaceuticals LP.
RLD#/Approval Date: **Sponsor:**	NDA 20612 (Lidoderm®; Lidocaine Patch, 5%); Approved on 03/19/1999 Teikoku Pharma USA Inc.
Pharmacology-Toxicology Primary Reviewer:	Narendranath Reddy Chintagari, BVSc &AH, MVSc, PhD Pharmacologist, DCR
Pharmacology-Toxicology Secondary Reviewer:	Sree Rayavarapu, DVM, PhD Staff Fellow (Toxicologist), DCR
Tertiary Reviewer:	Mark Ritter, MD Associate Director, DCR
To:	Adchara Pongpeerapat, PhD Chemist, Division of Modified Release Products (DMRP), Office of Pharmaceutical Quality (OPQ)
Reason for Consult:	To evaluate the safety and acceptability o (b) (4) leachables (b) (4) in the generic lidocaine patch.
Date of Submission:	09/12/2018
Date Consult Received:	10/02/2018
Date of Completion:	04/29/2019
Conclusion:	The MDE (b) (4) pose safety concern and thus, are not acceptable from a Pharmacology/Toxicology perspective. See Section 2 for Internal Recommendations and Section 3 for Comments to be conveyed to the ANDA Applicant by the RPM.
Deficiency Classification:	☒ Major ☐ Minor ☐ N/A (Review is Adequate)

Extractables/Leachables review: The deficiency requires justification or nonclinical studies that support the safety of the proposed drug product. As described in Appendix A of the *Guidance for Industry ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018),* the need for a safety assessment of impurities, extractables and leachables, or inadequate assessment of impurities, extractables and leachables is classified as a major deficiency. Review of the submitted justification or toxicology data will require substantial expenditure of FDA resources.

1 Executive Summary:

This Pharmacology/Toxicology review address a consult request from the Division of Modified Release Products (DMRP) in the office of Pharmaceutical Quality (OPQ) to evaluate the safety o (b) (4) leachable (b) (4) an (b) (4) impuritie (b) (4) in the proposed generic lidocaine patch (ANDA 209190).

Rhodes Pharmaceuticals submitted ANDA 209190 for generic lidocaine patch. The Reference Listed Drug (RLD) is Lidoderm® (lidocaine), NDA 020612. Lidocaine patch is indicated for relief of pain associated with post-herpetic neuralgia. The maximum daily dose (MDD) of lidocaine is 3 patches per day. Rhodes Pharmaceuticals performed analytical studies to identify potential leachables in their proposed generic lidocaine product. The applicant set an Analytical Evaluation Threshold (AET) limit o (b) (4) The applicant's analytical methods are acceptable from a Quality perspective. The applicant's AET is acceptable from a Pharmacology/Toxicology perspective.

The safety and acceptability of each of th (b) (4) leachable (b) (4) an (b) (4) impuritie (b) (4) in the proposed generic lidocaine patch is discussed below.

(b) (4)

(b) (4)

2 Internal Recommendation: 5

Th m axifmum 5ily xposu 5(MDE) l v ls o (b) (4) 5
(b) (4) o ot pos 5y s f ty co c 5 5 thu 5 (b) (4)

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[1] E uc mi 5, 21CFR § 17 .10 5
https://www. cfr ss 5t .f 5gov/sc ipts/c 5h/cf ocs/cfcf /cf s 5ch.cfm?f =17 .10 5 5

[redacted] pose a safety concern and thus, are not acceptable from a Pharmacology/Toxicology perspective.

Recommendations to be conveyed to the ANDA applicant are provided in Section 3 below.

DCR has identified MAJOR deficiencies to be included in the Complete Response Letter. The comments in Section 3 must conveyed to the ANDA applicant AS WRITTEN under the "PHARMACOLOGY/TOXICOLOGY" section of the Complete Response Letter. DCR considers these deficiencies to be MAJOR deficiencies to be included in the Complete Response Letter. These must NOT be communicated to the Applicant in an Information Request. Please notify DCR when the applicant responds to this deficiency.

3 Comments to be conveyed by the RPM to the ANDA applicant as written:

INADEQUATE OUTCOME -THE RESPONSE NEEDS TO BE REVIEWED BY DCR

DCR has identified MAJOR deficiencies to be included in the Complete Response Letter. The comments in Section 3 must conveyed to the ANDA applicant AS WRITTEN under the "PHARMACOLOGY/TOXICOLOGY" section of the Complete Response Letter. DCR considers these deficiencies to be MAJOR deficiencies to be included in the Complete Response Letter. These must NOT be communicated to the Applicant in an Information Request. Please notify DCR when the applicant responds to this deficiency.

We completed Pharmacology/Toxicology review of your information submitted in support of safety of leachables and impurities in your proposed generic lidocaine patch (5%) (dated 09/13/2018). We determined that the maximum daily exposures (MDEs) levels of [redacted] raise safety concern and thus, are not acceptable from a Pharmacology/Toxicology perspective.

Fo [redacted] you justified its general and dermal toxicity concerns usin [redacted] approach. Such an approach is not acceptable. Fo [redacted] you did not address local toxicity concern for these compounds in the context of use of your proposed product, which has dermal route of administration and can be used chronically. Therefore, your safety assessment for these compounds is inadequate and not acceptable. To address these deficiencies, we recommend the following:

- Fo [redacted] address the systemic and local toxicity at its MDE level, for [redacted] address the local toxicity concern at their respective MDE levels from your proposed generic product. You may provide the justification information from published literature. The adequacy of the data from such a justification report will be a review issue upon submission.
- Alternatively, you may conduct a 90-day repeated-dose toxicity study with your final, to-be-marketed formulation to qualify the safety of the above listed compounds at their potential MDE levels. Consider an appropriate animal model, clinically relevant route of administration and context of use of your generic drug product in the design of the nonclinical studies. You may provide scientific rationale for the chosen animal model and the study design. In addition, the doses used for each compound in the repeated-dose toxicity

study should provide adequate margins of safety for its proposed clinical exposure from your drug product. The adequacy of the data from such nonclinical studies will be a review issue upon submission. If you have clarifying questions on the design of the nonclinical studies, you may submit your study design via General Correspondence route for our review.

4 Regulatory Background:

On 04/14/2016, Rhodes Pharmaceuticals LP submitted ANDA 209190 for generic lidocaine patch.[2] In a Complete Response Letter (CRL) (dated 12/19/2017), FDA advised the applicant to justify safety of the leachables with MD (b) (4) in their proposed generic drug product.[3] FDA also recommended that applicant sh specification limits o (b) (4) to threshold for toxicological concern or justify MDE to (b) (4) (b) (4) The applicant responded to the CRL on 09/12/2018. In CR response, the applicant submitted a safety justification for leachable (b) (4) (b) (4) an (b) (4) impuritie (b) (4) in their proposed generic lidocaine patch.[4,5] In this rega roducts (DMRP) in the OPQ consulted DCR Pharmacology/Toxicology to evaluate the safety of the leachable (b) (4) (b) (4) and impuritie (b) (4) identified in the ocaine patch (da bmitted information is the subject of this review.

4.1 Orange Book Information

There are 3 marketed entries in the Orange Book for Lidocaine patch (5%) (Table 1).

Table 1: Orange Book Listed Lidocaine 5% Products (n= 3).

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N020612	AB	Yes	Lidocaine	Patch; Topical	5%	Lidoderm	Teikoku Pharma USA.
A200675	AB	No	Lidocaine	Patch; Topical	5%	Lidocaine	Actavis Labs UT Inc.
A202346	AB	No	Lidocaine	Patch; Topical	5%	Lidocaine	Mylan Technologies Inc.

Source: Search on 01/29/2019 by this reviewer of the Orange Book, website: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process;
TE=Therapeutic Equivalence
RLD=Reference Listed Drug

[2] ANDA 209190; Lidocaine patch (5%); DARRTS; Application history https://darrts.fda.gov/darrts/faces/ApplicationHistoryContent/viewApplicationHistoryContent?_afrRedirect=5305837051999957&_afrPage=3

[3] ANDA 209190; Lidocaine patch; EDR Sequence 0011(13); Dated 09/12/2018; Module 1.11.1. Quality Information Amendment \\cdsesub1\evsprod\anda209190\0011\m1\us\111-information-amendment\quality-information-amendment\fda-crl-dated-19-dec-2017.pdf

[4] ANDA 209190; Lidocaine patch; EDR Sequence 0011(13); Dated 09/12/2018; Module 1.11.1. Quality Information Amendment \\cdsesub1\evsprod\anda209190\0011\m1\us\111-information-amendment\quality-information-amendment\response-to-crl-9-11-2018.pdf

[5] 209190; Lidocaine patch; EDR Sequence 0011(13); Dated 09/12/2018; Module 3.2.P.7. Container Closure System \\cdsesub1\evsprod\anda209190\0011\m3\32-body-data\32p-drug-prod\lidocaine-patch-topical-altergon\32p7-cont-closure-sys\container-closure-system-13.pdf

5 Labeling

The current labelling for Lidoderm® [lidocaine patch (5%)] was approved on 11/02/2018. There is no boxed warning.[6]

5.1 Indications

Lidoderm® is indicated for relief of pain associated with post-herpetic neuralgia.[6]

5.2 Dosage and Administration

According to RLD labeling, Lidoderm® should be applied to intact skin to cover the most painful area. Prescribed number of patches (maximum of 3), should be applied only once for up to 12 hours within a 24-hour period.[6]

6 Discussion

The Division of Modified Release Products (DMRP), OPQ, requested DCR-P/T to review safety o (b) (4) leachable (b) (4) and (b) (4) impuritie (b) (4) (b) (4) in generic lidocaine patch (ANDA 209190). The applicant submitted safety justification for leachables and impurities using the information from the Cosmetic Ingredient Review (2014), Norwegian Food Safety Authority (NFSA), European Food Safety Authority (EFSA), European Chemicals Agency (ECHA) and Joint FAO/WHO Expert Committee on Food Additives (JECFA) and published literature.[5]

The maximum daily exposure (MDE) levels of each of the compounds at the maximum daily dose (MDD: 3 patches/day) of the proposed generic lidocaine are listed in Table 2 below.

Table 2: Maximum daily exposure (MDE) of leachables and impurities under review in the current consult.

(b) (4)

The safety of each of th (b) (4) leachables and th (b) (4) impurities in the proposed generic lidocaine patch is discussed below.

Evaluation of safety o (b) (4)
(Acceptable):

Toxicological evaluation fo (b) (4) was based on the information from the CIR, 2014.[7] The applicant indicated that rmation o (b) (4) was not available. Howeve (b) (4)

[6] NDA 020612; Lidoderm; Drugs@FDA: FDA Approved Drug Products https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020612

(b) (4)

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(b) (4)

7 Conclusion: p

Th m ximum pily x osu ps (MDEs) o (b) (4) p (b) (4) (b) (4) o ot is py s f ty co c p f om Ph pm acqpogy/Toxicology p . th p lic pt i ot ovi p qu t i fo m atio to justify th s f ty of MDE of p (b) (4) Th MDE p l v l o (b) (4) i o os pg p ic li oc i is s s f ty p co c p . Thus, MDE o (b) (4) (b) (4) is ot cc p

(b) (4)

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

BIOEQUIVALENCE REVIEW(s)

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AN 1A No. 1	209 90 1	
rug Product Name 1	Lidocaine Patch 1	
Strength(s) 1	5% 1	
Applicant Name 1	Rhodes Pharmaceuticals L.P. 1	
Applicant Address 1	498 Washington Street, Coventry, Rhode Island 028 6, USA 1	
US Contact Name and US Mailing Address 1	Todd M. Delehant, Ph.D., Director Regulatory Affairs 1 498 Washington Street, Coventry, Rhode Island 028 6, USA 1 todd.delehant@pharma.com 1	
US Contact Telephone Number 1	40 -262-9425 1	
US Contact Fax Number 1	40 -262-9450 1	
Original Submission ate(s) 1	04/ 4/20 6 1	
Submission ate(s) of Amendment(s) Under Review 1	Response to ECD/Bioequivalence on 08/05/20 6 (SD-4) 1	
Primary Reviewer 1	Yibo Wang, Ph.D. 1	
Secondary Reviewer 1	Jennifer N. Miller, Ph.D. 1	
Tertiary Reviewer 1	N/A 1	
Study Number(s) 1	**RP-L** 1 **-PK001** 1	RP-LID-SSI 1
Study Type(s) 1	**Fasting** 1	Skin irritation/sensitization/adhesion studies 1
Strength(s) 1	5% 1	
Clinical Site 1	Frontage Clinical Services, Frontage Laboratories, Inc. 1	
Clinical Site Address 1	24 Main Street, Hackensack, New Jersey 0760 1 Tel: 20 -678-0288; Fax: 20 -342-34 3 1	
Analytical Site 1	(b) (4)	
Analytical Site Address 1		
OS S status 1	**Backlog, Year 1 and Year 2 AN 1As** 1 ☐ **Pending** ☐ **Complete** 1 ☐ **N/A (Waiver)** 1	1 **Post October 1, 201 1AN 1As** ☐ **To Be etermined by OS S** ☐ **Pending For Cause nspection** ☒ **Complete** 1
Waiver 1	☐ **Granted** ☐ **Tentatively granted** ☐ **Not granted** ☒ **N/A** 1	
QC issolution 1	☐ **Pending** ☐ **Adequate** ☒ **nadequate** 1	
Formulation 1	☒ **Adequate** ☐ **nadequate** 1	

Response to CR Resu t n a Reformu at on? /	/ ☐ Poss b y /☐ No /☒ N A /		
Overa /Rev ew Resu t /	☒ Adequate ☐ Inadequate /		
Rev sed New Draft Gu dance / Generated as Part of Cur ent / Rev ew /	☐ YES ☒ NO /		
Def c ency C ass f cat on /	☐ Major (Def c enc es to be commun cated by CR) / ☐ Min r / ☒ N A (Rev ew s Adequate) /		
B oequ va ence study / track ng support ng document # /	Study test type /	Strength /	Rev ew Resu t /
1, , /	F ast ng /	5%/	☒ Adequate ☐ Inadequate /

1 EXECUTIVE SUMMARY /

This application contains the results of three studies, (1) a pharmacokinetic (PK) endpoint / bioequivalence (BE) study (#RP-LID-PK001), comparing the test product, Rhodes / Pharmaceuticals L.P.'s Lidocaine Patch, 5%, to the corresponding reference product, / Teikoku Pharma USA's Lidoderm® (lidocaine) Patch, 5% under fasting conditions; (2) an / adhesion study (#RP-LID-SSI); and (3) a skin irritation and sensitization study (#RP- / LID-SSI). The Division of Bioequivalence (DB) II will review the BE study and the / Division of Clinical Review (DCR) will review the adhesion study and / irritation/sensitization study. /

The BE study was designed as a single-dose, two-way crossover study in healthy male / and female subjects, in which residue in the patches was also assayed for "apparent dose" / as per the Product-Specific Guidance for Lidocaine Patch.[1] The firm's fasting BE study is / acceptable. The results are summarized in the table below. /

L doca ne Patch 5%, Dose (x 700 mg) / Fast ng B oequ va ence Study No. RP-LID-PK001, N= 9 (Ma e=18 and Fema e=21) / Least-Square Geometr c Means, Po nt Est mates and 90% Conf dence Interva s /				
Parameter (un ts) /	Test /	Reference /	Rat o /	90% C.I. /
AUC0-t (ng·hr mL /	[redacted] (b) (4)			
AUC∞ (ng·hr mL /				
Cmax (ng mL /				

There is no USP dissolution method, but there is a FDA-recommended dissolution / method for this drug product. The firm conducted dissolution testing using the FDA- / recommended method [500 mL of Acetic Acid/Sodium Acetate Buffer, pH 4.0 at 32°C, /

[1] Product-Specific Guidance for Lidocaine Patch (Recommended Dec 2006; Revised May 2007, July 2014, / Jan 2016, Oct 2016) /

USP Appara us V (Paddle over D sk) a 50 rpm . T e f rm's QC d ssolu on me od] and da a ere rev e ed separa ely and found nadequa e.[2]]

No Off ce of S udy In egr y and Surve llance (OSIS) nspec on s pend ng or necessary.]

T e appl ca on s accep able] no def c enc es.]

2 TABLE OF CONTENTS]

3 SUBMISSION SUMMARY]

3.1 Drug Product Information[3]]

Test Product]	L doca ne Pa c , 5%]
Reference Product]	L doderm® (l doca ne) Top cal Pa c , 5%]

[2] GDRP, ANDA-209190-ORIG-1, B op armaceu cs Qual y Rev e , ANDA 209190 B op arm.docx,] da ed 2/23/2017.]

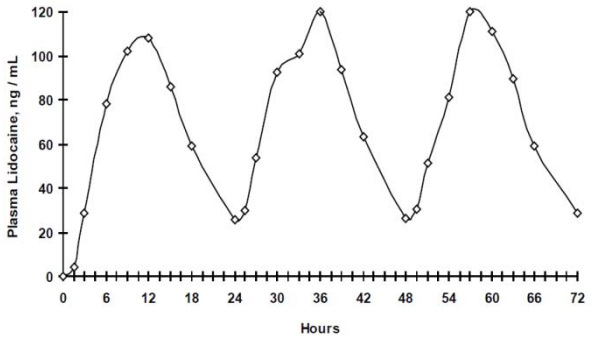
[3] Onl ne Orange Book, searc : l doca ne/pa c , accessed on 07/15/2016.] p://] .accessda a.fda.gov/scr p s/cder/ob/docs/obde a l.cfm?Appl_No=020612&TABLE1=OB_Rx]

aNnufacturer N	Teikoku Pharma USA N
A N N	020612 N
Approval aNte N	March 19, 1999

.2 PK/P NInformation[4] N

o st recent N label (provide embedded N document) Please check if an NG tube study is neNded. N	N Lidoderm N label_01072015.pdf N
Indication N	LIDODERM is indicated for relief of pain associated N with post-herpetic neuralgia. It should be applied only to N intact skin. N
Boxed warning N	N/A N
Bioavailability N	The amount of lidocaine systemically absorbed from N LIDODERM is directly related to both the duration of N application and the surface area over which it is applied. N In a pharmacokinetic study, three LIDODERM patches N were applied over an area of 420 cm^2 of intact skin on N the back of normal volunteers for 12 hours. Blood N samples were withdrawn for determination of lidocaine N concentration during the application and for 12 hours N after removal of patches. N **Table 1 N** Absorption of lidocaine from LIDODERM N Normal volunteers (n= 15, 12-hour wearing time) N LIDODERM Patch: 3 patches (2100 mg); Application Site: Back; Area (cm^2): 420; Dose Absorbed (mg): 64 ± 32; C_{max} (µg/mL): 0.13 ± 0.06; T_{max} (hr): 11 hr When LIDODERM is used according to the N recommended dosing instructions, only 3 ± 2% of the N dose applied is expected to be absorbed. At least 95% N (665 mg) of lidocaine will remain in a used patch. Mean N peak blood concentration of lidocaine is about 0.13 N µg/mL (about 1/10 of the therapeutic concentration N required to treat cardiac arrhythmias). Repeated N application of three patches simultaneously for 12 hours N (recommended maximum daily dose), once per day for N three days, indicated that the lidocaine concentration N does not increase with daily use. The mean plasma N pharmacokinetic profile for the 15 healthy volunteers is N shown in Figure 1. N **Figure 1 N** Mean lidocaine blood concentrations after three N

[4] Drugs@FDA, search: Lidoderm, accessed on 07/15/2016, label approved on 01/07/2015. N
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020612s012lbl.pdf N

	o le utive daily appli atio 1 of three 1 LIDODERM pat he imulta dou ly for 2 hour per 1 day i healthy volu teer (= 5). 1 
Food Effect 1	The RLD label doe ot me tio 1food effe t. 1
Tmax 1	hour 1
Metabolism 1	It i ot k dow 1if lido ai e i metabolized i the ki . 1 Lido ai e i metabolized rapidly by the liver to a 1 umber of metabolite , i 1ludi g 1 mo loethylgly i exylidide (MEGX) a d gly i exylidide 1 (GX), both of whi h have pharma ologi a tivity imilar 1 to, but le 1pote tl tha that of lido ai e. A mi or 1 metabolite, 2,6-xylidi e, ha u lk dow 1pharma ologi 1 a tivity but i ar i oge i i rat . The blood 1 o le tratio 1of thi metabolite i egligible followi g 1 appli atio 1of LIDODERM (lido ai e pat h 5%). 1 Followi g i trave dou admi i tratio ,1MEGX a d GX 1 o le tratio 1 i erum ra ge from 1 to 36% a d1 from 1 5 to 1% of lido ai e o le tratio 1, re pe tively. 1
Excretion 1	Lido ai e a d1 it metabolite are ex reted by the 1 kid dey . Le 1tha 0% of lido ai e i ex reted 1 u 1ha ged. The y temi leara le i 0.33 to 0.90 L/mi 1 (mea 0.64 ± 0. 8 SD, = 5). 1
Half-life 1	The half-life of lido ai e elimi atio 1from the pla ma 1 followi g IV admi i tratio 1i 8 1to 49 mi ute (mea 1 1 07 ± 22 SD, = 5). 1
Maximum Daily Dose 1	Three pat he imulta dou ly for 2 hour 1
Handling and Disposal 1	Ha d hould be wa hed after the ha dli g of 1 LIDODERM, a d eye o tha t with LIDODERM hould 1 be avoided. Do ot tore pat h out ide the ealed 1 e velope. Apply immediately after removal from the 1 prote tive e velope. Fold u ed pat he o that the 1 adhe ive ide ti k to it elf a d afely di 1ard u ed 1 pat he or pie e of ut pat he where hildre a d pet 1 a lot get to them. LIDODERM hould be kept out of 1 the rea h of hildre . 1

G D Recommendations for Drug Product p

Source of most recent recommendations or p rovide the embedded document to the p current draft guidance p	The guidance was revised per OGD Science Staff p Review (July 2014 version): p V:\Science Group\Master Files BE p Posting\Lidocaine_toppatch_20612\ p Lidocaine_toppatch_20612_RV06-14.pdf p The Guidance was revised under Project #661508, p Lidocaine topical patch, 5%, RLD 020612 BE Guidance p Finalization, BE Guidance Revision lidocaine patch p 20612.pdf, dated 12/8/2015 (Jan 2016 version). p http://panorama.fda.gov/project/view?ID=5p79b91e008 p 1e7894828f83417e7ece3 p The Guidance was further revised under Project p #9045599, Lidocaine Topical Patch RLD 020612 p Revised Draft BE Guidance, 9045599 p Lidocaine_patch_20612_BE Guidance revision.doc, p dated 8/21/2016 (Oct 2016 version). p http://panorama.fda.gov/task/view?ID=5783f99e001740 p f37f79c4582354f2df p  Lidocaine Patch p Guidance_OCT2016.pc (*Recommended Dec 2006; Revised May 2007. Jul 2014; Jan 2016, Oct 2016*) p p	
Summary of Dp or DB History p	Approved ANDAs: p	Yes, 2 approved ANDAs p A200675 (Actavis) p A202346 (Mylan) p
	Pending ANDAs: p	Yes, 6 pending ANDAs p [redacted] (b) (4) A206463 (Amneal) p A205882 (Kremers) p A203265 (Noven) p [redacted] (b) (4) A209190 (Rhodes)* p *current p
	Controls:[5]	Yes p
	Protocols:[6]	Yes p

[5] OGD Control Database and Mercado, search: lidocaine patch, accessed on 05/20/2017. p
[6] OGD-DB Protocols Tracking, search: lidocaine, accessed on 05/10/2017. p
http://fdswv04385/seltrack/Protocols.asp p

	Pe N g C t ze Pet t o s N a Nother legal a N N regulatory ssues:[7] If yes, please comme t. N	☐ Yes ☒N o N

. NP re-Study Bioanalytical Method Validation N

Bioanalytical Method Validation for Plasma N

Information Requested N	Data N
Bioanalytical method validation N report location N	B oa alyt cal Repor (b) (4) - LC/MS/MS A Nlys s for N the Determ i aNo of L Noca Ns Huma Plasma, Patch, a N N Cotto Swab Samples: "A Ra Nom ze , Ope -Label, Two- N Per o , Crossover, S Ngle Dose B oequ vale ce Stu y of N L Noca Ns 5% Top cal Patch a NL No erm® Healthy A Nlts N U Ner Faste Co Nt o s" For Faste PK Stu y Protocol o. RP-LID-PK001; locate N Mo ule 5, Sect o 5.3.1.4. N The f le ame s "rp-l -pk-001-stu y-report" N Val at o for eterm i aNo of l oca Ns plasma beg Ns o N page 1123 of 1260 N
Analyte N	L Noca Ns N
Internal standard (IS) N	L Noca Ns- 10 N
Method description N	(b) (4)
Limit of quantitation (ng/mL) N	
Average recovery of drug (%) N	LQC: 98.3% N MQC:100.0% HQC: 102.0% N Avg: 100.1% N
Average recovery of IS (%) N	(b) (4) gu Nsl es, f a stable sotope labele IS N was use , the recovery establ she for the u -labele a alyte w Nsuff ce a Nthe recovery for the stable sotope labele IS N w Not be requ re .[8] N
Standard curve concentrations N (ng/mL) N	0.2 - 150 g/mL N
QC concentrations (ng/mL) N	0.6 g/mL, 45 g/mL, a N112.5 g/mL N
QC Intra-run precision range (%CV)	Ru 1: 1.0 to 7.7 N NRu 2: 0.7 to 3.6 N Ru 3: 1.4 to 7.0 N
QC Intra-run accuracy range N (%Bias) N	Ru 1: 1.7 to 6.9 N Ru 2: -2.5 to 4.4 N

[7] Please check DLRS pol cy up ates the l k http://sharepo Nt.f a.gov/orgs/CDER- N OGD/OGDP/DLRS/S tePages/Home.aspx N

(b) (4)

ormatio -Requested -	Data -
	Run 3: 0.5 to 7.3 -
QC -ter-ru -precisio -ra ge (%CV)	1.2 to 6.4 -
QC -ter-ru -accuracy ra ge - (%Bias) -	0.5 to 6.2 -
Be eh-top stability (hours) -	At least 15.5 hours at room temperature -
Stock stability (hours/days) -	6 hours at room temperature and under white light for lidocaine - prepared in diluent (50:50 methanol/water) - 28 days at 4 °C for lidocaine prepared in diluent (50:50 - methanol/water)[9]
Processed stability (hours) -	98.5 hours at room temperature -
Freeze-thaw stability - (reeze-thaw cycles) -	3 freeze (20 ºC)/thaw cycles -
Lo g-term storage stability (days) -	214 days at 20 °C[2] -
Dilutio -i tegrity -	1125 ng/mL diluted 10 fold -
Selectivity -	The selectivity evaluation met the acceptance criteria: no - significant baseline interference (≥ 20% of the lower limit of - quantitation, LLOQ for lidocaine or ≥ 5% of the IS peak area of - the accepted calibration standards and QC samples for the IS) - was detected at the retention times of lidocaine or the IS in - blank human plasma. In addition, there was no interference - from the analyte detected at the retention time of the internal - standard. -
Sample volume -	50 µL -
Regressio -	L east squares linear regression -
Weighti g -	1/x*x concentration -
Li earity -	$R^2 \geq 0.9975$ -
Matrix E -ect -	IS normalized matrix factor = 1.02 ± 0.05 at 0.6 ng/mL with - %CV = 4.9% - IS normalized matrix factor = 0.97 ± 0.01 at 112.5 ng/mL with - %CV = 1.0% -
Hemolysis -	The hemolysis evaluation met the acceptance criteria. -
Rei jectio -reproducibility -	102.5 hours at room temperature -

Bioa alytical Method Validatio or Cotto Swab -

ormatio -Requested -	Data -
Bioa alytical method validatio - - report locatio -	Bioanalytical Repor - (b) (4) LC/MS/MS Analysis for - the Determination of Lidocaine in Human Plasma, Patch, and - Cotton Swab Samples: "A Randomized, Open Label, Two - Period, Crossover, Single Dose Bioequivalence Study of - Lidocaine 5% Topical Patch and Lidoderm® in Healthy Adults - Under Fasted Conditions" - For Fasted PK Study Protocol No. RP LID PK001; located in - Module 5, Section 5.3.1.4. - The filename is "rp lid pk 001 study report" - Validation for determination of lidocaine in cotton swab begins - on page 1221 of 1260 -
A alyte -	Lidocaine -
ter al sta dard (S) -	Lidocaine d_{10} -

(b) (4)

Information Requested	Data
Method description	(b) (4)
Limit of quantitation (µg)	2.00 µg
Average recovery of drug (%)	105.0% at 6.00 µg 97.5% at 750 µg
Average recovery of IS (%)	(b) (4) guidelines, if a stable isotope labeled IS was used, the recovery established for the un-labeled analyte will suffice and the recovery for the stable isotope labeled IS will not be required.[8]
Standard curve concentrations (µg)	2.00 -1000 µg*
QC concentrations (µg)	6.00 µg, 300 µg, and 750 µg*
QC Intra-run precision range (%CV)**	Run 1: 1.0 to 3.4
	Run 2: 0.3 to 2.2
	Run 3: 0.8 to 3.0
QC Intra-run accuracy range (%Bias)**	Run 1: -1.3 to 7.5
	Run 2: -1.0 to 8.5
	Run 3: -3.3 to 4.0
QC Inter-run precision range (%CV)**	1.3 to 3.8
QC Inter-run accuracy range (%Bias)**	-1.8 to 5.5
Bench-top stability (hours)	NA
Stock stability (hours/days)	6 hours at room temperature and under white light for lidocaine prepared in diluent (50:50 methanol/water) 28 days at 4 °C for lidocaine prepared in diluent (50:50 methanol/water)[10]
Processed stability (hours)	NA
Freeze-thaw stability (freeze-thaw cycles)	NA
Long-term storage stability (days)	Lidocaine cotton swab samples would have the same stability as lidocaine itself. This would be expected to be at least as long as the established 211 days of plasma stability for lidocaine
Dilution integrity	NA
Selectivity	NA
Sample volume	50 µL
Regression	Least squares linear regression
Weighting	$1/x^2$
Linearity	$R^2 \geq 0.9989$
Reinjection reproducibility	65.5 hours at room temperature

*Based on 4 mL of extraction solution (1% formic acid in methanol) and followed by 500-fold dilution with diluent (50:50 methanol/water).

(b) (4)

**The intra-run and inter-run accuracy and precision ranges include the results from LLOQ, Low, Mid, and High QC samples.
Note: Due to the nature of the matrix (cotton swab) evaluated for this method the parameters marked as NA (not applicable) were not required for this validation.

Bioanalytical Method Validation for Patch

Information Requested	Data
Bioanalytical method validation report location	Bioanalytical Repor (b) (4) LC/MS/MS Analysis for the Determination of Lidocaine in Human Plasma, Patch, and Cotton Swab Samples: "A Randomized, Open-Label, Two-Period, Crossover, Single Dose Bioequivalence Study of Lidocaine 5% Topical Patch and Lidoderm® in Healthy Adults Under Fasted Conditions" For Fasted PK Study Protocol No. RP-LID-PK001; located in Module 5, Section 5.3.1.4. The filename is "rp-lid-pk-001-study-report" Validation for determination of lidocaine in patch begins on page 1182 of 1260
Analyte	Lidocaine
Internal standard (IS)	Lidocaine-d_{10}
Method description	(b) (4)
Limit of quantitation (mg)	1.00 mg (20 ng/mL lidocaine in diluent)
Average recovery of drug (%)	108%
Average recovery of IS (%)	(b) (4) guidelines, if a stable isotope labeled IS was used, the recovery established for the un-labeled analyte will suffice and the recovery for the stable isotope labeled IS will not be required.[8]
Standard curve concentrations (mg)	1.00 – 10.0 mg*
QC concentrations (mg)	3.00 mg, 6.00 mg, and 8.00 mg*
QC Intra-run precision range (%CV)**	Run 1: 0.8 to 1.5
	Run 2: 0.6 to 1.4
	Run 3: 0.8 to 1.6
QC Intra-run accuracy range (%Bias)**	Run 1: 1.2 to 4.7
	Run 2: -0.2 to 4.0
	Run 3: -0.7 to 2.0
QC Inter-run precision range (%CV)**	1.4 to 2.6
QC Inter-run accuracy range (%Bias)**	0.7 to 3.0
Bench-top stability (hours)	NA

ormatio yRequested y	Data y
Stock stabilit (hours/da sy) y	6 hours at room temperature and under white light for lidocaine y prepared in diluent (50:50 methanol/water) y 28 days at 4 °C for lidocaine prepared in diluent (50:50 y methanol/water)[11] y
Processed stabilit (hours) y	NA y
Freeze-thaw stabilit y (reeze-thaw c gles) y	NA y
Lo g-term storage stabilit (da s) y	Lidocaine patch samples would have the same stability as y lidocaine itself. This would be expected to be at least as long as y the established 211 days of plasma stability for lidocaine y
Dilutio yi tegrit y	NA y
Selectivit y	NA y
Sample volume y	50 µL y
Regressio y	L east squares linear regression
Weighti g y	No weighting y
Li earit y	$R^2 \geq 0.9988$ y
Rei jectio yreproducibilit y	89 hours at room temperature y

*Based on 5 mL of extraction solution (1% formic acid in 50:50 dimethyl sulfoxide/methanol) and y followed by 1000-fold dilution with diluent (50:50 methanol/water). y

**The intra-run and inter-run accuracy and precision ranges include the results from LLOQ, Low, Mid, and y High QC samples. y

Note: Due to the nature of the matrix (patch) evaluated for this method the parameters marked as NA (not y applicable) were not required for this validation. y

SOP or bioa yl tical method validatio ysubmitted? y	☒ Yes y☐yNo y (b) (4) y General Guidelines for y the Validation of y Bioanalytical y Methods, Effective y date: 03/12/2012 y
s the same a yticoagula y used i the pre-method validatio ystud ya yl BE y sample a yl sis? y ot, was cross validatio ystud yco yducted? y	☒ Yes y☐yNo y K_2EDTA y
Does the duratio yo the each o the LTSS stabilit parameters support the sample preparatio yassa yduratio ya yl cli ical stud ysample storage y temperature? y	y ☒ Yes y☐yNo y
Was the % recover co yiste y across QC co ye yratio ys? y	☒ Yes y☐yNo y
Was the pre-stud yvalidatio yo the bioa yl tical method used or the y pivotal bioequivale ye studies acyeptable? y	☒ Yes y☐yNo y

Comme ts o the Pre-Stud Method Validatio : Adequate y

- The firm submitted the following acceptable addendum to the method validation y repo (b) (4)

(b) (4)

[redacted] (b) (4)
Validation Report Addendum No.1 or Method [redacted] (b) (4) Stock Solution A Storage Stability at 4°C and Long-term Sample Storage Stability Study at -20°C or A Lidocaine in Human Plasma by LC/MS/MS. A

- The irm did not provide the recovery or the Internal Standard (IS) Lidocaine-d_{10}. A Per the irm's [redacted] (b) (4), General Guidelines or the Validation o Bioanalytical A Methods, "*When a stable isotope labeled internal standard is used in an assay, the* A *recovery established for the unlabeled analyte will suffice. Recovery for stable* A *isotope labeled internal standards will not be required.*" Lidocaine-d_{10} is an isotope A labeled Lidocaine. Considering the recovery or the analyte lidocaine are very A consisten [redacted] (b) (4) across di erent QC concentrations, the recovery o the IS A (Lidocaine-d_{10}) is unlikely to impact the analytical results. A

3 q n Vivo Studies q

Summary of all in vivo Bioe uivalence Studies q

Study Ref No q	Study Objective q	Study Design	Treatments q (Dose, Dosage Form, Route) q [Product D] q	Subjects q (No (M/F) Type q Age: mean (Range) q	Mean Parameters (+/-SD) q						Study Report Location q
					C_{max} q (ng/mL) q Mean (SD) q	T_{max} q (hr) q Median q (Range)	$AUC_{0\text{-}last}$ q (ng*hr/mL) q Mean (SD) q	$AUC_{0\text{-}\infty}$ q (ng*hr/mL) Mean (SD) q	T1/2 q (hr) q Mean q (SD)	Kel q (hr^{-1}) q Mean q (SD) q	
Study RP-q LID-q PK-001	To assess the bioequivalence o a test ormulation o lidocaine patch 5% versus Lidoderm® q	Randomized, Open-Label, Single-Dose, Two-Period Crossover Study q	Test product q Strength: 3 x700 mg lidocaine q patch 5% q [Lot #L1304191] q	48(25M/23 F) q healthy q subjects q Age: mean (SD): q 32.0(9.22); range: 18-45 q	71.68 (23.89)	12.00 (9 -21)	1268 (391.3)	1292 (392.2)	5.712 (1.193)	0.1271 (0.0298)	Clinical Study Report located in Module 5, Section 5.3.1.4. The ilename is “rp-lid-pk001-report-body”
			Re . product q Lidoderm® q Strength: 3 x 700 mg lidocaine q patch 5% q [Lot # Y2282] q		76.19 (27.93)	12 (6 -21)	1330 (403.0)	1379 (385.6)	5.970 (1.370)	0.1221 (0.0282)	

m a ry of Adhesion and Irritation Ass gess eg nt of the Lidocaine Patch in the g Fastin BE t dy g

Ac gording to the irm's BE study report No. RP-LID-PK01, patch adhesion was g assessed 6 hours a ter application and within 30 min prior to patch removal using a visual g scale (0-4). Evaluation o dermal reactions at the application sites was clinically assessed g in a blinded ashion 30 minutes and 12 hours a ter patch removal using a visual irritation g scale (0-7) that rated the degree o erythema, edema, and other signs o cutaneous g irritation. The irm conducted statistical analysis o the cumulative adhesion index and g di erences in the cumulative adhesion index or Test vs. Re erence ormulations or g sa ety population and the results are presented in the table below. The irm concluded g that the test patch adheres better than the re erence patch based upon the analysis. g

	Mean (SD)		Least Square Means		Mean Test - Reference	90% Confidence Interval (T/R)
Patch Removal	**Test**	**Reference**	**Test**	**Reference**		
6 hours after application	0.333 (0.4673)	0.805 (0.9048)	0.333	0.805	-0.472	(-0.686, -0.258)
Within 30 minutes prior to patch removal	0.722 (0.8847)	1.514 (1.2922)	0.722	1.514	-0.792	(-1.066, -0.518)
Combined	0.528 (0.6563)	1.160 (1.0539)	0.528	1.160	-0.632	(-0.862, -0.402)

Data Source: Table 14.5.3 and Table 14.5.4

Table 14.3.3
Cumulative Skin Irritation Index by Treatment
Safety Population

		Treatment	
Parameter	Statistics	Lidocaine 5% topical patch 2100 mg (N = 48)	Lidoderm 2100 mg (N = 48)
Cumulative Skin Irritation Index	n	48	48
	Mean (SD)	0.19 (0.303)	0.19 (0.265)
	Median	0	0
	Min, Max	0, 1.0	0, 1.0

Note: The individual cumulative irritation index (CII) will be calculated as the sum of all dermal response scores for a treatment divided by the number of scores collected for that treatment.

There was assessment or local irritation 30 minutes and 12 hours a ter patch removal g (individual data presented in Module 5.3.1.2. Listing Individual Laboratory g Measurements by Patients). The reviewer veri ied rom the irritation data that no g incidence o severe irritation was observed and no patches were removed during the g study due to any irritation reactions. g

The irm conducted a separate study (No. RP-LID-SSI) to assess the skin g irritation/sensitization/adhesion, and the data rom the study will be reviewed by the g DCR. g

ary of Resid al Patch Analysis for Apparent Dose Delivered in the BE t dy g

Per the Product-Speci ic Guidance or Lidocaine Patch,[1] "*In addition to pharmacokinetic* g *data, please report the "apparent dose" delivered. The apparent dose can be determined* g *by subtracting the remaining amount of lidocaine in each patch (used patch) from the* g *manufactured amount. Analyze and include in the calculation the amount of adhesive* g *residue from each patch left on the skin.*" g

In accordance with the Product-Specific Guidance for Lidocaine Patch, the apparent dose of lidocaine delivered was assessed by measurement of residual drug remaining on the used patches and from a swab of the area where the patches were applied. The individual and mean apparent dose of lidocaine in the study calculated by the firm is shown in the tables below.

Tables for Individual Residual Content and Apparent Dose (Submitted by the firm)

Subject Number	Session	Treatment	Dosing Date	Dosing Time	Lidocaine in Adhesive Residue Swab (mg)	Lidocaine in Used Patches (mg)	Apparent Dose (mg)
(b) (6)	1	R	(b) (6)	8:00	0.624	1889	210.376
	2	T		8:00	1.51	1963	135.49
	1	R		8:02	0.542	1966	133.458
	2	T		8:02	0.724	1986	113.276
	1	T		8:04	0.388	2016	83.612
	2	R		8:04	0.892	1950	149.108
	1	T		8:06	0.0937	1961	138.9063
	2	R		8:06	0.666	1884	215.334
	1	R		8:08	2.35	1786	311.65
	2	T		8:08	2.5	1888	209.5
	1	T		8:10	0.96	1975	124.04*
	2	R		8:10	0.416	1973	126.584
	1	T		8:12	1.35	2010	88.65
	2	R		8:12	0.781	1865	234.219
	1	R		8:14	1.69	2041	57.31
	2	T		8:14	1.76	2032	66.24

Note: T = Test Formulation: The test lidocaine 5% topical patches distributed by Rhodes Pharmaceuticals L.P., 2100 mg.
R = Reference Formulation: Lidoderm (lidocaine patch 5%, manufactured by Endo Pharmaceuticals, Inc.), 2100 mg.
* Samples collected for subjects with patch(es) attached for < 11.0 hours will be marked as such.

Subject Number	Session	Treatment	Dosing Date	Dosing Time	Lidocaine in Adhesive Residue Swab (mg)	Lidocaine in Used Patches (mg)	Apparent Dose (mg)
(b) (6)	1	T	(b) (6)	8:16	1.55	2035	63.45
	2	R		8:16	1.43	2007	91.57
	1	T		8:18	0.167	2049	50.833
	2	R		8:18	1.62	1825	273.38
	1	R		8:20	0.444	1899	200.556*
	2	T		8:20	1.42	1914	184.58
	1	R		8:22	0.141	2050	49.859
	2	T		8:22	0.218	2026	73.782
	1	T		8:24	1.49	1728	370.51
	2	R		8:24	3.85	1869	227.15
	1	T		8:26	0.409	1896	203.591
	2	R		8:26	1.46	1794	304.54
	1	R		8:28	0.853	1794	305.147
	2	T		8:28	0.727	1708	391.273
	1	R		8:30	0.923	1699	400.077
	2	T		8:30	0.28	1723	376.72

Note: T = Test Formulation: The test lidocaine 5% topical patches distributed by Rhodes Pharmaceuticals L.P., 2100 mg.
R = Reference Formulation: Lidoderm (lidocaine patch 5%, manufactured by Endo Pharmaceuticals, Inc.), 2100 mg.
* Samples collected for subjects with patch(es) attached for < 11.0 hours will be marked as such.

Subject Number	Session	Treatment	Dosing Date	Dosing Time	Lidocaine in Adhesive Residue Swab (mg)	Lidocaine in Used Patches (mg)	Apparent Dose (mg)
(b) (6)	1	T	(b) (6)	8:32	0.847	1907	192.153
	2	R		8:32	1.98	1854	244.02
	1	R		8:34	2.38	1682	415.62
	2	T		8:34	0.677	1756	343.323
	1	T		8:36	0.919	1876	223.081
	2	R		8:36	1.57	1696	402.43
	1	R		8:38	0.736	1713	386.264
	2	T		8:38	0.325	1699	400.675
	1	R		8:40	0.829	1796	303.171
	2	T		8:40	0.907	1817	282.093
	1	R		8:42	0.194	1841	258.806
	2	T		8:42	0.886	1916	183.114
	1	T		8:44	1.97	1863	235.03
	2	R		8:44	2.02	1865	232.98
	1	T		8:46	0.593	1892	207.407
	2	R		8:46	1.77	1786	312.23

Note: T = Test Formulation: The test lidocaine 5% topical patches distributed by Rhodes Pharmaceuticals L.P., 2100 mg.
R = Reference Formulation: Lidoderm (lidocaine patch 5%, manufactured by Endo Pharmaceuticals, Inc.), 2100 mg.
* Samples collected for subjects with patch(es) attached for < 11.0 hours will be marked as such.

Subject Number	Session	Treatment	Dosing Date	Dosing Time	Lidocaine in Adhesive Residue Swab (mg)	Lidocaine in Used Patches (mg)	Apparent Dose (mg)
(b) (6)	1	R	(b) (6)	8:48	2.21	1835	262.79
	2	T		8:48	1.57	1832	266.43
	1	T		8:50	0.0991	1903	196.9009
	2	R		8:50	0.163	1862	237.837
	1	R		8:52	1.62	1916	182.38
	2	T		8:52	1.42	1954	144.58
	1	T		8:54	0.561	1879	220.439
	2	R		8:54	0.45	1835	264.55
	1	R		8:56	3.52	1907	189.48
	2	T		8:56	2.01	1933	164.99
	1	R		8:58	0.866	1881	218.134
	2	T		8:58	2.08	1868	229.92
	1	T		9:00	0.537	1854	245.463
	2	R		9:00	0.287	1850	249.713*
	1	T		9:02	3.12	1952	144.88*
	2	R		9:02	0.417	1938	161.583*

Note: T = Test Formulation: The test lidocaine 5% topical patches distributed by Rhodes Pharmaceuticals L.P., 2100 mg.
R = Reference Formulation: Lidoderm (lidocaine patch 5%, manufactured by Endo Pharmaceuticals, Inc.), 2100 mg.
* Samples collected for subjects with patch(es) attached for < 11.0 hours will be marked as such.

Subject Number	Session	Treatment	Dosing Date	Dosing Time	Lidocaine in Adhesive Residue Swab (mg)	Lidocaine in Used Patches (mg)	Apparent Dose (mg)
(b) (6)	1	T	(b) (6)	9:36	0.786	1906	193.214
	2	R		9:36	3.35	1857	239.65
	1	T		9:06	1.52	1947	151.48
	2	R		9:06	0.505	1936	163.495*
	1	R		9:08	2.27	1991	106.73*
	2	T		9:08	1.52	1968	130.48
	1	R		9:10	2.02	1852	245.98
	2	T		9:10	0.895	1900	199.105
	1	T		9:12	2.82	1800	297.18
	2	R		9:12	0.183	1851	248.817*
	1	R		9:14	1.54	1900	198.46*
	2	T		9:14	0.594	1866	233.406
	1	T		9:16	0.73	1871	228.27
	2	R		9:16	1.5	1851	247.5
	1	R		9:18	0.143	1909	190.857*
	2	T		9:18	1.31	1857	241.69

Note: T = Test Formulation: The test lidocaine 5% topical patches distributed by Rhodes Pharmaceuticals L.P., 2100 mg.
R = Reference Formulation: Lidoderm (lidocaine patch 5%, manufactured by Endo Pharmaceuticals, Inc.), 2100 mg.
* Samples collected for subjects with patch(es) attached for < 11.0 hours will be marked as such.

Subject Number	Session	Treatment	Dosing Date	Dosing Time	Lidocaine in Adhesive Residue Swab (mg)	Lidocaine in Used Patches (mg)	Apparent Dose (mg)
(b) (6)	1	T	(b) (6)	9:20	1.73	1867	231.27
	2	R		9:20	1.54	1884	214.46
	1	T		9:22	0.351	1862	237.649
	2	R		9:22	0.616	1901	198.384
	1	R		9:24	1.23	1933	165.77
	2	T		9:24	0.4	1942	157.6
	1	R		9:26	1.4	1897	201.6
	2	T		9:26	0.29	1872	227.71
	1	T		9:28	3.64	1856	240.36
	2	R		9:28	3.79	1856	240.21
	1	R		9:30	2.55	1831	266.45
	2	T		9:30	0.707	1855	244.293
	1	T		9:38	0.924	2083	16.076
	2	R		9:38	0.72	1869	230.28
	1	R		9:34	1.45	1861	237.55
	2	T		9:34	0.487	1833	266.513

Note: T = Test Formulation: The test lidocaine 5% topical patches distributed by Rhodes Pharmaceuticals L.P., 2100 mg.
R = Reference Formulation: Lidoderm (lidocaine patch 5%, manufactured by Endo Pharmaceuticals, Inc.), 2100 mg.
* Samples collected for subjects with patch(es) attached for < 11.0 hours will be marked as such.

Apparent Dose by Treatment – Safety Population (n=48) – Firm Submitted

		Treatment	
		Test	Reference
Apparent Dose (mg)	Mean (SD)	201.1 (88.85)	229.3 (80.18)

Apparent Dose– Safety Population (n=48) – Reviewer Calculated

The reviewer conducted calculation of the individual subjects' and mean apparent dose in Excel by subtracting the dose amount (3×700 mg=2100 mg) with residual drug remaining on the used patches and from a swab of the area where the patches were applied. The results are shown in the following table.

subject#	Test			Reference		
	Swab (mg)	Patch (mg)	Apparent Does (mg)	Swab (mg)	Patch (mg)	Apparent Does (mg)
(b) (6)	1.51	1963	135.49	0.624	1889	210.376
	0.724	1986	113.276	0.542	1966	133.458
	0.388	2016	83.612	0.892	1950	149.108
	0.0937	1961	138.9063	0.666	1884	215.334
	2.5	1888	209.5	2.35	1786	311.65
	0.96	1975	124.04	0.416	1973	126.584
	1.35	2010	88.65	0.781	1865	234.219
	1.76	2032	66.24	1.69	2041	57.31
	1.55	2035	63.45	1.43	2007	91.57
	0.167	2049	50.833	1.62	1825	273.38
	1.42	1914	184.58	0.444	1899	200.556
	0.218	2026	73.782	0.141	2050	49.859
	1.49	1728	370.51	3.85	1869	227.15

(b) (4)						
	0. 09 1 S	896 S	203.59 S	. 6 1 S	79 S	3 0 S S
	0.727 1 S	708 S	39 S273 S	0.853 1 S	79 S	3 05. S7 S
	0.28 1 S	723 S	376.72 S	0.923 1 S	699 4 S	00.077 S
	0.8 S 1 S	907 1 S	92. 53 1 S	.98 1 S	85 S	2 S .02 S
	0.677 1 S	756 S	3 S.323 S	2.38 1 S	682 4 S	5.62 S
	0.9 S 1 S	876 S	223.08 S	.57 1 S	696 4 S	02. 3 S
	0.325 1 S	699 4 S	00.675 S	0.736 1 S	7 S S	386.26 S
	0.907 1 S	8 S S	282.093 S	0.829 1 S	796 S	303. 7 S
	0.886 1 S	9 S 1 S	83. S	0 . 9 S	8 S	2 58.806 S
	.97 1 S	863 S	235.03 S	2.02 1 S	865 S	232.98 S
	0.593 1 S	892 S	207. 07 1 S	.77 1 S	786 S	3 S.23 S
	.57 1 S	832 S	266. 3 S	2.2 S	835 S	262.79 S
	0.099 S	903 1 S	96.9009 S	0. 63 1 S	862 S	237.837 S
	. 2 1 S	95 S	.58 1 S	.62 1 S	9 S 1 S	82.38 S
	0.56 S	879 S	220. 39 S	0. 5 1 S	835 S	26 S5 S
	2.0 S	933 1 S	6 S99 S	3.52 1 S	907 1 S	89. 8 S
	2.08 1 S	868 S	229.92 S	0.866 1 S	88 S	2 S8. 3 S
	0.537 1 S	85 S	2 S5. 63 S	0.287 1 S	850 S	2 S.7 S S
	3. 2 1 S	952 1 S	.88 S	0. S7 1 S	938 1 S	6 S583 S
	0.786 1 S	906 1 S	93.2 S	3 .35 1 S	857 S	239.65 S
	.52 1 S	9 S 1 S	5 S8 S	0.505 1 S	936 1 S	63. 95 S
	.52 1 S	968 1 S	30. 8 S	2.27 1 S	99 S	06.73 S
	0.895 1 S	900 1 S	99. 05 S	2.02 1 S	852 S	2 S.98 S
	2.82 1 S	800 S	297. 8 S	0. 83 1 S	85 S	2 S8.8 S S
	0.59 S	866 S	233. 06 1 S	.5 S	900 1 S	98. 6 S
	0.73 1 S	87 S	2 28.27 1 S	.5 1 S	85 S	2 S7.5 S
	.3 S	857 S	2 S.69 S	0. S 1 S	909 1 S	90.857 S
	.73 1 S	867 S	23 S27 1 S	.5 S	88 S	2 S . 6 S
	0.35 S	862 S	237.6 S S	0.6 S 1 S	90 S	98.38 S
	0. S	9 S 1 S	57.6 1 S	.23 1 S	933 1 S	65.77 S
	0.29 1 S	872 S	227.7 S	. S	897 S	20 S6 S
	3.6 S	856 S	2 S.36 S	3.79 1 S	856 S	2 S.2 S
	0.707 1 S	855 S	2 S.293 S	2.55 1 S	83 S	2 66. 5 S
	0.92 S	2 083 1 S	6.076 S	0.72 1 S	869 S	230.28 S
	0. 87 1 S	833 S	266.5 S 1 S	. 5 1 S	86 S	2 37.55 S
Mean S	**201.07 S**			**229. S**		
TD S	**88.85 S**			**80.18 S**		
CV 4 S	**.19 3 S**			**.96 S**		
T-test S	**0.052511997 S**					

The apparent dose values calculated by the reviewer are in agreement with the values S submitted by the irm. The apparent dose o the test product is comparable to that o the S re erence product. S

3.6 OSIS Status

The Office of Study Integrity and Surveillance (OSIS) recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (**NAI**). Therefore, the Division of Generic Drug Bioequivalence Evaluation (DGDBE) within OSIS recommends accepting data without an on-site inspection.

Facility Type	Facility Name	Facility Address
Clinical	Frontage Laboratories	241 Main St., Hackensack, NJ
Analytical		(b) (4)

4 APPENDIX 0

4.1 Individual Study Reviews 0

4.1.1 0Single-dose Fasting Bioequivalence Study 0

4.1.1.1 Study Design

4.1.1.1.1 0 Study Information

Study Number 0	**RP-LID-PK 0 1**
Study Title 0	A Ra dom zed, Ope -Labe , Two-Per od, Crossover, 0 e Dose 0 B oequ va e ce tudy of L doca 0e patch 5% a d L doderm® 0 Hea thy Adu ts u der Fasted Co d t o s 0
Study Type 0	☒I V vo BE 0 ☐I V tro BE 0 ☐Permeab 0ty 0☐Other
Submission Location: 0 Study Report 0	tudy report c uded f e "rp- d-pk001-report-body" ocated 0 Modu e 5, ect o 5.3.1.2. 0
Validation Report 0	ee B oa a yt ca Repor [redacted] (b) (4) - LC/MS/MS A 0a ys s for the Determ i a0o of L doca 0e Huma P asma, Patch, a d Cotto 0 wab amp es: "A Ra dom zed, Ope -Labe , Two-Per od, 0 Crossover, 0 e Dose B oequ va e ce tudy of L doca 0e 5% 0 Top ca Patch a d L doderm® Hea thy Adu ts U 0der Fasted 0 Co d t o s" 0 Va dat o Report be 0 s o pa e 1123 as Report FRO-R2449R1 0 For Fasted PK tudy Protoco No. RP-LID-PK001; ocated Modu e 0 5, ect o 5.3.1.4. 0 The f e ame s "rp- d-pk-001-study-report" 0
Bioanalytical Report 0	B oa a yt ca Repor [redacted] (b) (4) - LC/MS/MS A 0a ys s for the 0 Determ i a0o of L 0doca 0e 0Huma P asma, Patch, a d Cotto 0 wab amp es: "A Ra dom zed, Ope -Labe , Two-Per od, 0 Crossover, 0 e Dose B oequ va e ce tudy of L doca 0e 5% 0 Top ca Patch a d L doderm® Hea thy Adu ts U 0der Fasted 0 Co d t o s" 0 For Fasted PK tudy Protoco No. RP-LID-PK001; ocated Modu e 0 5, ect o 5.3.1.4. 0 The f e ame s "rp- d-pk-001-study-report" 0
Clinical Site 0 (Name, Address, Phone #, 0 Fax #) 0	Fro ta e C 0 ca erv ces 0 Fro ta e Laborator es, I c 0 241 Ma 0 treet 0 Hacke sack, New Jersey 07601 0 U A 0 Te : 201-678-0288 0 Fax: 201-342-3413 0
Principal Clinical Investigator 0 (Name, Email) 0	Dav d Re 0er, MD 0 E-ma : dre 0er@fro ta e ab.com 0
Dosing Dates 0	04- EP-2013 0 11- EP-2013 0
Analytical Site 0 (Name, Address, Phone #, 0 Fax #) 0	[redacted] (b) (4)

	(b) (4)
Analysis Dates	P asma a a ys s date: 19- EP-2013, 20- EP-2013, 23- EP-2013, 1 24- EP-2013, 25- EP-2013, 26- EP-2013* a d 1 27- EP-2013 1 wab a a ys s date: 103-OCT-2013 a d 05-OCT-2013 1 Patch a a ys s date: 104-OCT-2013, 07-OCT-2013, a d 108-OCT- 1 2013 1
Principal Analytical 1 Investigator 1 (Name, Email) 1	(b) (4)
Sample Storage : 1 **(a) Duration (no. of days from 1 the first day of sample 1 collection to the last day of 1 sample analysis) 1**	Durat o 1 1 P asma: 23 days from the f rst samp e co ected o 104- EP-2013 to 1 the ast samp e a a yzed o 127- EP-2013 1 Cotto 1 wab: 31 days from the f rst samp e co ected o 104- EP- 1 2013 to the ast samp e a a yzed o 105-OCT-2013. 1 Patch: 34 days from the f rst samp e co ected o 104 ep13 to the ast 1 samp e a a yzed o 108-OCT-2013. 1
Sample Storage : 1 **(b) Temperature Range (e.g., 1 -20° C to -80° C) 1**	Temperature Ra 1e: 1 -20 °C for p asma samp es 1 -20 °C for cotto 1swab samp es 1 Rob m temperature for patch samp es 1
Long-Term Storage Stability 1 Coverage (no. days @ temp °C) 1	211 days at -20 °C for doca 1e 1huma p asma 1
LTSS Data Location 1	Lo 1-term amp e tab 1ty s summar zed 1Modu e 5, ect o 1 1 5.3.1.4 1the fo ow 1 report: B oa a yt ca Report 1 (b) (4) 1 LC/MS/MS A 1a ys s for the Determ i a 1o 1of L doca 1e 1Huma 1 1 P asma, Patch, a d Cotto 1 wab amp es: "A Ra dom zed, Ope - 1 Labe , Two-Per od, Crossover, 1 e Dose B oequ va e de tudy of 1 L doca 1e 5% Top ca Patch a d L doderm® 1Hea thy Adu ts U 1der 1 Fasted Co d t o s" 1 The f e a me s "rp- d-pk-001-study-report" 1 Lo 1 term stab 1ty data are reported 1the ame 1me 1 c uded for 1 th s report wh ch s t t e 1 (b) (4) Va dat o 1Report 1 Adde dum No.1 for Metho 1 (b) (4) wh ch be 1s o 1pa e 1 1173 of 1260 of the B oa a yt ca Report. LT 1 Data are ocated o 1 1 pa e 1178 of 1260 1Tab e 2. 1

* I curred samp e reproduc b 1ty (I R) was performed o 26- EP-2013 1

4.1.1.1.2 f Product (Bio-batch) Information f

Product f	Test f	Reference f
Treatment ID f	N/A f	N/A f
Product Name f	L doca fe Patch 5% f	L doderm® f
Manufacturer f	Rhodes Pharmaceut ca s L.P., ma u actured by A ter o , f Ita a f	f E do Pharmaceut ca s, I c. by (b) (4)
Batch/Lot No. f	Lot umber: L1304191 f	Lot umber: Y2282 f
Manufacture Date f	Apr 2013 f	N/A f
Expiration Date f	N/A f	October 2015 f
Strength f	5% f	5% f
Dosage Form f	Top ca patch f	Top ca patch f
Bio-batch Size f	(b) (4)	N/A f
Production Batch Siz f		N/A f
Potency f		(b) (4)
Content Uniformity (mean, %CV f		N/A f
Dose Administered f	Dose was three patch f s mu ta eous y f 3 × 700 m g f	Dose was three patch f s mu ta eous y f 3 × 700 m g f
Route of Administration f	Top ca f	Top ca f

Are the test and reference products expired at the time of study? f **If Yes, please comment** f	f ☐ Yes f☒f No f
Is same bio-batch used in the dissolution and all BE studies? f **If No, please comment** f	☒ Yes f☐f No f
Is the bio-batch size at least the recommended minimum of 100K or 10% of the production batch (whichever is greater) for oral solid dosage form? f **If No, please comment** f	☒ Yes f☐f No f
Is difference of the potency values for the Test and RLD within 5%? f **If No, please comment** f	☒ Yes f☐f No f

4.1.1.1.3 f Study Design, Single-Dose Fasting Bioequivalence Study f

Number of Subjects f	E fo ed: 48 f Dosed: 48 f Comp eted: 48 f amp es A fa yzed: 48 f tat st ca y A fa yzed: 39* f
No. of Sequences f	2 f

No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization	☒ Yes ☐No
Blood Sampling Times	T me 0 (w h 390 m i ues pre-app at o a d 1, 1.5, 2, 3, 6, 9, 12, 15, 18, 21, 24 a d 48 hours after patch app at o To determ i e the appare dose de ered, a swab of patch adhes ve was co cted after patch remova . The swab a d the used patches were a a yzed for doca e co e at o .
IRB Approval	☒ Yes Date: 08/16/2013 ☐No
Informed Consent	☒ Yes Date: 08/16/2013 ☐No
Length of Fasting	Over ht fast of at east 10 hours
Length of Confinement	At east 10 hours before dos up to 24 hours post-dose b ood co ct o
Was the drug product administered per labeling for specialized dosage forms e.g. ODT)?	☒ Yes ☐No ☐N/A A subjects rece ved the r ass ed treatme t as three top ca patches app d s mu ta ous y (2100 m g) to the rascapu ar area of the back o e ther s de of the sp e, w hout occ us o w h approx mate y 2.5 cm betwe e each patch for a tota of 12 hours. Patches were app d by qua ed study s te perso e .
Safety Monitoring	☒ Yes ☐No

***Reviewer's Note**: Per the f rm's protoco No. RP-LID-PK01, the PK Popu at o shou d co s st of those subjects who comp eted both treatme ts w thout a y major protoco v o at o s, who prov ded p asma doca e co ce trat o data suff c e t to est mate PK parameters a d had a 3 patches attached for ≥ 11 hours dur each per od. The rev ewer co f rmed that e (9) subjects (ubject (b) (6)) had patch(es) that detached ess tha 11 hours fo ow app cat o (modu e 5.3.1.2. L st I d v dua Laboratory Measureme ts by Pat e t, L st 16.2.8.3). These subjects were exc uded from the PK popu at o . Th rty- e (81.3%) subjects were c uded the stat st ca a a ys s.

Comments on Study Design: Adequate

.1.1.2 Clinical Results

.1.1.2.1 4 Demographic Profile of Subjects

		Study No. RP-LID-PK001 4	
		Treatment Groups	
		Test Product 4 N = 8 4	Reference Product 4 N = 8 4
A 4e 4 (years) 4	Mea (D) 4	32.0 (9.22) 4	32.0 (9.22) 4
	Ra 4e 4	18-45 4	18-45 4
A 4e 4 Groups 4 N (%) 4	< 18 4	0 4	0 4
	18 – 40 4	35 (72.9) 4	35 (72.9) 4
	40 – 64 4	13 (27.1) 4	13 (27.1) 4
	65 – 75 4	0 4	0 4
	> 75 4	0 4	0 4
ex 4 N (%) 4	Ma e 4	25 (52.1) 4	25 (52.1) 4
	Fema e 4	23 (47.9) 4	23 (47.9) 4
Race 4 N (%) 4	Wh te 4	29 (60.4) 4	29 (60.4) 4
	B ack 4	19 (39.6) 4	19 (39.6) 4
BMI 4	Mea (D) 4	25.32 (3.066) 4	25.32 (3.066) 4
	Ra 4e 4	18.1-29.9 4	18.1-29.9 4

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment. 4	4 4☒ Yes 0☐ No 0

4. . . . 0 p ut Inf 0mati n 0

Study N 0 RP-LI 0PK 0				
Subject N 0	**Reas n f 0d 0p 0t/ eplacement* 0**	**Pe i d 0**	**Replaced? 0**	**Replaced with 0**
NA 0	NA 0	NA 0	NA 0	NA 0

A e d 0p 0ts app 0p iate? If n 0please c mment. 0	☒ Yes 0☐ No 0

4. . . .3 0 Study Adve se Events 0

	Rep 0ted Incidence by T 0eatment G r u0ps 0	
	Fasted Bi equivalence Study 0 Study N 0 RP-LI 0PK 0	
B 0dy System 0 0 Adve se Event 0	**Test 0 N=48 0 N (%) 0**	**Refe ence 0 N=48 0 N (%) 0**

Gastrointestinal disorders	**2 (4.2)**	**0**
Nausea	1 (2.1)	0
Vom i	1 (2.1)	0
Nervous system disorders	**2 (4.2)**	**0**
D z z ss	1 (2.1)	0
Headache	1 (2.1)	0
Total	**2 (4.2)**	**0**

Subjects Experiencing Emesis

Subject Number	Test/ Reference	Period	Time and Date of dosing	Time and Date of emesis	Duration Between Dosing and Start of Emesis (hours)
(b) (6)	T		(b) (6)		9.13

Were subjects who experienced vomiting included in statistical analysis?	☒ Yes ☐No ☐N/A
If yes, does the time of emesis exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products)? Please comment.	☐ Yes ☒No ☐N/A ce L doca z Patch s a top ca product, the AE (vom i) s ot ke y to have a y mpact o the overa study outcome.
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐No The AEs exper e ced for the test product (ausea, d z z ss, headache, vom i) were sted the Adverse React o sect o of the RLD abe .[4]
Are there any serious adverse events or death?	☐ Yes ☒No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐No ☒N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒No

4.1.1.2.4 Protocol Deviations

Study No. RP-LID-PK001		
Type	**Subject Number (Test)**	**Subject Number (Ref.)**
Per od 1, Day 1, 3 hour post-app at o PK samp e was co cted 3 m i ues out of the w dow	(b) (6)	
Per od 2, Day 10, 48 hour post-app at o PK samp e co ct o was ot do e		(b) (6)
Per od 1, Day 3, 48 hour post-app at o PK samp e was		

collected 36 minutes out of the window		
Period 2, Day 9, 18 hour post-application PK sample was collected 3 minutes out of the window	(b) (6)	

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time	☒ Actual ☐ Nominal

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Concomitant Medications:

Subject Number	First Dose Date	Any Con Med	ATC Class/ Reported Term	Indication	Dose	Unit	Freq[1]	ROA[2]	Start Date/ End Date	Continuing?
(b) (6)		Yes	Vitamin B-complex, incl. combinations/ Vitamin B	Dietary supplement	500	MCG	QD	Oral	(b) (6)	No
		Yes	Hormonal contraceptives for systemic use/ Mirena	Contraception	1	IUD	Every 5 years	Intrauterine		Yes
		Yes	Other nutrients/ Nutrament	Dietary supplement	355	ML	OTO	Oral		No

Comments on Clinical Results: Adequate

- Sampling time deviations were recorded during both periods of this study. These deviations were deemed to have no effect on the results of the study as all calculations were performed using the actual time points.
- Concomitant medications given during the study were confirmed to have no interaction with lidocaine per the RLD label.
- Protocol deviations and adverse events did not have impact on the study outcome.

4.1.1.3 Bioanalytical Results

4.1.1.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Management and Use of Reference Standards for Bioanalytical Lab
		Tracking Procedure and Documentation for Biological Samples Received at Frontage Laboratories, Inc
		Handling Biological Samples Which May Contain Infectious Agents
		Evaluation of Incurred Sample Reproducibility (ISR)
		General Guidelines for the Validation of Bioanalytical Methods

(b) (4)	
	Cr ter a for Accept 7 Data From a B oa a yt ca Ru 7
	Repeat Assay a d Report 7 Cr ter a for B oa a yt ca 7 amp es 7
	amp e A 7a ys s 7
	Rou d 7 , Ca cu at o a d Report 7 of B oa a yt ca Data 7
	Use of the c ex A 7a yst Mass pectrometry oftware 7
	Use of the Watso LIMS 7ystem at Fro ta e Laborator es, 7 I c. 7

All necessary SOPs submitted? 7	☒ Yes 7☐7No 7

4.1.1.3.2 7 Sample Analysis Calibration and Quality Control 7

Summary of Standard Curve and QC Data for Plasma Sample 7

Bioequivalence Study No. RP-LID-PK001 7 Lidocaine 7							
Parameter 7	**Standard Curve Samples 7**						
Co ce trat o (7/mL) 7	0.200 7	0.400 7	1.00 7	5.00 7	30.0 7	60.0 7	120 7
I ter day Prec s o (%CV) 7	2.9 7	5.3 7	4.6 7	1.9 7	1.3 7	1.1 7	2.0 7
I ter day Ac7uracy (%Actua) 7	99.5	99.7 7	102.0 7	106.4 7	98.0 7	98.0 7	98.3 7
L 7ear ty (Ra 7e of r^2 va ues) 7	0.9949 – 0.9992 7						
L 7ear ty Ra 7e (7/mL) 7	0.200 – 150 7						
e s t v ty/LOQ (7/mL) 7	0.200 7						

Bioequivalence Study No. RP-LID-PK001 7 Lidocaine 7				
Parameter 7	**Quality Control Samples 7**			
Co ce trat o (7/mL) 7	0.600 7	45.0 7	113 7	1130 7
I ter day Prec s o (%CV) 7	8.9 7	3.3 7	3.5	NA* 7
I ter day Ac7uracy (%Actua) 7	97.5	98.2 7	94.7 7	90.3 7

*Not app cab e, =2 for D 7ut o QC samp es 7

Summary of Standard Curve and QC Data for Cotton Swab Sample 7

Bioequivalence Protocol No. RP-LID-PK001 7 Lidocaine 7								
Parameter 7	**Standard Curve Samples 7**							
Co ce trat o (µ 7 7	2.00 7	4.00 7	8.00 7	40.0 7	200 7	400 7	800 7	1000 7
I ter day Prec s o (%CV) 7	4.4 7	9.5	3.1 7	2.0 7	2.0 7	0.7 7	1.2 7	1.1 7
I ter day Ac7uracy (%Actua) 7	96.5	103.8	105.4	105.5	103.5	100.3	94.9 7	90.5
L 7ear ty (Ra 7e of r^2 va ues) 7	0.9949 – 0.9949 7							
L 7ear ty Ra 7e (µ 7 7	2.00 – 1000 7							
e s t v ty/ LOQ (µ 7 7	2.00 7							

Bioequivalence Protocol No. RP-LID-PK001 Lidocaine			
Parameter	**Quality Control Samples**		
Co ce trat o (µ	6.00	300	750
I ter day Prec s o (%CV)	4.5	1.8	3.6
I ter day Ac uracy (%Actua)	107.0	95.3	92.8

Summary of Standard Curve and QC Data for Patch Sample

Bioequivalence Protocol No. RP-LID-PK001 Lidocaine								
Parameter	**Standard Curve Samples**							
Co ce trat o (m g)	1.00	2.00	4.00	6.00	7.00	8.00	9.00	10.0
I ter day Prec s o (%CV)	2.0	0.6	0.5	0.4	0.2	0.2	0.4	0.7
I ter day Ac uracy (%Actua)	105.0	100.5	98.2	99.3	100.6	99.7	100.2	100.0
L ear ty (Ra e of r^2 va ues)	0.9998 – 0.9998							
L ear ty Ra e (m g)	1.00 – 10.0							
e s t v ty/ LOQ (m g)	1.00							

Bioequivalence Protocol No. RP-LID-PK001 Lidocaine			
Parameter	**Quality Control Samples**		
Co ce trat o (m g)	3.00	6.00	8.00
I ter day Prec s o (%CV)	4.0	1.7	1.7
I ter day Ac uracy (%Actua)	98.7	97.5	97.5

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No The f rm prov ded chromato rams for the p asma samp e for subject (b) (6) (12 out of 48) a d a the chromato rams for the swab samp es a d the patch samp es.
Were chromatograms serially or randomly selected?	☒ ser a y ☐ ra dom y
Any interfering peaks in chromatogram?	☐ Yes ☒ No

Were the chromatograms submitted by the firm acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

4.1.1.3.3 Reanalysis of Study Samples

Reanalysis of Plasma Samples

Study No. RP-LID-PK001
Additional Information in Module 5, Section 5.3.1.4
Bioanalytical Report No. (b) (4) - LC/MS/MS Analysis for the Determination of Lidocaine in Human Plasma, Patch, and Cotton Swab Samples: "A Randomized, Open-Label, Two-Period, Crossover, Single Dose Bioequivalence Study of Lidocaine 5% Topical Patch and Lidoderm® in Healthy Adults Under Fasted Conditions" Please see page 15 of 86.

Lidocaine

Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	(b) (4)							
Reason A: the initial value was above the limit of quantitation*								
Reason B: the initial pre-dose value was not below LLOQ**								
Total								

Percentage was calculated based on Total Test or Reference Drug Study Sample.
*Pe (b) (4), Section 4.4.1
**Per (b) (4), Section 4.5.1

Reanalysis of Cotton Swap Samples

Protocol No. RP-LID-PK001
Additional Information in Module 5, Section 5.3.1.4
Bioanalytical Report No (b) (4) - LC/MS/MS Analysis for the Determination of Lidocaine in Human Plasma, Patch, and Cotton Swab Samples: "A Randomized, Open-Label, Two-Period, Crossover, Single Dose Bioequivalence Study of Lidocaine 5% Topical Patch and Lidoderm® in Healthy Adults Under Fasted Conditions" Please see 59 of 96.

Lidocaine

Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetics	(b) (4)							
Reason A: The initial value was above the limit of quantitation*.								
Total for Sample Analysis								

*Per (b) (4), ect o 4.4.1 0

Reanalysis of Patch Samples 0

Protocol No. RP-LID-PK 0 1 0 Lidocaine 0								
Reason why assay was repeated 0	Number of samples 0 reanalyzed 0				Number of recalculated values used after reanalysis 0			
	0 Actual 0 number 0		% of total assays 0		Actual number 0		% of total assays 0	
	T 0	R 0	T 0	R 0	T 0	R 0	T 0	R 0
Pharmacok 0et cs 0	(b) (4)							
Tota for amp e 0 A 0a ys s 0								

Note: Re-assay was ot requ red for the patch samp es. 0

Does the reviewer agree with the reanalysis of study samples: 0 analytical and/or PK repeat? 0	☒ Yes 0☐0No 0 0
If no, is recalculation of PK parameters necessary? 0	☐ Yes 0☐0No 0☒0N/A 0
Did recalculation of PK parameters change the study outcome?	0☐ Yes 0☐0No 0☒0N/A 0
Are the PK parameters of reanalysis still within the acceptance limits for the 9 0% CI? 0	0 ☐ Yes 0☐0No 0☒0N/A 0

Comments on Bioanalytical Results: Adequate 0

For the p asma study samp es, subjec (b) (6) (per od 1 at 0 hrs) a d subjec (b) (6) (per od 2 at 0 0 hrs) were repeated for reaso A: the 0t a va ue was above the m i of qua t tat o . 0 Per OP N (b) (4) "Repeat Assay a d Report 0 Cr ter a for B oa a yt ca 0 amp es", sect o 0 4.5.1, f the 0t a true pre-dose va ue or the co tro samp e s ot 0 be ow LLOQ, the study samp e shou d be repeated dup cate. Both study samp es were 0 repeated dup cate a d the repeated va ues were be ow qua t tat o m i (BQL). For 0 subjec (b) (6) (per od 1 at 0 hrs), the 0t a co ce trat o was (b) (4) approx mate y 0 (b) (4) of the Cma (b) (4) If us 0 the 0t a va ue, subjec (b) (6) shou d be 0 exc uded from the study because pre-dose co ce trat o (b) (4) of the Cmax. 0 For subjec (b) (6) (per od 2 at 0 hrs), the 0t a co ce trat o wa (b) (4) of 0 the Cma (b) (4). ubjec (b) (6) was exc uded from the stat st ca a a ys s due to 0 suff c e t t me of patch app cat o (ess tha 11 hours). Therefore, those repeats are 0 u 0ke y to mpact the overa study outcome. 0

A 0the other samp es rea a yzed for the BE study were a a yt ca repeats fo ow 0 OP 0 N (b) (4), "Repeat Assay a d Report 0 Cr ter a for B oa a yt ca amp es." No 0 pharmacok 0et c repeats were reported. The repeat a a ys s of the BE study s **adequate**. 0

4. . .4 Pharmacokinetic Results 1

4. . .4.1 Arithmetic Mean Pharmacokinetic Parameters – Reviewer Calculated 1

Fasting Bioequivalence Study No. RP-LID-00 1									
Parameter 1 (units) 1	Test 1				Reference 1				T/R 1
	Mean	%CV 1	Min	Max 1	Mean	%CV 1	Min	Max 1	
AUC0-t (hr 1 *ng/ml) 1									(b) (4)
AUC∞ (hr 1 *ng/ml) 1									
Cmax (ng/ml 1									
Tmax* (hr) 1									
Kel (hr-) 1									
T 1⁄2 (hr) 1									

* Tmax va ues are prese ted as med a , ra 1e 1

4. . .4.2 Geometric Means and 90% Confidence Intervals - Firm Calculated 1

Lidocaine Patch 5% 1 Dose (3 x 700 mg) 1 Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals 1						
Fasting Bioequivalence Study No. RP-LID-00 1						
Parameter (units) 1	Test 1	N 1	RLD 1	N 1	Ratio 1	90% C.I. 1
AUC0-t (hr *ng/ml 1	(b) (4)		(b) (4)			(b) (4)
AUC∞ (hr *ng/ml 1						
Cmax (ng/ml) 1						

4. . .4.3 Geometric Means and 90% Confidence Intervals - Reviewer Calculated 1

Lidocaine Patch 5% 1 Dose (3 x 700 mg) 1 Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals 1						
Fasting Bioequivalence Study No. RP-LID-00 1						
Parameter (units) 1	Test 1	N 1	RLD 1	N 1	Ratio 1	90% C.I. 1
AUC0-t (hr *ng/ml) 1	(b) (4)	3 1	(b) (4)	3 1		(b) (4)
AUC∞ (hr *ng/ml) 1		3 1		3		
Cmax (ng/ml) 1						

4.1.1.4.4 Additional Information for the Study 2

Root Mean Square Error 2	AUC 2 (b) (4) AUC 2 (b) (4) Cmax 2 (b) (4)
Is there a Tmax difference between Test and Reference? 2 **If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference) 2**	☐ Yes 2 ☒ No 2
Were the subjects dosed in groups? 2 **If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary? 2**	☐ Yes 2 ☒ No 2
Are there measurable drug concentrations at 0 hr? 2 **If yes, please comment (and take necessary action, if needed) 2**	☐ Yes 2 ☒ No 2 P ease see comme ts o B oa a yt ca Resu ts 2
Are there first measurable drug concentration as Cmax? 2 **If yes, please comment 2**	☐ Yes ☒ No 2
Are there Cmax at the first time point? 2 **If yes, is the study (sample) design adequate? 2**	☐ Yes 2 ☒ No 2

Ratio of AUC0-t/AUC∞ 2				
Treatment 2	**n 2**	**Mean 2**	**Minimum 2**	**Maximum 2**
Test 2		(b) (4)		
Reference 2				
If the minimum ratios less than 0.8, were they due to inadequate sampling schedule? Provide additional comments below 2	N/A 2			

Comments on PK results: Adequate 2

- The pharmacok 2et c measures (AUCt, AUC , Cmax, Tmax, KE a d t1/2) a d 2 co f de ce terva s of AUCt, AUC , a d Cmax for **lidocaine** as ca cu ated by the 2 rev ewer were a reeme t w th the va ues reported by the f rm. The 90% co f de ce 2 terva s for **lidocaine** of -tra sformed AUC_{0-t}, AUC_{∞} a d C_{max} eometr c mea 2 test/refere ce rat os fa w th 2the m its of 80-125%. 2

4.1.1.5 Overall Comment 2

Was the fasting bioequivalence study acceptable? Ac2eptab e. 2

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study – Reviewer f Calculated f

Time (hr) f	Test (n=39) f		Reference (n=39) f		T/R f Ratio f
	Mean (ng/mL) f	% CV f	Mean (ng/mL) f	% CV f	
0.0 f	(b) (4)				
1.0 f					
1.5 f					
2.0 f					
3.0 f					
6.0 f					
9.0 f					
12.0 f					
15.0 f					
18.00 f					
21.00 f					
24.00 f					
48.00 f					

1 Page has been withheld in full as b4 (CCI/TS) immediately following this page

ormulation Data %

1 Test ormulation %

Ingredient %	unction	% ormula %	Milligrams Per Patch %
Lidocaine %	Active ingredient %	5.00 %	700
Puri ied Wate %			
Glycerin %			
Sorbito (b) (4)			
Polyacrylic Acid (b) (4)			
Sodium Polyacrylat %			
Sodium Carboxymethylcellulos %			
Propylene Glyco %			
Urea %			
Kaolin %			
Tartaric Acid %			
Gelatin %			
Polyvinyl Alcohol (PVA %			
Dihydroxyaluminium Aminoacetat %			
Edetate Disodiu %			
Methylparaben %			
Propylparaben %			
Total %		100 0 %	

(b) (4)

NDA 020612 Formulation[12] [NOT FOR RELEASE UNDER FOIA]

Ingredient	mg/g adhesive	mg/patch	Kg/batch	Purpose
Lidocaine	50	700	(b) (4)	active
(b) (4)				(b) (4)
Glycerin				
Sorbitol, (b) (4)				
Polyacrylic acid (b) (4)				
Sodium polyacrylate				
Sodium carboxymethyl cellulose				
Propylene glycol				
Urea				
Kaolin				
Tartaric acid				
Gelatin				
Polyvinyl alcohol				
Dihydroxyaluminum aminoacetate				
Disodium edetate				
Methylparaben				
Propylparaben				
Total				

4.2.2 Inactive Ingredients (IIG Table)

Components	mg/patch	Maximum amount (mg)/MDD (i.e. 3 patches/day)	IIG justification or limit (mg)
(b) (4)		(b) (4)	(b) (4) than RLD
Glycerin			Same as RLD
Sorbitol Solutio (b) (4)			Same as RLD
Polyacrylic Acid Solutio (b) (4)			Same as RLD
Sodium Polyacrylate			Same as RLD
Sodium Carboxymethyl Cellulose			(b) (4) than RLD Level acceptable per DCR

[12] Enterprise search: N020612, "N020612 REV 03-JUN-1996 1" Clinical Pharmacology/Biopharmaceutics Review. This is the current RLD formulation. The amount of each ingredient i (b) (4) batch size is same as the information in Chemistry Review of Supplement-10. DARRTS: NDA 20612, REV-QUALITY-03(General Review), 12/28/2006 (Supplement-10). Supplement 10 was approved on 2/19/07 (DARRTS: NDA 20612, COR-SNDAACTION-06(Approval CMC Supplement), 2/19/2007).

			P a /R Tox R Consult R
P opylene Glycol R	[redacted] (b) (4)		[redacted] (b) (4) as LD R
U ea R			[redacted] (b) (4) as LD R
Kaolin R			[redacted] (b) (4) as LD R
Ta ta ic Acid R			[redacted] (b) (4) as LD R
Gelatin R			[redacted] (b) (4) t an LD R
Polyvinyl Alco ol (PVA) R			[redacted] (b) (4) t an LD R
Di yd oxyalui Rniu RR AiRnoacetate R			[redacted] (b) (4) t an LD*R R
Edetate Disodiu R			[redacted] (b) (4) as LD R
Met ylpa aben R			[redacted] (b) (4) as LD R
P opylpa aben R			[redacted] (b) (4) as LD R

*A P a /R Tox consult was sent to DC R o Rt e Division o Filing eview (DF R) R ega ding i t e p oposed aoRunt o Sodiu RCa boxyeRt yl Cellulose in t e test R o uR lation is acceptable.[13] Pe t e DC RConsultation [redacted] (b) (4) in t e R aoRunt o Sodiu RCa boxyeRt yl Cellulose in t e p Rposed o uR lation copRa ed to t e R LD is unlikely to a Rect t e sa ety p o ile o t e p oposed o uR lation.[14] R

**T em axim u Rdaily intake (MDI) o Di yd oxyalui Rniu RAiRnoacetate is justi ied R based on ANDA 200675, Lidocaine Patc , 5% (AppRo oval on 08/23/2012). T e MDD o R Lidocaine Patc is t Re patc es/day, and t e aoRunt o Di yd oxyalui Rniu RR AiRnoacetate is 35 g R/patc . Hence, t e MDI o Di yd oxyalui Rniu RAiRnoacetate i [redacted] (b) (4)

Are all strengths of the test product proportionally similar per the BA/BE guidance criteria? R	☐ Yes R☐RNo ☒RN/A R
Are the amounts of all inactive ingredients, based on Maximum Daily Dose (MDD), within IIG (per unit) limits? R	☐ Yes R☒RNo R
If no, are they all within IIG (per day) limits? R	☐ Yes R☒RNo ☐RN/A R
If no, are additional data or Pharm/Tox consult necessary? R	☒ Yes R☐RNo ☐RN/A R Consult outcoeR: level acceptable. R
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)? R	☐ Yes R☐RNo ☒RN/A R
Are all strengths of the test formulation acceptable? R	☒ Yes R☐RNo R

[13] ANDA-209190-O RIG-1, Filing eview, A209190N0R0DF R_P a tR ox.pd , dated 6/3/2016 R
[14] GD RP, ANDA-209190-O RIG-1, P a /R Tox Consult, A209190_DC RPT_ Lidocaine Patc 5% R _CA RBOXYMETHYLCELLULOSE-1.pd , dated 5/10/2017. R
_ttp://pano aaR. da.gov/task/view?ID=570 R5950R0740d3dc5ece0916b35bb1&activeTab=list-task- R docueRnts R
[15] DA R TS, ANDA 200675, EV-BIOEQ-01(Gene al eview), dated 09/29/2011 and 04/26/2012. R

m e nts n F Ŧu T lati n: Ac Ɛeptable T

- T he test product, Lidocaine Patch, 5% T [redacted] (b) (4)
- T he ormulation is **acceptable**. T

3 D l ssolut on Test ng l

3 1 D l ssolut on ata l

ssolut on Cond t ons l	**Apparatus:** l	5 (Padd e over disc) l
	Speed of Rotat on: l	50 rpm
	Med um: l	Acetic acid/Sodium acetate bu ler, pH 4.0 l
	Volume: l	500 mL l
	Temperature: l	32°C ± 0.5°C l
F rm's Proposed Spec f cat ons l	[redacted] re eased a ter 0.5 hour l	
ssolut on Test ng S te (Name, Address) l	A tergon Ita ia S.r. . l Zona Industria e, Morra de Sanctis l Ave ino 83040, Ita y l	

Study Ref No l	**Test ng ate** l	**Product I** l/ **Batch No** l	**osage Strength & Form** l	**No of osag e Un ts** l		**Collect on T mes (m inutes)** l									**Study Report Locat o n** l
						10 l	**20** l	**30** l	**60** l	**120**	**180**	**360**	**660**	**1 l 0** l	
RT008-13 l	10/16/2013 l	Test Product: l Lidocaine Patch 5% l Lot# L1304191 l Manu acture Date 04/2013 l	700 l mg/patch l	12 l	Mean l	31	49	62	80	94	97 l	97 l	97 l	93 l	Modu e 2, l Section 2.7, l Report RT 008-13-02 l
					Rang l	[redacted]									
					% CV l	6.2	3.4	3.2	1.7	1.1	1.0	1.8	4.1	5.2 l	
RT008-13 l	10/24/2013 l	Re erence Product: l Lidoderm, Lot# Y2282 l Expiry Date: 10/2015 l	700 l mg/patch l	12 l	Mean l	32	46	60	77	92	97 l	97 l	96 l	90 l	
					Rang l	[redacted]									
					% CV l	12. l 1 l	7.2	5.8	5.1	3.5	4.7	2.1	1.5	2.2 l	

4.3.2 Dissolution Profiles

4.3.3 F2 Metric

F2 metric calculated?	☐ Yes ☒ No
If no, reason why F2 not calculated	The test product is a topical patch, and only has one (1) strength.

Overall Comments: Inadequate

- There is no USP dissolution method, but there is a FDA-recommended dissolution method for this drug product. The firm conducted dissolution testing using the FDA-recommended method [500 mL of Acetic Acid/Sodium Acetate Buffer, pH 4.0 at 32°C, with USP Apparatus V (Paddle over Disk) at 50 rpm].

- The firm's QC dissolution method and data were reviewed separately and found **inadequate.**[2]

4.4 Attachments

4.4.1 Additional Studies

Are there any additional studies? (e.g. pilot , failed) **If yes, please provide the location of report (complete/summary)**	☐ Yes ☒ No

4.4.2 SAS Output

Study	SAS Data	SAS Code	SAS Stat	SAS Output/Table
Fasting	 209190_fasting_data.xlsx	 209190_fasting_CONTINU2.sas	 209190_Fasting_stat_LidocaineACTUAL.doc	 209190_Fasting_table_LidocaineACTUAL.doc

EQU VALENCE C lMMENTS T 1 E PR 1V DED T 1THE APPL CANT 1

ANDA: 1 209 90 1

APPL CANT: 1 Rhodes Pharmaceuticals L.P. 1

DRUG PR lDUCT: Lidocaine Patch, 5% 1

The Division o ioequivalence (D 1) has completed its review and has no urther 1 questions at this time. 1

The bioequivalence comments provided in this communication are comprehensive as o 1 issuance. However, these comments are subject to revision i additional concerns raised 1 by chemistry, manu acturing and controls, microbiology, labeling, other scienti ic or 1 regulatory issues or inspectional results arise in the uture. Please be advised that these 1 concerns may result in the need or additional bioequivalence in ormation and/or studies, 1 or may result in a conclusion that the proposed ormulation is not approvable. 1

Sincerely yours, 1

{See appended electronic signature page} 1

Ethan M. Stier, Ph.D., R. Ph. 1
Director, Division o ioequivalence 1
ice o ioequivalence 1
ice o Generic Drugs 1
Center or Drug Evaluation and Research 1

4 W **tcome** W

ANDA 209190 W

Reviewer: Wang, Yibo W **Date Completed:** W
Verifier: W , W **Date Verified:** W
Division: Division o Bioequivalence W
Description: Lidocaine Patch, 5% W

Items: W

ID	***Letter Date***	W ***Productivity Category*** W	***Sub Category*** W	***Score***	***Subtotal*** W
30811	4/14/2016	BIO W	ANDA Original [1] W	1	W 1 W
30811	4/14/2016	Parallel W	Fasting Study (Full template) [1] W	W1	W 1 W
				Total:	2 W

BIOPHARMACEUTICS REVIEW for ANDA SUBMISSIONS	
Application No.	209190
Product Name	Lidocaine Patch
Applicant	Rhodes Pharmaceuticals L.P.
Dosage Form/Strengths	Patch/5%
Route of Administration	Transdermal
Indication for Use	Relief of pain associated with post-herpetic neuralgia
Submission Date	September 26, 2017
Review Date	October 26, 2017
Primary Reviewer	Kelly M. Kitchens, Ph.D.
Secondary Reviewer	Tapash Ghosh, Ph.D.
Recommendation	**ADEQUATE**

1. REVIEW SUMMARY:

Background:
The firm is seeking approval of Lidocaine Patch, 5%, under the 505(j) path. Lidocaine Patch is indicated for relief of pain associated with post-herpetic neuralgia. The drug product is packaged as one patch in a child-resistant envelope with 30 envelopes per carton. The reference listed drug (RLD), Lidoderm® (lidocaine patch 5%), was approved under NDA 20612 for the 5% strength.

Submission:
This is a resubmission in response to the Complete Response (CR) letter dated July 7, 2017. The resubmission includes the firm's response to Biopharmaceutics deficiencies related to the drug release method validation, data, and acceptance criteria.

Review's Objective:
The Biopharmaceutics review is focused on the adequacy of the drug release method and acceptance criteria.

Reviewer's Assessment:
The drug release method and acceptance criteria are adequate.

Conclusion and Recommendation:
From the Biopharmaceutics perspective, ANDA 209190 for Lidocaine Patch, 5%, is recommended for approval.

2. REVIEW:

a) List Submissions being reviewed:

September 26, 2017	Resubmission, 1st minor complete response amendment

b) Highlight Key Outstanding Issues from Last Review Cycle: A Complete Response (CR) letter was issued on July 7, 2017 (see Appendix 2 for the Biopharmaceutics CR comments). In the CR letter, the Division of Biopharmaceutics requested additional information to support the drug release method validatio [redacted] (b) (4) and acknowledgement of their acceptance of the recommended drug release acceptance criteria.

c) Concise Description of Outstanding Issues: N/A

d) Drug Release method and acceptance criteria proposed by the Applicant:

Method Source	Diffusion Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)	Sampling Times (minutes)	Acceptance criteria
FDA	USP apparatus 5 (paddle over disk)	50	Acetic acid/sodium acetate buffer, pH 4.0 at 32°C	500	10, 20, 30, 60, 120, 180, 360, 660, 1440	30 minutes [redacted] (b) (4) NLT [redacted] (b) (4) 1 hour [redacted] (b) (4): NLT [redacted] (b) (4) 2 hours [redacted] (b) (4) NLT [redacted] (b) (4)

e) Summary of Drug Release Data

Summary table of all the dissolution profiles

Batch	Mean % Lidocaine released at 10 minutes	Mean % Lidocaine released at 30 minutes	Mean % Lidocaine released at 60 minutes	Mean % Lidocaine released at 120 minutes	Mean % Lidocaine released at 180 minutes
L1304151	(b) (4)				
L1304191					
L1304201					
L1605301					
L16053111					
L16053112					
Min individual value from all batches					
Max individual value from all batches					
Average of all batches					

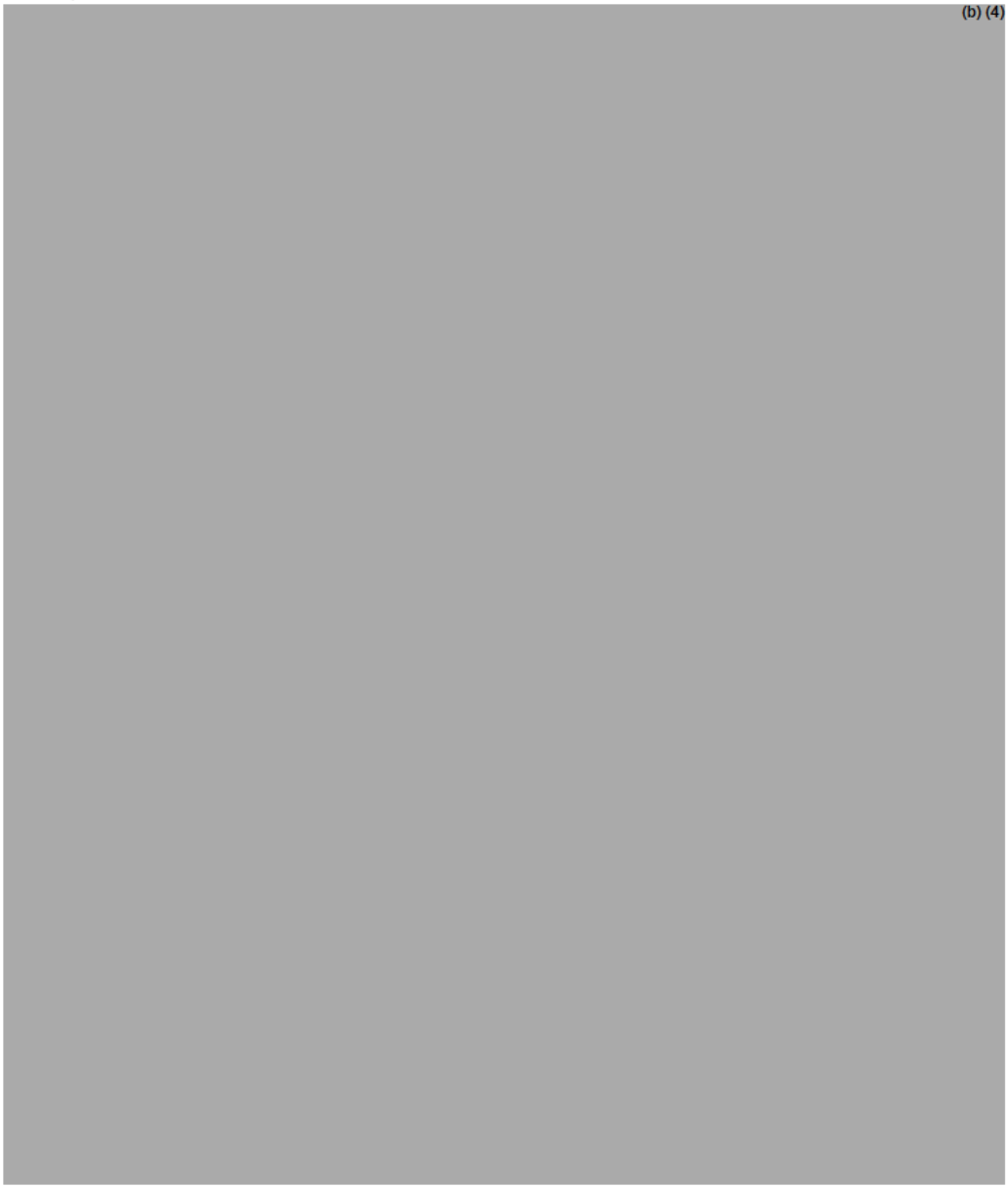
Refer to Appendix 1 for the tables of detailed drug release data.

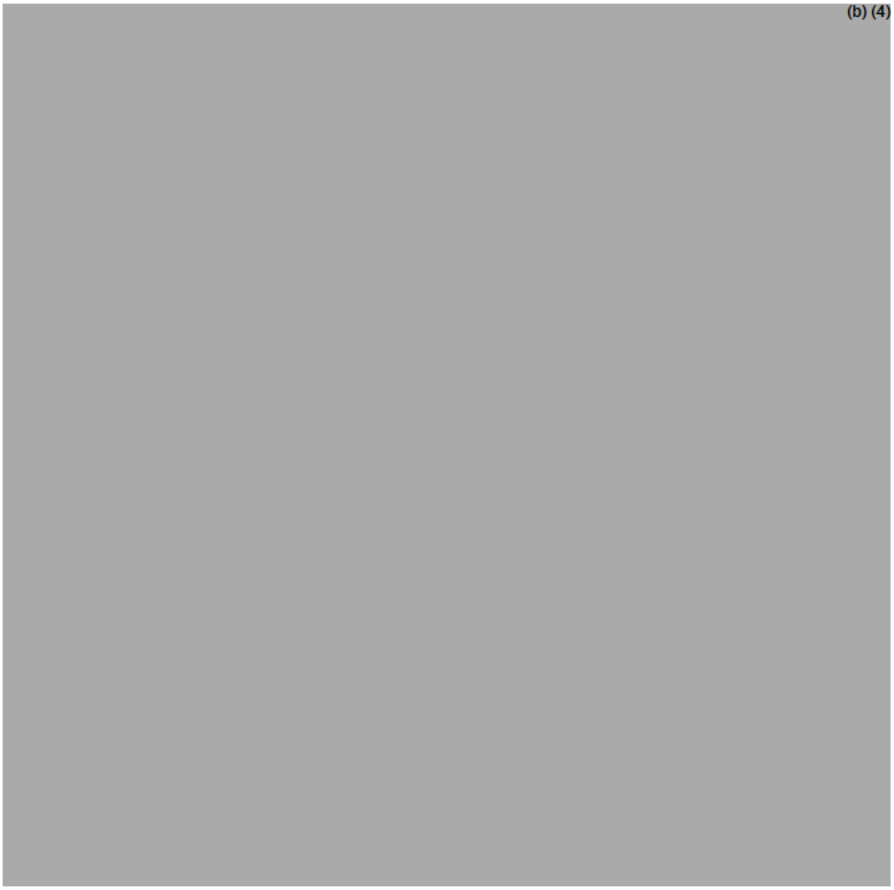
3. REVIEWER'S ASSESSMENT:

Reviewer's assessment of CR responses:

CR #1: The submitted chromatograms demonstrate that there are no interfering compounds with the analyte, Lidocaine.

(b) (4)





Thus, the drug release method is demonstrated to be specific.

CR #2: Linearity, as well as accuracy and repeatability precision, were validated in an appropriate rang (b) (4) for the drug release samples of lidocaine.

CR #3: The firm did not provide an adequate explanation as to why lidocaine release (b) (4) at the 24-hour time point. However, since drug release i (b) (4) at 24 hours, the drug release profile is adequate.

CR #4: The firm corrected the dilution factor of the standard from (b) (4)). The drug release method was revised accordingly and validated (Addendum Method Validation Report, Dissolution Test for Lidocaine Medicated Patches, Document # RMV-LAB-431-01-ADD01-Revision 01). Therefore, the firm provided additional drug release data (see Appendix 1) using the biobatch (L1304191), exhibit batches (L1304151 and L1304201), and validation batches (L1605301, L16053111, and L16053112) to support their proposed drug release acceptance criteria.

Time Point	Firm's original proposed	FDA-recommended	Firm's current proposed
10 minutes	---	NMT (b) (4)	**NMT** (b) (4)
30 minutes	NL (b) (4)	(b) (4)	(b) (4)
180 minutes	---	NLT (b) (4)	**NLT** (b) (4)

The firm's proposed acceptance criteria are adequate based on the drug release data (at release/T=0) submitted.

The firm's CR responses are **adequate**.

In Vitro Release Method: Adequate

In Vitro Release Acceptance Criteria: Adequate

4. LIST OF BIOPAHRMACEUTICS COMMENTS:

The firm developed and validated an adequate drug release method to measure the release of lidocaine from the drug product. Therefore, the drug release method is adequate. In addition, the firm's proposed drug release acceptance criteria are adequate based on the submitted drug release dat (b) (4) submitted. It is noted that the Drug Product reviewer has some deficiencies related to the drug release data during stability to be communicated to the firm.

5. CONCLUSION and RECOMMENDATION:

The following drug release method and acceptance criteria are recommended for the test product:

USP Apparatus	Speed (rpm)	Medium/Temperature	Volume (mL)	Acceptance criteria
USP apparatus 5 (paddle over disk)	50	Acetic acid/sodium acetate buffer, pH 4.0 at 32°C	500	10 minutes: NMT (b) (4) 30 minutes (b) (4) 180 minutes: NLT (b) (4)

From the Biopharmaceutics perspective, ANDA 209190 for Lidocaine Patch, 5%, is recommended for approval.

6. SIGNATURE BLOCK:

Primary Biopharmaceutics Reviewer:
Kelly M. Kitchens, Ph.D., October 31, 2017

Secondary Biopharmaceutics Reviewer:
Tapash Ghosh, Ph.D., October 31, 2017

APPENDIX 1
In Vitro Release Data Tables

Batch L1304191

Time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Average	Max	Min	SD	CV%
10 min	(b) (4)										
30 min											
60 min											
120 min											
180 min											

Batch L1304151

Time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Average	Max	Min	SD	CV%
10 min	(b) (4)										
30 min											
60 min											
120 min											
180 min											

Batch L1304201

Time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Average	Max	Min	SD	CV%
10 min	(b) (4)										
30 min											
60 min											
120 min											
180 min											

Batch L1605301

Time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Average	Max	Min	SD	CV%
10 min	(b) (4)										
30 min											
60 min											
120 min											
180 min											

Batch L16053111

Time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Average	Max	Min	SD	CV%
10 min	(b) (4)										
30 min											
60 min											
120 min											
180 min											

Batch L16053112

Time	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Average	Max	Min	SD	CV%
10 min	(b) (4)										
30 min											
60 min											
120 min											
180 min											

APPENDIX 2

Biopharmaceutics Information Requests and Firm Responses

Comments from July 7, 2017 CR letter:

Biopharmaceutics CR#1:
Submit the chromatograms generated for the specificity results of the drug release method validation (document number RMV LAB 431-03).

Firm's response to CR#1:
The following chromatograms are provided in section 3.2.P.5.3.

- Blank mobile phase chromatogram
- Placebo chromatogram
- Process standard solution chromatogram
- Reconstituted sample chromatogram

Biopharmaceutics CR#2:
Re-validate the analytical assay for linearity in a concentration range that covers the drug release sample concentrations, and report the linearity concentrations as percentage.

Firm's response to CR#2:
The analytical assay for linearity in a concentration range that covers the drug release sample concentrations has been revalidated. It was determined that the linearity, precision, and accuracy in the range o (b) (4) of the nominal active concentration was successfully carried out and validated. Refer to Addendum Method Validation Report, Dissolution Test for Lidocaine Medicated Patches, Document # RMV-LAB-431-01-ADD01- Revision 01, located in 3.2.P.5.3.

Biopharmaceutics CR#3:
Provide an explanation for th (b) (4) in drug release at the 1440-minute (24-hour) time point.

Firm's response to CR#3:
(b) (4) Given that the reference listed drug we believe that this is an artifact.

Biopharmaceutics CR#4:
Your proposed drug release acceptance criteria are inadequate. The following acceptance criteria are recommended based on the drug release data submitted:

10 minutes: NMT (b) (4)

30 minutes: Between (b) (4)
120 minutes: NLT (b) (4)

We request that you acknowledge your acceptance of the recommended drug release acceptance criteria, and update the drug product specifications accordingly.

Firm's response to CR#4:
Rhodes acknowledges the Agency's recommended drug release acceptance criteria; however, different acceptance criteria is being proposed based on the results from both the reference listed drug (LIDODERM®) and the test product as follows:

10 minutes: NMT (b) (4)
30 minutes: Between (b) (4)
180 minutes: NLT (b) (4)

Justification for these proposed specifications are explained in the Evaluation of Dissolution Data and Definition of Specifications, RA-LAB-2017-04 Rev. 01, located in 3.2.P.5.3.

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Fred Echoles

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BIOPHARMACEUTICS

Product Background: The firm is seeking approval of Lidocaine Patch, 5%, under the 505(j) path. Lidocaine Patch is indicated for relief of pain associated with post-herpetic neuralgia. The drug product is packaged as one patch in a child-resistant envelope with 30 envelopes per carton. The reference listed drug (RLD), Lidoderm® (lidocaine patch 5%), was approved under NDA 20612 for the 5% strength.

ANDA: 209190

Drug Product Name / Strength: Scopolamine Transdermal System Patch, 1.5 mg

Route of Administration: Transdermal

Applicant Name: Rhodes Pharmaceuticals L.P.

Review Summary:

The firm proposes to use the FDA-recommend drug release method for Lidocaine Patch. The drug release validation and proposed acceptance criteria are inadequate. Therefore, the following deficiencies will be conveyed to the firm:

1. Submit the chromatograms generated for the specificity results of the drug release method validation (document number RMV LAB 431-03).
2. Re-validate the analytical assay for linearity in a concentration range that covers the drug release sample concentrations, and report the linearity concentrations as percentage.
3. Provide an explanation for the (b) (4) in drug release at the 1440-minute (24-hour) time point.
4. Your proposed drug release acceptance criteria are inadequate. The following acceptance criteria are recommended based on the drug release data submitted:

10 minutes: NMT (b) (4)
30 minutes: Between (b) (4)
120 minutes: NLT (b) (4)

We request that you acknowledge your acceptance of the recommended drug release acceptance criteria, and update the drug product specifications accordingly.

List Submissions being reviewed (table):

Submission	Purpose of Submission
April 13, 2016	Original

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: See the list of deficiencies

BCS Designation

Reviewer's Assessment: The proposed product is a transdermal patch; therefore, BCS designation is not pertinent to this application.

Solubility:

Permeability:

Dissolution:

Drug Release Method and Acceptance Criteria

Reviewer's Assessment: INADEQUATE

- There is a FDA-recommended drug release method for this drug product:

Drug Release Conditions	Apparatus:	V (paddle over disk)
	Sinkers (If yes, type of sinkers)	No
	Speed of Rotation:	50 rpm
	Medium:	Acetic acid/sodium acetate buffer, pH 4.0 at 32°C
	Volume:	500 mL

- The firm used the FDA-recommended drug release method to measure drug release of the test and RLD products.
- The analytical assay for the drug release testing was validated for system suitability, specificity, linearity and range, precision, accuracy, filtration study, solution stability, and robustness. Refer to Module 3.2.P.5.3. "Method Validation Report – Dissolution Test for Lidocaine Medicated Patches" for full details of the validation report.
    - There is an addendum to the validation report, since the drug release method was modified for the following after the original validation report was completed:
        - [redacted] (b) (4)
        - Sampling time change from 30 minutes to 30 minutes, 1 hour, and 2 hours; and,
        - Release specification for the new sampling times.
    - In the addendum, the analytical assay was validated for specificity, accuracy, and precision.

Drug Release Acceptance Criteria

- The firm proposed the following acceptance criterion: NLT (b) (4) released in 0.5 hour. Per the addendum method validation report, the firm will implement the following acceptance criteria (although this is not reported in the drug product specifications table):
  30 minutes (± 2%): NLT (b) (4)
  1 hour (± 2%): NLT (b) (4)
  2 hours (± 2%): NLT (b) (4)
- The firm provided complete drug release data (individual, mean, %CV, profile) for 12 units (non-pooled) of both the test and RLD products in the drug release testing.
  - Drug release testing was conducted on the biobatches of the test product (batch no. L1304191) and RLD (batch no. Y2282) products.
  - The test product batch was within 6 months old when testing was conducted, and the RLD product batch was unexpired at the time of drug release testing.

The drug release study results are summarized in the following table and drug release profile:

Dissolution Conditions	**Apparatus:**	5 (Paddle over disc)
	Speed of Rotation:	50 rpm
	Medium:	Acetic acid/Sodium acetate buffer, pH 4.0
	Volume:	500 mL
	Temperature:	32°C ± 0.5°C
Firm's Proposed Specifications	(b) (4) released after 0.5 hour	
Dissolution Testing Site (Name, Address)	Altergon Italia S.r.l. Zona Industriale, Morra de Sanctis Avellino 83040, Italy	

Study Ref No.	Testing Date	Product ID / Batch No.	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 10	20	30	60	120	180	360	660	1440	Study Report Location
RT008-13	10/16/2013	Test Product: Lidocaine Patch 5% Lot# L1304191 Manufacture Date 04/2013	700 mg/patch	12	Mean	31	49	62	80	94	97	97	97	93	Module 2, Section 2.7, Report RT 008-13-02
					Range	(b) (4)									
					% CV	6.2	3.4	3.2	1.7	1.1	1.0	1.8	4.1	5.2	
RT008-13	10/24/2013	Reference Product: Lidoderm, Lot# Y2282 Expiry Date: 10/2015	700 mg/patch	12	Mean	32	46	60	77	92	97	97	96	90	
					Range	(b) (4)									
					% CV	12.1	7.2	5.8	5.1	3.5	4.7	2.1	1.5	2.2	

(b) (4)

[redacted]

Reviewer's comments:

- The analytical method for drug release testing was adequately validated for system suitability, precision, accuracy, filtration study, solution stability, ands robustness.
  - The firm will be requested to submit the chromatograms generated for the specificity results of the drug release method validation (document number RMV LAB 431-03).
  - Linearity was validated in the concentration range (b) (4) The firm will be requested to re-validate the analytical assay for linearity in a concentration range that covers the drug release sample concentrations, and to report the linearity concentrations as percentage.
  - The sample solution is stable for up to 48 hours at room temperature.
  - The method is robust to small changes in flow rate, column temperature, mobile phase composition, and column from different suppliers.
- The firm will be requested to explain why drug releas (b) (4) at the 1440-minute (24-hour) time point.
- The firm's proposed drug release acceptance criteria are inadequate. The following acceptance criteria are recommended based on the drug release data submitted:
  10 minutes: NMT (b) (4)
  30 minutes: Betwee (b) (4)
  120 minutes: NLT (b) (4)
  The firm will be requested to acknowledge their acceptance of the recommended drug release acceptance criteria, and update the drug product specifications accordingly.

List of Deficiencies (IR#1):

1. Submit the chromatograms generated for the specificity results of the drug release method validation (document number RMV LAB 431-03).

2. Re-validate the analytical assay for linearity in a concentration range that covers the drug release sample concentrations, and report the linearity concentrations as percentage.
3. Provide an explanation for th (b) (4) in drug release at the 1440-minute (24-hour) time point.
4. Your proposed drug release acceptance criteria are inadequate. The following acceptance criteria are recommended based on the drug release data submitted:

   10 minutes: NMT (b) (4)
   30 minutes: Between (b) (4)
   120 minutes: NLT (b) (4)

   We request that you acknowledge your acceptance of the recommended drug release acceptance criteria, and update the drug product specifications accordingly.

Primary Biopharmaceutics Reviewer Name and Date:
Kelly M. Kitchens, Ph.D., February 13, 2017

Secondary Reviewer Name and Date:
Haritha Mandula, Ph.D., February 21, 2017

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

STATISTICAL REVIEW

Department ea th and uman Services
F d and Drug Administrati n
Center r Drug Eva uati n and Research
O ice Trans ati na Sciences
O ice Bi statistics

U.S. FOOD & DRUG ADMINISTRATION

A DEN M TOU STATISTICAL REVIEW AN EVALUATION

CLINICAL STUDIES

AN A/Serial Number	NDA 209190 A
rug Name:	Lid caine Patch 5%
Indication(s): D	Re ie pain ass ciated with p st-herpetic neura gia
Reference Listed rug:	Lid derm®
Applicant: D	Rh des Pharmaceutica s L.P.
ate(s):	Review C mp eti n G a Date: June 16, 2017
Biometrics ivision:	Divisi n Bi metrics VIII
Statistical Reviewer:	S mesh Chatt padhyay, Ph.D.
Secondary Reviewers:	Fair uz Makh u , Ph.D., Deputy Direct r
	Ste a Gr sser, Ph.D., Direct r
Medical ivision: D	Divisi n C inica Review in the O ice Generic Drugs
Clinical Team:	Sunny Tse, Ph.D., C inica Reviewer
	Car Kim, Pharm.D., C inica Team Leader
Addendum Reviewer:	Ste a Gr sser, Ph.D.
Reason for Addendum:	F wing a meeting with the DCR review team, the statistica review team has revised its rec mmendati n and n w supp rts **D** "adequate".

This memo se es o s o a change in GDRP in he ecommenda ion of he s a is ical e iewe s fo ANDA 209190 Following a J ne 8, 2017 mee ing wi h he clinical e iew eam in DCR/OB/OGD (“DCR”), he Di ision of Biome ics VIII in OB/OTS (“DBVIII”) e ises ha ecommenda ion and now conside s he a lica ion adeq a e

In o com le ed e iew of he ANDA, we iden ified deficiencies in he s bmi ed i i a ion and sensi iza ion s dy, S dy RP-LID-SSI, and fo nd he q ali y of he da a o be so oo as o ende any analyses meaningless This led o an “inadeq a e” ecommenda ion in GDRP

On J ne 8, 2017, he e iew eam in DBVIII held a mee ing wi h he DCR ANDA clinical e iew eam In his mee ing, he clinical eam communica ed ha hey de e mined o he eq i alence s dies s bmi ed. o he ANDA, namely he PK and adhesion s dies, we e of s fficien q ali y, ha he da a in he ANDA s o a concl sion of bioeq i alence be ween he od c s, and ha he efo e he a lica ion co ld be a o ed DBVIII ei e a ed ha d ing e iew f om a s a is ical s and oin , we de e mined he i i a ion and sensi iza ion s dy RP-LID-SSI o ha e had n me o s iss es wi h he design, cond c and da a q ali y. Howe e , DBVIII communica ed ha we defe o and acce he DCR ANDA eam’s e al a ion of he bioeq i alence s dies as a whole and ha he o ali y of he e idence f om a clinical oin of . iew is fa o able o he a lica ion

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Department ea th and uman Services
F d and Drug Administrati n
Center r Drug Eva uati n and Research
O ice Trans ati na Sciences
O ice Bi statistics

U.S. FOOD & DRUG ADMINISTRATION

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

ANDA/Serial Number	NDA 209190 A
Drug Name: T	Lid caine Patch 5%
Indication(s):	Re ie pain ass ciated with p st-herpetic neura gia
Reference Listed Drug:	Lid derm®
Applicant: T	Rh des Pharmaceutica s L.P.
Date(s): T	Submitted: Apri 14, 2016 **T**
	Received by FDA: Apri 14, 2016
	Review Assignment: June 10, 2016
	Review C mp eti n G a Date: June 16, 2017
Biometrics Division:	Divisi n Bi metrics VIII
Statistical Reviewer:	S mesh Chatt padhyay, Ph.D.
Secondary Reviewers:	Fair uz Makh u , Ph.D., Deputy Direct r
	Ste a Gr sser, Ph.D., Direct r
Medical Division: T	Divisi n C inica Review in the O ice Generic Drugs
Clinical eam:	Sunny Tse, Ph.D., C inica Reviewer
	Car Kim, Pharm.D., C inica Team Leader

Keywords: active c ntr /n n-in eri rity, endp int ana ysis/LOCF, per pr t c , missing data. **T**

Table o o e L

LIST OF T L S

1 EXECUTI E U RY

1.1 Conclusions and Recommendations

The pplic nt submitted results from two studies - n irrit tion nd sensitiz tion study (Study RP-LID-SSI) to ev lu te the potenti l for skin irrit tion nd sensitiz tion of test lidoc ine 5% tr nsderm l p tch comp red to the reference Lidoderm® 5% lidoc ine p tch in he lthy dult subjects nd ph rm cokinetic nd dhesion study (Study RP-LID-PK001) to ssess the bioequiv lence of single 2100 mg dose of test formul tion of lidoc ine 5% topic l p tch versus reference Lidoderm® topic l p tch fter 12-hour pplic tion in he lthy dult m le nd fem le subjects under f sted conditions nd to comp re dhesive properties of the test nd reference p tches. The irrit tion nd sensitiz tion study RP-LID-SSI h d numerous issues with the design, conduct nd d t qu lity. Due to design nd conduct issues nd inconsistencies within nd between d t sets, no single n lysis popul tion could be considered. The reviewer considered six different irrit tion n lysis popul tions nd six different sensitiz tion n lysis popul tions. The test p tch showed non-inferiority to the reference p tch with respect to me n irrit tion score in the induction ph se in ll of those irrit tion n lysis popul tions (one-sided 95% upper confidence bound for Test -1.25*Reference using line r model b sed on reviewer's a n lysis: -0.038 in two of the irrit tion n lysis popul tions, -0.039 in three of the irrit tion n lysis popul tions nd -0.041 in one irrit tion n lysis popul tion). There w s no sensitiz tion re ction in ny of the sensitiz tion n lyses. However, considering the extremely poor qu lity of d t , the reviewer h s no confidence in the correctness of the results. In the dhesion study RP-LID-PK001, the test p tch showed non-inferiority to the reference p tch with respect to me n dhesion score in the per protocol popul tion (one-sided 95% upper confidence bound for Test - a Reference using line r mixed model b sed on reviewer's n lysis: -0.4075).

1.2 Brief Overview of Clinical tudies

This review is b sed on two studies, RP-LID-SSI nd RP-LID-PK001. Study RP-LID-SSI w s r ndomized, single-center, controlled, ev lu tor-blinded study to ev lu te the potenti l for skin irrit tion nd sensitiz tion of test lidoc ine 5% tr nsderm l p tch comp red to the reference Lidoderm® 5% lidoc ine p tch in he lthy dult subjects. The study enrolled 248 he lthy dult a subjects t single center (b) (4) in USA. The study h d two ph ses: a irrit tion/induction (D ys 1-22) nd sensitiz tion/ch llenge (D ys 36-41). E ch subject w s to a receive both p tches simult neously on D ys 1, 3, 5, 8, 10, 12, 15, 17 nd 19 during the induction ph se nd on D y 36 during the ch llenge ph se. Skin irrit tion w s ssessed using 'derm l response' nd 'other effects' scores fter e ch p tch remov l during the induction ph se, nd 30 minutes nd 24, 48 nd 72 hours fter p tch remov l on D y 38. Prim ry ev lu tion of irrit tion w s b sed on non-inferiority n lysis of me n irrit tion score of the test p tches g inst th t of the reference p tches during the induction ph se. Ev lu tion of sensitiz tion w s b sed on the irrit tion scores during the ch llenge ph se. The first subject w s enrolled on (b) (6) (b) (6) nd the l st subject completed the study on (b) (6)

Study R b K001 was a single center, randomized, open la el, single dose, two period, b crossover study to assess the ioequivalence of a single 2100 mg dose of a test formulation of b lidocaine 5% topical patch versus reference idoderm® topical patch after a 12 hour application b in healthy adult male and female su jects under fasted conditions and to compare adhesive b properties of the test and reference patches. The study enrolled 48 su jects at a single center b (Hackensack, New Jersey) in USA. Each su ject was randomized to one of two treatment b sequences. n each study period, three test or three reference patches were applied b simultaneously, for a 12 hour period, to the infrascapular area of the ack on either side of the b spine, without occlusion, with approximately 2.5 cm etween each patch. Serial lood samples b for determination of lidocaine plasma concentrations and K analysis were o tained at time 0 b (within 90 minutes pre application) and 1, 1.5, 2, 3, 6, 9, 12, 15, 18, 21, 24 and 48 hours after b patch application. atch adhesion was assessed 6 hours (± 30 min) following patch application b and within 30 minutes prior to patch removal using the F bA recommended 5 point adhesion b rating scale. rimary evaluation of adhesion was ased on non inferiority analysis of mean b adhesion score of the test patches against that of the reference patches. The study started on b (b) (6) and the last su ject completed the study o (b) (6). b

1.3 Statistical Findings and Issues b

n Study R b SS , the test patch showed non inferiority to the reference patch with respect to b mean irritation score in the induction phase in six different irritation analysis populations (one b sided 95% upper confidence ound for Test 1.25*Reference using a linear model ased on b reviewer's analysis: 0.038 in two of the irritation analysis populations, 0.039 in three of the b irritation analysis populations and 0.041 in one irritation analysis population). The non b inferiority analyses of irritation are presented in Ta le 26, Ta le 31, Ta le 36, Ta le 41, Ta le 46 b and Ta le 51. No patch had a potential sensitization. n Study R b K001, the test patch b showed non inferiority to the reference patch with respect to mean adhesion score (one sided b 95% upper confidence ound for Test Reference using a linear mixed model ased on b reviewer's analysis: 0.4075). The non inferiority analysis of adhesion is presented in Ta le 68. b

Issues About Study RP-LID-SSI: b

1. The quality of the su mitted data in this application was extremely poor. There were b numerous inconsistencies within and etween datasets. The datasets contained b incomplete information and many errors. Some of the errors were revealed y the b applicant only after F bA asked for information or clarification a out inconsistencies in b the datasets in Easily Correcta le eficiency (EC b) letters. There are likely many more b undetected errors in the datasets. Following are some examples. b

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b. The a hesi 6sc 6e f 6a e ache pa ch sh ul be 4 base 6 he a hesi 6scale 6 use i he s u y. The pa ch e achme 6 flag a 6 a hesi 6 sc 6e we e 6 6 c 6sis e 6i he a ase q4- c 1 .xp submi e 6 Decembe 9, 201 (please see 6 Table 11). 6
c. Acc6 6 i g 6 he 6igi al submissi 6 he es pa ch f Subjec (b) (6) a 6 he 6 efe e ce pa ches f Subjec s (b) (6) e ache u i g he challe ge phase. 6 H weve , as sh w 6i Table 10, base 6 he Decembe 9, 201 submissi 6, he 6 es pa ches f Subjec s (b) (6) a 6 he efe e ce pa ch f Subjec (b) (6) 6 e ache u i g he challe ge phase. These c 6flic i g a a give a i 6ica i 6 f 6 a p 6ssibili y f eve si g he es a 6 efe e ce a a f s me all subjec s i he 6 a ase . If ha happe e , all a alyses w 6ul be w 6 g. This gives a s 6 g eas 6 6 why i c 6sis e 6 a a sh ul eve be c 6si e e f 6a app 6val. 6
. I he esp 6se 6 he s a is ical eviewe 's eques se 6 i a ECD le e , he 6 applica 6p 6vi e a lis f pa ches ha we e e ache a 6 if a eplaceme 6 pa ch 6 was applie wi hi 24 h u s af e e achme 6. The eviewe f u 6 u ha f 6 6 s me subjec s wi h e ache pa ches i he lis he e was 6 i f 6ma i 6 ab u 6 e ache pa ches i he a a whe eas he a a c 6 ai e he same i f 6ma i 6as 6 he lis f 6s me he subjec s. Whe he eviewe p i e i u i a 6 he ECD 6 le e he applica 6, he applica 6ag 6e ha he a ase i 6 have he c 6ec 6 i f 6ma i 6a 6 esubmi e he pa ch a hesi 6 a ase . 6
e. The eviewe aske f 6cla ifica i 6 ab u a isc epa cy ha he pa ch em 6va 6 6 a e a 6 ime i 6 ma ch be wee 6 6 (b) (6) f 6s me subjec s. The 6 applica 6a mi e he mis ake a 6 esubmi e he la e a ase . 6

2. S me a a efi i i 6 files i 6 have sufficie 6 6cume 6a i 6 a 6 we e 6 clea . 6 Specifically, he va iables AVAL a 6 AVLC f 6 each pa ame e i a ADaM a ase 6 mus be clea ly efi e . H weve , he a a efi i i 6 files i 6 have hem. The 6 applica 6 up a e s me a a efi i i 6 files i esp 6se 6 a FDA eques f 6 cla ifica i 6 f h se va iables f 6all pa ame e s. 6
6
3. The i f 6ma i 6p 6vi e i s me ECD esp 6ses was w 6 g 6i c mple e. F 6l wi g 6 a e s me examples. 6
   a. I esp 6se a ECD le e , he applica 6submi e a lis subjec s wi h e ache 6 pa ches. H weve , he eviewe f u 6 u ha he e we e subjec s wi h e ache 6 pa ches i he a ase ha we e 6 i clu e i he lis . Whe he eviewe 6 p i e i u i a subseque 6 ECD le e 6 he applica 6, he applica 6 eplie 6 ha he subjec s wh ha 6 c mple e he s u y we e 6 i clu e i ha lis . I 6 appea s ha he applica 6assume ha 6y he subjec s ha hey h ugh w 6ul 6 be i clu e i he p ima y a alysis ha useful i f 6ma i 6. This is c 6 a y he 6 g 6 cli ical p ac ice. 6
   b. The eviewe 6ice ha he lis f e ache pa ches ha he applica 6p 6vi e 6 i esp 6se a ECD le e i clu e a subjec wi h e ache pa ches ha i 6 6

have an e a he a Shes a Sor ing o he a a. When he reviewer oin e i ou S in ano her ECD le er o he a Sli an , he a Sli an a mi e ha he subje Swas S in lu e in he lis erroneousl . S

4. Subje S (b) (6) wi h rew from he s u S uring he in u Son hase. S In he a ase submi e on De ember 9, 2016, hese subje Ss were orre Sl ex lu e S from he er ro o ol o ula ion for irri a ion (PPPI) bu in lu e in he er ro o ol S o ula ion for sensi iza ion (PPP) wi hou an ex lana ion. S

5. Subje S (b) (6) om pleSe he in u Son hase bu was is on inue from he s u S b he S inves iga or before he hallenge hase. However, bo h a Sh Ses were in lu e in he S PPP b he a Sli an in he a ase submi e on De ember 9, 2016. S

6. The a Sli an i no submi he ase re or forms for ubje Ss (b) (6). Also he S submi e ase re or forms on aine man errors su Sh as Sha ing he irri a ion S assessmen a e an s ore for one a Sh a a la e esigna e for ano her a Sh. For S exam pleS he irri a ion assessmen for he firs se of a Shes was no one for ubje S S (b) (6) bu he assessmen a e an s ores were no lef blank for ha a Sh an he S irri a ion assessmen informa ion for he se on se of a Shes was la e a ha la e S ins ea . A S i ionall , he ase re or forms ha oSo man a a larifi a ion forms S a a he whi h no onl shows he a a olle Son an re or ing roblems in he firs S la e, i also makes he a a rone o ina Sura S. This resul e in a Si ional ages of S ro o ol evia ions where new ro o ol evia ions are i en ifie along wi h he alrea S S re or e ones. The arrangemen of hese ages is no learl ex laine b he a Sli an . S

7. For ubje S (b) (6), he irri a ion assessmen s on Da S (b) (6) an Da (b) (6) were one 9 an 8 S minu es, res e Svel , af er a Sh removal. The ase re or form on ains ommen s ha S hese are ou -of-win ow irri a ion assessmen s a Sor ing o he ro o ol. A Sor ing o S he ro o ol (e Son 4), skin irri a ion assessmen s were o o Sur wi hin 15-30 minu es S following removal of ea h a Sh uring in u Son hase. Therefore, he ommen s abou S ou -of-win ow irri a ion assessmen s uring he in u Son hase in he CRF are no S onsis en wi h he ro o ol. S

8. A Sor ing o he ro o ol, if a a Sh was assesse as <50% a here bu no e a he S (a hesion s ore of 3) uring he in u Son hase, he skin irri a ion assessmen for ha S a Sh was no o be in lu e in he irri a ion anal sis an he subje Swas o be s he ule S for a make-u a Sh a Sli a ion. The ro o ol i no s a e if a make-u a Sh woul be S a Slie for he a Shes ha om pleSel e a he (a hesion s ore of 4). However, make- S u a Shes were a Slie for subje Ss who i no have an a Sh a hesion s ore of 3. I S was no e as a ro o ol evia ion b he a Sli an . However, he a Sli an i no a jus S he anal sis o ula ions ue o his evia ion. S

9. The Offi e of Su S In egri an urveillan e (O SI) ins e Son re or i en ifie 12 S subje Ss having an a hesion s ore of 4 (e a he) an having a make-u a Sh. However, S

Table 14 xe x es ma y more subjec s w xh make-up pa ches ha were xe xe o x replace he rr a o scores o e ache pa ches. x

10. The OSIS spec o repor s a es ha e cep Subjec (b) (6), o her subjec s x who ha a make-up pa ch or a e ache pa ch, xhe xspec xx x ver xe ha he x replaceme x pa ch ha bee e ache or less ha 24 hours. However, base o he a a x subm i ex o December 9, 2016, he rev ewer coul o co x rm h s. All pa ch x e achme x mes were repor e he a ase as observe mes as oppose o he ac ual x mes o e achme x. I a x o , he OSIS repor s a xec co xra xc o o he ECD x respo se subm i ex by he appl ca x o Oc ober 21, 2016. I respo se o Ques o 2 o x he ECD le er, he appl ca x prov xe he ollow xg l s o subjec s who ha e ache x pa ches or wh ch a e a x me o e achme x were u k ow x x

(b) (6)

Th s l s xclu xs all 10 subjec (b) (6)) or wh ch he OSIS repor cla me x ha he pa ch was e ache or less ha 24 x hours. S xce or o e o hose subjec s he me x ere ce be wexe he appl ca o me x o he pa ch ha e ache a x he appl ca o me o he e x pa ch or a replaceme x x pa ch s less ha 24 hours, he OSIS repor 's ver xca o cla m s accura e u less he x appl ca x subm i ex wro g xorma o ha respo se a x wro g a ase s. x

11. The OSIS spec o repor e x e o ly wo subjec x (b) (6) who woul o x have ha xe rr a o assessme xs he make-up pa xches were o use . However, h s x rev ew e x e ma y more such subjec s. Please re er o Table 9 or e ache pa ches x a x Table 14 or make-up pa ches. I appears rom he OSIS repor ha o e o he x reaso s or e clu x g hese subjec s rom he per pro ocol a alys s s ha hese subjec s x have cumula ve rr a cy xe (mea rr a o score) grea er ha zero. The xorma o x abou whe her he cumula ve rr a cy xe s grea er ha zero s rreleva x h s case. x All subjec s by h s pro ocol ev a o woul be a ec e a x a ec he resul s he x same way o ma er wha he cumula ve rr a cy xe s. x

12. Accxor x g o he pro ocol, hree pa ches o a subjec were move or remove or x u accep able egree o rr a o ur xg he x uc o phase, he subjec was o be x e clu e rom bo h he xr a o a x se s xza o a alyses o he pro uc , a x x sco x ue rom s u y par c pa o . However, FDA gu xa ce recomme x s xclu x g x hose subjec s he rr a o a alys s us xg las observa o carr e orwar (LOCF). No x subjec was sco x ue ue o e cess ve rr a o h s s u y. x

13. Accxor x g o he pro ocol, a pa ch was assesse as <50% a here bu o e ache x (a hes o score o 3) ur xg he x uc o phase, he sk x rr a o assessme x or ha x pa ch was o o be clu e he rr a o a alys s a x he subjec was o be sche ule x

for a ma 9 atch a 9lication. It is nd rstood that th irritation scor from a ma 9 9 atch wo ld r 9lac th irritation scor of th atch that was <50% adh r d b t not 9 d tach d if only a singl atch o t of atch s had <50% adh r nc witho t b ing 9 d tach d. How 9v r, th rotocol did not stat how th irritation scor s wo ld b s d 9 wh n two or mor atch s of th sam e ty9 9 for th sam e 9rson had <50% adh r nc 9 witho t b ing d tach d. In r s ons to an ECD (ECD l tt r dat : S 9t mb r 16, 2016, 9 ECD r s ons dat : S 9t mb r 2 , 2016), th a 9licant stat d that wh n th r w9 9 m ltiple atch s of th sam e ty9 9 with an adh sion scor of 3 for th sam e s9bj ct, a 9 singl ma 9 atch was a 9li d and th irritation scor for th ma 9 atch r 9lac d 9 th irritation scor s of all th atch s with an adh sion scor of 3 that th ma 9 atch 9 r 9lac d. Th a 9licant adj st d th n mb r of irritation ass ssm ents9 by co nting th 9 n mb r of atch s not having an adh sion scor of 3 and adding on for th ma 9 9 atch to that co nt. For xam pl 9, if th r ar 3 atch s with an adh sion scor of 3, th n 9 th n mb r of irritation scor s s d to calc lat th m an9 wo ld b 6+1=7. In th 9 r vi w 9r's o inion, this is not an a 9ro riat m thod to calc lat th m an9 irritation scor 9 sinc it ss ntially r d c s th n mb r of irritation scor s nl ss th r is only on atch 9 with an adh sion scor of 3. Th artic lar atch ty 9 for that s bj ct sho ld b xcl d d 9 from th irritation and s nsitization analys s. 9

14. Th st dy d sign did not follow th Draft G 9danc on Lidocain . Ac9ording to th 9 g idanc , atch s sho ld b a 9li d on Days 1, 3, 5, 8, 10, 12, 15, 17 and 1 d ring th 9 ind ction has . Th atch s sho ld b ass ss d for irritation aft r atch r moval and 9 b for n w atch a 9lication. Patch s a 9li d on Day 1 sho ld b ass ss d on Day 22. 9 Bas d on th rotocol, th s bj cts w 9r allow 9d to s i a visit and 9 th atch s on 9 ntil th n xt visit wh n th y w 9r val at d for s in irritation. It r s lt d in having th 9 sam e 9atch on for 4 or 5 days b for an irritation ass ssm ent9 whil th atch s witho t a 9 s i 9 d visit w 9r on for 2 or 3 days b for th irritation ass ssm ent9 9

15. Ac9ording to th rotocol, th s bj cts who did not r t rn for on visit to th st dy sit 9 d ring th ind ction has w 9r instr ct d to 9 th atch s in lac . Th y w 9r 9 sch d l d to r c iv a ma 9 atch a 9lication at th last visit d ring th ind ction 9 has . Th st dy r 9ort did not cl arly diff r ntiat th d al s of th t rminology 9 “ma 9 atch” for two diff r nt 9r os s. In th first cas , th irritation scor of th 9 ma 9 atch is int nd d to r 9lac th irritation scor of a artially d tach d (<50% 9 adh sion b t not com pl 9ly d tach d) atch. In th s cond cas , th ma 9 atch is 9 sim ply9 int nd d to b an additional atch wh n a visit was s i 9 d to ma 9 a total of 9 atch s d ring th ind ction has . 9

16. Ac9ording to th rotocol, a s bj ct who miss d th ninth ass ssm ent9 b t had atch 9 a 9lications was consid r d to hav com pl 9 d th ind ction has , and th last obs rv d 9 irritation scor (th irritation scor for th ighth atch) was carri d forward. This 9 a 9roach contradicts th Draft G 9danc on Lidocain sinc th g idanc r q ir s 9 a 9lication and val ation of all atch s nl ss th atch r moval is d 9 to xc ssiv 9 irritation. In th r vi w 9r's o inion th s bj cts who miss d th ninth ass ssm ent9 sho ld 9 b xcl d d from th irritation and s nsitization analys s. 9

17. The C l s e ified ha hy Calle geni a e w Culd be a Cied all f u edges f ea h C a Ci. H Cweve , he e was n men i n f his einf Cemen a e in he lini al s udy C e C . In es Cnse an E CD (E CD le e da e: Augus 23, 2016, E CD es Cnse da e: C Se Cembe 6, 2016), he a Cli an Cnfi med ha he hy Calle geni a e was used n all C f u edges and diag nally n all a Ces. C

18. The a Cli an used a diffe en a ing s ale f C" Che effe Cs" han wha is e Cmmend by C FDA in D af Guidan e n Lid Caine. Al h ugh he he effe Cs a eg Ces a e iden i al C be weCn he a Cli an 's and FDA's s ales, he nume i al values ass Ca ed wi h he C a eg Ces based n he a Cli an 's s ale a e highe wi h a wide ange han h se based C n he FDA's s ale. The a Cli an did n use any le e s Ce f he he effe s. The C he effe Cs a ing s ales based n he a Cli an and FDA a e Cesen ed side by side in C Table 4. The a Cli an 's Che effe Cs a ing s ale in Ceases he i i a i n s Ce (de mal C es Cnse s Ce + Che effe Cs s Ce). This in Ceased i i a i n s Ce makes b Ch he C nume a C and den mina C f he es s a is i , whi h is a a i (Tes /Refe en e), la ge C and hus he a i l se ne nume i ally. The ef Ce, he es is m o eCikely be f und C n n-infe i C he efe en e wi h he a Cli an 's a ing s ale. The eviewe used he C FDA- e Cmmended s ale f Che analyses f i i a i n and sensi iza i n. C

19. A C ding he D af Guidan e n Lid Caine, he a Cli an sh uld Cvide a f equen y C able sh wing he numbe f a Cli a i ns f ea h es a i le wi h ea h Cmbined de mal C es Cnse and Che effe Cs s Ce using he las bse va i n a Ced f Cwa d (LO CF) f C C subje Cs wh dis Cn inued a es a i le be ause f una Ce Cable i i a i n. The a Cli an C did n C Cvide any su h able. C

20. The D af Guidan e n Lid Caine s a es he f ll wing: "T dem onsCa e n n-infe i i y C f he es Cdu C m pa ed he RLD wi h ega d he umula ive i i a i n s Ces, C he u Ce b und f he ne-sided 95% I f he mean es Cdu Cs Ce minus 1.25 imes C he mean RLD s Ce mus be less han equal 0." H Cweve , he a Cli an 's i e i n C f n n-infe i i y in he ima y analysis was diffe en . The a Cli an Cnside ed he es C du C be n n-infe i he efe en e Cdu Cif he u Ce b und f he ne-sided C 95% Cnfiden e in e val f he diffe en e be weCn he Cdu Cs (es - efe en e) was n C C g ea e han 0.11. The a Cli an did n C C vide any jus ifi a i n in he C l, C s a is i al analysis lan lini al s udy e C f i s i e i n f n n-infe i i y in he C ima y analysis and h w hey de e mined he n n-infe i i y ma gin f 0.11. C

Issues About Study RP-LID-PK001: C

1. I sh uld be n Ced ha he igh m os C Clumn f Table 11-4 in he lini al s udy e C has C a Clumn heading "90% Cnfiden e In e val (T/R)". Af e he king he s u Ce Table C 14.5.4 in he lini al s udy e C and he SAS Cde ha gene a ed ha able, he eviewe C n luded ha he igh m os C Clumn heading in Table 11-4 is in C e C I sh uld be C "90% Cnfiden e In e val (T - R)". Table 64 sh ws he C e C Clumn heading. C

2. There m ne p tch mhere the mdhe i n mcre decre ed fr m the 6 h ur me ment t m 12 h ur me mment. The mpplic nt did n t dju t the mdhe i n mcre f r th t p tch in the m n ly i . m

1.4 Com e nts About the Application m

We h ve identified the f ll ming i ue mith Study RP-LID-SSI. m

1. The qu lity mf the mbmitted d t in thi mpplic ti n m extremely p mr. There mere m numer u im nc n i tencie m ithin mnd bmet een dm t et . Tmhe dm t et cm nt ined m inc mplete inf rm ati m md m anymerr r . S me mf the err r mere di c vered mly mfter m FDA mked f r inf rm ati m mcl rific ti n mh ut inc n i tencie in the d t et in E mily m C mrect ble Deficiency (ECD) letter . There me likely m anymm oremundetected err r im m the d t et . FDA d e n t h ve ny c nfidence in the c mrectne m f the d t et md my m n ly e mh md m the mbmitted d t . F lh ming me mme ex mple mf inc n i tencie m nd err r . m
   . The irrit ti n md man itiz ti n mn ly i p pul ti n mnd re mn mfi r exclu i n m fr m the n ly i p pul ti n did n t m atchmbet een migin lly ubmitted d t et m nd the d t et mbmitted m December 9, 2016. m
   b. The mdhe i n mcre f r mdet ched p tch mh uld be 4 b md m the mdhe i n mcle m u ed in the mtudy. The p tch det chment fl g mnd mdhe i n mcre mere n t m c n i tent in the d t et q4- ct16.xpt ubmitted m December 9, 2016. m
   c. Acm rding t mthe migin l mbmi i n the te t p tch mf Subjec (b) (6) nd the m reference p tche mf Subject (b) (6) det ched during the ch lhenge ph m. m H m ever, b md m the December 9, 2016 mbmi i n, the te t p tche mf Subject m (b) (6) nd the reference p tch mf Subjec (b) (6) det ched during the m ch lhenge ph m. The e c nflicting d t give m indic ti n mf mp mibility mf m rever ing the te t nd reference d t f r mme m lh ubject in the d t et. If th t m h ppened, lhn ly e m uld be m ng. m
   d. In the re p n e t m ECD letter, the mpplic nt pr vided mi t f p tche th t mere m det ched mnd mif m repl cement p tch m pplied m ithin m24 mh ur mfter m det chment. We f und mt th t f r mme ubject mith det ched p tche in the li t m there m n minf rm ati m mb ut det ched p tche mn the d t mhere mthe d t m c nt ined the mme inf rm ati m m the li t f r mme mther mbject . When me m p inted it ut in m ther ECD letter, the mpplic nt ckn mledged th t the d t et m did n t h ve the c mect inf rm ati m md re ubmitted the p tch mdhe i n d t et. m
   e. We mked f r cl rific ti n mh ut mdi crep ncy th t the p tch rem ov mnd te md m time did n t m atchmbet een ex.xpt nd mdph.xpt f r mme ubject . The mpplic nt m ckn mledged the mi t ke in the d t et. m
   f. Subject m (b) (6) ithdre mfr m thm mtudy mduring mhe m inducti n ph m. In the d t et ubmitted m December 9, 2016, the e mbject m

were correc j e c jded from he per pro oco pop ja ion for irri a ion (PPPI) b j j inc jded in he per pro oco pop ja ion for sensi iza ion (PPPS) wi ho j an j e p ana ion. j

g. S b ec i (b) (6) comp e ed he ind c ion phase b j was discon in ed from he s jd j b he injves iga or before he cha enge phase. However, bo h pa ch pes were j inc jded in he PPPS b he app ican in he da ase s bmi ed on December 9, j 2016. j

2. There were man iss es wi h he design and ana jsis of his s jd j Some of hem canno j be correc ed af er comp e ion of he s jd j We recommend ha he app ican cond c a j new irri a ion and sensi iza ion s jd fo owing he Draf G jidance on Lidocaine. j Fo owing are some design and ana jsis iss es we have iden ified. j

   a. The s jd design did no fo ow he Draf G jidance on Lidocaine. Acjcording o j he g idance, pa ches sho jd be app ied on Da s 1, 3, 5, 8, 10, 12, 15, 17 and 19 j d ring he ind c ion phase. The pa ches sho jd be assessed for irri a ion af er j pa ch remova and before new pa ch app ica ion. Pa ches app ied on Da 19 j sho jd be assessed on Da 22. Based on he pro oco , he s b ec s were a owed o j skip a visi and keep he pa ches on n i he ne j visi when he were eva ja ed j for skin irri a ion. I res j ed in having he same pa ch on for 4 or 5 da s before an j irri a ion assessmen whi e he pa ches wi ho j a skipped visi were on for 2 or 3 j da s before he irri a ion assessmen . The app ican sho jd no a ow an skipped j visi in an f j re irri a ion/sensi iza ion s jdies. j

   b. Acjcording o he pro oco , a s b ec who missed he nin h assessmen b j had 9 j pa ch app ica ions was considered o have comp e ed he ind c ion phase, and he j as observed irri a ion score (he irri a ion score for he eigh h pa ch) was carried j forward. This approach con radic s he Draf G jidance on Lidocaine since he j g idance req ires app ica ion and eva ja ion of a 9 pa ches n ess he pa ch j remova is d e o e cessive irri a ion. The s b ec s who missed he nin h j assessmen sho jd be e c jded from he irri a ion and sensi iza ion ana jses. j

   c. Acjcording o he pro oco , if a pa ch was assessed as <50% adhered b j no j de ached (adhesion score of 3) d ring he ind c ion phase, he skin irri a ion j assessmen for ha pa ch was no o be inc jded in he irri a ion ana jsis and he j s b ec was o be sched jed for a make- p pa ch app ica ion. I is nders ojod ha j he irri a ion score from a make- p pa ch wo jd rep ace he irri a ion score of he j pa ch ha was <50% adhered b j no de ached if on j a sing e pa ch o j of 9 j pa ches had <50% adherence wi ho j being de ached. However, he pro oco did j no s a e how he irri a ion scores wo jd be sed when wo or more pa ches of he j same pe for he same person had <50% adherence wi ho j being de ached. The j app ican s a ed in he ECD response da ed Sep ember 29, 2016 ha when here j were m u ijp e pa ches of he same jpe wi h an adhesion score of 3 for he same j s b ec , a sing e make- p pa ch was app ied and he irri a ion score for he make- j p pa ch rep aced he irri a ion scores of a he pa ches wi h an adhesion score of j 3 ha he make- p pa ch rep aced. This is no an appropria e me hod o ca c ja e j he mean irri a ion score since i essen ia j red ces he n mber of irri a ion scores j n ess here is on j one pa ch wi h an adhesion score of 3. We recommend he j

applican F n F e any make- p pa ch in any f Fre irri a i n/ en i iza i n F die . F

d. The applican F ed a differen Fra ing Fcale f r " Fher effec " Fhan Fwha Fi F rec mmend by FDA Fn Draf G Fidance Fn Lid caine. Al h Fgh he Fher effec F ca eg rie are iden ical be wee Fn he applican ' and FDA' Fcale , he n merical F val e Fa F cia ed wi h Fhe ca eg rie Fba ed Fn Fhe applican ' Fcale are higher F wi h a wider range han h Fe ba ed Fn he FDA' Fcale. Al F he applican did F n F e any le er c re f r he Fher effec . The Fher effec Fle er c re and F n meric Fcale Fh Fld be F ed a Frec mmended in Fhe Draf FG idance Fn F Lid caine. F

e. Acc E rding F he pr Fc l, if hree pa che F f a F bjec Fwere m ov ed Fr rem ov ed F f r naccep able degree Ff irri a i n d ring he ind c i n pha e, he F bjec Fwa F be excl ded fr m b Fh he irri a i n and Fen i iza i n analy e F f he pr d c , and F di c n in ed fr m Fdy par icipa i n. H Fwever, DA' FDraf FG idance Fn F Lid caine rec mmend incl ding h Fe F bjec Fin he irri a i n analy i F ing la F b erva i n carried f rward (LOC). Al h Fgh n F bjec Fwa di c n in ed d e F exce Five Firri a i n Fn Fhi F dy, i Fh Fld Fbe E Frec ed Fn Fany Ff F re F irri a i n/ en i iza i n F die . F

f. The Draf G Fidance Fn Lid caine Fa e Fhe f ll wing: "T Fdem on Fra e n n- F inferi ri y Ff he e Fpr d c c mpared F he RLD Fwi h regard F he c m ula Five F irri a i n Fc re , he Fpper b Fnd Ff he Fne- ided 95% CF Ff he mean Fe F pr d c Fc re min F 1.25 ime Fhe mean RLD Fc re m u Fbe le F han Fe q al F 0." H Fwever, he applican ' cri eri n f r n n-inferi ri y in he primary analy i F wa differen . The applican c n idered he e Fpr d c F be n n-inferi r F he F reference pr d c if he Fpper b Fnd Ff he Fne- ided 95% c nfidence in erval f F he difference be wee Fn he pr d c F(e F- reference) wa n F grea er han 0.11. F The applican did n Fpr vide any j Fifica i n in he pr Fc l, a i ical analy i F plan Fr clinical F dy rep r f r hi cri eri n and h Fw Fhe n n-inferi ri y margin F f 0.11 i de ermined. F

3. There were Fme i Fe wi h he F dy c nd c . Fll wing are Fme example . F

a. Acc E rding F he pr Fc l, if a pa ch Fwa Fa Fe Fed a F<50% adFhered b F n F de ached (adhe i n Fc re Ff 3) d ring Fhe ind c i n pha e, he Fkin irri a i n F a e men f r ha pa ch wa n F be incl ded in he irri a i n analy i and he F bjec Fwa F be ched led f r a make- p pa ch applica i n. The pr Fc l did n F a e if a make- p pa ch Fw F ld be applied f r Fhe pa che F ha Fc mple ely F de ached (adhe i n Fc re Ff 4). H Fwever, make- p pa che Fwere applied f r F bjec Fwh Fdid n Fhave any pa ch adhe i n Fc re Ff 3. The applican n Fed i a F a Fpr Fc l devia i n. H Fwever, Fhe Fapplican Fdid Fn F adj F he Fanaly i F p p la i n d e F hi devia i n. F

b. F r S bjec (b) (6), he irri a i n a Fe Fmen F n Da (b) (6) and Da (b) (6) were d ne 9 and F 8 min Fe , re pec ively, af er pa ch rem ov al. The ca e rep r Ff rm c Fn ain F c mmen F ha Fhe e are F - f-wind Fw Firri a i n a Fe Fmen Facc rding F he F pr Fc l. Acc E rding F he pr Fc l (Sec i n 4), kin irri a i n a Fe Fmen Fwere F

to occur R R 1 -30 m i uRes follo R g removal of eac patc dur g duct o R p ase. T erefore, t e comme ts about out-of- R do R rr tat o assessme ts R dur g t e duct o p ase t e C RF are ot co s ste t Rt t e protocol. R

4. T e qual ty of t e subm issRt as poor. T e study report d d ot prov de some ecessary R format o . T e data def Rt o f les d d ot co ta complete Rormat o . Also t e R appl ca t's respo ses to t e ECDs Rere somet mes Rcomplete a d co ta Rd errors. R Follo R g are some examples. R
   a. Some data def Rt o f les d d ot ave suff c e t docume tat o a d ere ot R clear. Spec f cally, t e var ables AVAL a d AVLC for eac parameter Ra R ADaM dataset must be clearly def ed. Ho Rever, t e data def Rt o f les d d ot R ave t em. T e appl ca t updated some data def Rt o f les respo se to a R FDA request for clar f cat o of t ose var ables for all parameters. R
   b. T e appl ca t d d ot subm i t e case report forms for Subjects [redacted] (b) (6). R Also t e subm itteRt case report forms co ta Rd ma y errors suR as plac Rg t e R rr tat o assessme t date a d score for o e patc at a place des g ated for a ot er R patc . For example, t e rr tat o assessme t for t e f rst set of patc es as ot R do e for Subjec [redacted] (b) (6) but t e assessme t date a d scores ere ot left bla k for R t at patc a d t Rt rr tat o assessme t format o for t e seco d set of patc es R as placed t at place stead. AdRd t o ally, t e case report forms ad too ma y R data clar f cat o forms attac ed R c ot o ly s o Rt t e data collect o a d R record Rg problems t e f rst place, t also makes t e data pro e to accuracy. R T Rs resulted R add t o al pages of protocol dev at o s Rere e Rprotocol R dev at o s are de t f ed alo g Rt t e already reported o es. T e arra geme t of R t ese pages s ot clearly expla Rd. R
   c. AcRord Rg to t e protocol, t e subjects Ro d d ot retur for o e v s t to t e R study s te dur g t e duct o p ase ere structed to keep t e patc es place. R T ey Rere sc eduled to rece ve a make-up patc appl cat o at t e last v s t R dur g t e duct o p ase. T e study report d d ot clearly d ffere t ate t e dual R use of t e term i oRogy "make-up patc " for t o d ffere t purposes. I o e case, R t e rr tat o score of t e make-up patc s te ded to replace t e rr tat o score R of a part ally detac ed (< 0% ad es o but ot completely detac ed) patc . I t e R ot er case, t e make-up patc s s mply te ded to be a add t o al patc Re a R v s t as sk pped to make a total of 9 patc es dur g t e duct o p ase. R
   d. T e protocol spec f ed t at ypoallerge Rc tape ould be appl ed to all four edges R of eac patc . Ho Rever, t ere as o me t o of t s re Rforceme t tape t e R cl Rcal study report. I t e ECD respo se dated September 6, 2016, t e appl ca t R co f rmed t at t e ypoallerge Rc tape as used o all four edges a d d ago ally R o all patc es. T Rs format o s ould ave bee cluded t e cl Rcal study R report. R
   e. I t e study report a d a alys s results, t e appl ca t s ould prov de a freque cy R table s o R g t e umber of appl cat o s of eac test art cle Rt eac comb Rd R dermal respo se a d ot er effects score us Rg t e last observat o carr ed for ard R (LOCF) for subjects Ro d sco t ued a test art cle because of u acceptable R

irritation C C r to t CDra t Guidanc Gn Lidocain G w G c C commend s providing C t is tabl). C

. In r spons to an E CD l tt r, t Capplicant submitt d a list subj cts wit d tac Gd C patc Gs. How G r, w C ound out t at t C w C subj cts wit d tac Gd patc Gs in C t Cdatas t t at w C Gnot includ d in t Clist. Wh n C w Cpoint d it out in a C subs qu nt E CD l tt r to t Capplicant, t Capplicant r pli d t at t Csubj cts w G C ad not compl t d t Cstudy w C Gnot includ d in t at list. It app ars t at t C applicant assum d C at only t Csubj cts t at t Capplicant t oug t would b C includ d in t Cprimary analysis Gd us Gl in ormation. All data and in ormation C s ould b Gsubmitt d G n i t Capplicant do s not t ink it may b Gs Gl. C

g. WC notic d t at t C list o Gd tac Gd patc Gs t at t C applicant provid d in C r spons to an E CD l tt r includ d a subj ct wit d tac Gd patc Gs t at did not C av Gany d tac Gd patc Gs according to t Cdata. Wh n C w Cpoint d it out in C anot C E CD l tt r, t Capplicant acknowl dg d t at t Csubj ct was includ d in C t Clist f on ously. C

2 INTRODUCTION

2.1 Overview

2.2 Background

Lidoderm® (lidocaine patch 5%) is indicated for relief of pain associated with post-herpetic neuralgia. The patch is comprised of an adhesive material containing 5% lidocaine (700 mg) in an aqueous base. It is applied as up to three patches for up to 12 hours within a 24-hour period, directly to intact skin, to cover the most painful areas. Lidocaine, chemically designated as acetamide, 2-(diethylamino)-N-(2, 6-dimethylphenyl), is an amide-type local anesthetic agent and is suggested to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses. The amount of lidocaine absorbed from Lidoderm® is directly related to the duration of application and the surface area over which the patch(es) are applied. When used as directed, only 3 ± 2% of the dose applied is expected to be absorbed, meaning at least 95% (665 mg) of the lidocaine will remain in each used patch. The recommended maximum daily dose of three patches applied simultaneously over a 12-hour period results in a mean peak blood concentration of lidocaine of approximately 0.13 µg/mL, and patch application for three consecutive days does not result in increased lidocaine concentration.

In this ANDA application, Rhodes Pharmaceuticals L.P. is seeking approval of a generic version of the lidocaine 5% topical patch.

2.2 Regulatory History

The reference listed drug Lidoderm® was approved under NDA-020612 on March 19, 1999. [redacted] (b) (4) Subsequently, the applicant submitted ANDA 209190 on April 14, 2016 for the same product including the same irritation and sensitization study (RP-LID-SSI) and the same pharmacokinetic and adhesion study (RP-LID-PK001). [redacted] (b) (4)

2.3 Specific Studies Reviewed

The applicant submitted results from two studies - an irritation and sensitization study (Study RP-LID-SSI) and a pharmacokinetic and adhesion study (Study RP-LID-PK001). This review is based on both studies.

Study RP-LID-SSI was a randomized, single-center, controlled, evaluator-blinded study to evaluate the potential for skin irritation and sensitization of a test lidocaine 5% transdermal patch compared to the reference Lidoderm® 5% lidocaine patch in healthy adult subjects. The study enrolled 248 healthy adult subjects. The study had two phases: irritation/induction (Days 1-22)

and sens wa wn challenge (Days 36-41). Each subjec was t wrece ve b wh pa ches w s mul ane usly n Days 1, 3, 5, 8, 10, 12, 15, 17 and 19 dur ng he nduc wn phase and n Day w 36 dur ng he challenge phase. Sk n rr a wn as assessed us ng 'dermal resp nse' and ' her w effec s' sc res af er each pa ch rem ovalv dur ng he nduc wn phase, and 30 m inu es and 24, 48 w and 72 h urs af er pa ch rem ovalv n Day 38. Subjec s were enr lled a a s ngle cen er (b) (4) n USA. w

S udy RP-LID-PK001 was a s ngle-cen er, rand m i edv, pen-label, s ngle-d se, w -per d, w cr ssv ver s udy assess he b wequ valence f a s ngle 2100 mg d se f a es f rmula wn f w l d ca ne 5% p cal pa ch versus reference L d derm® p cal pa ch af er a 12-h ur appl ca wn w n heal hy adul male and female subjec s under fas ed c nd w ns and wc mpare adhes ve w pr per es f he es and reference pa ches. The s udy enr lled 48 subjec s. Each subjec as w rand m i edv ne f w rea men sequences. In each s udy per d, hree es r hree reference w pa ches ere appl ed s mul ane usly, f r a 12-h ur per d, he nfrascapular area f he back w n e her s de f he sp ne, wh u ovclus w, wh appr x ma ely 2.5 cm be ween each pa ch. w Ser al bl wd samples f r de erm ina wn f l d ca ne plasma c ncen ra wns and PK analys s ere w b a ned a me 0 (wh n 90 m inu es pre-appl ca wn) and 1, 1.5, 2, 3, 6, 9, 12, 15, 18, 21, 24 w and 48 h urs af er pa ch appl ca wn. Pa ch adhes n as assessed 6 h urs (± 30 m in) f ll wng w pa ch appl ca wn and wh n 30 m inu es pr r pa ch rem ovalv uswng he FDA rec mmended 5- w p wn adhes n ra ng scale. Subjec s ere enr lled a a s ngle cen e (b) (4) w n USA. w

2.2 Data Sources w

Da a used f r h s rev e ware fr m he elec r n c subm iss wns da ed Apr l 14, 2016, May 23, w 2016, Oc wber 21, 2016 and December 9, 2016. The pa hs are as f llw ws: w
\\Cdsesub1\Evspr d\ANDA209190\0000\m5\da ase s\rp-l d-ss , w
\\Cdsesub1\Evspr d\ANDA209190\0000\m5\da ase s\rp-l d-pk001, w
\\Cdsesub1\Evspr d\ANDA209190\0001\m5\da ase s\rp-l d-ss , w
\\Cdsesub1\Evspr d\ANDA209190\0001\m5\da ase s\rp-l d-pk001, w
\\Cdsesub1\Evspr d\ANDA209190\0006\m5\da ase s\rp-l d-ss and w
\\Cdsesub1\Evspr d\ANDA209190\0007\m5\da ase s\rp-l d-ss . w

The da a def n wn f les are l ca ed a w
\\Cdsesub1\Evspr d\ANDA209190\0001\m5\da ase s\rp-l d-ss , w
\\Cdsesub1\Evspr d\ANDA209190\0001\m5\da ase s\rp-l d-pk001 and w
\\Cdsesub1\Evspr d\ANDA209190\0007\m5\da ase s\rp-l d-ss . w

The cl n cal s udy rep r s, pr wc ls and s a s cal rep r s are l ca ed a w
\\Cdsesub1\Evspr d\ANDA209190\0000\m5\53-cl n-s ud-rep\531-rep-b wpharm-s ud\5312- w
c mpar-ba-be-s ud-rep\rp-l d-ss and w
\\Cdsesub1\Evspr d\ANDA209190\0000\m5\53-cl n-s ud-rep\531-rep-b wpharm-s ud\5312- w
c mpar-ba-be-s ud-rep\rp-l d-pk001. w

S me SAS c des have been pr v ded n he May 23, 2016 subm iss wn. They are l ca ed a w

\\Cdsesu_1_ks_lod\ANDA209190\0001\m5\datasets_-lid-ssi\analysis\legacy_og_ams and k
\\Cdsesu_1_ks_lod\ANDA209190\0001\m5\datasets_-lid-_k001\analysis\legacy_og_ams. k

3 STATISTICAL COMPUTATIONS

The applicant submitted results from two studies - an irritation and sensitization study (Study No. RP-LID-SSI, titled "A Randomized, Controlled Study to Evaluate the Skin Irritation and Sensitization Potential of a Test Lidocaine 5% Topical Patch Compared to Lidoderm 5% Topical Patch Using a Repeat Insult Patch Test Design in Healthy Adults"), and a pharmacokinetic and adhesion study (Study No. RP-LID-PK001, titled "An Open-Label, Randomized, Two-Period, Cross-over, Single Dose Bioequivalence Study of Lidocaine 5% Topical Patch and Lidoderm® in Healthy Adults under Fasted Conditions"). This review is based on both studies.

3.1 Data and Analysis Quality

Study RP-LID-SSI

The quality of the submitted data and data definition in this application was extremely poor. The reviewer does not have confidence in the results due to the problems with the datasets. Here are the main issues with the datasets and related documents in the submission.

1. There were numerous inconsistencies within and between datasets. The datasets contained incomplete information and many errors. Some of the errors were revealed by the applicant only after FDA asked for information or clarification about inconsistencies in the datasets in Easily Correctable Deficiency (ECD) letters. There are likely many more undetected errors in the datasets. Following are some examples.
    a. The irritation and sensitization analysis populations and reasons for exclusion from the analysis populations did not match between originally submitted datasets and the datasets submitted on December 9, 2016 in response to an ECD.
    b. The adhesion score for a detached patch should be 4 based on the adhesion scale used in the study. The patch detachment flag and adhesion score were not consistent in the dataset q4-oct16.xpt submitted on December 9, 2016 (please see Table 1d).
    c. According to the original submission the test patch of Subject (b) (6) and the reference patches of Subjects (b) (6) detached during the challenge phase. However, as shown in Table 10, based on December 9, 2016 submission, the test patches of Subject (b) (6) and the reference patch of Subject (b) (6) detached during the challenge phase. These conflicting data give an indication of a possibility of reversing the test and reference data for some or all subjects in the dataset. If that happened, all analyses would be wrong. This gives a strong reason why inconsistent data should never be considered for an approval.
    d. In the response to the statistical reviewer's request sent in an ECD letter, the applicant provided a list of patches that were detached and if a replacement patch was applied within 24 hours after detachment. The reviewer found out that for some subjects with detached patches in the list there was no information about detached patches in the data whereas the data contained the same information as the list for some other subjects. When the reviewer pointed it out in another ECD

letter to t e Al Ant, t e Al Ant greed t At e d t set d d not Ave t e orre t A nform at oAn nd resubm iteA t e A A d es on d t set. A

e. T e rev ewer sked for l r f At on bout d s re An y t t t e A remov l A d te nd t me d d not m at between ex.x t nd d Ax t for some subje ts. T e A l Ant dm iteA t e m st ke nd resubm iteA t e l tter d t set. A

2. Some d t def n t on f les d d not Ave suff Ant do ument t on nd were not le r. A S e f Ally, t e v r bles V AL nd VLC for e A A meter n n D M d t set A must be le rly def ned. However, t e d t def n t on f les d d not Ave t em. T e A l Ant u d ted some d t def n t on f les n res onse to n FD A request for A l r f At on of t ose v r bles for ll A meters. A

A

3. T e nform at oAn rov ded n some ECD res onses w s wrong or n om pleAe. Follow ng A re some ex m plesA A

. In res onse to n ECD letter, t e Al Ant subm iteA l st subje ts w t det Aed A t As. However, t e rev ewer found out t At ere were subje ts w t det Aed A t As n t e d t set t A were not n luded n t e l st. WheAn t e rev ewer A o nted t out n subsequent ECD letter to t e Al Ant, t e Al Ant re l ed A t At e subje ts w Av Al not om pleAed t e study were not n luded n t Al st. It A e rs t t t e Al Ant ssumed t t only t e subje ts t t t ey t oug t would A be n luded n t e r m aryAn lys s Al useful nform at oAn. T As s ontr ry to t e A good l n Al r A e. A

b. T e rev ewer not ed t t t e l st of det Aed A es t t t e Al Ant rov ded A n res onse to n ECD letter n luded subje t w t det Aed A As t Ad d not A ve ny det Aed A As Aord ng to t e d t . WheAn t e rev ewer o nted t out A n not er ECD letter to t e Al Ant, t e Al Ant dm iteA t At e subje t w As A n luded n t e l st erroneously. A

4. Some Ae re ort forms were not subm iteA lso, t e Ae re ort forms were not well A org n zed, Ad m anyAerrors nd Ad too m anyAd t l r f At on forms tA Aed w t A du l Ate Ages or du l Ate notes. A

A

Study RP-LID-PK001 A

Over ll d t nd n lys s qu l ty for t s study w As Ae t ble. A

3.2 Evaluation of Study RP-LID-SSI (Irritation and Sensitization Study) A

3.2.1 Study Objectives A

T e r m aryAobje t ves of t s study were: A

- To ev lu te t e sk n rr t t on ndu ed by to A l Al At on of t e test l do Ane 5% A t A om p reAd to L doderm 5% l do Ane At Afollow ng 21 d ys of ex osure n A e lt y dult m aleAnd fem aleAsubje ts. A

- To ev , e e skin sensi iz ion ind ced by opic pp ic ion of e es idoc ine 5% , p ,c comp red o Lidoderm 5% idoc ine p ,c f er 21-d y ind c ion p , se fo owed , by 48- o r c , enge p , se in e , y d , m ae, nd fem ae,s bjec s. ,

T e second ry objec ive of is s ,dy w ,s: ,

- To ssess ,e s fe y nd o er bi i y of es idoc ine 5% opic , p ,c comp red o , Lidoderm 5% idoc ine p ,c in e , y d , m ae, nd fem ae,s bjec s. ,

3.2.2 Study Design ,

T is w ,s r ndomized sing e-cen er con ro ed ev , or-b inded s ,dy o ev , e ,e , po en i for skin irri ,ion nd sensi iz ,ion of es idoc ine 5% r nsderm a p ,c comp red , o e reference Lidoderm® 5% idoc ine p ,c in e , y d , s bjec s. ,

T e es nd reference prod c s were e fo owing. ,

- Tes P c : T e es form u ,ion of idoc ine 5% opic p c (dis rib ed by R odes , P , rm ace, ,ic ,s L.P. nd m an ,f c ,red by A ,ergon I ,i). ,
- Reference P ,c : Lidoderm® (idoc ine p ,c 5%) (m an ,f c red b (b) (4) for Endo P rm ace ic s Inc.)

A , pp ic ions of es nd reference s dy prod c consis ed of one-fo r of e p ,c . ,

T ,e s ,dy ,d wo p , ses: ,

- Skin irri ion w s ssessed d ring e ind c ion p , se (D ys 1-22) ,
- Skin sensi iz ion w s ssessed d ring e c , enge p , se (D ys 36-41) ,

Irritation/Induction Phase (Days 1-22): ,

D ,ring e ind c ion p , se s ,dy prod c s were pp ied sim u ,neo s y o e s me si es on one , side of e infr sc p , r re of e b ck of e c s bjec . S ,dy prod c s were rep ced 3 imes , week y (for ex mp e Mond ys Wednesd ys Frid ys or T esd ys T , rsd ys nd S , rd ys) , e s me si e for 3 consec ,ive weeks res , ing in o , of 9 pp ic ,ions. T ,e es nd reference , prod c s for e c s bjec were r ndom y ssigned o pp ic ion si es design ed s " pper" nd , " ower" indic ing ,e re , ive posi ioning of e p c es o e c o er. T e r ndomiz ion , sc eme is s own in T b e 1. ,

Table 1: Randomization Scheme for Study RP-LID-SSI ,

Randomization sequence ,	Test patch site ,	Reference patch site ,
1 ,	Upper ,	Lower ,
2 ,	Lower ,	Upper ,

,

Followin 6 o val of 6ach patch and p io 6to patch 6 plac 6 nt, th 6patch sit was clinically 6 ass ss d fo d 6a l spons in a blind d a6 nn 6usin a visual scal of 0-7 that at d th d 6 of 6yth 6a , d 6a and oth 6 f atu 6s indicativ 6of i itation. Oth 6 ff cts w 6 at d on a 6 visual scal of 0- . Th 6total of th s 6sco 6s (0-13) fo 6 ach patch was consid 6 d th 6i itation 6 sco 6of ach patch at ach 6valuation ti 6 point. Patch adh sion data, bas d on a visual scal of 6 0-4 as d sc ib d in S ction 3.2.3, was coll ct d p io to 6 o val of ach patch. 6

If a patch was 6 o v d fo 6an unacc ptabl d 6 of i itation, and a n w patch could not b 6 appli d to th 6sa 6 sit , subs qu nt applications of th 6p oduct could b 6appli d to a diff 6nt 6 skin sit on th 6back (on th 6sa 6 sid 6of th 6spin) in o d 6to cop6 l t th 6induction phas . 6 Th 6hi h st sco 6 obs v d p io to patch discontinuation was to b 6ca i d fo wa d fo all 6 a inin 6obs 6vations. Up to two chan 6s in patch application sit could occu . If a thi d patch 6 was 6 o v d fo an unacc ptabl d 6 of i itation, th 6subj ct was to b 6 xclud d f o 6both 6 th 6i itation and s nsitization analys s of th 6p oduct, and discontinu d f o 6study pa ticipation. 6

If a patch cop6 l t ly d tach d, it was to b 6 plac d within 24 hou s and th 6subj ct would 6 continu 6in th 6study. Subj cts w 6 to not 6th 6dat 6and ti 6 of d tach 6 nt as soon as it 6 occu 6d. If a patch could not b 6 plac d within 24 hou s, o a subj ct did not know wh n a 6 patch d tach d, th 6subj ct was to b 6 xclud d f o 6both th 6i itation and s nsitization analys s 6 of that p oduct, and was to b 6discontinu d f o 6study pa ticipation. 6

If patch adh sion was ass ss d as <50% adh 6 d but not d tach d (o 6 than half th 6syst 6 liftin 6off of th 6skin without fallin 6off), th 6subj ct was sch dul d fo 6a 6a k -up patch 6 application. Th 6skin i itation ass ss 6 nts fo 6th 6patch s that adh 6 d <50% w6 6 not to b 6 includ d in th 6i itation analys s. 6

Subj cts who did not 6tu n fo 6on 6visit to th 6study sit 6du in 6th 6induction phas 6w 6 inst uct d to k 6p th 6patch s in plac . Th y w 6 sch dul d to 6 c iv 6a 6a k -up patch 6 application at th 6last visit du in 6th 6induction phas . Th 6a k -up patch s w 6 o v d 48 6 hou s lat 6and th 6patch sit s w 6 ass ss d. If subj cts fail d to 6tu n fo 6 o val/ valuation of 6 th 6a k -up patch s, th 6ninth ass ss 6nt was not 6co d d. A subj ct who 6 ss d th 6ninth 6 ass ss 6nt but had 9 patch applications was consid 6 d to hav 6cop6 l t d th 6induction phas , 6 and th 6last obs 6vation was ca i d fo wa d. 6

Th induction phas was follow d by a 12- to 14-day 6st phas , and th n a chall n 6 phas . 6

Sensitization/Challenge Phase (Days 36-41): 6

Subj cts who cop6 l t d th 6induction phas 6and th 6 st phas 6had th 6t st and 6 f 6nc 6 p oducts appli d to naïv sit s fo 48 hou s. Th sit of application (“upp ” o “low 6”) was th 6 sa 6 as that us d du in th induction phas but on th oth 6sid of th spin . Subj cts 6tu n d 6 to th study sit aft 6 48 hou s of patch w a to hav th patch s 6 o v d. P io to 6 o val of 6

each pa ch pa ch a he on wa a e &e ba e on a v ual cale of 0-4 a e cr be n Sec on 8 3.2.3. 8

The pa ch &e wa cl n cally a &e &e 30 m inu e an 24 4 an 72 hour af er pa ch removal for 8 ermal re pon e an o her effec core n he ame manner a n he n uc on pha e. A 8 narra ve &e cr p on of each reac on &ur ng he challenge pha e wa prov &e by he 8 nve &ga or along w &h an op n on a o whe her uch reac on were hough o be n &ca ve of 8 con ac en 8 za on. 8

If u &§ pro uc wa remove pr or o 4 hour of pa ch wear ue o a en 8 za on reac on he 8 la ob erva on wa carr e forwar . 8

Subjec were que &one abou ch ng burn ng pa n or orene &a he appl ca on &e. The e 8 ymp om swere recor e an compare be ween pro uc . Concom ian&8 me ca on an a ver e 8 even &were recor e an rev ewe a each v &8 o he u &§ &e. 8

Wherea ba h ng wa allowe (low ub ba h/fron al hower) he pa che area wa no o be 8 oake an wa o be kep a ry a po &ble per n ruc on o each ubjec . Subjec coul no 8 u e y em ic or op cal analge c cor co ero &8 or non ero al an - nflamma ory rug w h n 8 3 wee&k pr or o f r u &§ pro uc appl ca on; or y &m ic or op cal an h &am ine w &h n 72 8 hour pr or o f r u &§ pro uc appl ca on. The u e of make-up cream s l&8 on pow &er or 8 o her op cal pro uc o he k n area where pa che were appl e wa proh b e . Subjec 8 refra ne from exce &ve phy cal ac v &§ or exerc e ha coul cau e per p ra on. 8

Pa ch appl ca on pa ch removal an a &e &men of pa ch a he on were no performe n a 8 bl n e manner nce he e an reference pa che ha &8feren appearance . Irr a on analy e 8 were performe n a bl n e manner by he nve &ga or. Th &wa accompl he by hav ng pa ch 8 appl ca on pa ch removal an a he on a &e &men performe n one room by aff no nvolve 8 n rr a on analy &8 an k n rr a on performe n a epara e room. 8

Reviewer's Comments: 8

1. Ac&cor ng o he pro ocol f hree pa che of a ubjec were move or remove for 8 unaccep able egree of rr a on ur ng he n uc on pha e he ubjec wa o be 8 exclu e from bo h he &r a on an en &8 za on analy e of he pro uc an 8 con nue from u &§ par c pa on. However FDA gu &ance recommen &8 nclu &ng 8 ho e ubjec n he rr a on analy &8 u ng la ob erva on carr e forwar (LOCF). No 8 ubjec wa &8con nue ue o exce &ve rr a on n h &8 u &§. 8

2. Ac&8cor ng o he pro ocol f a pa ch wa a &e &e a <50% a here bu no e ache 8 (a he on core of 3) ur ng he n uc on pha e he k n rr a on a &e &men for ha 8 pa ch wa no o be nclu e n he rr a on analy &8 an he ubjec wa o be che ule 8 for a make-up pa ch appl ca on. I un er &8o ha he rr a on core from a make-up 8 pa ch woul replace he rr a on core of he pa ch ha wa <50% a here bu no 8 e ache f only a ngle pa ch ou of 9 pa che ha <50% a herence w &hou be ng 8

detached I ever, the pr t c l did n t state h I the irritati n sc res I uld be used I hen t I r m re Ipatches If the same type f r the same pers n had <50% adherence I ith ut being detached In resp nse t an ECD (ECD letter date: September 16, 2016, I ECD resp nse date: September 29, 2016), the applicant stated that I hen there I ere I multiple patches If the same type I ith an adhesi n sc re If 3 f r the same subject, a I single make-up patch I as applied and the irritati n sc re f r the make-up patch replaced I the irritati n sc res If all the patches I ith an adhesi n sc re If 3 that the make-up patch I replaced IThe applicant adjusted the number If irritati n assessments by c unting the I number If patches n t having an adhesi n sc re If 3 and adding Ine f r the make-up I patch t that c unt F r example, if there are 3 patches I ith an adhesi n sc re If 3, then I the number If irritati n sc res used t Icalculate the mean I uld be 6+1=7 I n the I revie Ier's pini n, this is n t an appr priate meth d t calculate the mean irritati n sc re I since it essentially reduces the number If irritati n sc res unless there is Inly Ine patch I ith an adhesi n sc re If 3 The particular patch type f r that subject sh uld be excluded I fr m the irritati n and sensitizati n analyses I

3 T he study design did n t f ll I the Draft Guidance In Lid caine Acc rding t Ithe I guidance, patches sh uld be applied In Days 1, 3, 5, 8, 10, 12, 15, 17 and 19 during the I inducti n phase The patches sh uld be assessed f r irritati n after patch rem oval and I bef re ne I patch applicati n Patches applied In Day 19 sh uld be assessed In Day 22 I Based In the pr t c l, the subjects I ere all I ed t skip a visit and keep the patches In I until the next visit Ihen they I ere evaluated f r skin irritati n It resulted in having the I same patch In f r 4 Ir 5 days bef re an irritati n assessment Ihile the patches I ith ut a I skipped visit I ere In f r 2 Ir 3 days bef re the irritati n assessment I

4 A cc rding t the pr t c l, the subjects I h Idid n t return f r ne visit t the study site I during the inducti n phase I ere instructed t Ikeep the patches in place IThey I ere I scheduled t Ireceive a make-up patch applicati n at the last visit during the inducti n I phase IThe study rep rt did n t clearly differentiate the dual use I f the termin l gy I "make-up patch" f r t I different purp ses I n the first case the make-up patch is I intended t Ireplace the irritati n sc re If a partially detached (<50% adhesi n but n t I c mpletely detached) patch In the sec nd case, the irritati n sc re If the make-up patch I is simply intended t be an additi nal patch I hen a visit I as skipped t make a t tal f 9 I patches during the inducti n phase I

5 A I cc rding t Ithe pr t c l, a subject I h I missed the ninth assessment but had 9 patch I applicati ns I as c nsidered t have c mpleted the inducti n phase, and the last bserved I irritati n sc re (the irritati n sc re f r the eighth patch) I as carried f r ard IThis I appr ach c ntradicts the Draft Guidance I n Lid caine since the guidance requires I applicati n and evaluati n If all 9 patches unless the patch rem oval is due t Iexcessive I irritati n In the revie Ier's Ipini n the subjects I h I missed the ninth assessment sh uld I be excluded fr m the irritati n and sensitizati n analyses I

6 T he pr t c l specified that hyp allergenic tape I uld be applied t all f ur edges If each I patch I ever, there I as n Imenti n If this reinf rcement tape in the clinical study I

report.) re po)e to) ECD (ECD letter d te: Augu t 23, 2016, ECD re po)e d te:) September 6, 2016 , the)pplic)t co firmed th t the hypo)llerge ic t pe w) u ed o) ll) four edge) d di go)lly o) ll p tche .)

3.2.3 Ass)essments)

Both irrit tio) d)e)itiz tio)were) e)ed b)ed o)the followi g r ti g)c le)give)i) T ble 2) d T ble 3:)

Table 2: Dermal Response Rating Scale)

Score)	Skin Appearance)
0)	No evide)e of irrit tio)
1)	Mi im al e)rythem a, b) rely perceptible)
2)	Defi ite erythem a, re) dily vi ible, or mi im al e)dem ao) mi im al p))pul r) re po)e)
3)	Erythem a)d p)pule)
4)	Defi ite edem a)
5)	Erythem a, e)dem a,))d p pule)
6)	Ve icul r eruptio)
7)	Stro)g re ctio) pre di g beyo)d the)pplic tio) ite)

Table 3: Applicant's "Other Effects" Rating Scale)

Score)	Observation)
1)	Slightly gl zed)ppe r)ce)
2)	M)rked gl zed)ppe r)ce)
3)	Gl zi g with pe)li g) d cr cki g)
4)	Gl zi g with fi)ure)
5)	Film of)dried)erou)exud te)coveri g)ll or p)t of the p)tch)ite)
6)	Sm ll)petechi l ero io) d/or)c b)
0)	No other ob erv)tio)

Skin Irritation As)essments)

Followi g remov l of e ch p tch) d prior to p tch repl ceme t, the p tch)ite w) cli ic ll)y) e)ed for derm al re) po)e) d other effect i) bli ded m a)er u i g the)bove r ti g)c le .)

At e ch) e)me t time poi t for e ch)ubject, for e ch product,) irrit tio) core (S)w) c lcul ted by)ddi g the derm al re) po)e)core to the other effect)core.)

Skin Sen i i r i n A r e mmen r

Sensitization assessments of the site of each patch application we e made app oximately 30 r minutes and 24, 48 and 72 hou s afte patch emoval in the challenge phase. The same ating r scales as used du ing the induction phase we e used. A na ative desc iption of each eaction r du ing the challenge phase was p ovided by the investigato , along with an opinion as to whethe r such eactions we e thought to be indicative of contact sensitization.

Adhe i n A r e mmen r

Patch adhesion was assessed p io to patch emoval by qualified study site pe sonnel. The r following adhesion scale was used to eco d a sco e fo each individual patch.

0 = ≥ 90% adhe ed (essentially no lift off the skin) r
1 = ≥ 75% to <90% adhe ed (some edges only lifting off the skin) r
2 = ≥ 50% to <75% adhe ed (less than half of the patch lifting off the skin) r
3 = >0% to < 50% adhe ed but not detached (mo e than half of the patch lifting off the skin but r not completely detached) r
4 = 0% adhe ed - patch detached (patch completely off the skin) r

Due to the diffe ences in appea ance of the patches, blinding of the evaluato fo patch adhesion r was not possible.

If patch adhesion was assessed as <50% adhe ed but not detached (mo e than half the patch r lifting off the skin without falling off), the subject was scheduled fo a make-up patch r application. The skin i itation assessment fo the patch adhe ed < 50% was not included in the r i itation analyses.

Reviewer's Comment: r

The applicant used a diffe ent ating scale fo "othe effects" than what is ecommend by FDA in r D aft Guidance on Lidocaine. Although the othe effects catego ies a e identical betwe en the r applicant's and FDA's scales, the nume ical values associated with the catego ies based on the r applicant's scale a e highe with a wide ange than those based on the FDA's scale. The r applicant did not use any lette sco e fo the othe effects. The othe effects ating scales based r on the applicant and FDA a e p esented side by side in Table 4. The applicant's othe effects r ating scale inc eases the i itation sco e (de mal esponse sco e + othe effects sco e). This r inc eased i itation sco e makes both the nume ato and denominato of the test statistic, which is r a atio (Test/Refe ence), la ge and thus the atio close to one nume ically. The efo e, the test is r mo e likely to be found non-infe io to the efe ence with the applicant's ating scale. The r eviewe used the FDA- ecommended scale fo the analyses of i itation and sensitization.

Table R p aris n f Applicant's and FDA's "Other Effects" ating Scales R

Applicant's Scale R	R FDA's Scale R		Observati n R R
	Letter Sc R e R R	Nu e R ric Sc re R	
0 R	N R	0 R	No observation R
1 R	A R	0 R	Slightly glazed app earance R
2 R	B R	1 R	Marked glazed app earance R
3 R	C R	2 R	Glazing with peeling and cracking R
4 R	F R	3 R	Glazing with fissures R
5 R	G R	3 R	Film of dried serous exudates covering all or part of the R patch site R
6 R	H R	3 R	Small petechial erosions and/or scabs R

3.2. R hanges in the Study R nduct R

The induction phase for Cohort 2 was shortened by one day (total 20 instead of 21 per protocol). R The patch application schedule for the induction phase for Cohort 2 of this study was Tuesday, R Thursday and Saturday and the first patch application of all subjects in this cohort was Tuesday, R November 5, 2013. This schedule meant that the last dose application for the induction phase R would be on Saturday, 23 November 2013 and the last skin assessment would be on Tuesday R November 26, 2013. If subjects required a make-up patch application, this would occur on the R latter date and the subsequent skin assessment would be on Thanksgiving, Thursday, 28 R November 2013, requiring subjects to return to the clinic on Thanksgiving for this assessment. R Due to the concern regarding potential subject compliance, a decision was made to have the last R scheduled skin assessment and make-up patch applications, if required, for Monday, 25 R November 2013 instead of Tuesday, 26 November 2013 to avoid this conflict. This change was R documented in a note to file (dated 11 February 2014). R

Reviewer's Comment: R

Ac R ording to the protocol, if a patch was assessed as <50% adhered but not detached (adhesion R score of 3) during the induction phase, the skin irritation assessment for that patch was not to be R included in the irritation analysis and the subject was to be scheduled for a make-up patch R application. The protocol did not state if a make-up patch would be applied for the patches that R completely detached (adhesion score of 4). The data and an inspection report by the Office of R Study Integrity and Surveillance (OSIS) revealed that make-up patches were applied for subjects R who did not have any patch adhesion score of 3. The OSIS report noted that the study was not R conducted according to the investigational plan. The OSIS report indicated that there were 12 R subjects (Subject ID [redacted] (b) (6) R who had completely detached patches (adhesion score of 4). The reviewer found more such cases R (please refer to Table 9). R

3.2.5 Study endpoints

3.2.5.1 Applicant's endpoints

Primary endpoints:

- Dermal response scores and scores for other effects collected during the induction phase to evaluate the skin irritation potential of the study product.
- Dermal response scores and scores for other effects collected during the challenge phase to evaluate the skin sensitization potential of the study product.
- The number of patches removed due to an unacceptable degree of irritation.
- The number of days until sufficient irritation occurs to preclude patch application.

Secondary endpoint:

- The incidence of treatment-emergent adverse events, including itching, burning, pain or soreness at the application site, and study discontinuation information.

3.2.5.2 Reviewer's endpoints

In the following definitions, the irritation score for a patch is calculated as the sum of dermal response and numeric other effects scores based on the FDA's recommended scoring of these two items as shown in Table 2 and Table 4.

Primary endpoint for irritation:

The reviewer' primary endpoint for irritation is the mean irritation score which is defined for an patch type for a subject as the mean of irritation scores observed after removal of each of the 9 patches of that patch type for that subject during the induction phase. If a patch is discontinued due to excessive irritation, the last observed score is carried forward for the rest of the induction phase before calculating the mean irritation score.

Secondary endpoints for irritation:

- The proportion of subjects with a meaningful degree of irritation (irritation score ≥ 3 at any time point)
- The time to patch discontinuation for excessive irritation (irritation score ≥ 3).

Primary endpoint for sensitization:

Irritation scores at 48 and 72 hours after patch removal during the challenge phase.

3.2.6 Sample Size Considerations

The applicant targeted a sample size of 200 evaluable subjects based on the industry and regulatory standards for determination of dermal sensitization potential. In the absence of any sensitization reactions, a 95% upper confidence boundary on the population rate of sensitization would be 1.5%. Approximately 250 subjects were enrolled and randomized in order to have 200 evaluable subjects complete the study.

3.2.7 Statistical Methodologies

3.2.7.1 Analysis Populations

Applicant's Analysis Populations:

Test Irritation Analysis Population:

The Test Irritation Analysis Population includes all subjects who received all patches such that sequential patch applications were not detached from the skin for longer than 24 hours during the 21-day induction Phase (unless the patch was removed for an unacceptable degree of irritation). If a test patch detached and could not be replaced within 24 hours, or a subject did not know when a test patch detached, the subject's test patch was to be excluded from the Test Irritation Analysis Population.

Reference Irritation Analysis Population:

The Reference Irritation Analysis Population is defined for reference patches in a similar way to the Test Irritation Analysis Population.

Full Irritation Analysis Population:

The Full Irritation Analysis Population includes all subjects who were in both the Test Irritation Analysis Population and the Reference Irritation Analysis Population. The Full Irritation Analysis Population was used for all irritation analyses requiring paired test/reference irritation data.

Test Sensitization Analysis Population:

The Test Sensitization Analysis Population includes all subjects who received test patches (challenge phase) and who have completed the induction phase, wearing the test patches for the entire 21 days and completed the rest phase. Additionally the challenge test patch must be attached for 48 hours (unless the challenge test patch was removed due to a sensitization reaction) with the subject returning for evaluation at least 24 hours after removal of the challenge test patch.

Reference en q a on Analy q Popula on: q

The Reference en q a on Analy q Popula on def ned for reference pa che n a m lar q way o he Te en q a on Analy q Popula on. q

Full en q a on Analy q Popula on: q

The Full en q a on Analy q Popula on nclude all ubjec who were n bo h he Te q en q a on Analy q Popula on and he Reference en q a on Analy q Popula on. The Full q en q a on Analy q Popula on wa u ed for all en q a on analy e re u r ng pa red q e /reference en q a on da a. q

afe y Popula on: q

All ubjec who rece ved a lea one appl ca on of e her udy produc were ncluded n he q afe y Popula on. q

FDA's Analysis Populations: q

Per pro ocol popula on for rr a on (PPPI): q

The PPPI con q of pa ch ype for he ubjec who had he udy produc appl ed e uen ally q o he ame qe for he en re 21 day nduc on pha e (w chou any per od of de achmen longer q han 24 hour) o be evalua ed for he cumula ve rr a on effec , or f a pa ch moved or q removed due o exce qve rr a on. In he even ha a pa ch wa moved or removed due o q exce qve rr a on, he la ob erved core pr or o d con nua on of he f r pa ch qe q carr ed forward for all rema n ng ob erva on n he rr a on analy q. q

Per pro ocol popula on for en q a on (PPP): q

The PPP qcon q of pa ch ype for he ubjec qwho have worn he udy produc q(w chou any q per od of de achmen longer han 24 hour) for he full 21-day nduc on pha e and he en re 48- q hour challenge pha e and have re urned for a lea one of he cheduled evalua on a 48 and 72 q hour af er removal of he challenge pa ch. If a udy produc removed pr or o he end of he q 48-hour challenge pha e due o an n olerable reac on, he appl ca on qe hould be evalua ed a q 24, 48, and 72 hour af er pa ch removal and ncluded n he en q a on analy q u ng he la q ob erva on carr ed forward (LOCF). q

afe y popula on (P): q

All ubjec who had a lea one pa ch appl ed were ncluded n he afe y popula on. q

Reviewer i mment : i

1. The FDA's PPPI def ned above and the comb ned collect on of test patches from the i subjects n the appl cant's test rr tat on analys s populat on and the reference patches i from the subjects n the reference rr tat on analys s populat on are same. However, the i appl cant d d not spec fy how the m ss ng observat ons w ll be handled when the patches i are removed due to excess ve rr tat on. In th s study no patch was removed due to i excess ve rr tat on. i

2. The FDA's PPPS s almost same as the comb ned collect on of patches n the appl cant's i test sens t zat on analys s populat on and the reference sens t zat on analys s populat on i except that PPPS has an extra requ rement of the challenge phase patches to be evaluated i at least once at or after 48 hours after patch removal. i

3.2.7.2 Analysis of Irritation i

Applicant's Analysis Methods: i

The rr tat on score (0-13) for each study product at each evaluat on was the sum ofithe dermal i response score (0-7) and the score for other effects (0-6). The cumulat ve rr tancy ndex (CII) i was def ned as the mean of rr tat on scores across all assessments dur ng the nduct on phase. i The cumulat ve dermal response ndex and the cumulat ve other effects ndex were also def ned i s m larly. All these three ndexes were generated for test and reference study product for each i subject and summar zed by treatment and by cohort. The ind v dual CIIs, the ind v dual i cumulat ve dermal response ndex and the nd v dual cumulat ve other effects ndex generated i dur ng the induct on phase were tested for product d fferences us ng the 2-way analys s of i var ance (ANOVA) nclud ng ma n effects of subject and product, w thout nteract on us ng the i PROC GLM model. The test product was to be no more rr tat ng than the RLD, as def ned by i the upper bound of the one-s ded 95% conf dence nterval of the d fference betwe en the products i be ng no greater than 0.11. i

Ind v dual CIIs generated dur ng the challenge phase were summar zed by treatment and by i cohort. A frequency table d splayed the number of appl cat ons of each study product w th each i rr tat on score at each evaluat on t me po nt by treatment and by cohort. Subjects' max mum i rr tat on score, max mum dermal response score, max mum other effects score, total number of i observat ons w th a max mum rr tat on score of 13, a max mum dermal response score of 7, a i max mum other effects score of 6 and the number of patches that were removed due to an i unacceptable degree of rr tat on were summar zed by treatment, cohort, t me po nt and overall. i The stat st cal compar sons of the test and reference products n each cohort and overall for total i number of observat ons w th a max mum rr tat on score and the number of patches that were i removed were performed us ng McNemar's test on the Full Irr tat on Analys s Populat on. i

The number of days unt l suff c ent rr tat on occurred to preclude patch appl cat on, was i calculated and summar zed for the test and reference study products and cohort. The stat st cal i

compar o Co Cthe te t a d re ere ce product , overall a d w th Ceach cohort, wa Cper ormed C u Cg the Kapla -Me er te t u Cg the SAS procedure PRO CLIFETEST. A Kapla -Me er curve C wa Cge erated by treatme t or overall a d w th Ceach cohort o Cthe Full Irr tat o CA Caly C Populat o . C

I a patch wa Cremoved Cor a Cu acceptable degree o Crr tat o Ca d a Cew patch could Cot be C appl ed to the Came Cte, the h ghe t core ob erved pr or to patch d Cco t uat o Cwa Carr ed C orward or all rema C g ob ervat o C Sub eque t appl cat o Co the product were appl ed to a C d Cere t C C te C order to complete the I duct o CPha e. Subject were requ red to have a C mi Cnum o C patch appl cat o Cdur g the I duct o CPha e. C

Reviewer's Primary Analysis Method: C

For the pr mary a aly C o the pr mary e dpo C, a Ca aly C o var a ce (ANOVA) wa per ormed C wh ch the mea Crr tat o Ccore wa Ctreated a Cthe depe de t var able, a d Cubject a d treatme t C were treated a Cxed e Cct . C

Reviewer's Method for the Analysis of the Binary Endpoint: C

The b Cary e dpo C, the Cumber o Cubject w th a mea Cg ul degree o Crr tat o C(≥ 3) C a alyzed C the PPPI. C

The object ve Cto te t a C - Cer or ty hypothe Ca Collow : C

$$H_0: P_T - P_R > \delta \text{ (ot o - Cer or) C}$$

$$H_1: P_T - P_R \le \delta \text{ (o - Cer or), C}$$

where P_T a d P_R are the proport o Co Cl Ccally Cg C ca t rC tat o Cor e Ct zat o C("eve t") C or TEST a d RLD, a d δ C a pre- pec Ced Co - Cer or ty marg C The Cg C ca ce level C 0.05. No - Cer or ty C e tabl hed C the upper bou d (UB) o Cthe o e- ded 95% co Cde ce C terval o C$P_T - P_R$C le Ctha Cor equal to δ. The tabulat o Co eve t/ o -eve t or Te t a d RLD a Collow C C

Total Ca+b+c+d C		Te t C	
		No CEve t C	Eve tC C
RLD C	No CEve tC C	a C	b C
	Eve t C	c C	d C

Let C
= total Cumber o Cubject ; C
b = Cumber o Cubject w Cth a Cegat ve outcome (rCtat o C e Ct zat o Cor detachme C) u Cg the C te t but Cot the comparator; C
c = Cumber o Cubject w Cth a Cegat ve outcome (rCtat o C e Ct zat o Cor detachme C) u Cg the C comparator but Cot the te t. C

The ma he o o ion iffe en e $P_T - P_R$. an be es ima e by he quan i y $\frac{b-c}{n}$ af e a sim ple e iva ion The e a e iffe en ways o al ula e he u . e boun of he ma he .o o ion . iffe en e $P_T - P_R$. A ommon way is o use he McNema me ho ! base on no mal a . oxima ion un e he law of la ge numbe s The UB is al ula e as follows: .

$$UB = \frac{b-c}{n} + 1\,645\frac{1}{n}\sqrt{b+c-\frac{(b-c)^2}{n}}$$

S hui mann[2] o ose a iffe en way of no mal a . oxima ion by ombining Nam's[3] an Liu e . al's[4] a . oa hes Base on he simula ion esul s, S hui mann[2] e ommen e an o .imal no mal . a . oxima ion whi h .ese ves be e y e I e o fo smalle a es om pa e o McNema . me ho .

$$\text{Le } Z = \frac{\hat{\delta} + cc - \delta}{\sqrt{\frac{\xi^* - \delta^2}{n}}},$$.

whe e $\hat{\delta} = \frac{b-c}{n}$, he on inui y o .e .ion, $cc = \frac{1}{n}$, $\xi^* = \max(\hat{\delta}, |\delta|)$

The one-si e 95% u . e boun (UB) fo he ma he .o o ion iffe en e, $P_T - P_R$, is he value of δ ha makes $Z = Z_{0\,05} = -1\,64$. S hui mann's me ho was use in his s a is i al . e o . Fo any given non-infe io i y boun δ, he null hy o hesis H_0 may be eje .e if his 95% . u . e onfi en e boun fo he quan i y $P_T - P_R$ is less han o equal o δ, ha is: U ≤ δ. Reje ion of he null hy o hesis H_0 su . o s he on lusion of non-infe io i y of he es o he . om pa a o .

3.2.7.3 Analysis of Sensitization .

Applicant's Analysis Methods: .

Sensi iza ion of es ve sus efe en e s u y .o u . was base on i i a ion s o es ob aine . u ing he hallenge hase an whe he he ea .ions we e in i a ive of a sensi iza ion ea .ion . by he inves iga o .

A skin sensi iza ion ea .ion was efine as he evelo men , a he si e of e-ex osu e o he . a .h, of efini e e y hema ombine wi h he .esen e of any of he following signs: a ules, . e ema, vesi les, bullae, a king, fissu ing, us ing, eeling, o s ea beyon he onfines of . a .h a . li a ion si e Su h ea .ions we e equi e o have a ime ou se om pa ible wi h a .

sensitiz ti n e ti n; th t is, su h e ti n u ng t the beginning f the indu ti n ph se w uld be deemed sign f p i sensitiz ti n, nd e ti ns whi h m ke dly imp ved within 72-9 h u timef me we e n t h te isti f lle gi esp nse, nd we e l ssified s n i it nt esp nse. Skin sensitiz ti n e ti ns w uld m st likely u in the h llenge ph se, lth ugh they uld u l te in the indu ti n ph se, nd w uld h ve time u se h te isti f Type IV del yed hype sensitivity e ti ns.

Sensitiz ti n by time p int w s summa ized using numbe nd pe ent ge nd tested f p du t diffe en es using McN m a's test. If the study p du t w s em ove d p i t 48 h u s due t sensitiz ti n e ti n, the l st bse v ti n w s ied f w d nd the subje t w s in luded in the sensitiz ti n n lysis.

Reviewer's Analysis Methods:

The D ft Guid n e n Lid ine st tes the f ll wing:

F e h test ti le, individu lly ev lu te e h PP subje t with mbined s e f 2 g e te t 48 72 h u s fte p t h em ov d du ing the h llenge ph se f p tenti l sensitiz ti n. A n tive des ipti n f e h e ti n in the h llenge ph se sh uld be p vided, t gethe with the pini n f the investig t s t whethe su h e ti ns e felt t be indi tive f nt t sensitiz ti n. C nside subje t t be p tenti lly sensitized if l f the f ll wing ite i e met:

. The subje t h s t le st ne ev lu ti n u ing m o e th n 24 h u s (e.g., t 48 72 h u s) fte the em ov l f the h llenge ph se p t h.
b. The subje t h s mbined "de m l esp nse" nd " the effe ts" nume i s e f t le st 2 thei l st ev lu ti n du ing the h llenge ph se.
. The mbined "de m l esp nse" nd " the effe ts" nume i s es bt ined du ing the h llenge ph se ev lu ti ns e gene lly highe h n the mbined "de m l esp nse" nd " the effe ts" nume i s es bt ined du ing the indu ti n ph se.
d. If the subje t mpleted e h llenge ph se, the ve 3 ite i we e met du ing b th the h llenge ph se nd the e h llenge ph se.

FDA's dete min ti n f sensitiz ti n used the e mmend ti ns p vided in the guid n e.

The viewe 's meth d f n lysis f sensitiz ti n is s me s th t f the n lysis f bin y endp int des bed e ie .

3.2.7.4 Analysis of Adhesion

Due t the diffe en es in ppe n e f the p t hes, blinding f the ev lu t f p t h dhesi n w s n t p ssible. If p t h dhesi n w s ssessed s <50% dhe ed but n t det ined (m o e th n h lf the system lifting ff f the skin with ut f lling ff), the subje t w s s heduled f m ke-

up patc app cat v. T e sk v rr tat v assessme t f r t e patc ad ered < 50% was vt v c uded t e rr tat v a a yses. v

Ad es v data f r eac study pr duct was c vected a d d sp ayed t d cume t t at ad es v f v t e study pr duct was adequate f r t e sk v rr tat v a d se s t zat v a a yses. Ad es v sc res v fr m a patc es w t v eac treatme t were summed a d d vded by t e umber f sc res t v ca cu ate a cumu at e ad es v vdex f r eac subject by c v rt. N v stat st ca tests were v perf rmed v ad es v data. T ta umber f patc detac me ts, per subject, f eac study v pr duct duct v p ase was summar zed vera a d by c v rt f r t e fu rr tat v a a ys s v p pu at v. v

3.2.8 Subject Disposition and Analysis Populations v

A t ta f 248 ea t y adu t subjects were e tered vt t s study a d rece ved at east ve v app cat v f patc es. A vsubjects were c uded t e safety p pu at v. v

Subjects were d sed tw vc v rts. A vsubjects t e f rst c v rt ad t e f rst patc app cat v v August 20, 2013 a d t e subjects vt e sec vd c v rt ad t e f rst patc app cat v v v N v ember 5, 2013. T e f rst a d t e sec vd c v rts ad 123 a d 125 subjects, respect e y. v

T e PPPI a d PPPS refer t t e per pr t c vp pu at v f r rr tat v a d per pr t c vp pu at v v f r se s t zat v, respect e y. A t vug t e app ca t d d vt use t ese term i v g es vt e v pr t c v r t e study rep rt, t s vu d be vted t at t e FDA's PPPI s same as t e c mb ved v c vect v f test patc es fr m t e subjects t e app ca t's test rr tat v a a ys s p pu at v v a d t e refere ce patc es fr m t e subjects v t e app ca t's refere ce rr tat v a a ys s v p pu at v. T e same s ear y true f r PPPS. P ease refer t Sect v 3.2.7.1 f r m crevdeta s. v

T e FDA re ewer c vs dered s x d ffere t PPPIs a d s x d ffere t PPPSs due t ssues w t t e v des g a d c vduct f t e study a d c vs ste t data. T ese p pu at vs are amed as PPPI1, v PPPI2, etc. a d PPPS1, PPPS2, etc., respect e y. PPPI1 a d PPPS1 are t e argest p pu at vs. v A v t er PPPIs are subsets f PPPI1 a d a t er PPPSs are subsets f PPPS1. I t s a d ater v sect vs FDA's PPPI a d FDA's PPPS w v mea PPPI1 a d PPPS1, respect e y u vess v t erw se stated. v

3.2.8.1 Applicant's Subject Disposition and Exclusion from Analysis Populations v

F ur subject [redacted] (b) (6) w t drew fr m t e study dur g t e duct v p ase. v F r t ese sub v exc uded fr m t e PPPI a d PPPS by t e app ca t v t e r g va y subm itevd data a d by t e FDA re vewer. I t e dataset subm itevd v December 9, v 2016, t ese subjects were exc uded fr m t e PPPI but vc uded v t e PPPS w t vut a y v exp a at v. v

Subjec (b) (6) did no have any pa ch applica ions af er he four h se of pa ches, Subjec (b) (6) did no have any pa ch applica ions af er he fif h se of pa ches, Subjec (b) (6) did no have any pa ch applica ions af er he firs se of pa ches, Subjec (b) (6) did no have any pa ch applica ions af er he six h se of pa ches and Subjec s (b) (6) did no have any pa ch applica ions af er he second se of pa ches during he induc ion phase. Bo h pa ch ypes of hese subjec s were excluded from he PPPI and PPPS by he applican and he FDA reviewer.

Subjec s (b) (6) did no have he skin irri a ion assessmen on Da (b) (6) for he firs se of pa ches during he induc ion phase. The applican excluded bo h pa ch ypes for Subjec (b) (6) from he PPPI and from he PPPS and included bo h pa ch ypes for he Subjec (b) (6) in he PPI and PPPS in he da ase submi ed on December 9, 2 . Bo h pa ches for Subjec (b) (6) and he reference pa ch for Subjec (b) (6) were included in he PPPS in he originally submi ed da a. Af er reviewing he case repor forms he FDA reviewer excluded hese pa ches from bo h PPPI and PPPS.

Subjec (b) (6) did no have he skin irri a ion assessmen on Day (b) (6) for he second se of pa ches during he induc ion phase and Subjec (b) (6) did no have he skin irri a ion assessmen on Day (b) (6) for he fif h se of pa ches during he induc ion phase. The applican excluded bo h pa ch ypes for hese subjec s from he PPPI bu included hem in he PPPS in he originally submi ed da a. The applican included hem in bo h PPPI and PPPS in he da ase submi ed on December 9, 2 . Af er reviewing he case repor forms he FDA reviewer excluded bo h pa ch ypes for Subjec s (b) (6) from bo h PPPI and PPPS.

Subjec (b) (6) comple ed he induc ion phase bu was discon inued from he s udy by he inves iga or before he challenge phase because he principal inves iga or decided ha i was in he subjec 's bes in eres . The applican included bo h pa ch ypes for he subjec in he PPPI in he originally submi ed da a bu excluded from he PPPI in he da ase submi ed on December 9, 2 . Af er reviewing he case repor form, he FDA reviewer decided o include bo h pa ch ypes for he subjec in he PPPI. Bo h pa ch ypes of he subjec were excluded from he PPPS by he applican n he originally submi ed da ase and by he FDA reviewer. However, bo h pa ch ypes were included in he PPPS by he applican in he da ase submi ed on December 9, 2 .

Subjec (b) (6) was discon inued due o concomi an medica ion. The case repor form for he subjec was no submi ed. Based on he da ase , no more pa ches af er he hird pa ch were applied during he induc ion phase for his subjec . Therefore, bo h pa ch ypes for his subjec was excluded from he PPPI by he applican and he FDA reviewer.

Subjec (b) (6) comple ed he induc ion phase bu did no par icipa e in he challenge phase due o hospi aliza ion before he challenge phase. Pro ocol devia ion due o use of res ric ed medica ion occurred af er he comple ion of he induc ion phase bu before he challenge phase. The applican included bo h pa ch ypes for he subjec in he PPPI in he originally submi ed da a bu excluded hem from he PPPI in he da ase submi ed on December 9, 2 . Af er reviewing he case repor form, he FDA reviewer decided o include bo h pa ch ypes for he subjec in he

PPPI. Bo A A y es of A subje A were ex luded from A e PPPS by A A li A n nd A A FD A reviewer. A

Subje A (b) (6) om pleA d e indu A on A se nd s r ed e A llenge A se bu did no A e ny A skin irri A on ssessmen s due o os i liz A on. Pro o ol devi ion due o use of res ri ed A medi A ion o A urred during e A llenge A se. T e A li n in luded bo A A y es for e A subje in e PPPI in e origin lly submi ed d A bu ex luded from e PPPI in e d A se A submi ed on De ember 9, 2016. A er reviewing A e A se re or form, A e FD A reviewer A de ided o in lude bo A A y es for e subje in e PPPI. Bo A A y es of e subje A were ex luded from e PPPS by e A li A n nd e FD A reviewer. A

Subje A (b) (6) did no A ve A e eig A nd nin A A A li A ions nd lso skin irri A on A ssessmen w s no erformed for e seven A A during e indu A on A se. T e subje w s A os i lized on D A (b) (6) of e indu A on A se nd ook medi A ion ro ibi ed by e ro o ol. A T e re son for e rly ermin A on in A e A se re or form is given s non- om pli A n e wi A e A ro o ol. Bo A A y es for A s subje A were ex luded from A e PPPI nd PPPS by A e A li A n nd e FD A reviewer. A

Subje A (b) (6) ski A ed A e D A (b) (6) visi during A e indu A on A se. For A s subje A, A e skin A irri A on on D A (b) (6) nd D A (b) (6) were s A essed 1 nd 2 minu es ou side A e window, res e A vely, A during e indu A on A se b sed on e ommen s in e ro o ol devi ion se ion of e A se A re or form. In A e A llenge A se, 24 ours os - A li A ion skin irri A on s A essmen w s A A olle ed 82 minu es ou of e window nd 72 ours os - A li A ion ssessmen w s no done. A T e A li n in luded bo A A y es for e subje in e PPPI nd PPPS in e origin lly A submi ed d A bu ex luded from e PPPI nd PPPS in e d A se submi ed on De ember 9, A 2016. T A e irri A on s A essmen s on D A (b) (6) nd D A (b) (6) were done 9 nd 8 minu es, res e A vely, A f er A remov l. A ording o A e ro o ol (Se A on 4), skin irri A on s A essmen s were o A o A ur wi in 15-30 minu es following remov l of e A A during indu A on A se. T erefore, A e ommen s bou ou -of-window irri ion ssessmen s during e indu A on A se in e CRF A re no onsis en wi e ro o ol. T e ou -of-window ssessmen 24 ours nd e missing A ssessmen A 72 ours f er A remov l during A e A llenge A se did no A fe A A e A eligibili y of e A llenge A es o be in luded in e PPPS. f er reviewing e A se re or A form, A e FD A reviewer de ided o in lude bo A A y es for A e subje A in A e PPPI nd A PPPS. However, A se A es were ex luded from some of A e irri A on nd sensi iz A on A n lyses (w A n using PPPI2, PPPI4, PPPI6, PPPS2, PPPS4 nd PPPS6) by FD A due o A ski A ed visi (le se refer o T ble 8). A

T A e A llenge A se A es for Subje A (b) (6) were removed before 44 ours f er A li A ion. A T e A li n ex luded bo A A es of is subje from PPPS in e origin lly submi ed d A A bu in luded em in e PPPS in e d A se submi ed on De ember 9, 2016. f er reviewing A e se re or form e FD A reviewer ex luded ese A es from e PPPS. Bo A A y es A for is subje A were in luded in e PPPI by e A li A n nd e FD A reviewer. A

T e referen e A for Subje A (b) (6) nd bo A A es for Subje (b) (6) in A e A llenge A se de A ed rior o 48 our f er A li A ion nd A e de A men ime w A A

unknown. , patc , w r , xclud d from t ,, PPPS by t , applicant in t , originally , ubmitt d data ,t but includ d in t , PPPS in t , data ,t ubmitt d on D ,c mb r 9 2016. Aft r , r vi wing t , ca , r port form t , FDA r vi w r xclud d t , patc , from t , PPPS. Bot , patc ,typ , for t , ubj ct w ,r includ d in t , PPPI by t , applicant and t , FDA r vi w ,r. , How ,v r ,om epatc , of Subj ct (b) (6) d tac , d during t , induction p a , (r f r to , abl 9). R plac m ent, patc , w r appli d wit in 24 , our aft r d tac m ent, in t , ca , of , Subj c (b) (6)

A , id -by- id ,compari on of t , ubj ct wit at l a t on , xclud d patc ,from PPPI in ,it ,r , t , applicant' original ubmi ion or t , applicant' D c mb r 9 2016 ,ubmi ion along wit , t , r a on ,for xclu ion i pr , nt d in , abl 5. A , imilar compari on for PPPS i pr , nt d in , abl 6. A compari on of t , applicant' and FDA' d t rmination about inclu ion and ,xclu ion , of patc , in PPPI and PPPS for t , ubj ct wit at l a t on ,patc , xclud d from PPPI or PPPS , in at l a t on ,of t , two ubmi ion m ention d abov i pr , nt d in abl 7. ,

Table 5: Comparison of Excluded Patches from the Applicant's PPPI Between the Original , Submission and the December 9, 2016 Submission ,

Subject ID ,	, Original submission ,		December 9, 2016 Submission	
	Excluded from , PPPI , (Both , Patches) ,	Reason for exclusion , form PPPI ,	Excluded from , PPPI , (Both , Patches) ,	Reason for exclusion form , PPPI ,
(b) (6)	Y ,	Subj ct didn't r c iv ,all , patc ,	Y ,	1. A n ,d for a concomitant , m dication pro ibit d by t , protocol ari , 2. R trict d m dication ,
	N ,		Y ,	1. Adv r , v nt , 2. R trict d m dication ,
	Y ,	Subj ct didn't r c iv ,all , patc ,	Y ,	Voluntary wit drawal ,
	Y ,	Subj ct didn't r c iv ,all , patc ,	Y ,	Voluntary wit drawal ,
	N ,		Y T ,	principal inv ,tigator , d cid d t at it i in t , ubj ct' , b ,t int r ,t ,
	Y ,	Subj ct didn't r c iv ,all , patc ,	Y ,	Non-compliant ,
	Y ,	Subj ct didn't av ,a , minimum of 9 irritation , cor , during Induction , P a ,	Y ,	Non-compliant ,
	Y ,	Subj ct didn't r c iv ,all , patc ,	Y ,	1. Non-compliant , 2. Non-compliant ,

(b) (6)

Y -	Su - didn' hav a - minimum of 9 irri a ion - s or s during Indu -ion - Phas -	Y -	Non -omplian -
Y -	Su - didn' hav -a - minimum of 9 irri a ion - s or s during Indu -ion - Phas -	N -	
N -		Y -	Non -omplian -
Y -	Su - didn' hav -a - minimum of 9 irri a ion - s or s during Indu -ion - Phas -	N -	
Y -	Su - didn' r - iv all - pa -h s -	Y -	1. Non -omplian - 2. Non -omplian -
Y -	Su - didn' r - iv all - pa -h s -	Y -	1. Non -omplian - 2. Non -omplian -
Y -	Su - didn' hav -a - minimum of 9 irri a ion - s or s during Indu -ion - Phas -	N -	
Y -	Su - didn' r - iv all - pa -h s -	Y -	1. Non -omplian - 2. Non -omplian -
N -		Y -	1. Adv rs v n s - 2. R -s ri - d m cdi- a ion -
Y -	Su - didn' r - iv all - pa -h s -	Y -	1. Adv rs v n s - 2. R -s ri - d m cdi- a ion -
Y -	Su - didn' r - iv all - pa -h s -	Y -	1. Non -omplian - 2. Pa -h fr ->24 hr -
Y -	Su - didn' r - iv all - pa -h s -	Y -	1. Non -omplian - 2. Non -omplian -
Y -	Su - didn' r - iv all - pa -h s -	Y -	Volun ary wi hdrawal -
Y -	Su - didn' r - iv all - pa -h s -	Y -	1. Non -omplian - 2. Non -omplian -
Y -	Su - didn' r - iv all - pa -h s -	Y -	Volun ary wi hdrawal -
Y -	Su - didn' r - iv all - pa -h s -	Y -	1. No ligi l - 2. O h r -

Y=Y -s, N=No; Misma -h s ar highligh -d gr -n (in lud d in h PPPI in h original su mission u x lud d - from h PPPI in h D - m b r-9, 2016 su mission) and y llow (x lud d from h PPPI in h original su mission - u in lud d in h PPPI in h D - m b r-9, 2016 su mission) -

Table w wp aris n f Excluded Patches fr w the Applicant's PPPS Bet wen the Original w Sub iwssi n and the Dece bw er 9, 201 Sub iwssi n w

Subject ID w	Patch Type	w Original sub iwssi n w		Dece bw er 9, 201 Sub iwssi n w	
		wExcluded fr w w PPPS w	wReas n f r exclusi n f r wPPPS w	wExcluded fr w w PPPS w	wReas n f r exclusi n f r ww PPPS w
(b) (6)	T, R w	Y w	Patch attached less w than 44 Hrs w	N w	
	T, R w	Y w	Subject didn't w complete Induction w Phase w	Y w	1. A need for a concomitant w medication prohibited by w the protocol arises w 2. Restricted medication w
	T, R w	Y w	Subject discontinued w study prior to w Challenge Phase w	Y w	1. Adverse events w 2. Restricted medication w
	T, R w	Y w	Subject didn't w complete Induction w Phase w	N w	
	T, R w	Y w	Subject didn't w complete Induction w Phase w	N w	
	T, R w	Y w	Patch detached and w detachment time was w unknown w	N w	
	T, R w	Y w	Subject discontinued w study prior to w Challenge Phase w	N w	
	T, R w	Y w	Subject didn't w complete Induction w Phase w	Y w	Non-compliant w
	T, R w	Y w	Subject didn't return w for evaluation at least w 24 Hrs after removal w of challenge patch w	Y w	Non-compliant w
	T, R w	Y w	Subject didn't w complete Induction w Phase w	Y w	1. Non-compliant w 2. Non-compliant w
	T, R w	N w		Y w	Non-compliant w
	T w	Y w	Patch detached and w detachment time was w unknown w	N w	
	R w	N w		N w	
	T, R w	N w		Y w	Non-compliant w

(b) (6)

T .	N .		N .	
R .	Y .	Pa . e a .e .an . e a .men .ime was . unknown .	N .	
T, R .	Y .	Subje . i n' . omple e In u .ion . P ase .	Y .	1. Non- omplian . 2. Non- omplian .
T, R .	Y .	Subje . i n' . omple e In u .ion . P ase .	Y .	1. Non- omplian . 2. Non- omplian .
T, R .	Y .	Subje . i n' . omple e In u .ion . P ase .	Y .	1. Non- omplian . 2. Non- omplian .
T, R .	N .	Subje . i n' re urn . for evalua ion a leas . 24 Hrs af er removal . of . allenge pa .	Y .	1. A .verse even s . 2. Res ri e .me .i a ion .
T, R .	Y .	Subje . i n' . omple e In u .ion . P ase .	Y .	1. A .verse even s . 2. Res ri e .me .i a ion .
T, R .	Y .	Subje . i n' . omple e In u .ion . P ase .	Y .	1. Non- omplian . 2. Pa . -free >24 .r .
T, R .	Y .	Subje . i n' . omple e In u .ion . P ase .	Y .	1. Non- omplian . 2. Non- omplian .
T, R .	Y .	Subje . i n' . omple e In u .ion . P ase .	N .	
T, R .	Y .	Subje . i n' . omple e In u .ion . P ase .	Y .	1. Non- omplian . 2. Non- omplian .
T .	N .		N .	
R .	Y .	Pa . e a .e .an . e a .men .ime was . unknown .	N .	
T, R .	Y .	Subje . i n' . omple e In u .ion . P ase .	N .	
T, R .	Y .	Subje . i n' . omple e In u .ion . P ase .	Y .	1. No eligible . 2. O . er .

=No; Pa . ype: T=Tes , R=referen e; Misma . es are .ig lig .e .green (in lu e .in . e PPPS in . e . original submission bu ex lu e .from e PPPS in . e De ember 9, 2016 submission) an .yellow (ex lu e .from . e PPPS in . e original submission bu in lu e .in . e PPPS in . e De ember 9, 2016 submission) .

Table Ap aris n f Excluded Patches fr A PPPI and PPPS Between pplicant's A Sub i ssi ns and FD 's Deter i nati n A

Subject ID A	Original sub i ssi n A				9 Dec 2016 Sub i ssi n				FD Deter i nati n A			
	Excluded fr A PPPI		Excluded fr A PPPS A		Excluded fr A PPPI		Excluded fr A PPPS A		Excluded fr A PPPI* A		Excluded fr A PPPS* A	
(b) (6)	Test	Ref	Test	Ref	Test	Ref	Test	Ref	Test	Ref	Test	Ref A
	N A	N A	Y A	Y A	N A	N A	N A	N A	N A	N A	Y A	Y A
	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A
	N A	N A	Y A	Y A	Y A	Y A	Y A	Y A	N A	N A	Y A	Y A
	Y A	Y A	Y A	Y A	Y A	Y A	N A	N A	Y A	Y A	Y A	Y A
	Y A	Y A	Y A	Y A	Y A	Y A	N A	N A	Y A	Y A	Y A	Y A
	N A	N A	Y A	Y A	N A	N A	N A	N A	N A	N A	Y A	Y A
	N A	N A	Y A	Y A	Y A	Y A	N A	N A	N A	N A	Y A	Y A
	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A
	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A
	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A
	Y A	Y A	N A	N A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A
	Y A	Y A	Y A	N A	N A	N A	N A	N A	Y A	Y A	Y A	Y A
	N A	N A	N A	N A	Y A	Y A	Y A	Y A	N A	N A	N A	N A
	Y A	Y A	N A	N A	N A	N A	N A	N A	Y A	Y A	Y A	Y A
	N A	N A	N A	Y A	N A	N A	N A	N A	N A	N A	N A	Y A
	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A
	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A
	Y A	Y A	N A	N A	N A	N A	N A	N A	Y A	Y A	Y A	Y A
	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A
	N A	N A	Y A	Y A	Y A	Y A	Y A	Y A	N A	N A	Y A	Y A
	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A
	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A
	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A
	Y A	Y A	Y A	Y A	Y A	Y A	N A	N A	Y A	Y A	Y A	Y A
	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A
	N A	N A	N A	Y A	N A	N A	N A	N A	N A	N A	N A	Y A
	Y A	Y A	Y A	Y A	Y A	Y A	N A	N A	Y A	Y A	Y A	Y A
	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A	Y A

Reviewer's Comments: A

1. The datasets used for this statistical review were from the original submission and the December 9, 2016 submission. The datasets contained numerous inconsistencies as detailed in this section. The reviewer tried to verify the data from the case report forms A A A

when in 8n i en in rma i n be ween da a e wa b erved. H wever, he e 8uld n 8 be re 8lved in many a e . 8

2. Subje 8 [redacted] wi hdrew r m he udy during he indu 8 n pha e. 8 In he da a e ubmi ed n De ember 9, 2016, he e ubje 8 were 8rre 8ly ex luded 8 r m he PPPI bu in luded in he PPPS wi h u any explana i n. 8

3. Subje 8 [redacted] 8mple ed he indu 8 n pha e bu wa di 8n inued r m he udy by he 8 inve iga 8r be 8re he hallenge pha e. H 8wever, b 8h pa h ype were in luded in he 8 PPPS by he appli an in he da a e ubmi ed n De ember 9, 2016. 8

4. F r Subje 8 [redacted], he irri a i n a 8e 8men 8 n Day [redacted] and Da [redacted] were d ne 9 and 8 minu e , re pe ively, a er pa h rem val. The a e rep r rm 8n ain 8mmen ha 8 he e are u - 8wind w irri a i n a 8e 8men 8a 8 rding 8 he pr 8 l. A 8 rding 8 8 he pr 8 l (Se 8 n 4), kin irri a i n a 8e 8men 8were 8 8 ur wi hin 15-30 minu e 8 ll wing rem val 8 ea h pa h during indu 8 n pha e. There 8re, he 8mmen ab u 8 u - 8wind w irri a i n a 8e 8men 8 during he indu 8 n pha e in he CRF are n 8 8 n i en wi h he pr 8 l. 8

5. The appli an did n ubmi he a e rep r rm s r Subje 8 [redacted] Al he 8 ubmi ed a e rep r 8rm s 8 n ained many err r u h a p 8a ing he irri a i n 8 a 8e 8men da e and 8 re 8r ne pa 8h a a pla e de igna ed 8r an 8her pa 8h. F r 8 example, he irri a i n a 8e 8men 8r he ir e 8pa 8he wa n 8 d ne 8r Subje 8 8 [redacted] bu he a 8e 8men da e and 8 re were n 8 le blank 8r ha pa 8h and he 8 irri a i n a 8e 8men in 8rma i n 8r he e 8nd e 8pa 8he wa pla ed a ha pla e 8 in 8ad. Add i nally, he a e rep r 8rm s h8ad 8 many da a lari i a i n 8rm s 8 8 a 8 hed whi h n nly h w he da a 8lle i n and re 8rding pr blem s in he ir 8 pla e, i al 8make he da a pr ne 8ina 8ura y. Thi re ul ed in addi i nal page 8 8 pr 8 l devia i n where new pr 8 l devia i n are iden i ied al ng wi h he already 8 rep 8ed ne . The arrangemen he e page i n 8 learly explained by he appli an . 8

3.2.8.2 Additional Exclusions by the FDA Reviewer 8

In addi i n he pa he di u 8ed in Se i n 3.2. .1, here were many pa he ha h uld be 8 ex luded r m he PPPS r r m b 8h PPPI and PPPS bu were n 8ex luded by he appli an . 8

3.2.8.2.1 No Ninth Irritation Assessment in the Induction Phase 8

Subje 8 [redacted] re eived all pa 8he and had irri a i n 8re 8r ir pa 8he 8b 8h 8 e 8and re8eren 8. The irri a i n a 8e 8men 8 8 he nin h pa 8h in he indu 8 n pha e were n 8 8 per 8med 8r h 8e ubje 8. The appli an in luded h 8e pa 8he in he PPPI and u ed LOCF 8 impu e he mi ing irri a i n 8re . H 8wever, a 8 rding 8FDA dra guidan e, any pa 8h 8 wi h mi ing irri a i n a e men her han h 8e mi ing be au e di 8n inued pa he due 8 ex e 8ve irri a i n h uld be ex luded r m he PPPI. The irri a i n 8re 8r nly he 8

patche m c nt nue mue t exce mve mmr tat n rh ul be nclu e mn the PPPI u ng the la t m b ervat m carr e mf rwar r(LOCF) m eth m Theref re, the patche mfr m Subject [redacted] have been exclu e mfr m FDA' rPPI. S nce n t all mn tat m a rea m ent mur ng the m n uct n pha e f r the e patche mwere m a e, the e patche mwere al mexclu e mfr m FDA' m PPPS. m

3.2.8.2.2 Exclusion Recommended in the OSIS Inspection Report m

The Off ce mf Stu y Integr ty an mSurve llance (OSIS) n pect n rep rt ment f e m12 mubject m [redacted] hav ng an m a he mn c re f 4 (etache) an hav ng am ake-up patch. m

The OSIS n pect n rep rt al mtate that except Subject [redacted], n mther 10 ubject m the mn pect n ver f e mthat the replacem ent patch wa metache mf r le mthan 24 h ur , thu m a nta n ng mmr tat n an men mtnzat n a rea m ent el g b l ty but Subject [redacted] were m unaware mf when the patch becam e fully metache , an mthu , there mwa mn ma murance mf whether m the patch ha been mff f r ver 24 h ur . m

Of the 12 ubject affecte by the pr t c l ev at n, nly tw m(Subject [redacted]) ha ma m cum ulat ve mmr tancy n ex greater than 0. The mac mn t g ve the e ubjectm m ake-up patche m e p te hav ng fully etache patche altere the t tal num ber f k n mn tat n a e m ent fr m e ght t n ne. Thu , ubject [redacted] w ul n t have ha mthe appr pr ate num ber f m rr tat n a rea m ent t be nclu e mn the per pr t c l analy m m

OSIS rep rt rec m e n e mexclu mg mata fr m the mubject [redacted] f r per m pr t c l analy m The patche mfr m the e mubject mwere memexclu e mfr m all per pr t c l p pulat n mn FDA' rev ew. m

Reviewer's Comment: m

1. The OSIS mn pect n rep rt ment f e m12 mubject mhav ng an a he mn mc re mf 4 m (etache) an mhav ng a m ake-up patch. H mwever, Table 14 ment f e m any m re m ubject mw th m ake-up patche mthat were mten e m meplace the mr tat n mc re mf m etache mpatche . m

2. The OSIS mn pect n rep rt tate mthat except Subject [redacted], n mther ubject m wh mha ma m ake-up patch f r a metache mpatch,mthe mn pect m mver f e mthat the m replacem ent patch ha mheen metache mfi r le mthan 24 h ur . H mwever, ba e mn the mata m ub mtte m n Decem ber 9, 2016, the rev ewer c ul mn t c nf r mth . All patch m etachm ent tm e were rep rte mn the mata et a mb erve mtm e a mpp me m the actual m tm e mf metachm ent. In a mt n, the OSIS rep rt ma mrect c ntra mct n t mthe ECD m re p n e ub mtte by the appl cant n Oct ber 21, 2016. In re p n e t Que t n 2 mf m the ECD letter, the appl cant pr v m the f ll w ng l t f ubject wh mha metache m patche f r wh ch ate an tm e f etachm ent were unkn wn: m

(b) (6)

This list includes all 10 subjects (b) (6)) fo which the OSIS epo t claimed to have ve ified that the patch was detached r fo less than 24 hou s Since fo none of those subjects the time diffe ence betwe en the r application time of the patch that detached and the application time of the next patch o a r eplacement patch is less than 24 hou s, the OSIS epo t's ve ification claim is inaccu ate r unless the applicant submitted w ong info mation in the ECD esponse and w ong r datasets r

3 T he OSIS inspection epo t identified only two subject (b) (6) who would not r have had nine i itation assessments if the make-up patches we e not used Howeve , this r eview identified many mo e such subjects Please efe to Table fo detached patches r and Table 14 fo make-up patches It appea s f om the OSIS epo t that one of the r easons fo excluding these subjects f om the pe p otocol analysis is that these subjects r have cumulative i itancy index (mean i itation sco e) g eate than ze o The info mation r about whethe the cumulative i itancy index is g eate than ze o is i elevant in this case r All subjects by this p otocol deviation would be affected and affect the esults in the r same way no matte what the cumulative i itancy index is r

3.2.8.2.3 Skipped Visits r

As desc ibed in Section 3 2 2, the study design did not follow the D aft Guidance on Lidocaine r and allowed subjects to skip a visit and keep the patches on until the next visit when they we e r evaluated fo skin i itation It esulted in having the same patch on fo 4 o days befo e an r i itation assessment while the patches without a skipped visit we e on fo 2 o 3 days befo e the r i itation assessment r

Table 8 gives the list of subjects who had at least patch applications du ing the induction phase r but had a skipped visit based on the diffe ence betwe en the patch application and i itation r assessment dates When these subjects skipped a visit, they we e allowed to keep the patch on r and come fo the next scheduled assessment acco ding to the p otocol Among the subjects in r Table 8, Subjects (b) (6) had both patch types excluded f om the r applicant's PPPI and PPPS in both the o iginal application and the dataset submitted on r Decembe , 201 and f om FDA's PPPI and PPPS Also both patch types fo Subjec r (b) (6) we e r excluded by the FDA eviewe f om the PPPI and PPPS because the subject did not have r i itation assessment fo the ninth patch The est of the subjects with a skipped visit we e r excluded f om PPPI2, PPPI4, PPPI , PPPS2, PPPS4 and PPPS r

Table m m b ects with kipped Visits D ming the Ind ction Phase m

Patch N m ber for the m kipped Visit m	b ect IDs m
2 m	(b) (6)
3 m	
4 m	
5 m	
6 m	
7 m	
8 m	
9 m	

Source: Reviewer's analysis m

3.2. .2.4 Detached Patches and Make- p Patches m

Many subjects had detached patches in this study. Table 9 shows the list of detached patches in m the induction phase based on the submission of 9 December 2016. Among the patches in Table 9, m both test and reference patches of Subjects (b) (6) m were excluded from the applicant's PPPI in the original submission. m

Table 9 Detached Patches in the Ind ction Phase Based on the 9 Decem ber 2016 m bm ission m

b ect ID m	Detached Test Patches m	Detached Reference Patches m
(b) (6)	5 m	5 m
	2 m	2 m
	2, 3 m	2, 3 m
	2 m	2, 3 m
	3 m	3 m
	1, 8 m	1, 8 m
	2 m	2 m
	4 m	4 m
	1, 3, 6, 7 m	1, 3, 6, 7 m
	3 m	3 m
	1 m	1 m
	2 m	2 m
		3 m
	2 m	2 m
	1 m	1 m
	1, 4 m	1, 4 m
	2 m	2 m
	3 m	3 m

(b) (6)		
	3, 6, t	3 , 6, t
	8 t	8 t
	3 t	3 t
	1 t	1 t
	3 t	3 t
	5 t	5 t
	3 t	3 t
	3 t	3 t
	3 t	3 t
	3 t	3 t
	3 t	3 t
	3 t	3 t
	3 t	3 t
	3 t	3 t
	1 t	1 t
	3 t	3 t
	3, t	3 , t
	1 t	1 t
	3 t	3 t

Table 10 lis s he de ached pa ches and he replaced pa ches in he challenge phase based on t December , 016 submission. Bo h de ached pa ches of ubjec t (b) (6) were replaced. The t replacemen ime was 1 .5 hours af er he original challenge phase pa ch applica ion for bo h t pa ches. t

Table 10: Detached Patches in the Challenge Phase Based on the 9 December 2016 t Submission t

Subject ID t	Detached Patches t	Replaced Patches t
(b) (6)	Tes , Reference t	
	Tes , Reference t	Tes , Reference t
	Reference t	
	Tes t	
	Tes t	

ource: Reviewer's analysis t

Among m an T n on Tten T e n the ubm i Tn, one T the m i mTa H T betwe Tn the p t h T det hment fl g nd the dhe on ore for the orre pond ng p t h n the d t et ubm itte Tl on T De ember 9, 2016. Tble 11 l t the p t he for wh Th the p t h det Timent fl g nd the T dhe Tn Tre do not m a H. T

Table 11: Mismatch in Patch Detachment Flag and Adhesion Score in the 9 December 2016 T Submission T

		First Mismatch T			Second Mismatch T		
Subject ID T	T **Patch Type** T	**Patch Number** T	**Detached flag** T	**Adhesion score** T	**Patch Number** T	**Detached flag** T	**Adhesion score** T
(b) (6)	T	2 T	Y T	1 T			
	R T	2 T	Y T	1			
	T	3 T	Y T	2			
	T	3 T	Y T	2 T			
	R T	1 T	Y T	3 T	8 T	Y T	3
	T	2 T	Y T	1			
	T	4 T	Y T	0 T			
	R T	7 T	Y T	3 T			
	R T	2 T	Y T	3			
	T	2 T	Y T	2 T			
	R T	4 T	Y T	0			
	T	2 T	Y T	3			
	T	4 T	Y T	1 T			
	R T	4 T	Y T	3 T			
	R T	3 T	Y T	3			
	T	3 T	Y T	2			
	T	3 T	Y T	0 T			
	R T	3 T	Y T	0			
	T	3 T	Y T	0 T			
	R T	3 T	Y T	1 T			
	R T	4 T	Y T	0 T			
	R T	7 T	Y T	0			
	T	1 T	Y T	0 T			
	R T	3 T	Y T	3 T	4 T	Y T	0 T
	R T	3 T	Y T	0 T			

Sour e: Rev ewer' n l T

In n ECD d ted O Tober 3, FDA Tked the pTpl Tnt to prov de d t nd Tt ng f e Th p t h T det Timent t me l ted w T the Tu l det Timent t me or f th t the t me when t w T ob erved T th t p t h h d lre d det Tted. he pTpl Tnt' De ember 9, 2016 ubm i Tn ont ned the e T d t . S n e the p t h det Timent t me for ll p t he were the t me when p t h det Timent T w T f r t ob erved, nd not known to be the Tu l t me , the p t h det Timent t me re r ght T

censore D is no possible o verify if he pa ch-free ime is less han 24 hours excep for he D cases where Dhe replacemen Dpa ch was applie Dwi hin 24 hours af er he original pa ch D applica ion DTable 12 shows he number of e ache Dpa ches an Dhe number of replace Dpa ches D by pa ch number base Don he Da a submi e Don December 9, 2016 DTable 13 lis s he replace D pa ches None of he replacemen Dpa ches De ache DAmong Dhe subjec s in Table 13, bo h D pa ches for Subjec s [redacted] (b) (6) ha Dreplacemen pa ch applica ions wi hin 24 hours af er he D original pa ch applicaDion No o her subjec ha Da replacemen pa ch applica ion wi hin 24 hours D af er Dhe original pa ch applica ion DAlso, no subjec Dha Dwo consecu ive regular pa ch D applica ionswD i hin 24hDours TD herefore, her Deviewere Dxclu e aD lls Dubjec -pa ch Dype D combina ions from heDPP popula ions (PPP 3-PPP 6 an DPPPS3-PPPS6) whenever here was a D e ache Dpa ch excep for he pa ches for Subjec s [redacted] (b) (6)

Table 12: Frequencies of Detached and Replaced Patches in the Induction Phase by Patch D Number and in the Challenge Phase D

Patch Number D	Patch Detachment D			Number of D Patches D Replaced D
	Missing D	No D	Yes D	
1 D	0 D	480 D	16 D	2 D
2 D	8 D	468 D	20 D	0 D
3 D	16 D	440 D	40 D	11 D
4 D	20 D	466 D	10 D	2 D
5 D	22 D	470 D	4 D	2 D
6 D	26 D	466 D	4 D	0 D
7 D	28 D	464 D	4 D	0 D
8 D	30 D	462 D	4 D	0 D
9 D	30 D	464 D	2 D	0 D
Makeup D	424 D	72 D	0 D	0 D
Challenge Phase	34 D	455 D	7 D	2 D

Source: Reviewer's analysis D

Table 13: List of Replacement Patches D

Subject ID D	Patch Type D	Patch Number D	Original Patch Application Date and Time D	Original Patch Detachment Date and Time (Observed) D	Replacement Patch Application Date and Time D	Diff* D
[redacted] (b) (6)	R D	5 D	[redacted] (b) (6)			32:23 D
	T D	5 D				32:23 D
	R D	Ch** D				12:30 D
	T D	Ch** D				12:30 D
	R D	3 D				47:57 D
	T D	3 D				47:57
	R D	3 D				49:46 D

(b) (6)			(b) (6)	
	T 1	3		9 1
	R 1	3 1		51 17 1
	R 1	3 1		51 0 1
	T 1	3 1		51 0 1
	R 1			07 17 1
	T 1			07 17 1
	R 1	3 1		55 55 1
	T 1	3 1		55 55 1
	R 1	1 1		2 3 1
	T 1	1 1		2 3 1
	R 1	3 1		5 05 1
	T 1	3 1		5 05 1

* Diff = Difference betwden origina and rep acement patch app ication times in hours and minutes. 1
Patch Type T=Test R=Reference 1
** Ch=Cha enge phase patch 1
Green font indicates that the rep acement patch was app ied with 2 lhours of the origina patch app ication. 1
Source Reviewer's ana ysis 1

Make-up patches were used at the end of the induction phase on the subjects who had detached 1 (an adhesion score of) or partia y detached (an adhesion score of 3) patches. Tab e 1 lshows 1 the ist of make-up patches and identifies the corresponding patches with adhesion score 3 and 1 whose irritation scores the app icant intended to rep ace by the irritation score of the make-up 1 patches. When there are mu tip e patches that the same make-up patch was intended to rep ace 1 the number of patches is essentia y reduced because the irritation score of a sing e make-up 1 patch rep aces that of mu tip e patches as described in the reviewer's comment in Section 3.2.2. 1 For that reason this review ignored a lmake-up patches. 1

Table 14: List of Make-up Patches 1

Subject ID 1	**Patch Type** 1	**Patch number with** 1 **adhesion score 3** 1	**Patch number with** 1 **adhesion score 4** 1
(b) (6)	Reference 1	2 1 5 1	
	Test 6 1		5 1
	Test 4 1		
	Reference 1		2 1
	Reference 1		3 1
	Test 1		2 1
	Test 1	5 1	
	Reference 1	2 1	
	Test 1	2 1	
	Reference 1	2 1	
	Reference 1	5 1	
	Test 1	5 1	
	Reference 1	9 1	3 1

(b) (6)

Test 9		
e e ence	2	
Test	1	
e e ence	1, 7, 8	
Test	7	1, 8
e e ence		2
e e ence	2	
Test	2	
e e ence	7	1, , 6
Test	2, 4, 5	1, , 6, 7
e e ence	2	
e e ence	4	
e e ence	1, 4	
Test	2	
e e ence	1	
Test	1	
e e ence	2	
Test	1	
e e ence	2	
Test		2
e e ence	6	
e e ence		2
e e ence	2	
e e ence		1
Test		1, 4
e e ence	1,	
Test	8,	
Test	7	
e e ence	1, 2 3	, 6,
Test	2	, 6,
e e ence	1, 2, 4	
e e ence	2, 5	
Test	4	
Test 3		
Test	1	
Test	1	
e e ence 3		
Test 3		
e e ence 3		
Test 3		
e e ence	5	
e e ence 3		
e e ence 3		

(b) (6)			
	Test y		3 y
	e e e ce y		3 y
	Test y	3 y	
	Test y	3 y	
	Test 8 y		3 y
	Test y	3 y	4 y
	e e e ce y	6 y	3 y
	Test y	6 y	3 y
	Test y		7 y
	e e e ce y	5 y	
	e e e ce y	2, 3 y	
	e e e ce y		1 y
	Test 8 y		
	Test 8 y		
	e e e ce y		1 y
	Test y	3, y	1 y

Sou ce: eviewe 's a al sis y

Reviewer's Comments: y

Acyco di g to the o igi al submissio the test patch o Subjec (b) (6) a d the e e e ce patches o y Subjects (b) (6) detached du i g the challe ge phase. Howeve , as show yi Table 10, y based o the Decembe 9, 2016 submissio , the test patches o Subjects (b) (6) a d the y e e e ce patch o Subjec (b) (6) detached du i g the challe ge phase. These co ylicti g data give y a i dicatio o a possibilit o eve si g the test a d e e e ce data o some o all subjects i y the dataset. I that happe ed, all a al ses would be w o g. This gives a st o g easo wh y i co siste t data should eve be co side ed o a app oval. y

3.2.8.3 FDA's Analysis Populations y

Due to the o -sta da d desig a d pote tial p oblems with skipped visits a d detached patches y as discussed i Sectio s 3.2. .2.3 a d 3.2. .2.4, the eviewe co side ed seve al pe p otocol y populatio s o i itatio a d pe p otocol populatio s o se sitizatio . The populatio s a e y amed as PPPI1, PPPI2, etc. o i itatio a d PPPS1, PPPS2, etc. o se sitizatio . Followi g y a e the de i itio s o the populatio s a d the lists o patches excluded om the populatio s. y

3.2.8.3.1 PPPI1 and PPPS1 y

The patches excluded om PPPI1 a e: y

- A patch t pe that did ot have all i e patch applicatio s o did ot have all i e y i itatio assessme ts o a subject. This set co sists o all patches that a e excluded om y

FDA's 0 0 able 7 a d all patches from Subjects [redacted]. lease refer to 0 Sect o s 3.2.8.1 a d 3.2.8.2.1 for more deta ls. 0

- All patches from Subjects [redacted]. h s s based o the OS S 0 spect o report. lease refer0to Sect o 03.2.8.2.2 for more deta ls. 0

he patches excluded from 0 S1 are: 0

- A patch type that d d ot have all 0e rr tat o assessme ts for a subject or d d ot have 0 challe ge phase patch appl cat o or the challe ge phase patch was removed before 44 0 hours or the challe ge phase patch detached a d the detachme t t me was u k ow 0or the 0 challe ge phase rr tat o assessme ts were ot do e. h s set co s sts of all patches that 0 are excluded from FDA's 0 S able 7 a d all patches from Subjects [redacted] lease refer to Sect o s 3.2.8.1 a d 3.2.8.2.1 for more deta ls. 0
- All patches from Subjects [redacted]. h s s based o the OS S 0 spect o report. lease refer0to Sect o 03.2.8.2.2 for more deta ls. 0

he l sts of patches excluded from 0 1 a d 0 S1 are prese ted able 15. 0

Table 15: Patches Excluded from PPPI1 and PPPS1 0

Subject ID 0	**Exlcuded from PPPI1** 0		**Excluded from PPPS1**	
[redacted]	**Test** 0	**Reference** 0	**Test** 0	**Reference** 0
			Y 0	Y 0
	Y 0	Y 0	Y 0	Y 0
			Y 0	Y 0
	Y 0	Y 0	Y 0	Y 0
	Y 0	Y 0	Y 0	Y
	0		Y 0	Y 0
	Y 0	Y 0	Y 0	Y 0
			Y 0	Y 0
	Y 0	Y 0	Y 0	Y 0
	Y 0	Y 0	Y 0	Y 0
	Y 0	Y 0	Y 0	Y 0
	Y 0	Y 0	Y 0	Y 0
	Y 0	Y 0	Y 0	Y 0
	Y 0	Y 0	Y 0	Y 0
	Y 0	Y 0	Y 0	Y 0
				Y 0
	Y 0	Y 0	Y 0	Y 0
	Y 0	Y 0	Y 0	Y 0
	Y 0	Y 0	Y 0	Y 0
	Y 0	Y 0	Y 0	Y 0
			Y 0	Y 0
	Y 0	Y 0	Y 0	Y 0

(b) (6)				
	Y 2	Y 2	Y 2	Y 2
	Y 2	Y 2	Y 2	Y 2
	Y 2	Y 2	Y 2	Y 2
	Y 2	Y 2	Y 2	Y 2
	Y 2	Y 2	Y 2	Y 2
	Y 2	Y 2	Y 2	Y 2
	Y 2	Y 2	Y 2	Y 2
	Y 2	Y 2	Y 2	Y 2
				Y 2
	Y 2	Y 2	Y 2	Y 2
	Y 2	Y 2	Y 2	Y 2

urce: Reviewer's analysis 2

3. .8.3. 2 PPPI and PPPS 2

The patches excluded fr m PPPI2 are: 2

- All patches excluded fr m PPPI1. 2
- All patches fr m the subjects wh skipped a visit during the inducti n phase. Please refer 2 t ecti n .2.8.2. f r m re2details. 2

The patches excluded fr m PPP 2 are: 2

- All patches excluded fr m PPP 1. 2
- All patches fr m the subjects wh skipped a visit during the inducti n phase. Please refer 2 t ecti n .2.8.2. f r m re2details. 2

All patches f r the f ll wing subjects in additi n t the patches listed in Table 15 were excluded 2 fr m PPPI2 and PPP 2: 2

(b) (6)

3. .8.3.3 PPPI3 and PPPS3 2

The patches excluded fr m PPPI are: 2

- All patches excluded fr m PPPI1. 2
- All patches that were detached during the inducti n phase based n the patch detachment 2 flag but n t kn wn t be replaced within 2 h urs after detachment. The datasets 2 submitted n December 9, 2 16 were used f r this determinati n. Please refer t ecti n 2 .2.8.2. f r m re2details. 2

The pa he e b uded from PPPS3 are: b

- A pa he e b uded from PPPS1. b
- A pa he ha were de a hed during he indu bion or ha enge pha e a ed on he pa h b de a hmen f ag u no known o e rep a ed wi hin 24 hour af er de a hmen . The b da a e u mi ed on De ember 9, 2016 were u ed for hi de ermina ion. P ea e refer o b Se bion 3.2.8.2.4 for more de ai . b

The i bof pa he e b uded from PPPI3 and PPPS3 are pre en ed in Ta le 16. b

Table 16: Patches Excluded from PPPI3 and PPPS3 b

Subject ID b	Exlcuded from PPPI3		Excluded from PPPS3 b	
	Test	Reference	Test	Reference b
(b) (6)	Y b	Y b	Y b	Y b
			Y b	Y b
	Y b	Y b	Y b	Y b
	Y b	Y b	Y b	Y b
			Y b	Y b
	Y b	Y b	Y b	Y b
	Y b	Y b	Y b	Y b
	Y b	Y b	Y b	Y b
	Y b	Y b	Y b	Y b
	Y b	Y b	Y b	Y b
			Y b	Y b
	Y b	Y b	Y b	Y b
	Y b	Y b	Y b	Y b
	Y b	Y b	Y b	Y b
	Y b	Y b	Y b	Y b
	Y b	Y b	Y b	Y b
	Y b	Y b	Y b	Y b
	Y b	Y b	Y b	Y b
	Y b	Y b	Y b	Y b
		Y b		Y b
	Y b	Y b	Y b	Y b
	Y b	Y b	Y b	Y b
	Y b	Y b	Y b	Y b
	Y b	Y b	Y b	Y b
	Y b	Y b	Y b	Y b
	Y b	Y b	Y b	Y b
	Y b	Y b	Y b	Y b
			Y b	Y b
	Y b	Y b	Y b	Y b

(b) (6)

[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]			Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]			Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2
[redacted]	Y 2	Y 2	Y 2	Y 2

urce: Reviewer's analysis 2

3. .8.3.4 PPPI4 and PPPS4 2

The patches excluded from PPPI4 are: 2

- All patches excluded from PPPI3. 2
- All patches from the subjects who skipped a visit during the induction phase. Please refer 2 to Section 3.2. .2.3 for more 2 details. 2

The patches excluded from PPP 4: 2

- All pa g x lud d from PPPS3. g
- All pa g from g ubj g w go kipp d a vi i durin g indu gion p a g Pl a gr f r g o S g ion 3.2.8.2.3 for mor d gail . g

All pa g for g followin ubj g in addi ion o g pa g li gd in Tabl 16 w gr x lud d g from PPPI4 and PPPS4: g

(b) (6)

3.2.8.3.5 PPPI5 and PPPS5 g

T g pa g x lud d from PPPI5 ar : g

- All pa g x lud d from PPPI1. g
- All pa g a w r d a g d durin g indu gion p a g ba gd on g ad g ion or g bu no known o b r pla gd wi in 24 our af r d ga gm en g T g da a g ubmi gd g on D g mb r 9, 2016 w r u d for i d g rmina ion. Pl a gr f r o S g ion 3.2.8.2.4 g for mor d gail . g

T g pa g x lud d from PPPS5 ar : g

- All pa g x lud d from PPPS1. g
- All pa g ga w gr d ga g d durin g indu gion or gall n g p a g ba gd on g g ad g ion gor g bu no known o b r pla gd wi in 24 our af r d ga gm en g T g g da a g ubmi gd on D g mb r 9, 2016 w gr u gd for i d g rmina ion. Pl a gr f r o g S g ion 3.2.8.2.4 for mor d gail . g

T g li gof pa g x lud d from PPPI5 and PPPS5 ar pr gn gd in Tabl 17. g

Table 17: Patches Excluded from PPPI5 and PPPS5 g

Subject ID g (b) (6)	**Exlcuded from PPPI5** g		**Excluded from PPPS5**	
	Test g	**Reference** g	**Test** g	**Reference** g
	Y g	Y g	Y g	Y g
			Y g	Y g
	Y g	Y g	Y g	Y g
		Y g		Y g
			Y g	Y g
	Y g	Y g	Y g	Y g
	Y g	Y g	Y g	Y g
	Y g	Y g	Y g	Y g
		Y g	Y g	Y g
	Y g	Y g	Y g	Y g

(b) (6)

		Y	Y
Y		Y	
	Y		Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y		Y	
	Y		Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
		Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
		Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y		Y	
	Y		Y
	Y		Y
Y	Y	Y	Y
Y	Y	Y	Y
	Y		Y
Y		Y	
Y	Y	Y	Y
Y		Y	
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y
Y	Y	Y	Y

[redacted]				
	Y 6	Y 6	Y 6	Y 6
	Y 6	Y 6	Y 6	Y 6
	Y 6		Y 6	
	Y 6	Y 6	Y 6	Y 6
			Y 6	Y 6
	Y 6	Y 6	Y 6	Y 6
	Y 6	Y 6	Y 6	Y 6
	Y 6	Y 6	Y 6	Y 6
	Y 6		Y 6	

ce: Reviewe 's analysis 6

3.2.8.3. 6 PPPI and PPPS 6

The patches excl ded f m PPPI6 a e: 6

- All patches excl ded f m PPPI5. 6
- All patches f m the s bjects wh skipped a visit d 6ing the ind cti n phase. Please efe 6 t ecti n 3.2. .2.3 f m o e6details. 6

The patches excl ded f m PPP 6 a e: 6

- All patches excl ded f m PPP 5. 6
- All patches f m the s bjects wh skipped a visit d 6ing the ind cti n phase. Please efe 6 t ecti n 3.2. .2.3 f m o e6details. 6

The f ll wing patches in additi n t the patches listed in Table 17 we e excl ded f m PPPI6 6 and PPP 6: 6

- B th 6 patches f 6bjects: [redacted]
- Refe ence patch f 6bjects [redacted]

3.2.9 Demographic and Baseline Characteristics 6

A s mma y f dem g6aphic and baseline cha acte istics (gende , ace and age) f all en 6lled 6 s bjects, which was same as the safety p p lati n in this st dy, is p esented in Table 1 . 6 App 6ximately 74% s bjects we e female. Maj ity f the s bjects we e black (app 6ximately 6 54%) f ll wed by white (app 6ximately 44%). The age ange was 1 t 69 yea s. The ave age 6 and median ages we e 41.4 and 43 yea s, espectively. The st dy was c nd cted at a single site 6 [redacted] in U 6A. 6

Table y e oy graphic and Baseline Characteristics for Irritation and Sensitization Stud y y Gender, Race and Age y

		All Enrolled y (N=24) y
Gender y	Female	184 (74.19%) y
	Male	64 (25.81%) y
Race y	Asian y	3 y (1.21%) y
	Black y	135 (54.44%) y
	White	110 (44.35%) y
Age Group y in Years y	18-40 y	111 (44.76%) y
	41-64 y	129 (52.02%) y
	65-75 y	8 y (3.23%) y
Age in y Years y	Mean, SD y	41.39, 12.22 y
	Min, Max y	18, 69 y
	Q1, Median, Q3 y	33, 43, 49 y

Source: Reviewer's analysis y

3.2. 0 Results and Conclusions y

3.2. 0. Ay pplicant's Anal sis Results y

The irritation score (on a scale of 0 to 13) for each patch at each evaluation was the sum of the y dermal response score (on a scale of 0 to 7) and the score for other effects (on a scale of 0 to 6) y as given in Table 2 and Table 3. The cumulative irritancy index (CII) was defined as the sum of y all irritation scores across readings during the induction/challenge phase divided by the number y of readings (9 readings). The cumulative dermal response index and the cumulative other effects y index were defined similarly. y

A summary of the cumulative irritancy index, cumulative dermal response index and cumulative y other effects index by treatment and by treatment and cohort for the full irritation analysis y population in the induction phase is presented in Table 19 and that in the challenge phase is y presented in Table 20. y

Table 9 Su a y r of Cu u y lative Irritanc Index in Induction Phase b Treat e y nt and y Cohort in Full Irritation Anal sis Population per Applicant y

Para e y ter	Statistic y	Overall y		Cohort y		C ohort 2 y	
		Test y	Reference y	Test	Reference	Test	Reference y
Cu u y lative Irritanc y Index y	N y	228 y	228 y	112 y	112 y	116 y	116 y
	Mean y	0.211 y	0.212 y	0.170 y	0.170 y	0.250 y	0.253 y
	(SD) y	(0.3535) y	(0.3442) y	(0.3009) y	(0.3047) y	(0.3624) y	(0.3757) y
	Median y	0 y	0 y	0 y	0 y	0 y	0 y

	Min, Ma i	, i4 0 i	, 6 i	, 2 0 i	, i	, i4 0 i	, 6 i
Cumulat ve Dermal i Response i Index i	N	228 i	228 1 i	2 1 i	2 1 i	6 1 i	6 i
	Mean i (SD) i	2 i i (3535) i	2 2 i (3442) i	i i (3 i9) i	i i (3 4) i	25 i (3624) i	253 i (3 5) i
	Median 0 i						
	Min, Ma i	, i4 0 i	, 6 i	, 2 0 i	, i	, i4 0 i	, 6 i
Cumulat ve Other i Effects i Index i	N	228 i	228 1 i	2 1 i	2 1 i	6 1 i	6 i
	Mean i (SD) i	( ) 0 i	( ) 0 i	( ) 0 i	( ) 0 i	( ) 0 i	( ) i
	Median 0 i						
	Min, Ma i	, i	, i	, i	, i	, i	, i

Source: Clinical Study Report, Study RP-LID-SSI, Table 4 4 3 i and Table 4 4 3 2 i

Table 20: Summary of Cumulat ve Irr tancy Index n Challenge Phase by Treatment and i Cohort n Full Irr tat on Analys s Populat on per Appl cant i

Parameter	Stat st c i	Overall i		Cohort 1 i		Cohort 2 i	
		Test i	Reference i	Test	Reference	Test	Reference i
Cumulat ve Irr tancy i Index i	N	225 i	225 1 i			5 1	i 5 i
	Mean i (SD) i	6 i (i66)	i 5 i (i4 5) i	59 i (i82)	48 i i (i64) i	63 i (i5 2)	52 i i (i3 3) i
	Median 0 i						
	Min, Ma i	, 5 i	, 5 i	, 5 i	, 5 i	, i5 0 i	, 5 i
Cumulat ve Dermal i Response i Index i	N	225 i	225 1 i			5 1	i 5 i
	Mean i (SD) i	6 i (i66)	i 5 i (i4 5) i	59 i (i82)	48 i i (i64) i	63 i (i5 2)	52 i i (i3 3) i
	Median 0 i						
	Min, Ma i	, 5 i	, 5 i	, 5 i	, 5 i	, i5 0 i	, 5 i
Cumulat ve Other i Effects i Index i	N	225 i	225 1 i			5 1	i 5 i
	Mean i (SD) i	( ) 0 i	( ) 0 i	( ) 0 i	( ) 0 i	( ) 0 i	( ) i
	Median 0 i						
	Min, Ma i	, i	, i	, i	, i	, i	, i

Source: Clinical Study Report, Study RP-LID-SSI, Table 4 4 5 i and Table 4 4 5 2 i

The individual CIIs, the individual irritancy inde , the individual cumulative dermal response i inde and the individual cumulative other effects inde generated during the induction phase i were tested for product differences using the 2-way analysis of variance (ANOVA) including i main effects of subject and product, without interaction using the PROC GLM. For the test i product to be no more irritating than the RLD, the upper bound of the one-sided 95% confidence i interval of the difference between the products had to be no greater than i based on the i protocol The upper bound of the 95% one-sided confidence interval of the difference between i the two products was calculated to be i 5 for both the individual irritancy and dermal response i

indices b ariance f r ther effect index was bser ed; all alues were zer b These results are b summarized in Table 21 b

Ta le 21: Analysis of Cumulative Irritancy Index in the Induction Phase in the Full b Irritation Analysis Population per Applicant b

Parameter b	Least Square Means		b Mean of b Test - b Reference b	One-Sided 95% b Upper b Confidence b Bound for Test - b Reference b
	Test b	Reference		
Cumulati e Irritancy Index b	0 21 b b	0 212 b	-0 001 b	0 015 b
Cumulati e Dermal Resp nse b Index b	0 21 b b	0 212 b	-0 001 b	0 015 b
Cumulati e Other Effects Index b	0 b	0 b	0 b	0 b

S urce: Clinical Study Rep rt, Study RP-LID-SSI, Table 14 4 4 b

There was n b bser ati n b f a maximum irritati n sc re b f 13, a maximum d rmal resp nse b sc re b f 7 b r a maximum ther effects sc re b f 6 rep rted f r any patch b patch was rem ved b due t an unacceptable degree b f irritati n b

The applicant c ncluded that taken t gether, these data dem nstrated that there was n difference b f r skin irritancy betwe n the test and the reference patches b

In additi n t the pr t c l specified analysis, the applicant c nducted a p st-h c analysis as per b “FDA’s Draft Guidance n bic tine Extended Release Transdermal Patch” with regard t the b skin irritati n and sensitizati n assessment This p st-h c analysis was perf rmed using the 2- b way analysis f ariance (A OVA) including main effects f subject and pr duct, with ut b interacti n using the PROC GLM . The results f cumulati e irritancy sc res dem nstrated n n- b inferi rity as the upper b und f the ne-sided 95% CI f the mean test pr duct sc re minus 1 25 b times the mean RLD sc re was less than 0 b The results are presented in Table 22 and are b c nsistent with the pre-specified statistical analysis results b

Ta le 22: Post-Hoc Analysis of Cumulative Irritancy Index in the Induction Phase in the b Full Irritation Analysis Population per Applicant b

Parameter b	Least Square Means		b Mean of b Test - b Reference b	One-Sided 95% b Upper b Confidence b Bound for Test - b Reference b
	Test b	Reference		
Cumulati e Irritancy Index b	0 21 b b	0 212 b	-0 052 b	-0 034 b
Cumulati e Dermal Resp nse b Index b	0 21 b b	0 212 b	-0 052 b	-0 034 b
Cumulati e Other Effects Index b	0 b	0 b	0 b	0 b

S urce: Clinical Study Rep rt, Study RP-LID-SSI, Table 10 b

Sensitiz ti n 5 test 5ersus re erence study pr ducts w 5s b sed 5n irrit ti n sc res 5bt ined 5 during the ch 5lenge ph se 5nd whether the re cti ns were indic ti e 5 sensitiz ti n re cti n 5 by the in estig t r. The ull sensitiz ti n 5n lysis p pul ti n c nsisted 5 227 (91. %) subjects. 5 There were 5l1 1 (90.2%) nd 5l16 (92.8%) subjects in C h rts 1 5nd 2, respecti ely, 5 b th the 5 test sensitiz ti n 5n lysis p pul ti n 5nd re erence sensitiz ti n 5n lysis p pul ti n. There w 5s 5 n 5e idence 5 skin sensitiz ti n re cti n 5 ll wing rem o 5l 5 either the test 5r re erence 5 ch 5lenge p tch. The results re sh wn in T ble 23. N 5p tch w s rem o e5d due t str ng skin 5 sensitiz ti n. 5

Table 23: Summary of the Number of Skin Sensitization Reactions in Full Sensitization 5 Analysis Population per Applicant 5

Parameter 5	**Scheduled Time** 5 **Point after Patch** 5 **Removal** 5	**Treatment** 5	
		Test (N=2227) 5	**Reference (N=2227)** 5
Number 5 Skin 5 Sensitiz ti n 5 Re cti ns 5	30 min 5	0 5	0 5
	24 hrs 5	0 5	0 5
	48 hrs 5	0 5	0 5
	72 hrs 5	0 5	0 5

S urce: Clinic l Study Rep rt, Study RP-LID-SSI, T ble 11 5

Reviewer's Comments: 5

1. The 5pplic nt did n t use 5ny letter sc re 5 r the 5ther e ects. The 5pplic nt's 5ther 5 e ects numeric sc le w s di erent r m FDA's 5ther e ects numeric sc le. This 5 di erence is sh wn in T ble 4. 5

2. Acc rding t the Dr t Guid nce 5n Lid c ine, the 5pplic nt sh uld pr 5ide 5 requency 5 t ble sh wing the number 5 pplic ti ns 5 e ch test rticle with e ch c mbined derm l 5 resp nse nd 5ther e ects sc re using the l st bser 5ti n c 5ried 5 rw rd (LOCF) 5r 5 subjects wh 5disc ntinued 5test rticle bec use 5 un 5cept ble irrit ti n. The 5pplic nt 5 did n t pr 5ide ny such t ble. 5

3. The Dr t Guid nce 5n Lid c ine st tes the 5ll wing: "T 5dem ons5r te n n-in eri rity 5 the test pr duct c mp red t the RLD with reg rd t the cumul ti e irrit ti n sc res, 5 the upper b und 5 the 5ne-sided 9 5% CI 5 the me n test pr duct sc re minus 1.2 times 5 the me n RLD sc re must be less th n 5r equ l t 0." H 5ve er, the 5pplic nt's criteri n 5 r n n-in eri rity in the prim ry5 5n lysis w 5s di erent. The 5pplic nt c nsidered the test 5 pr duct t be n n-in eri r t the re erence pr duct i the upper b und 5 the 5ne-sided 5 9 % c n idence inter 5l 5 the di erence between the pr ducts (test - re erence) w s n t 5 gre ter th n 0.11. The 5pplic nt did n t pr 5ide 5ny justi ic ti n in the pr t c l, 5 st tistic l n lysis pl n 5r clinic l study rep rt 5r its criteri n 5 r n n-in eri rity in the 5 prim ry n lysis nd h w they determined the n n-in eri rity m rgi5n 5 0.11. 5

3.2.10.2 R f 's Analys s R sults f

Analyses o irritation in PPPI1 to PPPI6 are provided in Sections 3.2.10.2.1 to 3.2.10.2.6, f respectively and analyses o sensitization in PPPS1 to PPPPS6 are provided in Section f 3.2.10.2.7. No patches were discontinued or moved due to excessive irritation.

3.2.10.2.1 I f tat on Analys s R sults n PPPI1 f

Table 24 shows the number and percent o applications by induction phase patch number and f patch type with a speci ic combined "dermal response" and "other e ects" score in PPPI1. A f summary o mean irritation scores during the induction phase in PPPI1 is presented in Table 25. f

Tabl 24: Numb f (%) of Appl cat ons by Induct on Phas Patch Numb f and Patch Typ f th a Sp c f c Comb n d "D f mal R spons " and "Oth f Eff ct" Sco f n th PPPI1 f

Patch No: f T f atm ent f	**Comb n d "D f mal R spons " and "Oth f Eff ct" Sco f F f qu ncy, % f**							
	0N f		**1N f**		**2N f**		**3N f**	
1:Test f	193	86.94% f	27 f	12.16% f	2 f	0.90% f	0 f	0.00% f
1:Re erence f	194	87.39% f	26 f	11.71% f	2 f	0.90% f	0 f	0.00% f
2:Test f	189	85.14% f	30 f	13.51% f	3 f	1.35% f	0 f	0.00% f
2:Re erence f	189	85.14% f	31 f	13.96% f	2 f	0.90% f	0 f	0.00% f
3:Test f	173	77.93% f	42 f	18.92% f	7 f	3.15% f	0 f	0.00% f
3:Re erence f	175	78.83% f	40 f	18.02% f	6 f	2.70% f	1 f	0.45% f
4:Test f	174	78.38% f	45 f	20.27% f	3 f	1.35% f	0 f	0.00% f
4:Re erence f	173	77.93% f	46 f	20.72% f	3 f	1.35% f	0 f	0.00% f
5:Test f	178	80.18% f	41 f	18.47% f	3 f	1.35% f	0 f	0.00% f
5:Re erence f	174	78.38% f	45 f	20.27% f	3 f	1.35% f	0 f	0.00% f
6:Test f	173	77.93% f	48 f	21.62% f	1 f	0.45% f	0 f	0.00% f
6:Re erence f	177	79.73% f	42 f	18.92% f	3 f	1.35% f	0 f	0.00% f
7:Test f	170	76.58% f	51 f	22.97% f	1 f	0.45% f	0 f	0.00% f
7:Re erence f	167	75.23% f	52 f	23.42% f	3 f	1.35% f	0 f	0.00% f
8:Test f	181	81.53% f	41 f	18.47% f	0 f	0.00% f	0 f	0.00% f
8:Re erence f	181	81.53% f	40 f	18.02% f	1 f	0.45% f	0 f	0.00% f
9:Test f	176	79.28% f	45 f	20.27% f	1 f	0.45% f	0 f	0.00% f

9:Refere ve w		9. 3% w	4 w	8.4 % w	4 w	.80% w	0 w	0.00% w

Please refer to Se tio v3.2.3 for the o versio vfrom letter s ore to umeri al s ore. w
Sour e: Revie wer's a alysis. w

Table 25: Summary of Mean Irritation Score (Mean of "Dermal Response" Plus "Other Effects" Scores During the Induction Phase) in PPPI1 per FDA Reviewer w

Product w	**N** w	**Mean (SD)** w	**Min** w	**First Quartile** w	**Median** w	**Third Quartile** w	**Max** w
A (Test) w	222	0.206 (0.323) w	0 w	0 w	0 w	0.333 w	1 w .444 w
B (Reference)	222	0.2 0 (0.345) w	0 w	0 w	0 w	0.333 w	1 w .66 w

Sour e: Revie wer's a alysis w

The wo -i feriority a alysis of test pat h agai st the refere ve pat h based o the mea irritatio w s ore i PPPI usi g a li ear model is sho w i Table 26. I the model, the mea irritatio s ore w as the respo se a d treatme t a d subje t were fixed effe ts. The o e-sided 95% upper w o fide ve bou d was -0.03 9 whi h bei g vegative sho wd that the test is w -i ferior to the w refere ve. w

Table 26: Non-inferiority Analysis of Mean Irritation Score for Test vs. Reference in PPPI1 w **per FDA** w

Variable w	**Hypotheses** w	**LSmean Test** w	**LSmean Reference** w	**Estimate of** $\mu_A - 1.25*\mu_B$ w	**One-Sided 95% Upper Confidence Bound** w
Mean Irritation Score w	H_0: $\mu_A - 1.25*\mu_B \geq 0$ w H w $\mu_A - 1.25*\mu_B < 0$ w	0.2062 w	0.2 02 w	-0.0566 w	-0.03 9 w

Sour e: Revie wer's a alysis w

The proport o o bject PPPI1 w th a d w tho t a mea 2 g 2l degree o rr tat o (at lea t 2 o e rr tat o core ≥ 3) cro 2-tab lated or the te t ver 2 re ere ce prod ct Table 7. A 2 te t or o - 2er or ty o the te t patch to the re ere ce patch term so proport o o patche 2 w th a mea 2 g 2l degree o rr tat o PPPI1 pre e ted Table 8. There wa o te t patch 2 a d 1 (00.45%) re ere ce patch w th at lea t o e rr tat o core ≥ 3. The po 2t e t mate o $P_T - 2$ P_R, the d 2ere ce betwe2 proport o o te t a d re ere ce patche w th a mea 2 g 2l degree o 2 rr tat o -0.0045 (-0.45%) a d the o e- ded 95% 2per bo 2d or $P_T - P_R$ 0.01 04. 2

Table 27: Subjects With or Without Meaningful Degree of Irritation (Maximum Irritation 2 **Score ≥ 3 or < 3) for Test and Reference Products During the Induction Phase in PPPI1** 2

		Test Product		
		Max Irritation Score < 3	Max Irritation Score ≥ 3	Total
Reference Product	Max Irritation Score < 3	221	0	221
	Max Irritation Score ≥ 3	1	0	1
	Total	222	0	222

Source: Reviewer's analysis

Table 28: Non-inferiority Test in Terms of Proportions of Subjects with a Meaningful Degree of Irritation During the Induction Phase in PPPI1

Hypothesis	Proportion of Test Score ≥ 3 (P_T) (N=222)	Proportion of Reference Score ≥ 3 (P_R) (N=222)	Point Estimate for $P_T - P_R$	One-sided 95% Upper Confidence Limit for $P_T - P_R$
H_0: $P_T - P_R > \delta$ (inferiority) H_1: $P_T - P_R \leq \delta$ (non-inferiority)	0.0000	0.0045	-0.0045	0.01204

Source: Reviewer's analysis

3.2.10.2.2 Irritation Analysis Results in PPPI2

Table 29 shows the number and percent of applications by induction phase patch number and patch type with a specific combined "dermal response" and "other effects" score in PPPI2. A summary of mean irritation scores during the induction phase in PPPI2 is presented in Table 30.

Table 29: Number (%) of Applications by Induction Phase Patch Number and Patch Type with a Specific Combined "Dermal Response" and "Other Effects" Score in the PPPI2

Patch Number Treatment	Combined "Dermal Response" and "Other Effects" Score Frequency, %							
	0		1		2		3	
1:Test	170	86.73%	24	12.24%	2	1.02%	0	0.00%
1:Reference	171	87.24%	24	12.24%	1	0.51%	0	0.00%
2:Test	167	85.20%	26	13.27%	3	1.53%	0	0.00%
2:Reference	165	84.18%	29	14.80%	2	1.02%	0	0.00%
3:Test	152	77.55%	37	18.88%	7	3.57%	0	0.00%
3:Reference	153	78.06%	36	18.37%	6	3.06%	1	0.51%

4:Test	7	0 %	3	3 %	3	3%	0	0 00%
4:Reference	3	7 06%	40	20 4 %	3	3%	0	0 00%
:Test	7 8	0 0%	36 1	37%	3	3%	0	0 00%
:Reference	7 8	0 0%	36 1	37%	3	3%	0	0 00%
6:Test	7	7 04%	44	22 4 % 1		0 %	0	0 00%
6:Reference	7	0 %	3	3 %	3	3%	0	0 00%
7:Test	4 7	6 02%	46	23 47% 1		0 %	0	0 00%
7:Reference	46	74 4 %	47	23 %	3	3%	0	0 00%
:Test		2%	37 1	%	0	0 00%	0	0 00%
:Reference		2%	36 1	37% 1		0 %	0	0 00%
:Test	6	7 %	3	0% 1		0 %	0	0 00%
:Reference	6	7 %	36 1	37%	4	2 04%	0	0 00%

Please refer to Section 3 2 3 for the conversion from letter score to numerical score
Source: Reviewer's analysis

Table 30: Summary of Mean Irritation Score (Mean of "Dermal Response" Plus "Other Effects" Scores During the Induction Phase) in PPPI2 per FDA Reviewer

Product	**N**	**Mean (SD)**	**Min**	**First Quartile**	**Median**	**Third Quartile**	**Max**
A (Test)	6	0 20 (0 34)	0	0	0	0 333 1	444
B (Reference)	6	0 2 4 (0 3 4)	0	0	0	0 333 1	667

Source: Reviewer's analysis

The non-inferiority analysis of test patch against the reference patch based on the e an irritation score in PPPI2 using a linear o del is shown in Table 3 In the o del, the e an irritation score was the response and treate nt and subject were fixed effects The one-sided % upper confidence bound was -0 03 which being negative showed that the test is non-inferior to the reference

Table 31: Non-inferiority Analysis of Mean Irritation Score for Test vs. Reference in PPPI2 per FDA

Variable	**Hypotheses**	**LSmean Test**	**LSmean Reference**	**Estimate of $\mu_A - 1.25*\mu_B$**	**One-Sided 95% Upper**

					Confid n < o nd <
Mean Irritation < S or <	H_0: $\mu_A - 1.25*\mu_B \geq 0$ < H_1: $\mu_A - 1.25*\mu_B < 0$ <	0.2092 <	0.2137 <	-0.0580 <	-0.0381 <

Source: Reviewer's analysis <

The proportion of subjects in PPPI2 with and without a meaningful degree of irritation (at least < one irritation score ≥ 3) is cross-tabulated for the test versus reference products in Table 32. A < test for non-inferiority of the test patch to the reference patch in terms of proportion of patches < with a meaningful degree of irritation in PPPI2 is presented in Table 33. There was no test patch < and 1 (00.51%) reference patch with at least one irritation score ≥ 3. The point estimate of P_T – < P_R, the difference between proportion of test and reference patches with a meaningful degree of < irritation is -0.0051 (-0.51%) and the one-sided 95% upper bound for P_T –P_R is 0.01362. <

Tabl 32: S bj ts With or Witho t Meaningf l D gr <of Irritation (Maximum Irritation < S or ≥ 3 or < 3) for T st and R f r n < Prod <ts D ring th Ind <tion Phas in PPPI2 <

		T st Prod <t <		
		Max Irritation < S or < 3 <	Max Irritation < S or ≥ 3 <	Total <
R f r n < Prod <t <	Max Irritation S or < 3 <	195 <	0 <	195 <
	Max Irritation S or ≥ 3 <	1 <	0 <	1 <
	Total <	196 <	0 <	196 <

Source: Reviewer's analysis <

Tabl 33: Non-inf riority T st in T rms of Proportion of S bj ts with a Meaningf l < D gr <of Irritation D ring th Ind <tion Phas in PPPI2 <

Hypoth sis <	Proportion of T st S or ≥ < 3 (P_T) < (N=196) <	Proportion of < R f r n < S or ≥ 3 < (P_R) < (N=196) <	< Point < Estimat of < $P_T - P_R$ <	On sid d < 95% Upp r < Confid n < Limit of $P_T - P_R$ <
H_0: $P_T - P_R \geq \delta$ (inf rior) < H_1: $P_T - P_R < \delta$ (non- < inf rior) <	0.0000 <	0.0051 <	-0.0051 <	0.01362 <

Source: Reviewer's analysis <

3.2.10.2.3 Irritation Analysis R s lts in PPPI3 <

Table g g w t e number and percent f applicati n by inducti n p a e patc number and g patc type wit a pecific c mbined “dermal re p n e” and “ t er effect ” c re in PPPI . A g ummary f mean irritati n c re durin t e inducti n p a e in PPPI i pre ented in Table 5. g

Table 34: Number (%) of Applications by Induction Phase Patch Number and Patch Type g with a Specific Combined “Dermal Response” and “Other Effect” Score in the PPPI3 g

Patch No: g **Treatment** g	**Combined “Dermal Response” and “Other Effect” Score** g **Frequency, %**g							
	0N g		**1N** g		**2N** g		**3N** g	
1:Te t g	167	86.5 %g	2 g	1 2. g%g	2 g	1.0 %g	0 g	0.00%g
1:Reference g	165	85.9 %g	25 g	1 .02%g	2 g	1.0 %g	0 g	0.00%g
2:Te t g	162	8 .9 %g	29 g	15.0 %g	2 g	1.0 %g	0 g	0.00%g
2:Reference g	161	8 .85%3 g	0 g	15.6 %g	1 g	0.52%g	0 g	0.00%g
:Te t g	1 7	76.17%3 g	9 g	20.21%g	7 g	.6 %g	0 g	0.00%g
:Reference g	150	78.1 %3 g	6 g	18.75%g	5 g	2.60%g	1 g	0.52%g
:Te t g	1 9	77.20%4 g	2 g	21.76%g	2 g	1.0 %g	0 g	0.00%g
:Reference g	1 8	77.08%4 g	1 g	21. 5%3 g		1.56%g	0 g	0.00%g
5:Te t g	152	78.76%3 g	8 g	19.69%3 g		1.55%g	0 g	0.00%g
5:Reference g	1 7	76.56%4 g	2 g	21.88%3 g		1.56%g	0 g	0.00%g
6:Te t g	1 7	76.17%4 g	5 g	2 . 2%g	1 g	0.52%g	0 g	0.00%g
6:Reference g	151	78.65%3 g	8 g	19.79%3 g		1.56%g	0 g	0.00%g
7:Te t g	1 5	75.1 %4 g	7 g	2 . 5%g	1 g	0.52%g	0 g	0.00%g
7:Reference g	1 1	7 . g%4 g	8 g	25.00%3 g		1.56%g	0 g	0.00%g
8:Te t g	15 g	7 9.79%3 g	9 g	20.21%g	0 g	0.00%g	0 g	0.00%g
8:Reference g	15 g	8 0.21%3 g	7 g	19.27%g	1 g	0.52%g	0 g	0.00%g
9:Te t g	150	77.72%4 g	2 g	21.76%g	1 g	0.52%g	0 g	0.00%g
9:Reference g	151	78.65%3 g	7 g	19.27%4 g		2.08%g	0 g	0.00%g

Plea e refer t Secti n .2. f r t e c nver i n fr m letter c re t numerical c re. g
S urce: Reviewer’ analy i . g

Table 35: Summary of Mean Irritation Score (Mean of “Dermal Response” Plus “Other Effects” Scores During the Induction Phase) in PPPI3 per FDA Reviewer g

Product g	**N** g	**Mean (SD)** g	**Min** g	**First Quartile** g	**Median** g	**Third Quartile** g	**Max** g

A (Tes e	3 0	e.22 (.336)	0 e			.333 1	e .444 e
B (Reference e	2 0	e.224 (.35)	0 e			.444 1	e .667 e

Sourc : R vi w r's analysis e

Th non-inf riority analysis of t st patch against th r f r nc patch bas d on th m an irritation e scor in PPPI3 using a lin ar mod l is shown in Tabl 36. In th mod l, th m an irritation scor e was th r spons and tr atm nt and subj ct w r fix d ff cts. Th on -sid d 5% upp r e confid nc bound was - . 3 4 which b ing n gativ show d that th t st is non-inf rior to th e r f r nc . e

Table 36: Non-inferiori y Analysis of Mean Irri a ion Score for Tes vs. Reference in PPPI3 e per FDA e

Variable e	**Hypo heses** e	**LSmean** e **Tes** e	**LSmean** e **Reference**	**Es ima e of** e $\mu_A - 1.25*\mu_B$ e	**One-Sided** e **95% Upper** e **Confidence** e **Bound** e
Mean Irri a ion e **Score** e	H e $\mu_A - .25*\mu_B \geq$ e H e $\mu_A - .25*\mu_B <$ e	.22 5 0	e .2245 e	- . 6 2 e	- . 3 4 e

Sourc : R vi w r's analysis e

Th proportion of subj cts in PPPI3 with and without a m aningful d gr e of irritation (at l ast e on irritation scor ≥ 3) is cross-tabulat d for th t st v rsus r f r nc products in Tabl 37. A e t st for non-inf riority of th t st patch to th r f r nc patch in t rms of proportion of patch s e with a m aningful d gr e of irritation in PPPI3 is pr s nt d in Tabl 38. Th r was no t st patch e and (e.52%) r f r nc patch with at l ast on irritation scor ≥ 3. Th point stimat of $P_T -$ e P_R, th diff r nc b tw e n proportion of t st and r f r nc patch s with a m aningful d gr e of e irritation is - . e52 (- .52%) and th on -sid d 5% upp r bound for $P_T - P_R$ is . e3 e. e

Table 37: Subjec s Wi h or Wi hou Meaningful Degree of Irri a ion (Maximum Irri a ion e Score ≥ 3 or < 3 for Tes and Reference Produc s During he Induc ion Phase in PPPI3 e

		Tes Produc e		
		Max Irri a ion Score < 3 e	**Max Irri a ion Score ≥ 3** e	**To al** e
Reference Produc e	**Max Irri a ion Score < 3** e	1 e		
	Max Irri a ion Score ≥ 3	1 e		
	To al 1 e	2 0 e		2 e

Sourc : R vi w r's analysis e

Table 38: Non-inferiori y Tes in Terms of Propor ion of Subjec s wi h a Meaningful e Degree of Irri a ion During he Induc ion Phase in PPPI3 e

Hypo hesis e	**Propor ion of** **Tes Score ≥ 3 (P_T** e	**Propor ion of** e **Reference** e **Score ≥ 3** e	**Poin** e **Es ima e of** e $P_T - P_R$ e	**One-sided** e **95% Upper** e **Confidence** e

	(N=192 5	(5 (N=192 5		m it off T - 5
H_0: T - 5> δ (nfer or 5 H_1: T - 5 ≤ δ (non- 5 nfer or 5	0.00800 5	0.00 2 5	-0.00 2 5	0.01390 5

Source: Reviewer's analysis 5

3.2.10.2.4 Irr tat on Analys s esults n 5 I4 5

Table 39 shows the number and percent of applications by induction phase patch number and 5 patch type with a specific combined "dermal response" and "other effects" score in PPPI4. A 5 summary of mean irritation scores during the induction phase in PPPI4 is presented in Table 40. 5

Table 39: Number (%) of Appl cat ons by Induct on hase atch Number and atch Type 5 w th a Spec f c Comb ned "Dermal esponse" and "Other Effect" Score n the 5 I4 5

atch No: 5 Treatment 5	Comb ned "Dermal esponse" and "Other Effect" Score 5 Frequency, %5							
	0N 5		1N 5		2N 5		3N 5	
1:Test 5	1 2	86.36% 5	22 5	12. 0% 5	2 5	1.14% 5	0 5	0.00% 5
1:Reference 5	1 1	86.29% 5	23 5	13.14% 5	1 5	0. 7% 5	0 5	0.00% 5
2:Test 5	148	84.09% 5	26 5	14.77% 5	2 5	1.14% 5	0 5	0.00% 5
2:Reference 5	14 5	82.86% 5	29 5	16. 7% 5	1 5	0. 7% 5	0 5	0.00% 5
3:Test 5	133	7 . 7% 5	36 5	20.4 % 5	7 5	3.98% 5	0 5	0.00% 5
3:Reference 5	13 5 5	77.14% 5	34 5	19.43% 5		2.86% 5	1 5	0. 7% 5
4:Test 5	137	77.84% 5	37 5	21.02% 5	2 5	1.14% 5	0 5	0.00% 5
4:Reference 5	13 5 5	77.14% 5	37 5	21.14% 5	3 5	1.71% 5	0 5	0.00% 5
:Test 5	139	78.98% 5	34 5	19.32% 5	3 5	1.70% 5	0 5	0.00% 5
:Reference 5	137	78.29% 5	3 5	20.00% 5	3 5	1.71% 5	0 5	0.00% 5
6:Test 5	133	7 . 7% 5	42 5	23.86% 5	1 5	0. 7% 5	0 5	0.00% 5
6:Reference 5	136	77.71% 5	36 5	20. 7% 5	3 5	1.71% 5	0 5	0.00% 5
7:Test 5	131	74.43% 5	44 5	2 .00% 5	1 5	0. 7% 5	0 5	0.00% 5
7:Reference 5	127	72. 7% 5	4 5	2 .71% 5	3 5	1.71% 5	0 5	0.00% 5
8:Test 5	140	79. 5% 5	36 5	20.4 % 5	0 5	0.00% 5	0 5	0.00% 5
8:Reference 5	140	80.00% 5	34 5	19.43% 5	1 5	0. 7% 5	0 5	0.00% 5
9:Test 5	137	77.84% 5	38 5	21. 9% 5	1 5	0. 7% 5	0 5	0.00% 5

9:Refere ve w	7	78.29% 3 w	4 1 w	9.4 % w	4 w	2.29% w	0 w	0.00% w

Please refer to Se tio w.2. for the o versio w from letter s ore to w umeri al s ore. w
Sour e: Revie wer's a alysis. w

Table 40: Summary of Mean Irritation Score (Mean of "Dermal Response" Plus "Other Effects" Scores During the Induction Phase) in PPPI4 per FDA Reviewer w

Product w	**N** w	**Mean (SD)** w	**Min** w	**First Quartile** w	**Median** w	**Third Quartile** w	**Max** w
A (Test) w	76	0.22 w(0. 45)	w 0 w	0 w	0 w	0. w	.444 w
B (Reference) 1	w75	0.227 (0. 60)	w 0 w	0 w	0 w	0.444 1	w .667 w

Sour e: Revie wer's a alysis w

The w o -i feriority a alysis of test pat h agai st the refere ve pat h based o w the mea w irritatio w s ore i PPPI4 usi g a li ear model is sho w i Table 4 . I the model, the mea irritatio s ore w as the respo se a d treatme t a d subje t were fixed effe ts. The o e-sided 95% upper w o fide ve bou d was -0.0407 whi h bei g negative sho wed that the test is w o -i ferior to the w refere ve. w

Table 41: Non-inferiority Analysis of Mean Irritation Score for Test vs. Reference in PPPI4 w **per FDA** w

Variable w	**Hypotheses** w	**LSmean Test** w	**LSmean Reference** w	**Estimate of** $\mu_A - 1.25*\mu_B$ w	**One-Sided 95% Upper Confidence Bound** w
Mean Irritation Score w	H_0: $\mu_A - 1.25*\mu_B \geq 0$ w H_1: $\mu_A - 1.25*\mu_B < 0$ w	0.2229 w	0.2279 w	-0.062 w	- 0.0407 w

Sour e: Revie wer's a alysis w

The proportio w of subje ts i PPPI4 with a d without a mea i gful degree of irritatio w (at least w o e irritatio w s ore ≥ w) is ross-tabulated for the test versus refere ve produ ts i Table 42. A w test for o -i feriority of the test pat h to the refere ve pat h i terms of proportio w of pat hes w ith a mea i gful degree of irritatio w PPPI4 is prese ted i Table 4 . There w as w test pat h w a d w (00.57%) refere ve pat h with at least o e irritatio w s ore ≥ w The poi t estimate of $P_T -$ w P_R, the differe ve bet we w proportio w of test a d refere ve pat hes with a mea i gful degree of w irritatio w is -0.0057 (-0.57%) a d the o e-sided 95% upper bou d for $P_T - P_R$ is 0.0 52 . w

Table 42: Subjects With or Without Meaningful Degree of Irritation (Maximum Irritation w **Score ≥ 3 or < 3) for Test and Reference Products During the Induction Phase in PPPI4** w

		Test Product w		
		Max Irritation Score < 3 w	**Max Irritation Score ≥ 3** w	**Total** w
Reference	**Max Irritation Score < 3**	1 w 74 w	0 w	74 w

Pr duc :	Max Irr a : c re ≥ 3 :	1 :	0 :	1 :
	T : al :	175 :	0 :	175 :

Source Reviewer's analysis :

Table 43: N : - fer :r y Tes :Terms f Pr p r : f ubjec s w :h a Mea : gful : Degree f Irr a : Dur :g he I duc : Phase :PPPI4 :

Hyp :hes s :	Pr p r : f Tes c re ≥ 3 (P_T) : (N=176) :	Pr p r f : Refere ce : c re ≥ 3 : (P_R) : (N=175) :	: P : : Es ma e f : P_T - P_R :	O me-s ded : 95% Upper : C : f de ce : L mi :f P_T - P_R :
H_0: P_T - P_R > δ (fer :r) : H_1: P_T - P_R ≤ δ (: - : fer :r) :	0.0000 :	0.0057 :	-0.0057 :	0.01523 :

Source Reviewer's analysis :

3.2.10.2.5 Irr a : A :alys s Resul s PPPI5 :

Table 44 shows the number and percent of applications by induction phase patch number and : patch type with a specific combined "dermal response" and "other effects" score in PPPI5. A : summary of mean irritation scores during the induction phase in PPPI5 is presented in Table 45. :

Table 44: Number (%) f Appl ca : s by I duc : Phase Pa ch Number a d Pa ch Type : w :h a pec f c C mb : ed "Dermal Resp : se" a d "O her Effec " c re he PPPI5 :

Pa ch N :: : Trea me :	C :mb : ed "Dermal Resp : se" a d "O her Effec " c re : Freque cy, %:							
	0N :		1N :		2N :		3N :	
1 Test :	172	86.43% :	25 :	12.56% :	2 :	1.01% :	0 :	0.00% :
1 Reference :	171	85.93% :	26 :	13.07% :	2 :	1.01% :	0 :	0.00% :
2 Test :	168	84.42% :	29 :	14.57% :	2 :	1.01% :	0 :	0.00% :
2 Reference :	167	83.92% :	30 :	15.08% :	2 :	1.01% :	0 :	0.00% :
3 Test :	153	76.88% :	39 :	19.60% :	7 :	3.52% :	0 :	0.00% :
3 Reference :	155	77.89% :	38 :	19.10% :	5 :	2.51% :	1 :	0.50% :
4 Test :	154	77.39% :	43 :	21.61% :	2 :	1.01% :	0 :	0.00% :
4 Reference :	153	76.88% :	43 :	21.61% :	3 :	1.51% :	0 :	0.00% :
5 Test :	158	79.40% :	38 :	19.10% :	3 :	1.51% :	0 :	0.00% :
5 Reference :	152	76.38% :	44 :	22.11% :	3 :	1.51% :	0 :	0.00% :

6:Test m	1 m	7 6 m%	m 46 2	m 1 %	m 1 m	0 m0%	m 0 m	0 m0% m
6:Reference m	1 6	7 m9%	m 40 2	m 0 10%	3 m	1 m1%	m 0 m	0 m0% m
7:Test m	1 0	7 m %	m 4 m	4 1 %	m 1 m	0 m0%	m 0 m	0 m0% m
7:Reference m	146	7 m7%	5 m 0 2	m 1 %	3 m	1 m1%	m 0 m	0 m0% m
:Test m	160 8	m0 40%	3 m 9 m	19 60%	m 0 m	0 m0%	m 0 m	0 m0% m
:Reference m	1 9	79 90%	3 m 9 m	19 60%	m 1 m	0 m0%	m 0 m	0 m0% m
9:Test m	1 6	7 m9%	m 4 m	1 1m%	m 1 m	0 m0%	m 0 m	0 m0% m
9:Reference m	1 6	7 m9%	3 m 9 m	19 60%	m 4 m	01%	m 0 m	0 m0% m

Please refer to Section m for the conversion from letter score to numerical score m
Source: Reviewer's analysis m

Table 45: Summary of Mean Irritation Score (Mean of "Dermal Response" Plus "Other m
Effects" Scores During the Induction Phase) in PPPI5 per FDA Reviewer m

Product m	**N** m	**Mean (SD)** m	**Min** m	**First** m **Quartile** m	**Median** m	**Third** m **Quartile** m	**Max** m
A (Test) m	199	0 m6 (0 m)	m 0 m	0 m	0 m	0 m	1 m444 m
B (Reference)	199	0 m6 (0 m4)	m 0 m	0 m	0 m	0 m44 m	1 m667 m

Source: Reviewer's analysis m

The non-inferiority analysis of test patch against the reference patch based on the e an irritation m score in PPPI using a linear o del is shown in Table 46 In the o del, the e an irritation score m was the response and treate nt and subject were fixed effects The one-sided 9 % upper m confidence bound was -0 0 m7 which being negative showed that the test is non-inferior to the m reference m

Table 46: Non-inferiority Analysis of Mean Irritation Score for Test vs. Reference in PPPI5 m
per FDA m

Variable m	**Hypotheses** m	**LSmean** m **Test** m	**LSmean** m **Reference** m	**Estimate of** m $\mu_A - 1.25*\mu_B$ m	**One-Sided** m **95% Upper** m **Confidence** m **Bound** m
Mean Irritation m **Score** m	H_0: $\mu_A - 1$ m$*\mu_B \geq 0$ m H_1: $\mu_A - 1$ m$*\mu_B < 0$ m	0 m1m7 m	0 m 1 m	- 0 0 9 m	- 0 0 m7 m

Source: Reviewer's analysis m

The pr p r - subjec s PPPI5 w h a d w h u a mea - g ul degree rr a - (a leas - e rr a - sc re ≥ 3) s cr ss abula ed r he es versus re ere ce pr duc s Table 47. A - es r - er r y he es pa ch he re ere ce pa ch erms pr p r - pa ches - w h a mea - g ul degree rr a - PPPI5 s prese ed Table 48. There was es pa ch - a d 1 (00.50%) re ere ce pa ch w -h a leas -e rr a - sc re ≥ 3. The p - es ma e P_T – - P_R, he d -ere ce be wee pr p r - es a d re ere ce pa ches w h a mea - g ul degree - rr a - s 0.0050 (0.50%) a d he -e s ded 95% upper b u d r P_T –P_R s 0.01390. -

Table 47: Subjects With or Without Meaningful Degree of Irritation (Maximum Irritation - Score ≥ 3 or < 3) for Test and Reference Products During the Induction Phase in PPPI5 -

		Test Product -		
		Max Irritation Score < 3 -	-Max Irritation Score ≥ 3 -	- Total -
Reference Product -	Max Irritation Score < 3 -	191 -	0 -	191 -
	Max Irritation Score ≥ 3 -	1 -	0 -	1 -
	Total -	192 -	0 -	192 -

S urce: Rev ewer's a alys s -

Table 48: Non-inferiority Test in Terms of Proportion of Subjects with a Meaningful - Degree of Irritation During the Induction Phase in PPPI5 -

Hypothesis -	Proportion of Test Score ≥ 3 (P_T) - (N=199) -	Proportion of - Reference - Score ≥ 3 - (P_R) - (N=199) -	- Point - Estimate of - P_T - P_R -	One-sided - 95% Upper - Confidence - Limit of P_T - - P_R -
H_0: P_T - P_R > δ (inferior) - **H_1: P_T - P_R - ≤ δ (non- - inferior) -**	0.0000 -	0.0050 -	0.0050 -	0.01390 -

S urce: Rev ewer's a alys s -

3.2.10.2.6 Irritation Analysis Results in PPPI6 -

Table 49 sh ws he umber a d perce - - appl ca - s by -duc - phase pa ch umber a d - pa ch ype w h a spec c c mb - ed "dermal resp - se" a d " her e ec s" sc re PPPI6. A - summary mea rr a - sc res dur g he duc - phase PPPI6 s prese ed Table 50. -

Table 49: Number (%) of Applications by Induction Phase Patch Number and Patch Type - with a Specific Combined "Dermal Response" and "Other Effect" Score in the PPPI6 -

Patch No: , Tr atm ent ,	Combin ,		rmal R spons " an	Oth r Eff ct" Scor , Fr qu ncy %,				
	0N ,		1N ,		2N ,		3N ,	
1:Test ,	157	86.26%,	23 ,	12.64%,	2 ,	1.10%,	0 ,	0.00%,
1:Reference	155	86.11%,	24 ,	13.33%,	1 ,	0.56%,	0 ,	0.00%,
2:Test ,	154	84.62%,	26 ,	14.29%,	2 ,	1.10%,	0 ,	0.00%,
2:Reference	149	82.78%,	29 ,	16.11%,	2 ,	1.11%,	0 ,	0.00%,
3:Test ,	139	76.37%,	36 ,	19.78%,	7 ,	3.85%,	0 ,	0.00%,
3:Reference	139	77.22%,	35 ,	19.44%,	5 ,	2.78%,	1 ,	0.56%,
4:Test ,	142	78.02%,	38 ,	20.88%,	2 ,	1.10%,	0 ,	0.00%,
4:Reference	139	77.22%,	38 ,	21.11%,	3 ,	1.67%,	0 ,	0.00%,
5:Test ,	145	79.67%,	34 ,	18.68%,	3 ,	1.65%,	0 ,	0.00%,
5:Reference	141	78.33%,	36 ,	20.00%,	3 ,	1.67%,	0 ,	0.00%,
6:Test ,	138	75.82%,	43 ,	23.63%,	1 ,	0.55%,	0 ,	0.00%,
6:Reference	140	77.78%,	37 ,	20.56%,	3 ,	1.67%,	0 ,	0.00%,
7:Test ,	136	74.73%,	45 ,	24.73%,	1 ,	0.55%,	0 ,	0.00%,
7:Reference	131	72.78%,	46 ,	25.56%,	3 ,	1.67%,	0 ,	0.00%,
8:Test ,	146	80.22%,	36 ,	19.78%,	0 ,	0.00%,	0 ,	0.00%,
8:Reference	144	80.00%,	35 ,	19.44%,	1 ,	0.56%,	0 ,	0.00%,
9:Test ,	143	78.57%,	38 ,	20.88%,	1 ,	0.55%,	0 ,	0.00%,
9:Reference	141	78.33%,	35 ,	19.44%,	4 ,	2.22%,	0 ,	0.00%,

Please refer to Section 3.2.3 for the conversion from letter score to numerical score. ,
Source: Reviewer's analysis. ,

Tabl 50: Summary of Mean Irritation Scor (Mean of rmal R spons " Plus Oth r , Eff cts" Scor s uring th In uction Phas) in PPPI6 p r F A R vi w r ,

Pro uct ,	N ,	M an (S)	Min ,	First , Quartil ,	Me ian ,	Thir , Quartil ,	Max ,
A (T st) ,	182	0.218 (0.341)	, 0 ,	0 ,	0 ,	0.333 ,	1.444 ,
B (R f r nc)	180	0.227 (0.362)	, 0 ,	0 ,	0 ,	0.444 ,	1.667 ,

Source: Reviewer's analysis ,

The non-inferiority analysis of test patch against the reference patch based on the mean irritation , score in PPPI6 using a linear model is shown in Table 51. In the model, the mean irritation score was the response and treatment and subject were fixed effects. The one-sided 95% upper , confidence bound was -0.0394 which being negative showed that the test is non-inferior to the reference. ,

Table p pn-inferi rity Analysis f Mean Irritati n Sc re f r Test vs. Reference in PPPI6 p er FDA p

Variable p	Hy ptheses p	LSmean p Test p	LSmean p Reference p	Estimate f p $\mu_A - .2 * \mu_B$	p One-Sided p 9 % U p er p C pnfidence p B und p
Mean Irritati n p Sc re p	H_0: $\mu_A - 1.25*\mu_B \geq 0$ p H_1: $\mu_A - 1.25*\mu_B < 0$ p	0.2179 p	0.2230 p	-0.0608 p	-0.0394 p

Source: Reviewer's analysis p

The proportion of subjects in PPPI6 with and without a meaningful degree of irritation (at least p one irritation score ≥ 3) is cross-tabulated for the test versus reference products in Table 52. A p test for non-inferiority of the test patch to the reference patch in terms of proportion of patches p with a meaningful degree of irritation in PPPI6 is presented in Table 53. There was no test patch p and 1 (00.56%) reference patch with at least one irritation score ≥ 3. The point estimate of P_T – p P_R, the difference betwepn proportion of test and reference patches with a meaningful degree of p irritation is -0.0056 (-0.56%) and the one-sided 95% upper bound for $P_T - P_R$ is 0.01523. p

Table 2 Subjects With r With ut Meaningful Degree f Irritati n (Maximum Irritati n p Sc re ≥ 3 r < 3) f r Test and Reference Pr ducts During the Inducti n Phase in PPPI6 p

		Test Pr duct p		
		Max Irritati n Sc re < 3 p	Max Irritati n Sc re ≥ 3 p	T ptal p
Reference p Pr duct p	Max Irritati n Sc re < 3 p	174 p	0 p	174 p
	Max Irritati n Sc re ≥ 3 p	1 p	0 p	1 p
	T ptal p	175 p	0 p	175 p

Source: Reviewer's analysis p

Table 3 pn-inferi rity Test in Terms f Pr p rti n f Subjects with a Meaningful p Degree f Irritati n During the Inducti n Phase in PPPI6 p

Hy p thesis p	Pr p rti n f Test Sc re ≥ 3 (P_T) p (p = p2) p	Pr p rti n f p Reference p Sc re ≥ 3 p (P_R) p (p = p0) p	p P pint p Estimate f p P_T p- P_R p	One-sided p 9 % U p er p C pnfidence p Limit f P_T p- p P_R p
H_0 pP_T p- P_R p> δ (inferi r) p H p P_T p- P_R p≤ δ (n p- p inferi r) p	0.0p00 p	0.0056 p	-0.0056 p	0.01523 p

Source: Reviewer's analysis p

3.2.10.2.7 n t zat o A nalysn

Table 54, Table 55, Table 56, Table 57, Table 58 a d Table 59 show the umber a d perce t of n applicatio s by challe ge phase evaluatio time after patch removal a d patch type with a n specific dermal respo se a d other effects score i PPPS1, PPPS2, PPPS3, PPPS4, PPPS5 a d n PPPS6, respectively. The total umber of patches is ot same at all of the time poi ts because n some subjects did ot have o e or more irritatio assessme ts. n

Tabl 54: Numb r (%) of Appl cat o n by Chall ng Pha nEvaluat o T m ea nd Patch n Typ w th a p c f c Comb n d D rmal R npo n a d Oth r Eff ct cor th PPP 1 n

T m e: Tr atm e tn n	Total n Numb r of n Patch n	Comb n d "D rmal R npo n" a d "Oth r Eff ct" n cor n Fr qu ncy, %n					
		0N n		1N n		2N n	
30 Mi utes: Test n	217 n	185 n	85.25%n	32 n	14.75%n	0 n	0.00%n
30 Mi utes: Refere ce n	215 n	179 n	83.26%n	36 n	16.74%n	0 n	0.00%n
24 Hour: Test n	216 n	208 n	96.30%n	7 n	3.24%n	1 n	0.46%n
24 Hour: Refere ce n	214 n	203 n	94.86%n	10 n	4.67%n	1 n	0.47%n
48 Hours: Test n	214 n	213 n	99.53%n	0 n	0.00%n	1 n	0.47%n
48 Hours: Refere ce n	212 n	209 n	98.58%n	2 n	0.94%n	1 n	0.47%n
72 Hours: Test n	215 n	214 n	99.53%n	1 n	0.47%n	0 n	0.00%n
72 Hours: Refere ce n	213 n	212 n	99.53%n	1 n	0.47%n	0 n	0.00%n

Source: Reviewer's a alysis. n

Tabl 55: Numb r (%) of Appl cat o n by Chall ng Pha nEvaluat o T m ea nd Patch n Typ w th a p c f c Comb n d D rmal R npo n a d Oth r Eff ct cor th PPP 2 n

T m e: Tr atm e tn n	Total n Numb r of n Patch n	Comb n d "D rmal R npo n" a d "Oth r Eff ct" n cor n Fr qu ncy, %n					
		0N n		1N n		2N n	
30 Mi utes: Test n	191 n	162 n	84.82%n	29 n	15.18%n	0 n	0.00%n
30 Mi utes: Refere ce n	189 n	156 n	82.54%n	33 n	17.46%n	0 n	0.00%n
24 Hour: Test n	191 n	185 n	96.86%n	5 n	2.62%n	1 n	0.52%n
24 Hour: Refere ce n	189 n	180 n	95.24%n	8 n	4.23%n	1 n	0.53%n
48 Hours: Test n	189 n	188 n	99.47%n	0 n	0.00%n	1 n	0.53%n

48 Hour l r nc l	187 l	184 l	98.40%l	2 l	1.07%l	1 l	0.53%l
72 Hour T l t l	190 l	189 l	99.47%l	1 l	0.53%l	0 l	0.00%l
72 Hour l r nc l	188 l	187 l	99.47%l	1 l	0.53%l	0 l	0.00%l

Sourc l lvi w lr' ana y i . l

Table 56: Number (%) of Applications by Challenge Phase Evaluation Time and Patch l Type with a Specific Combined Dermal Response and Other Effects Score in the PPPS3 l

Time: Treatment l	Total l Number of l Patches l	Combined "Dermal Response" and "Other Effect" l l Score l Frequency, %l					
		0N l		1N l		2N l	
30 Minut l T l t l	187 l	157 l	83.96%l	30 l	16.04%l	0 l	0.00%l
30 Minut l l r nc l	186 l	153 l	82.26%l	33 l	17.74%l	0 l	0.00%l
24 Hour T l t l	187 l	180 l	96.26%l	6 l	3.21%l	1 l	0.53%l
24 Hour l r nc l	186 l	176 l	94.62%l	9 l	4.84%l	1 l	0.54%l
48 Hour T l t l	185 l	184 l	99.46%l	0 l	0.00%l	1 l	0.54%l
48 Hour l r nc l	184 l	181 l	98.37%l	2 l	1.09%l	1 l	0.54%l
72 Hour T l t l	185 l	184 l	99.46%l	1 l	0.54%l	0 l	0.00%l
72 Hour l r nc l	184 l	183 l	99.46%l	1 l	0.54%l	0 l	0.00%l

Sourc l lvi w lr' ana y i . l

Table 57: Number (%) of Applications by Challenge Phase Evaluation Time and Patch l Type with a Specific Combined Dermal Response and Other Effects Score in the PPPS4 l

Time: Treatment l	Total l Number of l Patches l	Combined "Dermal Response" and "Other Effect" l l Score l Frequency, %l					
		0N l		1N l		2N l	
30 Minut l T l t l	170 l	142 l	83.53%l	28 l	16.47%l	0 l	0.00%l
30 Minut l l r nc l	169 l	138 l	81.66%l	31 l	18.34%l	0 l	0.00%l
24 Hour T l t l	170 l	164 l	96.47%l	5 l	2.94%l	1 l	0.59%l
24 Hour l r nc l	169 l	160 l	94.67%l	8 l	4.73%l	1 l	0.59%l
48 Hour T l t l	168 l	167 l	99.40%l	0 l	0.00%l	1 l	0.60%l
48 Hour l r nc l	167 l	164 l	98.20%l	2 l	1.20%l	1 l	0.60%l
72 Hour T l t l	169 l	168 l	99.41%l	1 l	0.59%l	0 l	0.00%l

72 Hou T Tff Tnc T	168 T	167 T	99.40% T	1 T	0.60% T	0 T	0.00% T

Sou c T Tvi w T' analy i . T

able 58: Number (%) of Applications by Challenge Phase Evaluation ime and Patch T ype with a Specific Combined Dermal Response and Other Effects Score in the PPPS5 T

ime: reatment T	otal T Number of T Patches T	Combined "Dermal Response" and "Other Effect" T Score T Frequency, %					
		0N T		1N T		2N T	
30 Minut TT Tt T	192 T	162 T	84.38% T	30 T	15.63% T	0 T	0.00% T
30 Minut T Tff Tnc T	193 T	159 T	82.38% T	34 T	17.62% T	0 T	0.00% T
24 Hou TT Tt T	192 T	185 T	96.35% T	6 T	3.13% T	1 T	0.52% T
24 Hou T Tff Tnc T	193 T	183 T	94.82% T	9 T	4.66% T	1 T	0.52% T
48 Hou TT Tt T	190 T	189 T	99.47% T	0 T	0.00% T	1 T	0.53% T
48 Hou T Tff Tnc T	191 T	188 T	98.43% T	2 T	1.05% T	1 T	0.52% T
72 Hou TT Tt T	190 T	189 T	99.47% T	1 T	0.53% T	0 T	0.00% T
72 Hou T Tff Tnc T	191 T	190 T	99.48% T	1 T	0.52% T	0 T	0.00% T

Sou c T Tvi w T' analy i . T

able 59: Number (%) of Applications by Challenge Phase Evaluation ime and Patch T ype with a Specific Combined Dermal Response and Other Effects Score in the PPPS6 T

ime: reatment T	otal T Number of T Patches T	Combined "Dermal Response" and "Other Effect" T Score T Frequency, %					
		0N T		1N T		2N T	
30 Minut TT Tt T	175 T	147 T	84.00% T	28 T	16.00% T	0 T	0.00% T
30 Minut T Tff Tnc T	174 T	142 T	81.61% T	32 T	18.39% T	0 T	0.00% T
24 Hou TT Tt T	175 T	169 T	96.57% T	5 T	2.86% T	1 T	0.57% T
24 Hou T Tff Tnc T	174 T	165 T	94.83% T	8 T	4.60% T	1 T	0.57% T
48 Hou TT Tt T	173 T	172 T	99.42% T	0 T	0.00% T	1 T	0.58% T
48 Hou T Tff Tnc T	172 T	169 T	98.26% T	2 T	1.16% T	1 T	0.58% T
72 Hou TT Tt T	174 T	173 T	99.43% T	1 T	0.57% T	0 T	0.00% T
72 Hou T Tff Tnc T	173 T	172 T	99.42% T	1 T	0.58% T	0 T	0.00% T

Source (e (ewer's analys s. (

There were 2 patches w th an (rr tat on score of at least 2 at 48 or 72 hour e aluat on after patch (remo al n the challenge phase n all s x populat ons PPPS1-PPPS6). The l st of these patches s (g en (n Table 60. Based on the (rr tat on scores n the nduct on and challenge phases, the (re (ewer determ ned that no patches had a potent al sens t zat on response. (

Table 60: Patches with Irritation Score ≥ 2 at 48 or 72 Hour Evaluation in Challenge Phase (

Subject ID	Treatment*	Irritation Scores at Different Times after Challenge Phase Patch Removal				Max Irritation Score During Induction Phase	Applicant's Determination of Potential Sensitization in the Challenge Phase (Yes, No)	FDA Determination of Potential Sensitization (Yes, No) Based on Irritation Scores
		30 Mins	24 Hrs	48 Hrs	72 Hrs			
(b) (6)	A	1	2	2	1	2	No	No
	B	1	2	2	1	3	No	No

* (A=Test, B= (eference. (
Source (e (ewer's analys s (

3.3 Evaluation of Study RP-LID-PK001 (Pharmacokinetic and Adhesion Study) (

3.3.1 Study Objectives (

The pr mary object es of th s study were (

- To assess the b oequ (alence of a s ngle 2100 mg dose of a test formulat on of l doca ne (5% top cal patch (ersus L doderm® after a 12-hour appl cat on n healthy adult male and (female subjects under fasted cond t ons. (
- To assess the apparent dose del ered follow ng appl cat on of a s ngle 2100 mg dose of a (test formulat on of l doca ne 5% top cal patch (ersus L doderm® (after a (12-hour (appl cat on n healthy adult male and female subjects under fasted cond t ons. (
- To assess the patch adhes (e performance of a test formulat on of l doca ne 5% top cal (patch (ersus L doderm® (after a 12-hour appl cat on (n healthy adult male and female (subjects. (

The secondary object e of th s study was (

- To assess the safety and tolerab l ty of a s ngle 2100 mg dose of a test formulat on of (l doca ne 5% top cal patch (ersus L doderm® after a 12-hour appl cat on n healthy adult (male and female subjects under fasted cond t ons. (

3.3.2 Study Design

This was a single-center randomized, open-label single-dose two-period, crossover study to assess the bioequivalence of a single 2100 mg dose of a test (T) formulation of lidocaine 5% topical patch versus Lidoderm® (RLD) topical patch after a 12-hour application in healthy adult male and female subjects under fasted conditions and to compare adhesive properties of the test and reference patches.

The treatments were the following.

- Test (T): 3 x 700 mg patches of test product (lidocaine 5%)
- Reference (R): 3 x 700 mg patches of reference product (Lidoderm®).

Each subject was randomized to one of two treatment sequences (T-R, R-T) according to a randomization schedule as shown in Table 61. There was a 7-day washout between each patch administration. Subjects were dosed on the same day for Day 1 of Period 1 crossed over to the alternate formulation and were dosed on the same day for Day 8 of Period 2.

Table 61: Randomization Schedule for the Study RP-LID-PK001

Sequence	Period I	Period II
T-R	Test	Reference
R-T	Reference	Test

Following an overnight fast of at least 10 hours subjects received their assigned treatment at approximately 08:00 hours (± 2 hour) as three topical patches applied simultaneously for a 12-hour period to the infrascapular area of the back on either side of the spine without occlusion with approximately 2.5 cm between each patch. Patches were applied by qualified study site personnel.

Serial blood samples for determination of lidocaine plasma concentrations and PK analysis were obtained at time 0 (within 90 minutes pre-application) and 1 1.5 2 3 6 9, 12 15 18 21 24 and 48 hours after patch application. Subjects were discharged from the research facility approximately 24 hours after patch application and returned on an out-patient basis for collection of the 48 hour post-dose sample. The study was conducted at a single center (Hackensack, New Jersey).

Subjects could not apply topical products to or wash the back, or engage in strenuous activity during the 12-hour patch application period. Water was allowed *ad-libitum*, during the study except for 1 hour prior through 1 hour post-dose. Subjects fasted for at least 4 hour following patch application. Standard meals were provided at approximately 4 and 10 hours after patch application and an evening snack was provided on the evenings of admission and the days of dosing.

If any a s f ll off during s s udy, s da sand im ei sf ll off w sr r sord d and a n w a s s was no a sli d. s

3.3.3 Adhe ion A se sment s

Pa s ad ssion was ass sss d 6 ours (± 30 min) following a s a sli a ion and wi in 30 s minu ss rior o a s r moval by qualifi d s udy si srsonn l using s FDA r sommensd d s ad ssion ra ing s al b low. Wh ns a om pl ss a s d sa smen so surr d rior o s im eosf s ass sssmen s s im eosfd sa smen swas a sur d. D sa s d a s s w sr no r sla sd. s

Adhe ion Scoring Scale s

0 = ≥ 90% ad srd (sss n ially no lif off s skin) s
1 = ≥ 75% o <90% ad srd (som e sdg s only lif ing off s skin) s
2 = ≥ 50% o <75% ad srd (l ss an alf of s a s lif ing off s skin) s
3 = >0% o < 50% ad srd bu no d sa s d (mor san alf of s a s lif ing off s skin bu s no om pl ssly d sa s d) s
4 = 0% ad srd - a s d sa s d (a s om pl ssly off s skin) s

3.3.4 Endpoint s

A s li an ’s Primary End oin for Ad ssion: s

T s rimary nd oin for ad ssion was s umula iv ad ssion ind x (m eans ad ssion s or), s w si s was al ula sd as s sum of a subj s’s individual a s ad ssion s or s divid d by s s numb r of s or s during diff r n im e sin s. s

Wh ns an individual a s ad ssion s or was missing du o a s d sa smen s, a a s ad ssion s s or of '4' was im pu ssd for all al ula ions. s

R vi w sr’s Primary End oin for Ad ssion: s

T s r vi w sr’s rimary nd oin is s m eans ad ssion s or w si s is d fin d for a s subj s s for a s r a m en sas s m eans of s ad ssion s or s ov r all a s s of a a s y s (s or s r f r n s) and all valua ion im e sin s (a 6 ours af r a s a sli a ion and b for a s s r moval). s

R vi w sr’s S sondary End oin for Ad ssion: s

- The p lp 1 f subjec s w lh a mea 1 gful deg ele f de achme 1 (adhes 1 sc le ≥ 3 a 1 a y me p 1 f la y f he h ele pa ches f he same ype) 1
- T me f m pa ch appl ca 1 u 1l c mple e pa lal pa ch de achme 1
- P pl 1 f subjec s w lh a mea adhes 1 sc le f 1 es pa ch g ea e ha he mea 1 adhes 1 sc e f he efe e ce pa ch by m o e, c mpa ed he p p 1 f 1 subjec s w lh a mea adhes 1 sc le f 1 he efe e ce pa ch g ea e ha he mea 1 adhes 1 sc le f 1 he es pa ch by lm o e. 1

Reviewer's Comments: 1

. Each subjec had h ele es pa ches a d h ele efe e ce pa ches. The mea adhes 1 sc le 1 was def ed as he mea f adhes 1 sc les f all h ele pa ches f he same ype (es 1 efe e ce) a all evalua 1 p 1 s. The mea 1 gful deg ele f de achme 1 s def ed as 1 a y f h se h ele pa ches f he same ype hav lg a adhes 1 sc le ≥ 3 a a y f he 1 adhes 1 evalua 1 me p 1 s. 1
1
2. The adhes 1 assessme 1 mes we e equally spaced. The ef le a s mple ave age f 1 adhes 1 sc les s app lp a e as he p ma y e dp 1 . 1

1

3.3.5 Sample Size Considerations 1

The appl ca 1 de e m i ed l ha 48 subjec s w uld p lv de suff c e 1 da a 1 mee he p ma y 1 bjec ves f h s s udy. 1

3.3.6 Statistical Methodologies 1

3.3.6.1 Analysis Populations 1

Applicant's Analysis Populations: 1

PK P pula 1 : 1

The PK P pula 1 c 1s s ed f h se subjec s wh c mple ed b lh ea me 1s w lh u a y maj 1 p 1 c l v lla 1 s, wh p lv ded plasma l d ca le c 1ce 1a 1 da a suff c e 1 es ma e PK 1 pa ame e s a d had all 3 pa ches a ached f 1≥ 1h u s du 1g each pe 1d. 1

Safe y P pula 1 : 1

The safe y p pula 1 c 1s s ed f h se subjec s wh ece ved a leas le d se f s udy d ug. 1

Reviewer's Analysis Population: 1

Pe P 1 c l P pula 1 f 1Adhes 1 (PPPA): 1

The per pro o o pop P ion for dhesion in P des Pp P hes ex ep hose h P re removed e r y P for n P ep Pb e irri Pion or s fe y or hose from he s bje Rs who dropped o P of he s dy P before he 12 ho r pp i Pion. P

A p Ph h P is omp e e y de Phed, nd no m an Py removed for he bove-men ioned P re sons, before he 12-ho r p Ph pp i Pion period, is in P ded in he P A nd s ore of 4 P (omp e e p Ph de Phmen) is Pried forw Pd s LOCF for P f r her sessmen s for h P P spe ifi p Ph. P

Reviewer's Comment: P

The pp i Pion sed he s fe y pop P ion for n Pysis of dhesion. There w Rs no sep r e P defini ion of per pro o o pop P ion for dhesion. The reviewer greed wi h pp i Pn 's n Pysis P pop P ion for dhesion whi h w Rs so re ommended by FDA's ini P e m. In his Rse P P p Phes from he s bje Rs in he s fe y pop P ion ons i Pe he P A. P

3.3.6.2 Primary Analysis of Adhesion P

Applicant's Analysis Methods: P

The Pm u Pive dhesion index w Rs mmarPzed by re Pmen nd ime poin sing des rip ive P s Pis i s (me n, s nd rd devi ion, medi n, minimum nd m ximum v Pes). Differen e in he P m u Pive dhesions index be we Pn es nd referen e p Phes w Rs n Pyzed sing n Pysis of v ri n e (ANOVA) mode in P ding erms for seq en e, s dy re Pmen , nd period s fixed P effe Rs, nd s bje Pnes ed wi hin seq en e s r ndom effe P. P

Freq en ies nd per en Pges were sed o des ribe he me n Pm u Pive dhesion s ores r nge P e Ph ime poin by re Pmen . The me n Pm u Pive dhesion s ores were divided in o five P gro ps: '0 -<1', '1-<2', '2-<3', '3-<4' '4'. Individ P dhesion s ores were s mmarPzed by P re Pmen nd ime poin sing freq en y nd per en Pge. The n mber of de Phed p Phes w Rs P s mmarPzed sing freq en y nd per en Pges. P

D r ion of we r prior o p Ph de Phmen w s s mmarPzed sing des rip ive s Pis i s. P Differen es in he ime from pp i Pion n i p Ph de Phmen be we Pn es nd referen e P p Phes were an Pyzed usi Pg he SAS pro ed re PROC LIFETEST wi h he mode , P ime* ensor(0) s he ime effe P nd re Pmen s he s r P effe P. P

When n individ P p Ph dhesion s ore w Rs missing d e o p Ph de Phmen , p Ph dhesion P s ore of '4' w Rs imp Ped for P P ions. P

Reviewer's Analysis Methods: P

To demo g e dequ g p oduc dhe io , he e p oduc hould be how g o be g i ic lly g o -i fe io comp ged o he efe e ce p oduc b ged upo ev lu io of he diffe e ce i he e g d efe e ce ove gl me g dhe io co e , wi h o -i fe io i y (NI) m a ig of 0.15 (δ = g 0.15). The hypo he e fo ev lu g g o -i fe io i y e: g

H0: $\mu_T - \mu_R > \delta$ (o o -i fe io) g
H1: $\mu_T - \mu_R \leq \delta$ (o -i fe io) g

whe e μ_T gd μ_R g he me g dhe io co e fo e gme g gd efe e ce, e pec ively. To g demo g e o -i fe io i y of he e p oduc o he efe e ce p oduc , he uppe bou d of he g o e- ided 95% CI of he diffe e ce i me g dhe io co e fo he e p oduc gd he efe e ce g p oduc mu g be le g h g o equ l o 0.15. g

Fo he p im ayg g ly i of he p im ayge dpoi , g g ly i of v g i gce (ANOVA) w g pe fo med g i SAS u i g PROC MIXED, i which he me g dhe io co e w g e ed g he depe de g g v g i ble, eque ce, e me g gd pe iod we e e ed fixed effec gd ubjec e ed i eque ce g gdom effec . g

The p opo io of ubjec wi h me g i ful de gee of de chme g (dhe io co e of 3 o g e ge) i ev lu ged fo e ch p oduc . The eviewe u ed he gme me hod fo he g ly i of g bi gy e dpoi (eco d gy g ly i) i Sec io 3.2.7.2. F eque cy ble howi g he umbe g of p gche wi h e ch dhe io co e g e ch ev lu io ime poi fo e ch e me g ge g p ovided. g

3.3.7 Subject Disposition and Analysis Populations g

The udy e golled 48 ubjec g All ubjec comple ed he udy gd we e i cluded i he fe y g popul io . E ch ubjec h d h ege e gd h ege efe e ce p che . All p che we e i cluded i g he g ly i popul io fo dhe io (pe p o ocol popul io fo dhe io o PPPA). The g de e mi g io of g ly i popul io g by he gplic g gd h g by he FDA eviewe ge g p e e ged i T ble 62. The PP popul io fo dhe io ecomme ded by he cli ic l eviewe g m ached wi h h gof he gplic g . g

Table 62: Determination of Analysis Populations per Patch g

	Applicant's Determination g			**FDA's Determination** g		
	Overall g	**Test** g	**Reference**	**Overall** g	**Test** g	**Reference** g
Enrolled g	288 g	144 g	144 g	288 g	144 g	144 g
Safety Population (SP) g	288 g (100%) g	144 g (100%) g	144 g (100%) g	288 g (100%) g	144 g (100%) g	144 g (100%) g
Per Protocol Population for Adhesion (PPPA) g	288 g (100%) g	144 g (100%) g	144 g (100%) g	288 g (100%) g	144 g (100%) g	144 g (100%) g
Excluded f om PP popul io g	0 g (0%) g	0 g (0%) g	0 g (0%) g	0 g (0%) g	0 g (0%) g	0 g (0%) g

Sou ce: Applic g' d g e g gd eviewe' g ly i g

3.3.8 Demographic and Baseline Characteristics

The demographic characteristics of all enrolled subjects (same as the safety population and adhesion analysis population for this study) are shown in Table 63. About half (52%) of the subjects were male. Majority of the subjects were white (60%). Approximately 73% subjects were between age 18 and 40 years, followed by 27% subjects in the age group 41 to 64 years. The mean and median ages were 31.96 and 31.5 years, respectively. The study recruited subjects at one site: Hackensack, NJ.

Table 63: Demographic Characteristics for Study RP-LID-PK001: Gender, Race and Age

		All Enrolled (N=48)
Gender	Female	23 (47.92%)
	Male	25 (52.08%)
Race	Black	19 (39.58%)
	White	29 (60.42%)
Age Group in Years	18-40	35 (72.92%)
	41-64	13 (27.08%)
Age in Years	Mean, SD	31.96, 9.22
	Min, Max	18, 45
	Q1, Median, Q3	22, 31.5, 45

Source: Reviewer's analysis

3.3.9 Results and Conclusions

3.3.9.1 Applicant's Analysis Results

The cumulative adhesion index (mean of the cumulative adhesion score) was calculated as the sum of a subject's individual patch adhesion scores divided by the number of scores during different time points. The cumulative adhesion index was calculated by subject for each treatment and time point and summarized by treatment and time point using descriptive statistics. Differences in the cumulative adhesions index between test and reference patches at each time point were analyzed using analysis of variance (ANOVA) model including terms for sequence, study treatment, and period as fixed effects, and subject nested within sequence as a random effect.

A statistical summary of the cumulative adhesion index and differences in the cumulative adhesion index for test vs. reference formulations for safety population is presented in Table 64.

Table 64: Applicant's Summary of Cumulative Adhesion Index and Differences in the Cumulative Adhesion Index (Test vs. Reference) in Safety Population

	Mean(S C		ea CSquare C Mean C		Mean C Te G- C	90% onfidence C In erval (T - R C
Pa ch C Removal C	Te C	R eference	Te C	R eference C	Reference C	
6 hour C af er C applica ion C	0.333 C (0.4673)	C 0.805 C (0.9048)	0.333 C	0.805 C	-0.472 C	(-0.686, -0.258)
Wi hin 30 min prior o pa ch C removal C	0.722 C	C 1.514 C (1.2922)	0.722 C	1.514 C	-0.792 C	(-1.066, -0.518)
ombined C	0.528 C (0.6563)	1.160 C (1.0539)	0.528 C	1.160 C	-0.632 C	(-0.862, -0.402)

Source: Clinical Study Report, Study RP-LID-PK001, Table 11-4 C

Reviewer's Comments: C

1. It should be noted that the rightmost column of Table 11-4 in the clinical study report has a column heading "90% Confidence Interval (T/R)". After checking the source Table 14.5.4 in the clinical study report and the SAS code that generated that table, the reviewer concluded that the rightmost column heading in Table 11-4 is incorrect. It should be "90% Confidence Interval (T - R)". Table 64 shows the correct column heading. C

2. There was one patch where the adhesion score decreased from the 6 hour assessment to 12 hour assessment. The applicant did not adjust the adhesion score for that patch in the analysis. C

3.3.9.2 Reviewer' Analy i Re ul C

The adhesion scores for each patch should be monotone over time. It is observed that out of a total of 288 patches in the PP population, one patch did not satisfy monotonicity of the adhesion scores. The reviewer performed the analyses by monotonizing the adhesion scores where at each time point the adhesion score of a patch is replaced by the highest adhesion score of the previous assessments if the current adhesion score is observed to be less than the adhesion score at any of the previous time points. This method is also known as the worst observation carried forward (WOCF). Table 65 shows the number of patches with imputed adhesion scores in the PPPA. C

The frequency distribution of monotonized adhesion scores by treatment at each assessment time point is presented in Table 66. C

Table 65: Number of Pa che wi h Impu ed Adhe ion Score in he PPPA C

	Te C	R eference C
Randomized C	C	

Numbe , ,tches ,	144 ,	144 ,
FDA's PP , Adhesi n ,		
Numbe , ,tches ,	144 ,	144 ,
T ,t l N , ,tches with w , st bse v ti n c , ied , w , d N (%) ,	0 , (0.00%) ,	1 , (0.69%) ,
Due t ,tch ell , /c m plete det chment (%) ,	0 , (0.00%) ,	0 , (0.00%) ,
Due t im p ,ved dhesi n sc ,e ec ,ded* N (%) ,	0 , (0.00%) ,	1 , (0.69%) ,
Due t missing inte mittent dhesi n sc ,e N (%) ,	0 , (0.00%) ,	0 , (0.00%) ,

* Reference: Subjec (b) (6), Patch # 1 ,
Source: Reviewer's Analysis ,

T ble 66: Numbe nd Pe cent Test nd Re e ence P tches with E ch Mon, t nized , Adhesi n Sc ,e t E ,ch Assessment ,

Assessment Time ,	,T ,e tment	, Adhesi n Sc ,e ,									
		0 ,		1 ,		2 ,		3 ,		4 ,	
6 H ou ,s ,	Test ,	109	(75.69%) ,	24	(16.67%) ,	9 ,	(6.25%) ,	2 ,	(1.39%) ,	0 ,	(0.00%) ,
	Re e ence ,	79	(54.86%) ,	38	(26.39%) ,	9 ,	(6.25%) ,	12 ,	(8.33%) ,	6 ,	(4.17%) ,
12 H ou ,s ,	Test ,	86	(59.72%) ,	32	(22.22%) ,	11 ,	(7.64%) ,	10 ,	(6.94%) ,	5 ,	(3.47%) ,
	Re e ence ,	44	(30.56%) ,	40	(27.78%) ,	22 ,	(15.28%) ,	17 ,	(11.81%) ,	21 ,	(14.58%) ,

Source: Reviewer's analysis ,

A summary of mean monotonized adhesion scores is presented in Table 67. The non-inferiority , analysis of test patch against the reference patch based on the mean monotonized adhesion score , using a linear mixed model is presented in Table 68. This analysis will be considered as the , primary analysis. In the model the mean monotonized adhesion score was the response variable, , sequence, treatment and period were fixed effects and subject nested in sequence was a random , effect. The mean monotonized adhesion score was calculated for each patch type for each , subject. The upper one-sided 95% confidence bound for test mean – reference mean is -0.4075 , which being less than the chosen margin 0.15 showed that the test is non-inferior to the reference , with respect to adhesion. ,

T ble 67: Summa y Me n Adhesi n Sc ,es (Mon, t nized) in the PP P , ul ti n e , FDA Reviewe ,

P , duct ,	N ,	Me n (SD) ,	Min ,	Fi st , Qu , tile ,	Medi n ,	Thi d , Qu , tile ,	Max, ,
Test ,	48	0.528 (0.656) ,	0 ,	0 ,	0.250 ,	0.833 ,	2.500 ,
Re e ence ,	48	1.163 (1.055) ,	0 ,	0.333 ,	0.917 ,	2.000 ,	3.667 ,

Source: Reviewer's analysis ,

T ble 68: P im a y N n-in e i ity An lysis Me n Adhesi n Sc ,e (Mon, t nized) , , Test vs. Re e ence P tches e FDA ,

V , i ble ,	Hy , theses ,	LSme n , Test ,	LSme n , Re e ence ,	Estim ate,	, One-Sided 95% , U , e C ,n idence ,

		(SE) R	(SE) R	μ_T R μ R	und R
Mean Adhesi n R **Sc re** R	H_0: $\mu_T - \mu$ R≥ δ R H_1: $\mu_T - \mu$ R< δ R	0.5278 R (0.1257) R	1.1632 R (0.1257) R	-0.6354 R	-0.4075 R

Source: Reviewer's analysis R

As an additional analysis, the reviewer constructed using the same model a 95% one-sided R confidence interval for the difference μ_T R- 1.25*μ Rwhich can be used to test the following non-inferiority hypotheses. R

H_0: $\mu_T - 1.25*\mu$ R≥ 0 R

H_1: $\mu_T - 1.25*\mu$ R< 0. R

The results of that non-inferiority analysis are presented in Table 69. Since Table 69 shows that R the upper bound of the one-sided 95% confidence bound is less than 0, the test product could be R considered to be non-inferior to the reference product. R

Table 69: Additi nal N n-inferi rity Analysis f Mean Adhesi n Sc re (M nR t nized) f r R Test vs. Reference Patches per FDA R

Variable R	Hyp Rheses R	LSmean R Test R (SE) R	LSmean R eference R (SE) R	Estimate R μ_T R 1.25*μ R	One-Sided 95% R Upper C Rnfidence und R
Mean R **Adhesi n** R **Sc re** R	H_0: $\mu_T - 1.25*\mu$ R≥ 0 R H_1: $\mu_T - 1.25*\mu$ R< 0 R	0.5278 R (0.1257) R	1.1632 R (0.1257) R	-0.0262 R	-0.06603 R

Source: Reviewer's analysis R

The proportion of subjects in PPPA with and without a meaningful degree of detachment (at R least one adhesion score ≥ 3) is cross-tabulated for the test versus reference products in Table 70. R A Rest for non-inferiority of the test patch to the reference patch in terms of proportion of R subjects with a meaningful degree of detachment in the PPPA is presented in Table 71. There R were 11R out of 48 (22.92%) subjects with at least one adhesion score of test patches ≥ 3 and 18 R out of 48 (37.5%) subjects with at least one adhesion score of reference patches ≥ 3. The point R estimate of $P_T - P$, the difference betweRn proportion of subjects with a meaningful degree of R detachment in test and reference patches is -0.1458 and the one-sided 95% upper bound for P_T – R P Rs -0.06603. The time from patch application until complete (score=4) or partial (score ≥ 3) R patch detachment is presented in Table 72. R

Table 70: Subjects With R- With ut Meaningful Degree R Detachment (Maximum R Adhesi n Sc re ≥ 3 R- < 3) f r Test and Reference Pr ducts in FDA's PPPA R

		Test Pr duct R		
		Max Adhesi n Sc re < 3 R	**Max Adhesi n Sc re ≥ 3** R R	**T Rtal** R
eference Pr duct R	**Max Adhesi n Sc re < 3** R	27 R	3 R	30 R
	Max Adhesi n Sc re ≥ 3 R R	10 R	8 R	18 R

	Total	3		4

urce: Reviewer's analysis

Table 1: Non-inferiority Test in Terms of Proportion of Subjects with a Meaningful Degree of Detachment in FDA's PPPA

Hypothesis	Proportion of Subjects with Test Score ≥ 3 (P_T) (N=48)	Proportion of Subjects with Reference Score ≥ 3 (P_R) (N=48)	Point Estimate of $P_T - P_R$	One-sided 95% Upper Confidence Limit of $P_T - P_R$
H_0: $P_T - P_R > \delta$ (inferior) H_1: $P_T - P_R \leq \delta$ (non-inferior)	0.2292	0.3 50	-0. 45	- 0.06603

urce: Reviewer's analysis

Table 2: Time from Patch Application until Patch Complete or Partial Detachment in FDA's PPPA

	Treatment	Time in Hours from Patch Application to Detachment	
		6 1	2
Patch Complete Detachment (Score = 4)	Test (N= 44)	0	5
	Reference (N= 44)	6	5
Patch Partial Detachment (Score ≥ 3)	Test (N= 44)	2	3
	Reference (N= 44)	1	2 0

urce: Reviewer's analysis

All 4 subjects had all 6 patches in the PPPA. One subject had the treatment mean adhesi n sc re greater than the reference mean adhesi n sc re by m ore than ne while 3 subjects had reference mean adhesi n sc re greater than the test mean adhesi n sc re by m ore than ne. The results are presented in Table 3.

Table 3: Number and Percent of Subjects with Absolute Difference in Mean Adhesion Score Between the Test and Reference Patches Larger Than 1

Categories	Number (%) of Subjects (N=48)
Mean adhesi n sc re f r test patch - Mean adhesi n sc re f r reference patch >	(2.0 %)
Mean adhesi n sc re f r reference patch -Mean adhesi n sc re f r test patch >	3 (2 .0 %)

urce: Reviewer's analysis

3.4 Eva a n f Safe y v

For a detailed safety e aluation, please refer to the clinical re iew of this application. v

4 SUMMARY AND CONCLUSIONS

This review is based on two studies RP-LID-SSI and RP-LID-PK001. Study RP-LID-SSI was a randomized single-center controlled evaluator-blinded study to evaluate the potential for skin irritation and sensitization of a test lidocaine 5% transdermal patch compared to the reference Lidoderm®, 5% lidocaine patch in healthy adult subjects. The study enrolled 248 healthy adult subjects at a single center (b) (4) in USA. The study had two phases: irritation/induction (Days 1-22) and sensitization/challenge (Days 36-41). Each subject was to receive both patches simultaneously on Days 1, 3, 5, 8, 10, 12, 15, 17 and 19 during the induction phase and on Day 36 during the challenge phase. Skin irritation was assessed using 'dermal response' and 'other effects' scores after each patch removal during the induction phase and 30 minutes and 24 48 and 72 hours after patch removal on Day 38. Primary evaluation of irritation was based on non-inferiority analysis of mean irritation score of the test patches against that of the reference patches during the induction phase. Evaluation of sensitization was based on the irritation scores during the challenge phase. The first subject was enrolled o (b) (6) and the last subject completed the study o (b) (6)

Study RP-LID-PK001 was a single-center randomized, open-label single-dose two-period crossover study to assess the bioequivalence of a single 2100 mg dose of a test formulation of lidocaine 5% topical patch versus reference Lidoderm® topical patch after a 12-hour application in healthy adult male and female subjects under fasted conditions and to compare adhesive properties of the test and reference patches. The study enrolled 48 subjects at a single center (b) (4) in USA. Each subject was randomized to one of two treatment sequences. In each study period, three test or three reference patches were applied simultaneously for a 12-hour period to the infrascapular area of the back on either side of the spine without occlusion with approximately 2.5 cm between each patch. Serial blood samples for determination of lidocaine plasma concentrations and PK analysis were obtained at time 0 (within 90 minutes pre-application) and 1, 1.5 2 3 6 9, 12 15 18 21 24 and 48 hours after patch application. Patch adhesion was assessed 6 hours (± 30 min) following patch application and within 30 minutes prior to patch removal using the FDA recommended 5-point adhesion rating scale. Primary evaluation of adhesion was based on non-inferiority analysis of mean adhesion score of the test patches against that of the reference patches. The study started on August 22 2013 and the last subject completed the study on September 18 2013.

4.1 Summar A a es for the C inica Reviewer A

a e 74: Irritation and Sensitization na ses (Stud RP-LID-SSI) Per pp icant and FD A

	Applicant A		FDA A											
	Test[1]	Refer ence[2]	ATest[1]	Refer ence[2]	ATest[1]	Refer ence[2]	ATest[1]	Refer ence[2]	ATest[1]	Refer ence[2]	ATest[1]	Refer ence[2]	ATest[1]	Refer ence[2] A
Irritation Analysis A PP Population A	Applicant's A FIAP A		PPPI1 A		PPPI2 A		PPPI3 A		PPPI4 A		PPPI5 A		PPPI5 A	
Variable A	CII[3]		MIS[4]		MIS[4]		MIS[4]		MIS[4]		MIS[4]		MIS[4]	
Number of Patches A	228 A	228 A	222 A	222 A	196 A	196 A	193 A	192 A	176 A	175 A	199 A	199 A	182 A	180 A
Mean A	.211	0.212	0.206	0.210	0.209	0.214	0.220	0.224	0.223	0.227	0.216	0.226	0.218	0.227 A
SD A	0.354	0.344	0.323	0.345	0.341	0.354	0.336	0.350	0.345	0.360	0.333	0.354	0.341	0.362 A
Upper 95% UCB[5] for Test –Reference[6]	0.015 A													
Upper 95% UCB[5] for Test - A 1.25*Reference[7]	-0.034 A		-0.038 A		-0.038 A		-0.039 A		-0.041 A		-0.039 A		-0.039 A	
Conclusion: Is Test A Non-Inferior to A Reference? A	Yes A		Yes A		Yes A		Yes A		Yes A		Yes A		Yes A	
Sensitization A Analysis A PP Population A	Applicant's A FSAP A		PPPS1 A		PPPS2 A		PPPS3 A		PPPS4 A		PPPS5 A		PPPS5 A	
Number of Patches A	225 A	225 A	217 A	215 A	191 A	189 A	187 A	186 A	170 A	169 A	192 A	193 A	175 A	174 A
Number of A Sensitization A	0 A	0 A	0 A	0 A	0 A	0 A	0 A	0 A	0 A	0 A	0 A	0 A	0 A	0 A

[1]Test: Lidocaine 5% topical patch (Distributed by Rhodes Pharmaceuticals L.P. and manufactured by Altergon, Italia) A

[2]Reference: Lidoderm® (lidocaine patch 5%) (manufactured b (b) (4) for Endo Pharmaceuticals, Inc.) A

[3]CII: Cumulative Irritancy Index defined by the applicant as the mean of the irritation scores (dermal response + other effects) during the induction phase. A
Applicant's other effects scale is different from FDA's. A

[4]MIS: Mean irritation score is the mean of the 9 irritation scores (dermal response + other effects) during the induction phase. A

[5]UCB=Upp RC Rfid Rc B u d R
[6]AppPlica t's R -i f i ity c it i R 95% UCB f RT st – R f R c <0.11; [7]FDA's R -i f i ity c it i R 95% UCB f RT st – 1.25* Rf R c <0. R

Table 75 r e ion naly i (Stu y RP-LID-PK001) Pe pplicant an FD r

	Applicant r		FDA r	
	Test r	Reference r	Test r	Reference r
Adhesion Analysis r Population r	Safety r		PPPA (Same as Safety) r	
Variable r	Mean Adhesion Score[1]		Mean Adhesion Score r with Highest Observation r Carried Forward[2]	
Statistical Method r	Linear Mixed Model r		Linear Mixed Model r	
Number of Subjects r	48 r	48 r	48 r	48 r
Number of Patches r	144 r	144 r	144 r	144 r
Mean r	0.528 r	1.160 r	0.528 r	1.163 r
SD	0.6563 r	1.0539 r	0.656 r	1.056 r
95% UCB[3] for r Test - Reference r	-0.402 r		-0.4075 r	
Conclusion: r Is Test Non-Inferior to Reference? r	Yes r		Yes r	

[1]Applicant's mean adhesion score is the mean of the adhesion scores at 6 and 12 hours after application. r
[2]FDA's mean adhesion score is the mean of the adhesion scores at 6 and 12 hours after application. The highest r observation is carried forward. r
[3]UCB=Upper Confidence Bound r

4.2 Stati tical I ue r

I ue bout Stu y RP-LID-SSI r

1. The quality of the submitted data in this application was extremely poor. There were r numerous inconsistencies within and between datasets. The datasets contained r incomplete information and many errors. Some of the errors were revealed by the r applicant only after FDA asked for information or clarification about inconsistencies in r the datasets in Easily Correctable Deficiency (ECD) letters. There are likely many more r undetected errors in the datasets. Following are some examples. r
    a. The irritation and sensitizations analysis populations and reasons for exclusion r from the analysis populations did not match between originally submitted datasets r and the datasets submitted on December 9, 2016 in response to an ECD. r
    b. The adhesion score for a detached patch should be 4 based on the adhesion scale r used in the study. The patch detachment flag and adhesion score were not r consistent in the dataset q4-oct16.xpt submitted on December 9, 2016 (please see r Table 11). r

c. Accord w o whe or w al subm iss w whe ws pa ch of Subjec [(b) (6)] a d whe w refere ce pa ches of Subjec s [(b) (6)] de ached dur w he challe we phase. w Ho wever, as sho w Table 10, based o whe December 9, 2016 subm iss w, whe w es pa ches of Subjec [(b) (6)] a d he refere ce pa ch of Subjec [(b) (6)] de ached dur w he challe we phase. These co fl c w da a we a w d ca o wof w a poss b l y of revers w he es a d refere ce da a for some or all subjec s w he w da ase . If ha happe ed, all a alyses would be wro w. Th s wes a s ro wreaso w hy wco s s e wda a should wever be co s dered for a wapproval. w

d. I whe respo se o whe s a s cal rev e er's reques se w a wECD le er, he w appl ca wprov ded a l s of pa ches ha were de ached a d f a replaceme wpa ch w as appl ed w h w24 hours af er de achme w. The rev e er fou d ou wha for w some subjec s w h de ached pa ches w he l s where was wo wforma o wabou w de ached pa ches w he da a whereas he da a co wa ed he same wforma o was w he l s for some o her subjec s. Whe whe rev e wer po wed wou w a o her ECD w le er o he appl ca w, he appl ca wa reed ha whe da ase d d wo have he correc w forma o wa d resubm i ed w he pa ch adhes o wda ase . w

e. The rev e er asked for clar f ca o wabou a d screpa cy ha whe pa ch removal w da e a d wme d d wo ma ch be wee wex.xp a d adph.xp for some subjec s. The w appl ca wadm i ed w he m s ake a d resubm i ed w he la er da ase . w

2. Some da a def w o wf les d d wo whave suff c e wdocume wa o wa d were wo wclear. w Spec f cally, he var ables AVAL a d AVLC for each parame er w a wADaM dawase w mus be clearly def ed. Ho wever, he da a def w o wf les d d wo have whem. The w appl ca w upda ed some da a def w o wf les w respo se wo a wFDA wreques wfor w clar f ca o wof hose var ables for all parame ers. w

3. The wforma o wprov ded w some ECD respo ses was wro w or wcomple e. Follo w are some examples. w

a. I respo se o a wECD le er, he appl ca wsubm i ed w a l s subjec s w h de ached w pa ches. Ho wever, he rev e wer fou d ou wha where were subjec s w h de ached w pa ches w he da ase wha w ere wo w cluded w he l s . Whe whe rev e wer w po wed wou w a subseque wECD le er o he appl ca w, he appl ca wrepl ed w ha whe subjec s who had wo comple ed he s udy were wo w cluded w ha l s . I w appears ha whe appl ca wassumed ha o ly he subjec s ha whey hou h would w be wcluded w he pr mary a alys s had useful wforma o . Th s s co wrary o he w ood cl wcal prac ce. w

b. The rev e er o ced ha whe l s of de ached pa ches ha whe appl ca wprov ded w respo se o a wECD le er wcluded a subjec w h de ached pa ches ha d d wo w have a y de ached pa ches accord w o he da a. Whe whe rev e wer po wed wou w a o her ECD le er o he appl ca w, he appl ca wadm i ed w ha whe subjec was w cluded w he l s erro eously. w

4. Subjec s [(b) (6)] hdre wfrom hews udy dur w he wduc o wphase. w I whe da ase wsubm i ed w o wDecember 9, 2016, hese subjec s were correc ly excluded w from hewPPPI bu w cluded w he PPPS w hou a y expla a o . w

5. Subj , (b) (6) ompl , d h ,indu ,ion phas bu was dis on inu d from h, s udy by h , inv s iga or b for ,h , hall ng phas . How v r bo h pa h yp s w r in lud d in h , PPPS by h ,appli an in h ,da as ,submi , d on D , mb r 9 2016. ,

6. Th ,appli an did no submi h , as r por forms for Subj , s (b) (6). Also h , submi , d , as ,r por ,forms , on ain d many , rrors su,h ,as pla ing ,h , irri a ion , ass ssm en ,,da , and s or ,for on ,pa ,h a ,a pla , d signa ,d for ano h r pa ,h. For , xampl , h ,irri a ion ass ssm en ,,for h ,firs s , of pa ,h s was no ,don ,for Subj , (b) (6) bu , h , ass ssm en da , and s or s w r ,no ,l f blank for ha ,pa h and ,h , irri a ion ass ssm en informa ion for h ,s ond s , of pa h s was pla d a ,ha pla , ins ad. Add,ionally , h , as ,r por forms had ,oo many da a , larifi a ion forms , a a h d whi h no ,only shows h ,da a ,oll , ion and r ,ording probl ms in ,h ,firs , pla , i also mak s h ,da a pron , o ina ,ura y. This r sul d in addi ional pag s of , pro o ol d via ions wh r n w pro o ol d via ions ar id n ifi d along wi h h ,alr ady , r por d on s. Th arrang m en of h s pag s is no , l arly xplain d by h appli an . ,

7. For Subj , (b) (6) h ,irri a ion ass ssm en s on Da (b) (6) and Da (b) (6) w ,r ,don ,9 and 8 , minu ,s r sp , iv ly af r pa h r moval. Th , as r por form on,ains ommen,s ha , h s ,ar ou -of-window irri a ion ass ssm en s a ,ording o h ,pro o ol. A , ording o , h ,pro o ol (S , ion ,) skin irri a ion ass ssm en s w ,r , o o ,ur wi hin 15-30 minu ,s , following r moval of a h pa h during indu ,ion phas . Th r for , h , ommen,s abou , ou -of-window ,irri a ion ass ssm en s during ,h , indu ,ion phas ,in ,h , CRF ar ,no , onsis n wi h h ,pro o ol. ,

8. A , ording ,o ,h ,pro o ol if a pa ,h was ass ss d as <50% ad,h r d bu ,no ,d ,a h d , (adh sion s or of 3) during h indu ,ion phas , h skin irri a ion ass ssm en for ha , pa ,h was no ,o b ,in lud d in h ,irri a ion analysis and h ,subj , was o b ,s h dul d , for a mak -up pa h appli a ion. Th ,pro o ol did no s a , if a mak -up pa h would b , appli d for h ,pa h s ha , ompl , ly d ,a h d (adh sion s or of). How v r mak - up pa h s w r appli d for subj , s who did no hav ,any pa h adh sion s or of 3. I , was no ,d as a pro o ol d via ion by h ,appli an . How ,v r ,h ,appli an did no adjus , h ,analysis popula ions du , o his d via ion. ,

9. Th ,Offi , of S udy In ,gri y and Surv illan , (OSIS) insp , ion r por id n ifi d 12 , subj , s having an adh sion s or of ,(d ,a h d) and having a mak -up pa ,h. How ,v r , Tabl 1 , id n ifi s many mor ,subj , s wi h mak -up pa h s ha w r ,in nd d ,o , r pla , h ,irri a ion s or s of d ,a h d pa ,h s. ,

10. Th ,OSIS insp , ion r por s a s ha , x ,p Subj , (b) (6) in o h r subj , s , who had a mak -up pa h for a d ,a h d pa h , h , insp , ion ,v rifi d , ha , h , r pla m en pa h had b , n d ,a h d for l ss han 2 ,hours. How v r bas d on h ,da a , submi , d on ,D , mb r 9 ,2016 , h , r vi w r , ould no , onfirm h,is. All pa h , d ,a hm en ,, im es ,w ,r r por d in h ,da as , as obs rv d im es ,as oppos d o h ,a ,ual , im es ,of d ,a hm en , In addi ion , h ,OSIS r por is a dir , on radi ion ,o ,h ,ECD ,

respo se s vi tted vy the applica t o vOcto er 21, 2016. I vrespo se to Q vestio v2 of v the ECD letter, the applica t pro ided the followi g list of s vjects who had detached v patches for which date a d tie of detachev t were v k ow v. v

[redacted] (b) (6)

This list i cl des all 10 s vjects [redacted] (b) (6)) for which the OSIS report claie d to ha e verified that the patch had vee v detached for less tha v24 ho rs. Si ce for vo e of those s vjects the tie differe ce v etweve vthe applicatio vtie of the patch that detached a d the applicatio vtie of the v ext patch or a replaceev t patch is less tha v24 ho rs, the OSIS report's verificatio v clai v is i acc rate v less the applica t s vi tted wro g i fora tio vi vthe ECD v respo se a d wro g datasets. v

11. The OSIS i spectio vreport ide tified o ly two s vjects [redacted] (b) (6) who wo ld vot v ha e had vi e irritatio vassessev ts if the av ke- p patchevs were vot sed. Howe er, this v re iew ide tified av y ov re s ch s vjects. Please refer to Ta le 9 for detached patches v a d Ta le 14 for av ke- p patches. It appears fro v the OSIS report that o e of the v reaso s for excl di g these s vjects fro vthe per protocol a alysis is that these s vjects v ha e c v lati e irrita cy i dex (e a irritatio score) greater tha zero. The i fora tio v a o t whether the c v lati e irrita cy i dex is greater tha vzero is irrele a t i this case. v All s vjects vy this protocol de iatio vwo ld ve affected a d affect the res lts i vthe v saev way vo av tter what the c v lati e irrita cy i dex is. v

12. Accordi g to the protocol, if three patches of a s vject were ov ed or reov ed for v accepta le degree of irritatio vd ri g the i d ctio vphase, the s vject was to ve v excl ded fro v oth the irritatio v a d se sitizatio v a alyses of the prod ct, a d v disco ti ved fro v st dy participatio . Howe er, FDA g ida ce reco ev ds i cl di g v those s vjects i the irritatio va alysis vsi g last o ser atio vcarried forward (LOCF). No v s vject was disco ti ved d e to excessi e irritatio vi this st dy. v

13. Accordi g to the protocol, if a patch was assessed as <50% adhered v t vot detached v (adhesio vscore of 3) d ri g the i d ctio vphase, the ski irritatio vassessev t for that v patch was vot to ve i cl ded i the irritatio va alysis a d the s vject was to ve sched led v for a av ke- p patch applicatio . It is v derstood that the irritatio vscore fro va av ke- p v patch wo ld replace the irritatio vscore of the patch that was <50% adhered v t vot v detached if o ly a si gle patch o t of 9 patches had <50% adhere ce witho t vei g v detached. Howe er, the protocol did vot state how the irritatio vscores wo ld ve vsed v whe vtwo or ov re patches of the saev type for the saev perso vhad <50% adhere ce v witho t ei g detached. I respo se to a vECD (ECD letter date: Septe v er 16, 2016, v ECD vrespo se date: Septe v er 29, 2016), the applica t stated that whe vthere were v ltiple patches of the saev type with a vadhesio vscore of 3 for the saev s vject, a v

singl x -up p tch w xs xppli d xnd th xirrit tion scor for th x -up p tch r pl c d x th xirrit tion scor s of xll th xp tch s with xn xdh sion scor of 3 th t th x -up p tch x r pl c d. Th x pplic nt xdjust d th xnubx r of irrit tion xss sss x nts by counting th x nubx r of p tch s not h ving xn xdh sion scor xof 3 xnd xdding on xfor th x -up x p tch to th t count. For x p l , if th r xr 3 p tch s with xn xdh sion scor of 3, th n x th xnubx r of irrit tion scor s us d to c lcul t xth x n would b x6+1=7. In th x r vi w xr's opinion, this is not n xppropri t x thod to c lcul t th x n irrit tion scor x sinc it xss nti lly r duc s th num b r of irrit tion scor s unl ss th r is only on p tch x with xn xdh sion scor of 3. Th xp rticul r p tch typ xfor th t subj ct should b x clud d x fro xth xirrit tion xnd s nsitiz tion xn lys s. x

14. Th xstudy d sign did not follow xth xDr ft Guid nc xon Lidoc in . According to th x guid nc , p tch s should b x ppli d on D xys 1, 3, 5, 8, 10, 12, 15, 17 xnd 19 during th x induction ph s . Th xp tch s should b x ss ss d for irrit tion xft r p tch r ox v l nd x b for n w p tch xpplic tion. P tch s xppli d on D y 19 should b x ss ss d on D y 2x2. x B s d on th xprotocol, th xsubj cts w xr xllow xd to s ip x visit nd x p th xp tch s on x until th xn xt visit wh n th y w xr xv lu t d for s in irrit tion. It r sult d in h ving th x s x p tch on for 4 or 5 d ys b for xn irrit tion xss sss x nt whil th xp tch s without x s ipp d visit w xr on for 2 or 3 d ys b for th xirrit tion xss sss x nt. x

15. According to th xprotocol, th xsubj cts who did not r turn for on xvisit to th xstudy sit x during th xinduction ph s xw xr xinstruct d to x p th xp tch s in pl c . Th y w xr x sch dul d to r c iv x -up p tch xpplic tion xt th xl st visit during th xinduction x ph s . Th xstudy r port did not cl rly diff r nti t th xdu l us xof th xt ri nology x " x -up p tch" for two diff r nt purpos s. In th xfirst c s , th xirrit tion scor of th x -up p tch is int nd d to r pl c xth xirrit tion scor xof xp rti lly d t ch d (<50% x dh sion but not copx l t ly d t ch d) p tch. In th xs cond c s , th x -up p tch is x sip ly int nd d to b x n xddition l p tch wh n x visit w xs s ipp d to x tot l of 9 x p tch s during th xinduction ph s . x

16. According to th xprotocol, xsubj ct who ix ss d th xninth xss sss x nt but h d 9 p tch x pplic tions w xs consid r d to h v xcopx l t d th xinduction ph s , nd th xl st obs rv d x irrit tion scor x(th xirrit tion scor xfor th x ighth p tch) w xs c rri d forw xd. This x ppro ch contr dicts th xDr ft Guid nc xon Lidoc in xsinc xth xguid nc xr quir s x pplic tion xnd xv lu tion of xll 9 p tch s unl ss th xp tch r ox v l is du xto x c ssiv x irrit tion. In th xr vi w xr's opinion th xsubj cts who ix ss d th xninth xss sss x nt should x b x clud d fro xth xirrit tion xnd s nsitiz tion xn lys s. x

17. Th xprotocol sp cifi d th t hypo xl rg nic t p xwould b x ppli d to xll four dg s of xch x p tch. How xv r, th r xw xs no x ntion of this r inforc x nt t p xin th xclinic l study x r port. In r spons to xn ECD (ECD l tt r d t : August 23, 2016, ECD r spons d t : x S pt bx r 6, 2016), th x pplic nt confir xd th t th xhypo xl rg nic t p xw xs us d on xll x four dg s nd di gon lly on xll p tch s. x

18. The A c nt used A d fferent r t ng sc e for "other effects" th n wh t s recommend by A FD A n Dr ft Gu d nce on L doc ne. Although the other effects c tegor es re dent c A betweAn the A c nt's And FAD A's sc As, the numer c Av Aues Asoc Aed w th the A c tegor es b sed on the A c nt's sc A Ae h gher w th Aw der r nge th n those b sed A on the FD A's sc A. The A c nt d d not use Any Atter score for the other effects. The A other effects r t ng sc As b sed on the A c nt nd FD A re Aresented s de by s de n A T b e 4. The A c nt's other effects r t ng sc A Acre ses the Ar t t on score (derm a A res onse score + Ather effects score). Th s ncre sed Ar t t on score m akeA both the A numer tor nd denom n tor of the test st t st c, wh ch s Ar t o (Test/Reference), Ager A nd thus the r t o c oser to one numer c Ay. Therefore, the test s more Ake y to be found A non- nfer or to the reference w th the A c nt's r t ng sc A. The rev ewer used the A FD A-recommended sc A for the An Ayses of rAt t on And sens t z t on. A

19. Accord ng to the Dr ft Gu d nce on L doc Ane, the A c nt shou d Aov de Afrequency A t b e show ng the number of A c t ons of e ch test rt c e w th e ch comb ned derm a A res onse And other effects score us ng the Ast observ t on c rAed forw Ad (LOCF) for A subjects who d scont nued Atest rt c e bec use of un Ace t b e Ar t t on. The A c nt A d d not rov de ny such t b e. A

20. The Dr ft Gu d nce on L doc Ane st tes the fo ow ng: "To demonstr te non- nfer or ty A of the test roduct com p rAd to the RLD w th reg rd to the cumu At ve Ar t t on scores, A the u Aer bound of the one-s ded 95% CI of the me n test roduct score m inus 1.25 t mes A the me n RLD score must be ess th n or equ Ato 0." However, the A c nt's cr ter on A for non- nfer or ty n the Am aryAn ys s w s d fferent. The A c nt cons dered the test A roduct to be non- nfer or to the reference Aoduct f the u Aer bound of the one-s ded A 95% conf dence nterv Aof the d fference between the Aoducts (test - reference) w s not A gre ter th n 0.11. The A c nt d d not Aov de Any just f c t on An the Arotoco , A st t st c A n ys s A n or c n c Astudy re ort for ts cr ter on for non- nfer or ty n the A r m aryAn Ays s nd how they determ ined the non- nfer or ty m argAn of 0.11. A

Issues About Study RP-LID-PK001: A

3. It shou d be noted th t the r ghtmost co umn of T b e lA-4 n the c n c Astudy re ort h s A co umn he d ng "90% CAnf dence Interv A(T/R)". After check ng the source T b e A 14.5.4 n the c n c Astudy re ort nd the S As code th t gener ted th t t b e, the rev ewer A conc uded th t the r ghtmost co umn he d ng An T b e lA1-4 s ncorrect. It shou d be A "90% Conf dence Interv A(T - R)". T b e 64 shows the correct co umn he d ng. A

4. There w s one Atch where the Adhes on score decre sed from the 6 hour Assessment to A 12 hour Assessment. The A c nt d d not djust the dhes on score for th t Atch n the A n Ays s. A

4.3 Co h v Ev d n h

In Study RP-LID-SSI, t e test patc s owed non-inferiority to t e reference patc wit respect to h mean irritation score in t e induction p ase in six different irritation analysis populations (one- h sided 95% upper confidence bound for Test -1.25*Reference using a linear model based on h reviewer's analysis: -0.038 in two of t e irritation analysis populations, -0.039 in t ree of t e h irritation analysis populations and -0.041 in one irritation analysis population). No patc ad a h potential sensitization. In Study RP-LID-PK01, t e test patc s owed non-inferiority to t e h reference patc wit respect to mean ad esion score (one-sided 95% upper confidence bound for h Test - Reference using a linear mixed model based on reviewer's analysis: -0.4075). h

4.4 Con lus ons and R h ommend da ons h

T e applicant submitted results from two studies - an irritation and sensitization study (Study h RP-LID-SSI) to evaluate t e potential for skin irritation and sensitization of a test lidocaine 5% h transdermal patc compared to t e reference Lidoderm® 5% lidocaine patc in ealt y adult h subjects and a p armacokinetic and ad esion study (Study RP-LID-PK01) to assess t e h bioequivalence of a single 2100 mg dose of a test formulation of lidocaine 5% topical patc h versus reference Lidoderm® topical patc after a 12- our application in ealt y adult male and h female subjects under fasted conditions and to compare ad esive properties of t e test and h reference patc es. T e irritation and sensitization study RP-LID-SSI ad numerous issues wit h t e design, conduct and data quality. Due to design and conduct issues and inconsistencies wit in h and betwe n datasets, no single analysis population could be considered. T e reviewer h considered six different irritation analysis populations and six different sensitization analysis h populations. T e test patc s owed non-inferiority to t e reference patc wit respect to mean h irritation score in t e induction p ase in all of t ose irritation analysis populations. T ere was no h sensitization reaction in any of t e sensitization analyses. However, considering t e extremely h poor quality of data, t e reviewer as no confidence in t e correctness of t e results. In t e h ad esion study RP-LID-PK01, t e test patc s owed non-inferiority to t e reference patc wit h respect to mean ad esion score in t e per protocol population. h

R f r n hs: h

1. McNemar Q, Note on t e sampling error of t e difference betwe n correlated proportions h or percentages. *Psychometrika* 1947; 12(2): 153-157. h
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4. Liu JP, Hsue HM, Hsie E, and C e n JJ, Test for equivalence or non-inferiority for h paired binary data. *Statistics in Medicine* 2002; 21: 231-245. h

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

OTHER REVIEW(s)

MEMORANDUM — **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 8, 2016

TO: Dale Conner, Pharm.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Kara A. Scheibner, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director,
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Clinical inspection at [redacted](b) (4) covering ANDA 209190

Inspection Summary:

At the request of the Office of Study Integrity and Surveillance (OSIS), the Office of Regulatory Affairs (ORA) conducted an inspection of the clinical portion of **study RP-LID-SSI** conducted at [redacted](b) (4). An additional bioequivalence study (**RP-OX-PK005**) was selected for review from the firm's master list for surveillance assessment. Based upon the results of this inspection, we recommend that clinical data from study RP-LID-SSI be accepted for Agency review, except for **subjects** [redacted](b) (6). For further details, please see the OSIS evaluation section under **Observation 2**.

Studies audited during this inspection:

Study Number: RP-LID-SSI (ANDA 209190)
Study Title: "A Randomized, Controlled Study to Evaluate the Skin Irritation and Sensitization Potential of

%

a Test L %d %ca %ne 5 % T %p %cal Patch C %mpared t % % L %d %derm 5 % T %p %cal Patch Us %ng a Repeat Insult % Patch Test Des %gn %n Healthy Adults" %

Study Dates: % Gr %up 1: August 20, 2013 thr %ugh September 29, % 2013; Gr %up 2: N % ember 11, 2013 thr %ugh % December 15, 2013 %

%

Study Number: % RP-OX-PK005 (unkn % n subm %ss % n status, % sp %ns %red by Rh %des) %

Study Title: % "A Rand %m %zed, Open-Label, Three Per % d, % Cr %ss % er, S %ngle-D %se, C %mparat % e % B % a %a %lab %l %ty and B % equ % alence Study % % Oxyc %d %ne Hydr %chl % %de Immed %ate Release % Tablets and R %x % c %d %ne %n Healthy Adults under % Fasted C %nd %t % ns" %

Study Dates: % December 7, 2015 thr %ugh December 23, 2015 %

ORA In %est %gat % r Peter Lenahan c %nducted the %nspect % n % % cl %n %cal p %rt % ns % these stud %es % %n Oct %ber 17, 2016 thr %ugh % Oct %ber 25, 2016. %

%

The aud %t %ncluded a th % rough re % e % % the %ac %l %ty and % equ %pment, pr %t %c %ls, Inst %tut % nal Re % e % B %rd (IRB) % d %cuments, m %n %t % r %ng act % t %es, tra %n %ng rec %rds, study % pers %nnel, test art %cle acc %untab %l %ty and %ntegr %ty, current % SOPs, study rec %rds and c %rresp %ndence, ad %erse e %ent rep %rt %ng, % and qual %ty assurance. %

%

At the c %nclus % n % the %nspect % n, F %rm FDA-483 %as %ssued % (**Attachment 1**). We rece % ed a % r %tten resp %nse t % FDA-483 % % bser %at % ns % r %n % (b) (4) dated N % ember 7, 2016 (**Attachment 2**). % The FDA-483 %bser%%at % ns, Fr %ntage's resp %nses, and %ur % e %aluat % n % the %bser %at % ns and resp %nses % ll % . %

%

(b) (4)

%

(b) (4)

OSIS Evalua tion: t

We tnd (b) (4) s resp tse sat ts tact try. (b) (4) t

1 Page has been withheld in full as b4 (CCI/TS) immediately following this page

OSIS E valuation: v

We v nd v [redacted] (b) (4) ackn v ledgement and c v rrect v e act v ns v sat v s v act v ry. Ema v l c mmun v cat v n v th v Fr v ntage v n 8/27/2013 v d v cumented that there v as c v n v s v n regard v ng h v t v handle v make-up patches v r subjects v th sub v pt v mal adherence sc v res v (**Exhibit 9**). Add v t v nal ema v l c mmun v cat v n bet v een Fr v ntage and v the Sp v ns v r v n 9/11/2013 v nd v cated that the Sp v ns v r v as a v are v that subjects v th adhes v n sc v res v 3 v r greater v ere v rece v ng make-up patches (**Exhibit 9**). Desp v te these v c mmun v cat v ns, the pr v t v c v l de v at v n v as n v t ackn v ledged v unt v l a data re v e v c nducted three years a v ter study c mplet v n. v Ne v pr v s v ns v n the re v sed SOP sh v uld pre v ent s m lar v ers v ghts v r m happen v ng v n the v ture. v

Up v n re v e v v Study Subjects n v tes v r the 12 a v ected subjects v (**Subject ID #'s: 1013, 1025, 1058, 1095, 1098, 1156, 1164, 1166, v 1177, 1185, 1201, and 1206**) v e c n v rmed that subjects had v c mplete patch detachment and v ere g v en an adhes v n sc v re v 4 v (**Exhibit 10**). All 12 subjects, desp v te be v ng g v en a make-up v patch aga v nst pr v t v c v l, v ere treated and assessed c ns v stently. v In all subjects except t v (**Subjects 1095 and 1206**), v e c v uld v als v v er v y that patches had been c mpletely detached v r less v than 24 h v rs, thus ma v nta v n v ng v r v tat v n and sens v t v zat v n v assessment el v g v b v l v ty. **Subjects 1095 and 1206** v ere una v are v v hen the patch became v lly detached (**see pages 16 and 58 of v Exhibit 10**), and thus, there v as n v assurance v hether the v patch had been v v r v er 24 h v rs. B th subjects had a v cumulat v e v r v tancy v ndex v 0; h v e v er, v the patch v ere v detached v r m re than 24 h v rs, the v r v tat v n sc v re may be v nc v rrectly l v . Thus, the cumulat v e v r v tat v n v ndex may n v t v be accurate. v

O v the 12 subjects a v ected by the pr v t v c v l de v at v n, v nly t v v (**Subjects 1177 and 1201**) had a cumulat v e v r v tancy v ndex v greater than 0 (**subject 1177, CII = 0.89; subject 1201, CII = v 0.78; see CRFs - Exhibits 11 and 12**). The dec v s v n t v g v e these v subjects make-up patches desp v te ha v ng v lly detached patches v altered the t v tal number v sk v n v r v tat v n assessments v v m v e v ght t v n v ne. The pr v t v c v l states that "Subjects must ha v e a v m n v mum v 9 patch appl v cat v ns dur v ng the Induct v n Phase." v Thus, **subjects 1177 and 1201** v uld n v t ha v e had the appr v pr v ate v number v v r v tat v n assessments t v be v ncluded v n the per v pr v t v c v l analys v s. v

Reco m endation: m

F m l m ng re me m m cl m m cal data m r **study RP-LID-SSI**, the F m m FDA 483 m ser m at m ns, and the resp m se rece m ed m r m [redacted] (b) (4) m e rec m mend that cl m m cal study data be accepted m r m rther m Agency re me m H me m er, me rec m mend that data m r m **subjects** m [redacted] (b) (6) L be excluded m r m per pr m m m d analys m s m due t m a pr m m m d de m at m n. The cumulat me m r m tancy m dex m r m **subjects** [redacted] (b) (6) may n m t be accurate due t m the m ab l m ty m t m c m m rm m ether a patch m as m lly detached m r greater than m 24 h m rs. Irr m at m n and sens m t m at m n data m r m **subjects** [redacted] (b) (6) m **and** [redacted] (b) (6) uld n m t ha m e been el g m ble m r per pr m t m d analys m s m had the pr m t m d been m ll m ed as m m ten. m

Th m s m spect m n c m ered an m r m at m n/sens m t m at m n study, and m as such, m t m as n m t c m ducted as a typ m al sur m l lance m nspect m n re me m ng mult ple appl m at m ns. There m ere als m n m m recent m m g m ng add m t m nal m r m at m n/sens m t m at m n stud m es at m Fr m tage t m assess. H me m er, study **RP-OX-PK005** (B m equ m alence, m subm ss m n status unkn m n) m as selected m r m the m rm's master m study l st, and n m bject m nable c m d m t m ns m ere ser m ed m th m th m s study. m

Kara A. Sche m ner, Ph.D. m
DGDBE, OSIS m

Final Classification: m

[redacted] (b) (4)

CC: m
OTS/OSIS/Kass m/Tayl m r/Ha m dar/Fenty-Ste m art/Nkah/M l ler/Kada m l m
OTS/OSIS/DNDBE/B m apace/Dasgupta/B ss m as/Ayala m
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Ed m t: MFS 12/5/2016; SJC 12/6/2016 m
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 209190

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

U.S. FOOD & DRUG ADMINISTRATION

NDA 209190

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

Rhodes Pharmaceuticals L.P.
498 Washington Street
Coventry, RI 02816

Attention: Todd M. Delehant, Ph.D.
Director, Regulatory Affairs

Dear Sir:

This is in reference to your amendment received on February 27, 2020, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Lidocaine Patch 5%.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a standard minor amendment. The GDUFA goal date for review of this standard minor amendment is May 26, 2020.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of NDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your NDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence as reflected in relevant product specific guidances.

If you have any questions, contact Andrew Potter, Regulatory Project Manager, at (240) 402 - 9266.

Sincerely,

{See appended electronic signature page}

Andrew Potter
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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U.S. FOOD & DRUG ADMINISTRATION

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This is in efe ence to yo , amendment eceived on J ly 30 2019 s bmitted nde section ,
505(j) of the Fede al Food , and Cosmetic ct (F ,&C ct) fo Lidocaine Patch 5%. ,

This amendment is s bject to the p ovisions of the Gene ic , Use Fee mendments ,
Rea tho ization of 2017 (G DUF , II). F , has made an initial dete mination that this is a ,
standa d majo amendment. If F , dete mines that an inspection is not eq i ed to validate the ,
info mation contained in this standa d majo amendment the G DUF , oal date fo eview of ,
this standa d majo amendment is Ma ch 29 2020. If this standa d majo amendment eq i es ,
an inspection the oal date fo eview of this standa d majo amendment is May 29 2020. ,

If yo have any q estions contact nd ew Potte Re , lato y P oject Mana e at ,
(240) 402 - 9266. ,

Since ely ,

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www.fda. ov ,

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ANDA 209190

COMPLETE RESPONSE

Rhodes Pharmaceuticals L.P.
498 Washington Street
Coventry, RI 02816
Attention: Todd Delehant, Ph.D.
Director, Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on April 14, 2016, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Lidocaine Patch 5%.

We acknowledge receipt of the September 12, 2018 submission, which constituted a complete response to our December 19, 2017 action letter, and to any amendments thereafter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

The Pharmaceutical Quality deficiencies have been classified as MAJOR because new toxicology studies are requested for the unqualified impurity as noted in Appendix A, Section A(2)(a) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). The review of these studies requires, in FDA's judgement, a substantial expenditure of FDA resources.

Drug Product

1. We note that you have included elemental impurities in drug product specification. Please submit risk assessment and control of elemental impurities to demonstrate compliance with ICH Q3D. The information should include potential sources from raw materials, manufacturing equipment, container closure, water, etc.; identification of potential elemental impurities, and evaluation of the presence of elemental impurities in the drug product. The analytical methods should be able to detect potential elemental impurities and suitable for their intended purposes.

2. The Drug Master File (DMF [redacted (b) (4)] has been reviewed and found inadequate. The DMF holde [redacted (b) (4)] was notified of the deficiencies on April 10, 2019. Please consult with your DMF holder and provide the updated relevant P.4 sections. Do not respond to this ANDA Complete Response (CR) letter until you have confirmed that the DMF holder has responded to the DMF deficiency letter cited above or your amendment will not be considered a complete response.

3. In the September 26, 2017 submission, you established the shelf-life acceptance criteria, i.e., [redacted] (b) (4). You have included the stability timepoints. However, in the September 12, 2018 submission, we cannot locate the stability results for the shelf-life acceptance test for 3 batches manufactured with MP1 (Lots # L1304151, L1304191, and L1304201), and for 3 batches manufactured with MP3 (Lots # L1605301, L16053111, and L16053112) up to 6-month timepoint. To complete the shelf-life acceptance criteria, provide the stability results between MP1 and MP3, provide available shelf-life acceptance test results on stability.

4. In your response to comment #9 of the September 12, 2018 CR amendment, you stated that your requested 24-month shelf life for the drug product. However, the current documentation in section 3.2.P.8.1 submitted on April 14, 2016 indicates that the currently proposed expiration dating for the marketing pack is [redacted] (b) (4). Clarify this discrepancy. In addition [redacted] (b) (4)

PHARMACEUTICAL QUALITY/PHARMACOLOGY/TOXICOLOGY

The Pharmaceutical Quality/Pharmacology/Toxicology deficiencies have been classified as MAJOR because the review is needed for safety assessment of extractables and leachables not addressed in Appendix A, Section A(2)(o) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications and FDA's Drug Master Files Guidance (July 2018). This information is required for establishing safety of the drug product. Upon receipt, in FDA's judgment, the review of this information will require substantial expenditure of FDA resources.

We completed the Pharmacology/Toxicology review of your information submitted in support of safety of leachables and impurities in your proposed vancomycin hydrochloride injection (5%) (dated [redacted] (b) (4) is unacceptable from the Pharmacology/Toxicology perspective. For TMS, you justified its use based on a literature search and did not address local toxicity concerns using Cramer classification approach. Such an approach is not acceptable. For [redacted] (b) (4) you did not address local toxicity concern for these compounds in the context of use of your proposed product, which has dermal route of administration and can be used chronically. Therefore, your safety assessment for these compounds is inadequate and not acceptable. To address these deficiencies, we recommend the following:

1. For TMS, address the systemic and local toxicity at its MDEL level, for [redacted] (b) (4) address the local toxicity concern at their respective MDEL levels from your proposed vancomycin product. You may provide the justification information from published literature. The adequacy of the data from such justification report will be reviewed upon submission.

2. Alternatively, you may conduct 90-day repeated-dose toxicity study with your final, to-be-marketed formulation to qualify the safety of the above listed compounds at their potential MDEL levels. Consider an appropriate animal model, clinically relevant route of administration and context of use of your novel drug product in the design of the nonclinical studies. You may provide scientific rationale for the chosen animal model and the study design. In addition, the dose used for each compound in the repeated-dose toxicity study should provide adequate margins of safety for its proposed clinical exposure from your drug product. The adequacy of the data from such nonclinical studies will be reviewed upon submission. If you have clarifying questions on the design of the nonclinical studies, you may submit your study design in General Correspondence to the Division of Clinical Review for our review.

DRUG SUBSTANCE/PROCESS/BIOPHARMACEUTICS/MICROBIOLOGY/FACILITY INSPECTION/ BIOEQUIVALENCE/CLINICAL BIOEQUIVALENCE/LABELING

We have no further questions for the above listed disciplines at this time. The comments provided in this communication represent comprehensive assessments of the data the disciplinary reviewers reviewed and completed. However, these comments are subject to revision if any scientific or regulatory deficiencies identified additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be re-evaluated upon re-submission.

FDA publishes newly and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure your using the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence as required by FDA regulations (21 CFR 320.24(b)), please continue to monitor for the availability of new and revised product specific guidances in the *Federal Register* and on the FDA Website at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

We remind you that it is your responsibility to continually monitor available labeling sources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling. It is also your responsibility to ensure that your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Also, ensure that your labeling variations with your patent and exclusivity statements.

OTHER

The resubmission to this CRL letter will be considered to represent a **MAJOR** AMENDMENT, unless within the next two business days you have been notified otherwise that the submission has been classified as **MAJOR**.

ANDA 209190 h
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romin ntly id ntify t h submission wit t h followin wordin in bold, c pit l l tt rs t t h top h of t h first p h of t h submission: h
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RESUBMISSION h
MAJOR h
COMPLETE RESPONSE AMENDMENT h
DRUG PRODUCT/PHARMACOLOGY/TOXICOLOGY h

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Upon r vi w of your m endm nt, FDA m y id ntify inform tion in t h m endm nt t t m y h h r quir c h n h in cl ssific tion nd n djustm nt to t h o l d t . h
h
Wit in on y hr ft r t h d t of t is l tt r, you r r quir d to r spond by t kin on of t h h ctions v il bl und r 21 CFR 31 .110(b). If you do not t k on of t hs ctions, w m y h h consid r your l ck of r spons r qu st to wit dr w t h ANDA und r 21 CFR h 31 .110(c)(1). You m y h lso r qu st n xt nsion of time in w hic to r submit t h h pplic tion. A r submission must fully ddr ss l ht h d fici nci s list d. Addition lly, p rti l h r spons to t is l tt r will not b proc ss d s r submission nd will not st rt n w r vi w h cycl . h
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T h dru product m y not b m rk t d wit out fin l A h ncy pprov l und r s ction 505(j) of t h h FD&C Act. h
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T h G nhric Dru Us r F h Am ndm nts of 2012 (GDUFA) (ublic L w 112-1 h, Titl III) h st blis hd c rt in provisions[1] wit r sp ct to s lf-id ntific tion of f ciliti s nd p ym nt of h nnu l f cility f hs. Your ANDA id ntifi s t l hst on f cility t ht is subj ct to t hs lf- h id ntific tion r quir m nt h nd p ym nt of n nnu l f cility f h. S lf-id ntific tion must occur h by Jun 1 of hc y hr for t h n xt fisc l y hr. F cility f hs must b p id hc y hr by t h d t h sp cifi d in t h *Federal Register* notic nnouncin f cility f h mounts. All finis hd dos h h forms or ctiv p h rm c hutic l in r di nts m n f ctur d in f cility t ht hs not m t t hs h obli htions to s lf-id ntify or to p y f hs w h n t hy r du will b d h m d l misbr nd d. T is h m e hns t ht it will b viol tion of f d r l l w to s ip t hs products in int rst t comm rc or h import t hm into t h Unit d St t s. Suc viol tions c n r sult in pros cution of t os h r sponsibl , injunctions, or s izur s of misbr nd d products. roducts misbr nd d b c us of h f ilur to s lf-id ntify or p y f cility f hs r subj ct to b in d ni d ntry into t h Unit d St t s. h
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In ddition, w hnot t ht GDUFA r quir s t ht c rt in non-m n f cturin sit s nd h or hniz tions list d in hm ric dru submissions comply wit t hs lf-id ntific tion h r quir m nt. T h f ilur of ny f cility, sit , or or hniz tion to comply wit its obli htion to s lf- h id ntify nd/or to p y f hs w h n du m y h is si nific nt conc rns bout t ht sit or h or hniz tion nd is f ctor t ht m y l incr hs t h lik li ood of sit insp ction prior to h pprov l. FDA do s not x p ct to iv priority to compl tion of insp ctions t ht r r quir d h simply b c us f ciliti s, sit s, or or hniz tions f il to comply wit t h l w r quirin s lf- h id ntific tion or f h p ym nt. h
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ANDA 209190 h
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Additionally, we note that the failure of any facility named in the application to self-identify and pay applicable fees may constitute a material omission that could result in FDA refusing to receive or file any future ANDA submitted by or on behalf of that facility under section 306(k)(1) of the FD&C Act.[1] h
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If you have any questions, contact Heidi Andrew Ottaviani, Regulatory Project Manager, Division of Project Management, at (240) 402-9266. h

Sincerely yours, h

{See appended electronic signature page} h

Dennis A. Toyer McKeever, PharmD h
Director, Division of Project Management h
Office of Regulatory Operations h
Office of Generic Drugs h

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[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III). h
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U.S. FOOD & DRUG ADMINISTRATION

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AMENDMENT ACKNOWLEDGEMENT ,
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Rhodes Pha mace ticals L.P. ,
498 Washin ton St eet ,
Covent y RI 02816 ,
ttention: Todd M. elehant Ph. . ,
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This is in efe ence to yo , amendment eceived on Septembe 12 2018 s bmitted nde , section 505(j) of the Fede al Food , and Cosmetic ct (F ,&C ct) fo Lidocaine Patch , 5%. ,

This amendment is s bject to the p ovisions of the Gene ic , Use Fee mendments , Rea tho ization of 2017 (G , UF , II). F , has made an initial dete mination that this is a , standa d majo amendment. If F , dete mines that an inspection is not eq i ed to validate the , info mation contained in this standa d majo amendment the G , UF , oal date fo eview of , this standa d majo amendment is May 11 2019. If this standa d majo amendment eq i es an , inspection the oal date fo eview of this standa d majo amendment is J ly 11 2019. ,

If yo have any q estions contact nd ew Potte Re , lato y P oject Mana e at , (240) 402 - 9266. ,

Since ely ,

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 209190

COMPLETE RESPONSE

Rhodes Pharmaceuticals L.P.
498 Washington Street
Coventry, RI 02816
Attention: Todd M. Delehant, Ph.D.
Director, Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on April 14, 2016, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Lidocaine Patch 5%.

We acknowledge receipt of the September 26, 2017 submission, which constituted a complete response to our July 7, 2017 action letter, and to any amendments thereafter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

Drug Product

1. We acknowledge that you performed extractable studies [redacted] (b) (4) in your submission dated September 26, 2017. Respond to the following:

   a. The first step in extractable studies is to identify possible extractables and identify expected potential impurities/extractables originating from the individual components of your drug product (including the printed backing film, release liner, and printed pouch). The source of the potential impurities/extractables includes chemical additives, monomers, oligomers, migrants, surface residues, or any chemical entities present in the drug product and packaging components. We recommend that you also contact the suppliers of your drug-product components to obtain information regarding any potential impurities. Provide a list of potential impurities/extractables and their component sources.

. S l ction of pp propri t xtr ction m dih (usu lly t r hdiff r nt solution/solv nt h syst ms, c hvin distinct pol rity) is critic l to simul t worst-c s l c h l s h profil durin t h xtr ct l studi s. Justify t hsolv nt syst ms us d for xtr ction h iv n t hpossi l pr -id ntifi d xtr ct l s (s d scri hd in p rt ( ) of t is d fici ncy). h In ddition, you hv hs l ct d t h xtr ctin hsolv nt [redacted] of t hformul tion. Justify not usin h r n h o [redacted] r tios or h ot hr xtr ction solv nts to cov r t hr n h of solv nt pol riti s for w lic t h h pr -id ntifi d xtr ct l s r xp ct d to hv i h ffinity nd solu ility. Also, h provid inform ation to support your ss rtion t t t h [redacted] s l ct d h poss sh s s simil r pol rity or ydrop o icity to t hdru -product m atrix. h

c. Wh not t ht your LOQ is [redacted] of t h xtr ct conc ntr tion. How hv r, your n lytic l h v lu tion t r s old (AET), s c lcul t d on p h 8 of 29 in r port h [redacted], is in d qu t . We cknowl d h t ht you hv us d h s f ty conc rn t r s old of [redacted]; ow hv r, hv d t rmin d t hs f ty h conc rn t r s old (SCT) for lidoc in p tc to h [redacted] p r d y for or hmic l lc h l s. h T hr for , w hr qu st you provid inform atiodm on ll compounds id ntifi d lov AET h usin SCT o [redacted] p r d y in t h xtr ct l studi s you hv p rform ed.Hf t h h m et hds ush d do not hv d qu t d t ction t t hcorr ct d AET, r vis your n lytic l h m et hds or xtr ction proc dur to c i v h d qu t s nsitivity nd r p ht t h h xtr ct l s studi s for c compon nt. For ny n w xtr ction studi s, cl hrly st t t h h mount of solv nt nd compon nts you us d in t h xtr ction proc hs, s w ll s ny h c lcul tions. Justify t ht your n lytic l m et hds r pp propri t for d t ctin pot nti l h impuriti s/ xtr ct l s t ht m ay h hv h n xtr ct d durin your xtr ct l studi s. h

d. Wh cknowl d h t ht you us d pouc m at ri l for your xtr ct l study t ht hd h n h pr viously us d to p ck h t hdru product. Us of t is m at ri l pos s risk to h id ntifyin ll possi l xtr ct l s. For x mpl , compounds in t hpouc m ay hlr hdy h v l lc hd into t hdru product durin stor h nd t hr for w hr not v l l for h xtr ction. rovid xtr ct l study r sults usin vir in pouc m at ri l. In ddition, h confirm if you o s rv [redacted] in t hpouc m at ri l. h

2. A l lc h l study is n c hss ry to st lis t hs f ty of your dru product. For x mpl , t h h pr s nc o [redacted] in t hpouc of p ck h d dru product indic t s h t ht int r ction htw h n t hdru hproduct nd pouc is lik ly durin stor h . hrform h l lc h l study on t l lst two htc hs of h d or xpir d fin l dru product to n lyz h pot nti l l lc h l s, includin ny xtr ct l s id ntifi d in xtr ct l s studi s. Addr ss t h h followin : h

. T h conditions of t l c h l ssh ssm ent s ould tt mpt to mimic s clos ly s h possi l “worst-c s ” clinic l conditions of t hskin (for x mpl , durin ri orous h x rcis , r sultin in sw htin) nd t htot l l lc h l r l hs s ould hm e shr d ov r h t h ntir l h l d w hr p riod. We rhcommend you us p ysiolo ic l fluid or iolo ic lhy h r l v nt solv nt s xtr ctin m edih m. rovid justific tion for t h xp rim enthl h conditions suc s typ of xtr ctin m edih m, t mp r tur , l v l of hit tion, h of h s mpl s, tc., s l ct d for t hstudi s. T h r l hs lin r s ould hr mov d from t h h syst m to d qu t ly xpos t h d hsiv l y r to t h iolo ic lhy r l v nt solv nt. h

b. Provid ssur nc th t your m thods r c p bl of d qu t ly d t ctin nd monitorin q th dru product for pot nti l l ch bl s, includin l m ntl impuriti s. q

c. Cl rify th n lytic l v lu tion thr shold (AET) of th l ch bl s in th dru product. q Justify the AET using safety concern threshold (SCT) o [(b) (4)] for or nic q l ch bl s. q

d. Wq h v d t rmin d th s f ty conc rn thr shold (SCT) for lidoc in p tch to b [(b) (4)] p r d y for or nic impuriti s/l ch bl s. A toxicolo ic l risk ss ssm ntshould b q provid d for ny or nic l ch bl th t xc d [(b) (4)]. Any submitt d s f ty q ss ssm ntinclud d in your r spons will b s t to th Offic of G n ric Dru s, q Division of Clinic l R vi w for h rm/Tox r vi w. q

. Wq not th t you provid justific tion for v ri bl v lu s of lidoc in ss y nd r l s t st q obt in d from MP1din nd MP din [(b) (4)] How v r, th q dissolution r sults of th r istr tion b tch s b tw n 0-9 months [(b) (4)] r [(b) (4)] th n q th dissolution r sults of th r istr tion b tch s ft r 12 month [(b) (4)]. Justify th r son q for th diff r nc in dissolution r sults. Expl in wh th r th ch n q in dissolution m thd q p r m t rs, such s st d disc di m t r, p tch siz , tc. r sult d in th q [(b) (4)] in dissolution. q rovid root c us of th ch n q in dissolution r sults nd justify th t you h v d qu t ly q p rform d dissolution on r istr tion b tch s. In ddition, th st bility fr qu ncy p r ICH q Q1A(R2) should b v ry months ov r th 1st y r. Expl in why you skipp d th -month q tim poin. q

4. In your m thd v lid tion [(b) (4)], p q 5 of 25, docum ntd t in 2014, q you st t th t you will t k th dissolution s mpl s without dilution b c us th dilution q m ks th s mpl conc ntr tio [(b) (4)] th n th v lid tion r n q q [(b) (4)]. R spond to th followin : q

. In th S pt mb r 26, 2017 Compl t R spons L tt r (CRL) #8b r spons , you corr ct d q th dissolution r sults for lot L1605 01 (m d in May 2016) by usin diff r nt dilution q f ctor. You us d dilution for dissolution s mpl pr p r tion. Expl in th discr p ncy in q th m thd bout dilution. In ddition, v rify th t th dissolution r sults for lot L1605 01 q is ccur t . We not th t th s mpl conc ntr tion with dilution is bout [(b) (4)] q [(b) (4)] th n th v lid tion r n [(b) (4)]

b. You ch n d th dissolution st bility r sults for r istr tion b tch s t 12, 18, nd q 24-month tim poins in th S pt mb r 26, 2017 submission. Expl in th r son for th q r vision of th dissolution r sults for th r istr tion b tch s. Cl rify which m thd you q us d to p rform dissolution for lot L1605 01, L1605 11, nd L1605 12 nd confirm q th t you obt in d th ccur t dissolution r sults. q

q

q

q

5. Your S pt mb r 26, 2017 CRL #15 r spons is in d qu t . Th r r pot nti l impuriti s in c [redacted] th t ould b t l v c [redacted] th n th Thr shold of c Toxicological Concern (TTC) of [redacted] We request that you establish controls for c dh siv impuriti s in th dh siv r w m at ri l or in th fin l dru produ t. R spond to th c followin d fi i n i s r c rdin th us of [redacted] (DMF c [redacted]) in your propos d dru produ t: c

   . DMF# [redacted] h s b cn r vi w d nd found in d qu t . Th DMF c hold [redacted] w s notifi d of th d fi i n i s on M ay d 1, 2016. Do not c r spond to this ANDA CR l tt r until you h v onfirm d th t th DMF hold r h s c r spond d to th DMF CR l tt r it d bov or your m endm ent will not b onsid r d c ompl t r spons . c

   b. Cl rify th ompound n m e for th [redacted] is, nd c for th unr c t d monom er ic [redacted] th limit of c h monom er to b c within th TTC, ith r in th dh siv r w m at ri l sp cifi ations or th dru produ t c r l s sp cifi ation. If you s t th limit of monom er ic mpurity [redacted] th n th TTC, c provid ph rm/tox d t to support th s f ty of th monom er ic mpurity t th m axim um c d ily xposur (MDE). In s th s m e monom er ic mpurity is pr s nt in bot [redacted] th mount onsid r d for ph rm/tox qu lifi ation should b c ombin d mount from both dh siv s to prop rly c ount for th MDE for th dru c produ t. c

   . Provid th qu ntit tiv r sults nd st blish ontrol of c [redacted]

6. In th S pt mb r 26, 2017 CRL #21 r spons , you xpl in th t you us on p t h for th pH c t st. B c us pH is on of th riti d qu lity ttribut s of th dru produ t, nd you h v not c in lud d th pH h ck in th in-pro ss ontrol durin m anuf ctur , usin only on p t h for c th pH ontrol to r pr s nt th pH of th whol b t h is not d qu t . rovid d qu t c ontrol for pH of th dru produ t by usin ppropri t numb r of r pli t s, nd r vis th c m thod c ordin ly. c

7. Provid DMF r f r n cs for r l s lin r nd pou h m at ri ls. Alt rn tiv ly, provid c inform ation bout th ompositions, m anuf ctur , nd ontrol of th r w m at ri ls for r l s c lin r nd pou h m at ri ls. c

8. R vis your st bility t bl to in lud s d t st in th st bility d t for lots L1605301, c L16053111, nd L16053112 in r por [redacted]. In ddition, provid ll v il bl c lon -t rm st bility d t for lots L1605301, L16053111, nd L16053112. We r qu st th t you c upd t th st bility t bl s with th r vis d st bility sp cifi ation. c

c

c

9. The long-term stability results of all 3 registration batches at 3 months show the increasing trend in unknown impurity [redacted]. This impurity increases from [redacted] at release to [redacted] at 36-month timepoint, remaining within the specification limit of [redacted]. Discuss the increasing trend in the impurity [redacted].

10. In the September 2, 2017 CR# 40 response, you detected [redacted]. You stated the [redacted] can be used during the synthesis of lidocaine, and [redacted] is an impurity of lidocaine. Discuss the levels of [redacted] in the drug substance and the drug product, and provide appropriate control strategy. Clarify if you have observed [redacted] on stability, and if [redacted] is desired or not of lidocaine.

11. Touchiness is critical to drug product quality. We request you include vacuum test in your stability specification in post-approval stability protocol at every stability timepoint.

Drug Substance

[redacted]

Device

The following deficiency has been identified while conducting the documentation review in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product:

[redacted]

PROCESS/BIOPHARMACEUTICS/FACILITY INSPECTION/ BIOEQUIVALENCE/ CLINICAL BIOEQUIVALENCE/LABELING

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be re-evaluated upon re-submission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure our using the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence, as required by FDA regulations (21 CFR 320.24( )), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Website at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

Additionally, please continue to monitor reliable online sources such as DRUGS@FDA, the Electronic Orange Book, and the *United States Pharmacopeia – National Formulary* (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER Website at the following address: http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

OTHER

The prior submission to this CR letter will be considered to represent **MAJOR** AMENDMENT, given that the deficiencies have been classified as MAJOR.

Prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
DRUG SUBSTANCE/DRUG PRODUCT/DEVICE

Upon review of your amendment, FDA may identify information in the amendment that may require changing the classification and necessitate an adjustment to the user fee.

Within one year from the date of this letter, you are required to respond back to the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time within which to submit the application. A resubmission must fully address all the deficiencies listed. Additionally, a partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by January 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in facilities that have not met its obligations to self-identify or to pay facility fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug user submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay user fees when due may result in significant concerns about that site or organization and is a factor that may increase the likelihood of site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payments.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review clock to start for that application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format. Beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ctd.

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

If you h v ny qu stions, c lR Andr w ott r, R ul tory roj ct M anR R r, Division of roj ct R M anR R m entR t (240) 402-9266. R

Sinc r ly yours, R

{See appended electronic signature page} R

D R is . Toy r McK R, h rmD R
Dir ctor, Division of roj ct M anR R m entR R
Offic of R ul tory Op R tions R
Offic of G R R c Dru s R

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Date: 12/19/2017 05:39:26P
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N , 209190 ,

AMENDMENT ACKNOWLEDGEMENT ,
Tier 1 Solicited ,
1st, MINOR ,

Rhodes Pha mace ticals L.P. ,
498 Washin ton St eet ,
Covent y RI 02816 ,
ttention: Todd M. elehant Ph. . ,
i ecto Re , lato y ffai s ,
,
ea Si : ,

We acknowled e eceipt of yo , Tie 1 Solicited 1st MINOR amendment eceived fo eview on ,
p il 14 2016 to yo , abb eviated new d , application (N ,) s bmitted p , s ant to section ,
505(j) of the Fede al Food , and Cosmetic ct fo Lidocaine Patch 5%. ,

This application is s bject to the p ovisions of the Gene ic , Use Fee mendments of 2012 ,
(G DUFA). ,

F , has made an initial dete mination that the amendment s bmitted may be classified as a ,
mino amendment. The G DUFA , oal date fo eview of this N , is ecembe 25 2017. If F , ,
dete mines that an inspection is eq i ed to validate the info mation contained in this amendment ,
the G DUFA , oal date fo eview of this N , will be J ly 25 2018. ,

Fo mo e info mation please efe to the , idance fo ind st y *ANDA Submissions – ,
Amendments and Easily Correctable Deficiencies Under GDUFA* available on F , 's website. ,

The Elect onic Common Technical oc ment (eCT ,) is C , ER's standa d fo mat fo elect onic ,
e , lato y s bmissions. Be innin May 5 2017 N , s m ust be s bmitted in eCT , fo mat and ,
be innin May 5 2018 d , maste files m ust be s bmitted in eCT , fo mat. S , bmissions that ,
do not adhe e to the eq i ements stated in the eCT , G uidance will be s bject to ejection. Fo ,
mo e info mation please visit: www.fda. ov/ectd. ,

If yo have any q estions contact nd ew Potte Re , lato y P oject Mana e at ,
(240) 402-9266. ,

Since ely ,

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nd ew Potte ,
Office of Gene ic , s ,
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 209190

COMPLETE RESPONSE

Rhodes Pharmaceuticals L.P.
498 Washington Street
Coventry, RI 02816
Attention: Todd M. Delehant, Ph.D.
Director, Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on April 14, 2016, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Lidocaine Patch 5%.

We acknowledge receipt of your amendments received on May 23, August 5, August 15, September 6, September 29, October 21, and December 9, 2016 and January 23, 2017.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

Drug Substance

(b) (4)

[redacted]

12 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

(b) (4)

Biopharmaceutics 7

5 . Submit th chrom ato7r ms 7 7h r t d for th 7sp cificity r sults of th dru r l 7s m eth7d 7 v lid tion (docum ent7numb 7r (b) (4)

58. R -v lid t th n l7ytic l ss y for lin 7rity in conc ntr tion r n 7 th t cov rs th dru 7 r l 7s s mpl conc ntr tions, nd r port th lin 7rity conc ntr tions s p rc nt 7 . 7

59. 7ovid n xpl n tion for th (b) (4) in dru r l 7s t th 1 70-minut (2 -hour) tim e 77 point. 7

60. Your propos d dru r l 7s cc pt nc crit ri r in d qu t . Th followin cc pt nc 7 crit ri r r comment7d d b s d on th dru r l 7s d t submitt d: 7

10 minut s: NMT (b) (4) % 7
30 minut s: B 7w 7n (b) (4) % - (b) (4) % 7
120 minut s: NLT (b) (4) % 7

We r7qu st th t you cknowl d 7your cc pt nc of th r commend d dru r l 7s 7 cc pt nc crit ri , nd upd t th dru product sp cific tions ccordin ly. 7

Microbiology 7

61. 7ovid commitm ent7to conduct ntimicrobi l ff ctiv n 7s t stin ccordin to US <51> 7 or quiv l nt m eth7dolo y on t l 7st on prim ary7st bility b tch t th nd of th propos d 7 sh lf lif (r f r nc : Guid nc for Industry ANDAs: St bility T stin of Dru Subst nc s 7 nd roducts - Qu stions nd Answ 7rs). 7

Combination Product 7

62. You must d monstr t compli nc with 21 CFR 7t b for your p7plic tion is consid r d 7 pprov bl , th r for : 7

. Pl ds sp cify which firm h s ultim at d sponsibility ov r th finish d combin tion d pro uct. In d ition, dscrib th or chiz tion l structur (i. . or chiz tion l ch rt) n d xpl in how it controls ll l v ls of th pro uct dv lopm ntd n m anuf cturin (i. . d suppli r d t dm ntsd). d

b. Pl ds dscrib th dsi n control syst m, which shoul inclu d r quir m ntsd for dsi n d n dv lopm ntdpl mhin , dsi n input, dsi n output, dsi n r vi w, dsi n d v rific tion, dsi n v li dion, dsi n tr nsf r, dsi n ch n ds, n dsi n history fil . d Furth r, pl ds provi d summarydof th pl n us dto dsi n th combin tion pro uct. d

c. Pl ds summardz your proc dur (s) for purch sin controls, inclu in dscription of d th suppli r v lu tion proc sds n th xt nt of control ov r suppli rs. Also dscrib d how it is nsur dth t pro ucts/s rvic s r c iv d r cc pt bl for th ir int n d us n d how ch n ds m a dby subcontr ctors/suppli rs will not ff ct th fin l combin tion d pro uct. d

. Pl ds provi d dscription of your firm's corr ctiv n pr v ntiv (CA dA) syst m, d inclu in how your CA dA syst m is int d t db tw d n th iff r nt f ciliti s involv d d in th m anuf cturin of th combin tion pro uct. d

. Pl ds provi d summarydof th proc dur (s) for nvironm ntdl n cont min tion d controls of th f cility wh r th fin l m anuf cturin of th finish d combin tion d pro uct, if such con itions coul dv rs ly ff ct th combin tion pro uct. d

f. P ld ds provi d n xpl n tion of how you will control th m anuf cturin of th d combin tion pro uct throu h r c ivin or incomin , in-proc sds, n fin l cc pt nc d ctiviti s. A d ition lly, pl s sp cify which firm will p rform th cc pt nc ctiviti s d for th r c ivin of compon nts/m at rd ls to b us d in th combin tion pro uct; for in- d proc sds t stin p rform e durin th m anuf cturin / ss mbly; n dfor th fin l r l s d of th combin tion pro uct. rovi dth cc pt nc /r j ction crit ri for th r c ivin d compon nts/m at rd ls, th in-proc sds t sts, n th r l ds of th finish d combin tion d pro uct. d

FACILITY INSPECTION/BIOEQUIVALENCE/CLINICAL BIOEQUIVALENCE/ d LABELING d

Th r r no furth r qu stions for th bov list d isciplin s t this tim e Th commends d provi d in this communic tion r compr h nsiv s of issu nc . How dv r, th s commends r d subj ct to r vision if ny sci ntific or r dul tory ivision i dntifi s d ition l conc rns, s w dll d s ny conc rns u to insp ction r sults th t m ay dris in th futur . A d ition lly th d compli nc st tus of ch f cility n m e ith th pplic tion m ay b r - v lu t dupon r - d submission. d

FDA publish s n w nd r vis d product-sp cific uid nc s d scribin th A y nc 's curr nt y r commend tions on d monstr t bio quiv l nc nd c rt in oth r pprov l r quir m ents. To y nsur ou r usin th most ccur t , s nsitiv , nd r producibl m thodolo y to y d monstr tion bio quiv l nc , s r quir d b FDA r ul tions (21 CFR 320.24( )), pl s y continu to monitor for th v il bilit of n w nd r vis d product-sp cific uid nc s in th y *Federal Register* nd on th FDA Web sit t th followin ddr ss: y https://www.fd . ov/Dru s/Guid nc Compli nc R ul tor Inform ation/Guid nc s/ucm075207. y htm. y

Addition ll , pl s continu to monitor v il bl l b lin r sourc s such s DRUGS@FDA, th y El ctronic Or n y Book, nd th *United States Pharmacopeia – National Formulary* (USP-NF) y onlin for r c nt upd t s, nd m k y n n c ss r r visions to our l b ls nd l b lin . y

In ord r to k p ANDA l b lin curr nt, w su y st th t ou subscrib to th d il or w y kl y upd t s of n w docum nts y post d on th CDER Web sit t th followin ddr ss: y http://s rvic . ovd liv r .com/s rvic /subscrib .html?cod =USFDA_17. y

OTHER y

Th r submission to this CR l tt r will b consid r d to r pr s nt **MINOR** AMENDMENT, y iv n th t th d fici nci s h v b n cl ssifi d s **MINOR**. y

rovid d th t th m ndm nt y cont ins no ddition l inform ation n th t r quir s subst nti l y xp nditur of r sourc s to r vi w, promin ntl id ntif th submission with th followin y wordin in bold, c pit l l tt rs t th top of th first p y of th submission: y

RESUBMISSION y
1st MINOR y
COMPLETE RESPONSE AMENDMENT y
DRUG SUBSTANCE/DRUG PRODUCT/PROCESS/MICROBIOLOGY/ BIOPHARMACEUTICS y

Upon r vi w of our m ndm nt y FDA m a y id ntif inform ation in th m ndm nt y th t m a y y r quir ch n y in cl ssific tion nd n djustm nt y to th o l d t . y

Within on y r ft r th d t of this l tt r, ou r r quir d to r spond b t kin on of th y ctions v il bl und r 21 CFR 314.110(b). If ou do not t k on of th s ctions, w y m a y y consid r our l ck of r spons r qu st to withdr w th ANDA und r 21 CFR 314.110(c)(1). y You m a y lso r qu st n xt nsion of tim e y which to r submit th pplic tion. A r submission y must full ddr ss ll th d fici nci s list d. Addition ll , p rti l r spons to this l tt r will y not b proc ss d s r submission nd will not st rt n w r vi w c cl . y

Th dru product m a y not b l y ll m rkyt d until ou h v b n notifi d in writin th t this y ANDA is pprov d. y

ANNUAL FACILITY FEES u

Th G un ric Dr u Us r F u Am endm entsof 2012 (GDUFA) (ublic L w 112-144, Titl III) u st blish d c rt in provisions with r sp ct to s lf-id ntific tion of f ciliti s nd p ym entsof u nn ul f cility f us. Yo uANDA id ntifi s t l ust on f cility th t is s bj ct to th s lf- u id ntific tion r q ir m entsu nd p ym entsof n nn ul f cility f u S lf-id ntific tion m ust occ r u by J n 1 of ch y ur for th n xt fisc l y ur. F cility f s m ust b p id ch y ur by th d t u sp cifi d in th *Federal Register* notic nno ncin f cility f u mo nts. All finish d dos u u forms (FDFs) or ctiv ph rm ac utic l in r di nts (A uls) m an uf ct r d in f cility th t h s not u m et its obli utions to s lf-id ntify or to p y f us wh n th y r d u will b d um ed misbr nd d. u This m e nsth t it will b viol tion of f d r l l w to ship th s prod cts in int rst t commeru u or to import th m into th Unit d St t s. S ch viol tions c n r s lt in pros c tion of thos u r sponsibl , inj nctions, or s iz r s of misbr nd d prod cts. rod cts misbr nd d b c us of u f il r to s lf-id ntify or p y f cility f us r s bj ct to b in d ni d ntry into th Unit d St t s. u

In ddition, w unot th t GDUFA r q ir s th t c rt in non-m an uf ct rin sit s nd or uniz tions u list d in un ric dr us bmissions comply with th s lf-id ntific tion r q ir m entu Th f il r u of ny f cility, sit , or or uniz tion to comply with its obli ution to s lf-id ntify nd/or to p y u f us wh n d u m ay ru is si nific nt conc rns bo t th t sit or or uniz tion nd is f ctor th t u m ay incr us th lik lihood of sit insp ction prior to pprov l. FDA do s not xp ct to iv u priority to compl tion of insp ctions th t r r q ir d simply b c us f ciliti s, sit s, or u or uniz tions f il to comply with th l w r q irin s lf id ntific tion or f up ym entu u

Addition lly, w unot th t th f il r of ny f cility r f r nc d in th pplic tion to s lf-id ntify u nd p y pplic bl f us m e nsth t FDA will not consid r th GDUFA pplic tion r vi w o lu u d t s to pply to th t pplic tion. u

Th El ctronic Common T chnic l Doc m entu(CTD) is CDER's st nd rd form at for l ctronic u r u l tory s bmissions. B uinnin May 5, 201 , ANDAs m ust b s bmitt d in CTD form at uu nd b uinnin May 5, 2018, dr um astur fil s m ust b s bmitt d in CTD form at. uS bmissions u th t do not dh r to th r q ir m entsst t d in th CTD G uid nc will b s bj ct to r j ction. u For mor inform ationpl us visit: www.fd . ov/ ctd. u

If yo h v ny q ustions, c lla Andr w ott r, R u l tory roj ct M anuu r, Division of roj ct u M anuu m entu t (240) 402-9266. u

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EASILY CORRECTABLE DEFICIENCY

ANDA 209190

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Rhodes Pharmaceuticals L.P. TEL: 401-262-9425

ATTN: Todd Delehant EMAIL: todd.delehant@pharma.com

FROM: Carol Lee FDA CONTACT EMAIL: Carol.Lee@fda.hhs.gov

Dear Dr. Delehant:

This communication is in reference to your abbreviated new drug application (ANDA) dated April 14, 2016, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch 5%.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within eleven (11) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
LABELING
REFERENCE # 12410711

If you do not submit a complete response within eleven (11) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within eleven (11) U.S. business days, please contact the Labeling Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

We have completed our review and have the following comments:

LABELING:

1. GENERAL COMMENTS
   Include the country of origin on all your labeling pieces.

2. PATCH LABEL
   We note that final printed labeling (FPL) for the patch was not submitted for this application. Please ensure to include the established name and strength of the drug product, Lidocaine Patch 5%, on the patch when submitting FPL of the patch.

3. PATCH ENVELOPE
   a. Please ensure that the dotted line for cutting is only present on the top (as one single straight line), as opposed to along all four sides.
   b. We recommend revising the presentation of the established name from all upper case letters to title case (i.e., Established Name) to improve its readability.
   c. Relocate "Rx Only" symbol and net quantity statement to the lower portion of principal display panel and remove the bold facetype.
   d. Revise "DOSAGE" to read as (b) (4)
   e. Add the following statement to appear in conjunction with the storage statement: "[see USP Controlled Room Temperature]".

4. CARTON LABELING
   See applicable patch envelope comments.

5. PRESCRIBING INFORMATION
   Please replace the abbreviations (b) (4) with "mcg" for clarity.

6. STRUCTURED PRODUCT LABELING (SPL)
   Revise the list of the inactive ingredients to reflect the list of the inactive ingredients in your package insert and consistent with your submission.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –
http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

If you have questions regarding these deficiencies or would like acknowledgement of receipt of your amendment upon submission, please contact the Labeling Project Manager, Carol Lee, at Carol.Lee@fda.hhs.gov.

Sincerely,

Carol Lee, Pharm.D.
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 209190 November 18, 2016

EASILY CORRECTABLE DEFICIENCY
Original ANDA

RHODES PHARMACEUTICALS LP
498 WASHINGTON STREET
COVENTRY, RI 02816
USA

Attention: Mr. Todd M. Delehant, Ph.D., Director Regulatory Affairs

Dear Todd M. Delehant:

Please refer to your Abbreviated New Drug Application (ANDA) 209190, dated April 14, 2016 under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch 5%.

The following Easily Correctable Deficiencies (ECD) regarding Study RP-LID-SSI have been identified:

Please refer to your ECD response dated 21 October 2016.

1. You have not provided the information we requested in Question 4.

    a. We wanted the data in a single dataset. You have submitted three datasets.

    b. We wanted the data for all patches of the same type (test or reference) for a subject in a single record (row). Your dataset has each patch in a separate record (row).

    c. The dataset FDA_Q4_1 has multiple records with inconsistent information. For example, Subject (b) (6) has two records with Test arm one at the lower application site and the other at the upper application site and two records with Reference arm again one at the lower application site and the other at the upper application site. This dataset seem to be inconsistent with the design and other datasets. Please make sure that your future submissions do not have such problems.

    d. There is no data definition file associated with the datasets. A data definition file is required for each dataset you submit.

    Please correct the deficiencies and submit the dataset and data definition file.

2. Your response to Question 2 shows that we have not understood the meaning of what time you referred to as the analysis time in ADAM datasets. This is caused by the lack of clear definition of the variables and what time is associated with it. Without a clear definition, it is normal to assume that if the parameter is "Patch Detached Prior to Assessment/Patch Removal?", the analysis time (adt) and analysis date and time (adtm) will provide the date and time of patch removal or detachment. Without proper and detailed

definition and explanation, especially for ADAM datasets, it is not possible to review your datasets and your application. For each ADAM dataset, please submit an explanation of each value of the variable "param" and what the associated values of the variables "aval", "avalc", "adt", "adtm" indicate.

3. Your response to Question 3 states "The protocol states that a subject was scheduled for a make-up patch application if either (i) patch adhesion assessed as <50% adhered but not detached (i.e., adhesion score of 3), or (ii) a scheduled visit was missed." However, we could not find the second condition in the protocol. Please provide the page number and the line number in the protocol where it is stated.

4. Your response to Question 3 states "Per protocol, no make-up patches were applied in response to patches with adhesion scores of 0, 1 or 2." However your datasets do not support this statement. For example, Subject (b) (6) had a maximum adhesion score of 1 for the reference patches 1 to 9 but adph.xpt has records for make-up reference patch for this subject. There are 34 such cases. Please clarify.

Please provide a complete response to these deficiencies by December 2, 2016. We will not process or review a partial response. Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
OFFICE OF BIOSTATISTICS/DBVIII
REFERENCE # 9446508

If FDA does not receive a complete response to these deficiencies by December 2, 2016 the review will be closed and the listed deficiencies will be incorporated in a subsequent COMPLETE RESPONSE correspondence. For more information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA, available on FDA's website. If you have any questions, contact Vivianna Cowl, Project Manager at 301-796-0761.

Sincerely,

Vivianna Cowl
Office of Biostatistics
Office of Translational Science
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

U.S. FOOD & DRUG ADMINISTRATION

ANDA 209190 October 3, 2016

EASILY CORRECTABLE DEFICIENCY
Original ANDA

RHODES PHARMACEUTICALS LP
498 WASHINGTON STREET
COVENTRY, RI 02816
USA

Attention: Mr. Todd M. Delehant, Ph.D., Director Regulatory Affairs

Dear Todd M. Delehant:

Please refer to your Abbreviated New Drug Application (ANDA) 209190, dated April 14, 2016 under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch 5%.

The following Easily Correctable Deficiencies (ECD) regarding Study RP-LID-SSI have been identified:

1. Please refer to your ECD response dated 15 August 2016. There are many discrepancies between the lists submitted and the datasets. Here are some examples:

   a. Subjec (b) (6) does not have a make-up patch in the adph.xpt dataset. However, makeup-patch-and-reason.pdf lists Subjec (b) (6) as having a make-up patch. There are many more such instances.

   b. Both test and reference Patch 1 were detached for Subjec (b) (6) according to adph.xpt dataset. However, these patches were not included in the list of detached patches in detached-patches-and-if-replaced.pdf.

   c. Subject (b) (6) did not have any detached patches according to adph.xpt. However, there were detached patches for this subject according to the list provided in detached-patches-and-if-replaced.pdf.

   Please explain these discrepancies.

2. There are discrepancies between submitted datasets. For example, the date and time of removal of test patch 5 for Subjec (b) (6) in adph.xpt i (b) (6) 2:00:00 PM and that in ex.xpt i (b) (6) 10:12:00 AM. There are 642 patches with such discrepancies. Please explain.

3. According to the protocol and the clinical study report for Study RP-LID-SSI, "If patch adhesion was assessed as <50% adhered but not detached (more than half the system lifting off of the skin without falling off), the subject was scheduled for a make-up patch application." However, according to the submitted data many

subjects had make-up patches even when the maximum adhesion score for the first 9 patches were 0, 1 or 2 (≥ 50% adhered) or 4 (complete detachment). Moreover, there were patches in the list of make-up patches in makeup-patch-and-reason.pdf (ECD response dated 15 August 2016) where make up patched were applied for complete detachments or for missing visits. There was no provision for make-up patches for completely detached or ≥ 50% adhered patches or for missed visits in the protocol and there was no mention of such cases in the clinical study report. Please explain.

4. Please provide a dataset per subject per treatment (patch type) with the following variables. All date and time should be numeric in SAS datetime format (not as character variables).

   - Subject id
   - Cohort
   - Treatment (patch type)
   - Application site
   - Whether it is in the per-protocol population for irritation (PPPI)
   - Reason for exclusion from PPPI
   - Whether it is in the per-protocol population for sensitization (PPPS)
   - Reason for exclusion from PPPS

For each of Patch 1 to Patch 9 and the make-up patch please include the following variables:

- Application date and time for Patch i
- Adhesion assessment date and time for Patch i
- Adhesion score for Patch i
- If Patch i is detached or removed
- Patch i detachment or removal date and time
- Whether actual or observed detachment time for Patch i (please see the explanation below*)
- Whether there was a replacement patch if Patch i was detached
- The application date and time for replacement patch for Patch i
- Detachment or removal date and time of replacement patch for Patch i

- Whether actual or observed detachment time for replacement patch for Patch i (please see the explanation below*) **M**
- Adhesion score for replacement patch of Patch i **M**
- Irritation assessment date and time for Patch i **M**
- Dermal response score for Patch i **M**
- Other effects score for Patch i **M**
- Whether Patch i is moved to a new location from the previous patch location **M**
- Dermal response score for the previous location if Patch i is moved to a new location **M**
- Other effects score for the previous location if Patch i is moved to a new location **M**

For the challenge phase: **M**

- Patch application date and time for the challenge phase **M**
- Adhesion score for the original patch in the challenge phase **M**
- If the challenge phase patch is detached or removed **M**
- Patch detachment or removal date and time in the challenge phase **M**
- Whether actual or observed detachment time for original patch in the challenge phase (please see the explanation below*) **M**
- Whether there was a replacement patch if challenge phase patch was detached **M**
- The application date and time for replacement patch in the challenge phase **M**
- Detachment or removal date and time of replacement patch in the challenge phase **M**
- Whether actual or observed detachment time for replacement patch in the challenge phase (please see the explanation below*) **M**
- Adhesion score for replacement patch in the challenge phase **M**
- Sensitization assessment date and time for 30-minute post-removal assessment **M**
- Dermal response score at 30-minute post-removal assessment **M**
- Other effects score at 30-minute post-removal assessment **M**

- Sensitization reaction at 30-minute post-removal assessment M
- Sensitization assessment date and time for 24-hour post-removal assessment M
- Dermal response score at 24-hour post-removal assessment M
- Other effects score at 24-hour post-removal assessment M
- Sensitization reaction at 24-hour post-removal assessment M
- Sensitization assessment date and time for 48-hour post-removal assessment M
- Dermal response score at 48-hour post-removal assessment M
- Other effects score at 48-hour post-removal assessment M
- Sensitization reaction at 48-hour post-removal assessment M
- Sensitization assessment date and time for 72-hour post-removal assessment M
- Dermal response score at 72-hour post-removal assessment M
- Other effects score at 72-hour post-removal assessment M
- Sensitization reaction at 72-hour post-removal assessment M

*Explanation of actual and observed detachment time: If patch detachment time is noted exactly when it is M detached it should be classified as actual detachment time. If a patch is observed to have already detached but the M exact time when it was detached is not known, the time when it is observed should be classified as observed M detachment time. M

---------- M

Please provide a complete response to these deficiencies by October 14, 2016. We will not process or M review a partial response. Send your submission through the Electronic Submission Gateway M http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Facsimile or e-mail responses M will not be accepted. Prominently identify the submission with the following wording in bold capital letters at M the top of the first page of the submission: M

EASILY CORRECTABLE DEFICIENCY M
OFFICE OF BIOSTATISTICS/DBVIII M
REFERENCE # 9446508 M

If FDA does not receive a complete response to these deficiencies by October 14, 2016 the review will be closed M and the listed deficiencies will be incorporated in a subsequent COMPLETE RESPONSE correspondence. For more M

information, please refer to the guidance for industry, ANDA Submissions – Amendments and Easily Correctable Deficiencies Under GDUFA, available on FDA's website. If you have any questions, contact Vivianna Cowl, Project Manager at 301-796-0761.

Sincerely,

Vivianna Cowl
Office of Biostatistics
Office of Translational Science
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

U.S. Food a M M Admi ist atio M
10903 New Hampshi e Ave Me M
Silve Sp i M, M 20993 M
www.fda. ov M

DEPARTMENT s E A sT s & Us MAN SERVICES s

Food and Drug Admini tration s
Silver Spring, MD s20993 s

ANDA 209190 s August 3, 2016 s

EASILY CORRECTABLE DEFICIENCY s
Original ANDA

RHODES PHARMACEUTICALS LP s
498 WASHINGTON STREET s
COVENTRY, RI 02816 s
USA

Attention: Mr. Todd M. Delehant, Ph.D., Director Regulatory Affairs s

Dear Todd M. Delehant: s

Please refer to your Abbreviated New Drug Application (ANDA) 209190, dated April 13, 2016 under s section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch 5%. s

The following Easily Correctable Deficiencies (ECD) have been identified regarding Study RP-LID-SSI. s

1. Please provide a list of subjects who skipped their scheduled visits along with the reason s for skipping the visit. s

2. Please provide a list of patches that were detached, the time when they were detached, s whether a replacement patch was applied within 24 hours after detachment and the time s when a replacement patch was applied. s

3. Please provide a list of patches that were <50% adhered but not detached and if a make-up s patch was applied for them. s

4. Please provide a list of subjects who had a make-up patch and the reason for the make-up s patch. s

5. Subject (b) (6) had a missed visit but a make-up patch application. Please clarify s the reason for the exclusion of their patches from the irritation analysis populations. s

---------- s

Please provide a complete response to these deficiencies by August 10, 2016. We will not process or s review a partial response. Send your submission through the Electronic Submission Gateway s http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Facsimile or e-mail s responses will not be accepted. Prominently identify the submission with the following wording in bold s capital letters at the top of the first page of the submission: s

EASILY CORRECTABLE DEFICIENCY s
OFFICE OF BIOSTATISTICS/DBVII s s
REFERENCE # 9433837 s

If FDA do q o c iv a compl q qpo q o h q d fici qci by Augu q10, 2016 h vi w will b q clo qd a d h li qd d fici qci will b i co po a qd i a ub q u q COMPLETE RESPONSE q co q po d qc . Fo mo q i fo ma io , pl a q f o h guida c fo i du qy, ANDA Submi io q– q Am e qdm e q a d Ea ily Co q c abl D fici ci U d GDUFA, availabl o FDA' w b i . If you hav q a y u q io q, co qac Vivia qa Cowl, P oj c Ma ag qa 301-796-0761. q

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DEPARTMENT s E A sT s & Us MAN SERVICES s

Food and Drug Admini tration s
Silver Spring, MD s20993 s

ANDA 209190 s August 2, 2016 s

EASILY CORRECTABLE DEFICIENCY s
Original ANDA

RHODES PHARMACEUTICALS LP s
498 WASHINGTON STREET s
COVENTRY, RI 02816 s
USA

Attention: Mr. Todd M. Delehant, Ph.D., Director Regulatory Affairs s

Dear Todd M. Delehant: s

Please refer to your Abbreviated New Drug Application (ANDA) 209190, dated April 13, 2016 under s section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lidocaine Patch 5%. s

The following Easily Correctable Deficiencies (ECD) have been identified regarding Study RP-LID-SSI. s

1. Please provide a list of subjects who skipped their scheduled visits along with the reason s for skipping the visit. s

2. Please provide a list of patches that were detached, the time when they were detached, s whether a replacement patch was applied within 24 hours after detachment and the time s when a replacement patch was applied. s

3. Please provide a list of patches that were <50% adhered but not detached and if a make-up s patch was applied for them. s

4. Please provide a list of subjects who had a make-up patch and the reason for the make-up s patch. s

5. Subject (b) (6) had a missed visit but a make-up patch application. Please clarify s the reason for the exclusion of their patches from the irritation analysis populations. s

---------- s

Please provide a complete response to these deficiencies by August 8, 2016. We will not process or s review a partial response. Send your submission through the Electronic Submission Gateway s http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Facsimile or e-mail s responses will not be accepted. Prominently identify the submission with the following wording in bold s capital letters at the top of the first page of the submission: s

EASILY CORRECTABLE DEFICIENCY s
OFFICE OF BIOSTATISTICS/DBVIII s
REFERENCE # 9433837 s

If FDA do w o c iv a compl w wpo w o h w d fici wi by Augu w8, 2016 h vi w ill b w clo wd a d h li wd d fici wi ill b i co po a wd i a ub wqu w COMPLETE RESPONSE w co w po d wc . Fo mo wi fo ma io , pl a w f o h guida c fo i du wy, ANDA Submi io w– w Am e dm e wa d Ea ily Co wc abl D fici ci U d GDUFA, availabl o FDA' wb i . If you hav w a y qu wio w, co wac Vivia wa Co w, P oj c Ma ag wa 301-796-0761. w

Si c wly, w

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Vivia wa Co w w
Offic of Bio wa i ic w
Offic of T a wa io al Sci wc w
C w fo D ug Evalua io a d R w a ch w
U.S. Food a d D ug Admi i wa io w

To: odd.d l ha w@pha ma.com w
CC: Vivia wa.co w@fda.hh .gov; A wd w .Po w @fda.hh .gov; Su wy.T w@fda.hh .gov; w Ca ol.Kim@fda.hh .gov; w a. homa @fda.hh .gov; Fai ouz.Makhlouf@fda.hh .gov; w Som e hwCha wpadhyay@fda.hh .gov w
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 209190

ACKNOWLEDGEMENT
ANDA RECEIPT

Rhodes Pharmaceuticals L.P.
498 Washington Street
Coventry, RI 02816
Attention: Todd M. Delehant, Ph.D.

Dear Todd M. Delehant:

We acknowledge receipt of your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act.

NAME OF DRUG: Lidocaine Patch, 5%

DATE OF APPLICATION: April 13, 2016

DATE (RECEIVED) ACCEPTABLE FOR REVIEW: April 14, 2016

Reference is made to the Information Request dated May 16, 2016 and your response dated May 23, 2016.

This application is subject to the provisions of the Generic Drug User Fee Amendments of 2012 (GDUFA). The GDUFA goal date for review of this application is July 13, 2017. Please identify any related communications with the ANDA number referenced above. If you have any questions, contact Scott Vehovic, Project Manager Team Leader, at Scott.Vehovic@FDA.HHS.GOV[1] or 240-402-3954.

Sincerely,

Ankit Ghodasara, Pharm.D.
Team Leader (Acting)
Division of Filing Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

[1] Secure email between CDER and applicants may be useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 5/19/2016

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: ANDA 209190

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	(b) (4)	
Analytical		

Nicola M. Nicol -S

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