CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 205878

Name: Diclofenac Sodium Topical Solution, 1.5% w/w

Sponsor: Novel Laboratories, Inc.

Approval Date: December 09, 2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA205878Orig1s000

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Tentative Approval Letter	**X**
Labeling	**X**
Labeling Review(s)	**X**
Medical Review(s)	
Chemistry Review(s)	**X**
Pharm/Tox Review	
Bioequivalence Review(s)	**X**
Statistical Review(s)	
Microbiology Review(s)	
Other Review(s)	
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 205878

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 205878

ANDA APPROVAL

Novel Laboratories, Inc.
400 Campus Drive
Somerset, NJ 08873
Attention: Scott Talbot
Vice President, Quality Assurance and Regulatory Affairs

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated June 24, 2013, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Diclofenac Sodium Topical Solution, 1.5% w/w.

Reference is also made to the complete response letter issued on January 7, 2015, and to your amendments dated June 5, and November 24, 2015. Your June 5, 2015 submission constituted a complete response to our January 7, 2015 action letter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the **ANDA is approved**, effective on the date of this letter. The Office of Bioequivalence has determined your Diclofenac Sodium Topical Solution, 1.5% w/w to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Pennsaid, 1.5% w/w of Nuvo Research, Inc. (Nuvo).

The RLD upon which you have based your ANDA, Nuvo's Pennsaid Topical Solution, , 1.5% w/w is subject to periods of patent protection. The following patents and expiration dates are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

U.S. Patent Number	Expiration Date
8,217,078 (the '078 patent)	July 10, 2029
8,546,450 (the '450 patent)	August 9, 2030
8,618,164 (the '164 patent)	July 10, 2029
8,741,956 (the '956 patent)	July 10, 2029

Your ANDA contains paragraph IV certifications to '078, '450, '164 and '956 patents under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Diclofenac Sodium Topical Solution 1.5%

w/w, under this ANDA.[1] You have notified the agency that Novel Laboratories, Inc. (Novel) complied with the requirements of section 505(j)(2)(B) of the FD&C Act, and that no action for infringement was brought against Novel within the statutory 45-day period.

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 & 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.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

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

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions 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 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 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

[1] The agency notes that the '956 patent, the '450 patent, and the '164 patent were submitted to the agency after submission of your ANDA and therefore, litigation, if any, with respect to these patents creates no statutory stay of approval.

failure to self-identify or pay facility fees are subject to being denied entry into the United States.

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 http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

William P. Rickman -A

Digitally signed by William P. Rickman -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300043242, cn=William P. Rickman -A
Date: 2015.12.09 13:04:38 -05'00'

For Carol A. Holquist, RPh
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 205878

LABELING

.5"
Code Area

NDC 40032-016-61 Rx only

Diclofenac Sodium
Topical Solution

1.5% w/w

Avoid contact with the eyes
or mucous membranes.

FOR EXTERNAL USE ONLY

Usual dosage: 40 drops to a knee, four times a day.
Each mL contains: Diclofenac Sodium USP, 16.05 mg

Dispense Enclosed Medication Guide to Each Patient

5 FL. OZ. (150 mL)

NOVEL LABORATORIES

Apply Diclofenac Sodium Topical Solution to clean, dry skin. Allow several minutes for Diclofenac Sodium Topical Solution to dry. Avoid skin to skin contact between other people and the treated knee(s) until completely dry. **After application, wash the hands.** See package insert for complete prescribing information.

WARNING: If persistent skin irritation develops, discontinue use of product and consult your physician.

Excipients: dimethyl sulfoxide, alcohol (11.79%), propylene glycol, glycerin, purified water.

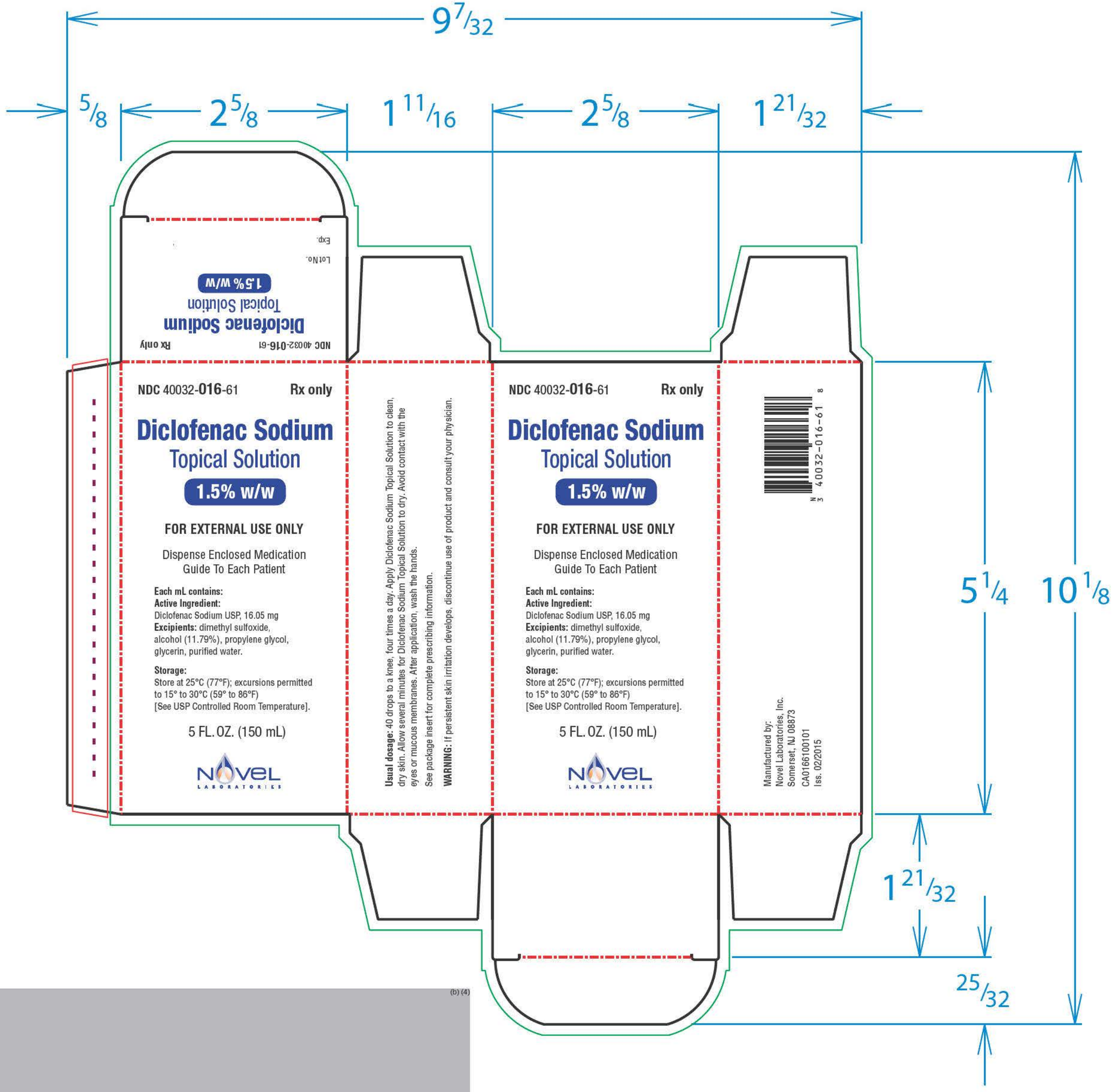
Storage: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Manufactured by:
Novel Laboratories, Inc. LA0166100101
Somerset, NJ 08873 Iss. 01/2015

N 3 40032-016-61 8

Lot No.:
Exp:

(b) (4)


9 7/32
5/8
2 5/8
1 11/16
2 5/8
1 21/32
Lot No.
Exp.
1.5% W/W
Topical Solution
Diclofenac Sodium
NDC 40032-016-61
Rx only
NDC 40032-016-61 Rx only
Diclofenac Sodium
Topical Solution
1.5% w/w
FOR EXTERNAL USE ONLY
Dispense Enclosed Medication Guide To Each Patient
Each mL contains:
Active Ingredient:
Diclofenac Sodium USP, 16.05 mg
Excipients: dimethyl sulfoxide, alcohol (11.79%), propylene glycol, glycerin, purified water.
Storage:
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].
5 FL. OZ. (150 mL)
NOVEL LABORATORIES
Usual dosage: 40 drops to a knee, four times a day. Apply Diclofenac Sodium Topical Solution to clean, dry skin. Allow several minutes for Diclofenac Sodium Topical Solution to dry. Avoid contact with the eyes or mucous membranes. After application, wash the hands.
See package insert for complete prescribing information.
WARNING: If persistent skin irritation develops, discontinue use of product and consult your physician.
N 3 40032-016-61 8
Manufactured by:
Novel Laboratories, Inc.
Somerset, NJ 08873
CA0166100101
Iss. 02/2015
5 1/4
10 1/8
1 21/32
25/32

(b) (4)

Diclofenac Sodium Topical Solution

40032-016-61

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use diclofenac sodium topical solution safely and effectively. See full prescribing information for diclofenac sodium topical solution.

DICLOFENAC sodium topical solution, 1.5% w/w is for topical use only.
Initial U.S. Approval: 1988

WARNING: CARDIOVASCULAR AND GASTROINTESTINAL RISK
See full prescribing information for complete boxed warning.

Cardiovascular Risk

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (5.1)**
- **Diclofenac sodium topical solution is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery. (4)**

Gastrointestinal Risk

- **NSAIDs, including diclofenac sodium topical solution, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. (5.2)**

RECENT MAJOR CHANGES

Dosage and Administration (2) 10/2013

INDICATIONS AND USAGE

Diclofenac sodium topical solution is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of signs and symptoms of osteoarthritis of the knee(s). (1)

DOSAGE AND ADMINISTRATION

For the relief of the signs and symptoms of osteoarthritis of the knee(s), the recommended dose is 40 drops on each painful knee, 4 times a day. (2)

- Apply diclofenac sodium topical solution to clean, dry skin. (2.1)
- Dispense diclofenac sodium topical solution 10 drops at a time either directly onto the knee or first into the hand and then onto the knee. Spread diclofenac sodium topical solution evenly around front, back and sides of the knee. Repeat this procedure until 40 drops have been applied and the knee is completely covered with solution. (2.1)
- Wash hands completely after administering the product.
- Wait until the area is completely dry before covering with clothing or applying sunscreen, insect repellent, cosmetics, topical medications, or other substances.
- Do not get diclofenac sodium topical solution in your eyes, nose or mouth.

DOSAGE FORMS AND STRENGTHS

- 1.5% w/w topical solution (3)

CONTRAINDICATIONS

- Known hypersensitivity to diclofenac sodium. (4)
- History of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. (4)
- Use in the perioperative period of coronary artery bypass graft (CABG) surgery. (4)

WARNINGS AND PRECAUTIONS

- Serious and potentially fatal cardiovascular thrombotic events, myocardial infarction, and stroke can occur with NSAID treatment. Use the lowest effective dose of diclofenac sodium topical solution in patients with known CV disease or risk factors for CV disease. (5.1)
- NSAIDs can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation. Prescribe diclofenac sodium topical solution with caution in those with a prior history of ulcer disease or gastrointestinal bleeding. (5.2)
- Elevation of one or more liver tests may occur during therapy with NSAIDs. Discontinue diclofenac sodium topical solution immediately if abnormal liver tests persist or worsen. (5.3)
- Hypertension can occur with NSAID treatment. Monitor blood pressure closely with diclofenac sodium topical solution treatment. (5.4)
- Use diclofenac sodium topical solution with caution in patients with fluid retention or heart failure. (5.5)
- Long-term administration of NSAIDs can result in renal papillary necrosis and other renal injury. Use diclofenac sodium topical solution with caution in patients at greatest risk of this reaction, including the elderly, those with impaired renal function, heart failure, liver dysfunction, and those taking diuretics and ACE-inhibitors. (5.6)
- Anaphylactoid reactions may occur in patients with the aspirin triad or in patients without prior exposure to diclofenac sodium topical solution. (5.7)
- NSAIDs can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. (5.8)
- Not for use during pregnancy. (5.9)
- Do not administer to patients with aspirin sensitive asthma and use with caution in patients with preexisting asthma. (5.10)
- Avoid exposure of treated knee(s) to natural or artificial sunlight. (5.11)
- Avoid contact of diclofenac sodium topical solution with eyes and mucosa. (5.12)
- Avoid concurrent use with oral NSAIDs. (5.13)

ADVERSE REACTIONS

The most common adverse events with diclofenac sodium topical solution are application site reactions. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Novel Laboratories, Inc., at 1-866-403-7592 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Concomitant administration of diclofenac and aspirin is not generally recommended because of the potential of increased adverse effects including increased GI bleeding. (7.1)
- Concomitant use of anticoagulants and diclofenac have a risk of serious GI bleeding higher than users of either drug alone. (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Not recommended for use during pregnancy. (8.1)
- Nursing Mothers: Use with caution, as it is not known if diclofenac is excreted in human milk. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2015

FULL PRESCRIBING INFORMATION: CONTENTS*
Warning : CARDIOVASCULAR AND GASTROINTESTINAL RISK

1. INDICATIONS AND USAGE
2. DOSAGE AND ADMINISTRATION
   2.1 General Instructions
   2.2 Special Precautions
3. DOSAGE FORMS AND STRENGTHS
4. CONTRAINDICATIONS
5. WARNINGS AND PRECAUTIONS
   5.1 Cardiovascular Thrombotic Events
   5.2 Gastrointestinal Effects – Risk of GI Ulceration, Bleeding, and Perforation
   5.3 Hepatic Effects
   5.4 Hypertension
   5.5 Congestive Heart Failure and Edema
   5.6 Renal Effects
   5.7 Anaphylactoid Reactions
   5.8 Skin Reactions
   5.9 Pregnancy
   5.10 Preexisting Asthma
   5.11 Sun Exposure
   5.12 Eye Exposure
   5.13 Oral Nonsteroidal Anti-Inflammatory Drugs
   5.14 Corticosteroid Treatment
   5.15 Inflammation
   5.16 Hematological Effects
   5.17 Monitoring
6. ADVERSE REACTIONS
   6.1 Clinical Studies Experience
   6.2 Postmarketing Experience
7. DRUG INTERACTIONS
   7.1 Aspirin
   7.2 Anticoagulants
   7.3 ACE-Inhibitors
   7.4 Diuretics
   7.5 Lithium
   7.6 Methotrexate
   7.7 Cyclosporine
   7.8 Oral Nonsteroidal Anti-Inflammatory Drugs
   7.9 Topical Treatments
8. USE IN SPECIFIC POPULATIONS
   8.1 Pregnancy
   8.2 Labor and Delivery
   8.3 Nursing Mothers
   8.4 Pediatric Use
   8.5 Geriatric Use
10. OVERDOSAGE
11. DESCRIPTION
12. CLINICAL PHARMACOLOGY
   12.1 Mechanism of Action
   12.2 Pharmacodynamics
   12.3 Pharmacokinetics
   12.4 Platelets
13. NONCLINICAL TOXICOLOGY
   13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
   13.2 Animal Toxicology and/or Pharmacology
14. CLINICAL STUDIES
   14.1 Pivotal Studies in Osteoarthritis of the Knee
16. HOW SUPPLIED/STORAGE AND HANDLING
17. PATIENT COUNSELING INFORMATION
   17.1 Patient/Caregiver Instructions
   17.2 Cardiovascular Effects
   17.3 Gastrointestinal Effects
   17.4 Hepatotoxicity
   17.5 Adverse Skin Reactions
   17.6 Weight Gain and Edema
   17.7 Anaphylactoid Reactions
   17.8 Effects During Pregnancy
   17.9 Eye Exposure
   17.10 Prevention of Secondary Exposure

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CARDIOVASCULAR AND GASTROINTESTINAL RISK

Cardiovascular Risk

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk *[see Warnings and Precautions (5.1)]*.**
- **Diclofenac sodium topical solution is contraindicated in the perioperative setting of coronary artery bypass graft (CABG) surgery *[see Contraindications (4)]*.**

Gastrointestinal Risk

- **NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events *[see Warnings and Precautions (5.2)]*.**

1. INDICATIONS AND USAGE

Diclofenac sodium topical solution is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of signs and symptoms of osteoarthritis of the knee(s).

2. DOSAGE AND ADMINISTRATION

2.1 General Instructions

For the relief of the signs and symptoms of osteoarthritis of the knee(s), the recommended dose is 40 drops per knee, 4 times a day.

Apply diclofenac sodium topical solution to clean, dry skin.

To avoid spillage, dispense diclofenac sodium topical solution 10 drops at a time either directly onto the knee or first into the hand and then onto the knee. Spread diclofenac sodium topical solution evenly around front, back and sides of the knee. Repeat this procedure until 40 drops have been applied and the knee is completely covered with solution.

To treat the other knee, if symptomatic, repeat the procedure.

Application of diclofenac sodium topical solution in an amount exceeding or less than the recommended dose has not been studied and is therefore not recommended.

2.2 Special Precautions

- Avoid showering/bathing for at least 30 minutes after the application of diclofenac sodium topical solution to the treated knee.
- Wash and dry hands after use.
- Do not apply diclofenac sodium topical solution to open wounds.
- Avoid contact of diclofenac sodium topical solution with eyes and mucous membranes.
- Do not apply external heat and/or occlusive dressings to treated knees.
- Avoid wearing clothing over the diclofenac sodium topical solution-treated knee(s) until the treated knee is dry.
- Protect the treated knee(s) from sunlight.
- Wait until the treated area is dry before applying sunscreen, insect repellant, lotion, moisturizer, cosmetics, or other topical medication to the same knee you have just treated with diclofenac sodium topical solution.
- Until the treated knee(s) is completely dry, avoid skin-to-skin contact between other people and the treated knee(s).

3. DOSAGE FORMS AND STRENGTHS

1.5% w/w topical solution

4. CONTRAINDICATIONS

Diclofenac sodium topical solution is contraindicated in patients with a known hypersensitivity to diclofenac sodium or any other component of diclofenac sodium topical solution.

Diclofenac sodium topical solution is contraindicated in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients *[see Warnings and Precautions (5.7, 5.10)]*.
Diclofenac sodium topical solution is contraindicated in the setting of coronary artery bypass graft (CABG) surgery *[see Warnings and Precautions (5.1)]*.

5. WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Clinical trials of several oral COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction (MI), and stroke, which can be fatal. All NSAIDs, including diclofenac sodium topical solution and COX-2 selective and nonselective orally administered NSAIDs, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Inform patients about the signs and/or symptoms of serious CV events and the steps to take if they occur.

Two large, controlled, clinical trials of an orally administered COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke *[see Contraindications (4)]*.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and NSAIDs, such as diclofenac, does increase the risk of serious GI events *[see Warnings and Precautions (5.2)]*.

5.2 Gastrointestinal Effects – Risk of GI Ulceration, Bleeding, and Perforation

NSAIDs, including diclofenac, can cause serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 to 6 months, and in about 2 to 4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

Prescribe NSAIDs, including diclofenac sodium topical solution, with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, use special care when treating this population.

To minimize the potential risk for an adverse GI event, use the lowest effective dose for the shortest possible duration. Remain alert for signs and symptoms of GI ulceration and bleeding during diclofenac therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. For high-risk patients, consider alternate therapies that do not involve NSAIDs.

5.3 Hepatic Effects

Borderline elevations (less than 3 times the upper limit of the normal [ULN] range) or greater elevations of transaminases occurred in about 15% of oral diclofenac-treated patients in clinical trials of indications other than acute pain. Of the markers of hepatic function, ALT (SGPT) is recommended for the monitoring of liver injury.

In clinical trials of an oral diclofenac-misoprostol combination product, meaningful elevations (i.e., more than 3 times the ULN) of AST (SGOT) occurred in about 2% of approximately 5,700 patients at some time during diclofenac treatment (ALT was not measured in all studies).

In an open-label, controlled trial of 3,700 patients treated for 2 to 6 months, patients with oral diclofenac were monitored first at 8 weeks and 1,200 patients were monitored again at 24 weeks. Meaningful elevations of ALT and/or AST occurred in about 4% of the 3,700 patients and included marked elevations (>8 times the ULN) in about 1% of the 3,700 patients. In this open-label study, a higher incidence of borderline (less than 3 times the ULN), moderate (3 to 8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Elevations in transaminases were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis. Almost all meaningful elevations in transaminases were detected before patients became symptomatic.

Abnormal tests occurred during the first 2 months of therapy with oral diclofenac in 42 of the 51 patients in all trials who developed marked transaminase elevations. In postmarketing reports, cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first 2 months of NSAID therapy.

Postmarketing surveillance has reported cases of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure. Some of these reported cases resulted in fatalities or liver transplantation.

In a European retrospective population-based, case-controlled study, 10 cases of oral diclofenac associated drug-induced liver injury with current use compared with non-use of diclofenac were associated with a statistically significant 4-fold adjusted odds ratio of liver injury. In this particular study, based on an overall number of 10 cases of liver injury associated with diclofenac, the adjusted odds ratio increased further with female gender, doses of 150 mg or more, and duration of use for more than 90 days.

Measure transaminases (ALT and AST) periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. Based on clinical trial data and postmarketing experiences, monitor transaminases within 4 to 8 weeks after initiating treatment with diclofenac. However, severe hepatic reactions can occur at any time during treatment with diclofenac. If abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, abdominal pain, diarrhea, dark urine, etc.), discontinue diclofenac sodium topical solution immediately.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms), and the appropriate action to take if these signs and symptoms appear.
To minimize the potential risk for an adverse liver-related event in patients treated with diclofenac sodium topical solution, use the lowest effective dose for the shortest duration possible. Exercise caution when prescribing diclofenac sodium topical solution with concomitant drugs that are known to be potentially hepatotoxic (e.g., acetaminophen, certain antibiotics, antiepileptics). Caution patients to avoid taking unprescribed acetaminophen while using diclofenac sodium topical solution.

5.4 Hypertension

NSAIDs, including diclofenac, can lead to new onset or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Use NSAIDs, including diclofenac sodium topical solution, with caution in patients with hypertension. Monitor blood pressure (BP) closely during the initiation of NSAID treatment and throughout the course of therapy.

Patients taking ACE-inhibitors, thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs.

5.5 Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients treated with NSAIDs, including diclofenac sodium topical solution. Use diclofenac sodium topical solution with caution in patients with fluid retention or heart failure.

5.6 Renal Effects

Use caution when initiating treatment with diclofenac sodium topical solution in patients with considerable dehydration.

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE-inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of diclofenac sodium topical solution in patients with advanced renal disease. Therefore, treatment with diclofenac sodium topical solution is not recommended in patients with advanced renal disease. If diclofenac sodium topical solution therapy is initiated, close monitoring of the patient's renal function is advisable.

5.7 Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without prior exposure to diclofenac sodium topical solution. Do not prescribe diclofenac sodium topical solution to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs *[see Contraindications (4) and Warnings and Precautions (5.10)]*. Seek emergency help in cases where an anaphylactoid reaction occurs.

5.8 Skin Reactions

Do not apply diclofenac sodium topical solution to open skin wounds, infections, inflammations, or exfoliative dermatitis, as it may affect absorption and tolerability of the drug.

NSAIDs, including diclofenac sodium topical solution, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin manifestations, and discontinue use of the drug at the first appearance of skin rash or any other signs of hypersensitivity.

5.9 Pregnancy

Diclofenac sodium topical solution should not be used by pregnant or nursing women or those intending to become pregnant.

5.10 Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, do not administer diclofenac sodium topical solution to patients with this form of aspirin sensitivity and use with caution in patients with preexisting asthma.

5.11 Sun Exposure

Instruct patients to avoid exposure to natural or artificial sunlight on treated knee(s) because studies in animals indicated topical diclofenac treatment resulted in an earlier onset of ultraviolet light-induced skin tumors. The potential effects of diclofenac sodium topical solution on skin response to ultraviolet damage in humans are not known.

5.12 Eye Exposure

Avoid contact of diclofenac sodium topical solution with eyes and mucosa. Advise patients that if eye contact occurs, immediately wash out the eye with water or saline and consult a physician if irritation persists for more than an hour.

5.13 Oral Nonsteroidal Anti-Inflammatory Drugs

Concomitant use of oral NSAIDs with diclofenac sodium topical solution resulted in a higher rate of rectal hemorrhage, more frequent abnormal creatinine, urea and hemoglobin. Therefore, do not use combination therapy with diclofenac sodium topical solution and an oral NSAID unless the benefit outweighs the risk and conduct periodic laboratory evaluations.

5.14 Corticosteroid Treatment

Diclofenac sodium topical solution cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-response illness. For patients on prolonged corticosteroid therapy, taper slowly if a decision is made to discontinue corticosteroids.

5.15 Inflammation

The pharmacological activity of diclofenac sodium topical solution in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

5.16 Hematological Effects

The effects of diclofenac sodium topical solution on platelet function were studied in 10 healthy subjects administered 80 drops four times a day for 7 days. There was no significant change in platelet aggregation following one week of treatment *[see Clinical Pharmacology (12.4)]*.

Anemia is sometimes seen in patients receiving NSAIDs. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Check hemoglobin or hematocrit of patients on diclofenac sodium topical solution if they exhibit any signs or symptoms of anemia or blood loss.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration and reversible. Carefully monitor patients receiving diclofenac sodium topical solution who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants.

5.17 Monitoring

Because serious GI tract ulcerations and bleeding can occur without warning symptoms in patients taking NSAIDs, monitor patients for signs or symptoms of GI bleeding. Check CBC and a chemistry profile periodically in patients on long-term treatment with NSAIDs. Discontinue diclofenac sodium topical solution if abnormal liver tests or renal tests persist or worsen.

6. ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to diclofenac sodium topical solution of 911 patients treated between 4 and 12 weeks (mean duration of 49 days) in seven Phase 3 controlled trials, as well as exposure of 793 patients treated in an open-label study, including 463 patients treated for at least 6 months, and 144 patients treated for at least 12 months. The population mean age was approximately 60 years, 89% of patients were Caucasians, 64% were females, and all patients had primary osteoarthritis. The most common adverse events with diclofenac sodium topical solution were application site skin reactions. These events were the most common reason for withdrawing from the studies.

Application Site Reactions

In controlled trials, the most common treatment-related adverse events in patients receiving diclofenac sodium topical solution were application site skin reactions. Application site reactions were characterized by one or more of the following: dryness, erythema, induration, vesicles, paresthesia, pruritus, vasodilation, acne, and urticaria. The most frequent of these reactions were dry skin (32%), contact dermatitis characterized by skin erythema and induration (9%), contact dermatitis with vesicles (2%) and pruritus (4%). In one controlled trial, a higher rate of contact dermatitis with vesicles (4%) was observed after treatment of 152 subjects with the combination of diclofenac sodium topical solution and oral diclofenac. In the open label uncontrolled long-term safety study, contact dermatitis occurred in 13% and contact dermatitis with vesicles in 10% of patients, generally within the first 6 months of exposure, leading to a withdrawal rate for an application site event of 14%.

Adverse Events Common to the NSAID Class

In controlled trials, subjects treated with diclofenac sodium topical solution experienced some adverse events associated with the NSAID class more frequently than subjects using placebo (constipation, diarrhea, dyspepsia, nausea, flatulence, abdominal pain, edema; see **Table 1**). The combination of diclofenac sodium topical solution and oral diclofenac, compared to oral diclofenac alone, resulted in a higher rate of rectal hemorrhage (3% vs. less than 1%), and more frequent abnormal creatinine (12% vs. 7%), urea (20% vs. 12%), and hemoglobin (13% vs. 9%), but no difference in elevation of liver transaminases.

Table 1 lists all adverse reactions occurring in ≥1% of patients receiving diclofenac sodium topical solution, where the rate in the diclofenac sodium topical solution group exceeded placebo, from seven controlled studies conducted in patients with osteoarthritis. Since these trials were of different durations, these percentages do not capture cumulative rates of occurrence.

Table 1: Adverse Reactions occurring in ≥1% of patients treated with diclofenac sodium topical solution in placebo and oral diclofenac-controlled trials.

Treatment Group:	Diclofenac sodium topical solution N=911	Topical Placebo N=332
Adverse Reaction*	**N (%)**	**N (%)**
Dry Skin (Application Site)	292 (32)	17 (5)
Contact Dermatitis (Application Site)	83 (9)	6 (2)
Dyspepsia	72 (8)	13 (4)
Abdominal Pain	54 (6)	10 (3)
Flatulence	35 (4)	1 (<1)
Pruritus (Application Site)	34 (4)	7 (2)
Diarrhea	33 (4)	7 (2)
Nausea	33 (4)	3 (1)
Pharyngitis	40 (4)	13 (4)
Constipation	29 (3)	1 (<1)
Edema	26 (3)	0
Rash (Non-Application Site)	25 (3)	5 (2)
Infection	25 (3)	8 (2)
Ecchymosis	19 (2)	1 (<1)
Dry Skin (Non-Application Site)	19 (2)	1 (<1)
Contact Dermatitis, vesicles (Application Site)	18 (2)	0
Paresthesia (Non-Application Site)	14 (2)	3 (<1)
Accidental Injury	22 (2)	7 (2)
Pruritus (Non-Application Site)	15 (2)	2 (<1)
Sinusitis	10 (1)	2 (<1)
Halitosis	11 (1)	1 (<1)
Application Site Reaction (not otherwise specified)	11 (1)	3 (<1)

*Preferred Term according to COSTART

6 2 Postmarketing Experience

In non-US postmarketing surveillance, the following adverse reactions have been reported during post-approval use of diclofenac sodium topical solution. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: abdominal pain, accidental injury, allergic reaction, asthenia, back pain, body odor, chest pain, edema, face edema, halitosis, headache, lack of drug effect, neck rigidity, pain

Cardiovascular: palpitation, cardiovascular disorder

Digestive: diarrhea, dry mouth, dyspepsia, gastroenteritis, decreased appetite, mouth ulceration, nausea, rectal hemorrhage, ulcerative stomatitis

Metabolic and Nutritional: creatinine increased

Musculoskeletal: leg cramps, myalgia

Nervous: depression, dizziness, drowsiness, lethargy, paresthesia, paresthesia at application site

Respiratory: asthma, dyspnea, laryngismus, laryngitis, pharyngitis

Skin and Appendages: At the Application Site: contact dermatitis, contact dermatitis with vesicles, dry skin, pruritus, rash; *Other Skin and Appendages Adverse Reactions:* eczema, rash, pruritus, skin discoloration, urticaria

Special Senses: abnormal vision, blurred vision, cataract, ear pain, eye disorder, eye pain, taste perversion

7. DRUG INTERACTIONS

Drug interactions with the use of diclofenac sodium topical solution have not been studied. The following drug interactions [sections 7.1 to 7.7] are noted for oral diclofenac sodium.

7.1 Aspirin

When diclofenac is administered with aspirin, the binding of diclofenac to protein is reduced, although the clearance of free diclofenac is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of diclofenac and aspirin is not generally recommended because of the potential of increased adverse effects.

7.2 Anticoagulants

The effects of anticoagulants such as warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

7.3 ACE-Inhibitors

NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors. Consider this interaction in patients taking NSAIDs concomitantly with ACE-inhibitors.

7.4 Diuretics

Clinical studies, as well as postmarketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. The response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, observe the patient closely for signs of renal failure *[see Warnings and Precautions (5.6)]*, as well as to assure diuretic efficacy.

7.5 Lithium

NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs, including diclofenac, and lithium are administered concurrently, observe patients carefully for signs of lithium toxicity.

7.6 Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Use caution when NSAIDs, including diclofenac, are administered concomitantly with methotrexate.

7.7 Cyclosporine

Diclofenac, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Therefore, concomitant therapy with diclofenac may increase cyclosporine's nephrotoxicity. Use caution when diclofenac is administered concomitantly with cyclosporine.

7.8 Oral Nonsteroidal Anti-Inflammatory Drugs

Concomitant use of oral NSAIDs with diclofenac sodium topical solution has been evaluated in one Phase 3 controlled trial and in combination with oral diclofenac, compared to oral diclofenac alone, resulted in a higher rate of rectal hemorrhage (3% vs. less than 1%), and more frequent abnormal creatinine (12% vs. 7%), urea (20% vs. 12%) and hemoglobin (13% vs. 9%). Therefore, do not use combination therapy with diclofenac sodium topical solution and an oral NSAID unless the benefit outweighs the risk and conduct periodic laboratory evaluations.

7.9 Topical Treatments

Instruct patients that before applying sunscreen, insect repellant, lotion, moisturizer, cosmetics, or other topical medication to the same skin surface of the knee treated with diclofenac sodium topical solution, they must wait until the treated area is completely dry.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C prior to 30 weeks gestation; Category D starting 30 weeks gestation.

Teratogenic Effects

There are no adequate and well-controlled studies of diclofenac sodium topical solution in pregnant women. Diclofenac sodium topical solution should not be used by pregnant women as its safe use has not been adequately determined and starting at 30 weeks gestation, diclofenac and other NSAIDs should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. Developmental studies in animals demonstrated that diclofenac sodium administration did not produce teratogenicity despite the induction of maternal toxicity and fetal toxicity in mice at doses up to 20 mg/kg/day (0.6-fold the maximum recommended human dose [MRHD] of 154 mg/day based on body surface area comparison), and in rats and rabbits at doses up to 10 mg/kg/day (approximately 0.6-fold and 1.3-fold the MRHD, respectively). Published reproductive and developmental studies of dimethyl sulfoxide (DMSO, the solvent used in diclofenac sodium topical solution) are equivocal as to potential teratogenicity.

Nonteratogenic Effects

In rats, maternally toxic doses of diclofenac were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival.

8.2 Labor and Delivery

The effects of diclofenac sodium topical solution on labor and delivery in pregnant women are unknown. In rat studies maternal exposure to diclofenac, as with other NSAID drugs, known to inhibit prostaglandin synthesis, increased the incidence of dystocia, delayed parturition, and decreased offspring survival.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk; however, there is a case report in the literature indicating that diclofenac can be detected at low levels in breast milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from diclofenac sodium topical solution, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 911 patients treated with diclofenac sodium topical solution in seven controlled, Phase 3 clinical trials, 444 subjects were 65 years of age and over. There was no age-related difference in the incidence of adverse events. Of the 793 patients treated with diclofenac sodium topical solution in one open-labeled safety trial, 334 subjects were 65 years of age and over including 107 subjects 75 and over. There was no difference in the incidence of adverse events with long-term exposure to diclofenac sodium topical solution for this elderly population. As with any NSAID, use caution in treating the elderly (65 years and older) and it may be useful to monitor renal function since they are more likely to have decreased baseline renal function.

10. OVERDOSAGE

There have been no known experiences of overdose with diclofenac sodium topical solution.

Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

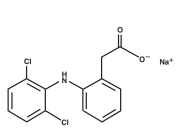
Manage patients using symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Emesis is not recommended due to a possibility of aspiration and subsequent respiratory irritation by DMSO contained in diclofenac sodium topical solution. Activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

For additional information about overdose treatment, call a poison control center (1-800-222-1222).

11. DESCRIPTION

Diclofenac sodium topical solution is a clear, colorless to faintly pink-orange solution for topical application.

Diclofenac sodium topical solution contains 1.5% w/w diclofenac sodium, a benzeneacetic acid derivative that is a nonsteroidal anti-inflammatory drug (NSAID), designated chemically as 2-[(2,6-dichlorophenyl)amino]-benzeneacetic acid, monosodium salt. The molecular weight is 318.14. Its molecular formula is $C_{14}H_{10}Cl_2NNaO_2$ and it has the following structural formula:



Each 1 mL of solution contains 16.05 mg of diclofenac sodium. In addition, diclofenac sodium topical solution contains the following inactive ingredients: dimethyl sulfoxide USP (DMSO, 45.5% w/w), propylene glycol, alcohol, glycerin and purified water.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of diclofenac is similar to that of other nonsteroidal anti-inflammatory drugs. Diclofenac inhibits the enzyme, cyclooxygenase (COX), an early component of the arachidonic acid cascade, resulting in the reduced formation of prostaglandins, thromboxanes and prostacylin. It is not completely understood how reduced synthesis of these compounds results in therapeutic efficacy.

12 2 Pharmacodynamics

Diclofenac, the active component of diclofenac sodium topical solution has anti- inflammatory, anti-nociception, and antipyretic effects.

12.3 Pharmacokinetics

After topical administration to healthy human volunteers of single and multiple maximum doses of diclofenac sodium topical solution, 40 drops (approximately 1.2 mL) to each knee (80 drops total dose), the following diclofenac pharmacokinetic parameters were obtained: (see **Table 2**).

Table 2: Single-Dose (80 drops) and Multiple Dose (80 drops four times daily for 7 days) diclofenac sodium topical solution Pharmacokinetic Parameters

Pharmacokinetic Parameters	Diclofenac sodium	
	Normal Adults [N=18] (Age: 18-55 years)	Normal Adults [N=19] (Age: 18-55 years)
	Single Dose	Multiple Dose Four times daily for 7 days
AUC_{0-t}	177.5 ± 72.6 ng.h/mL	695.4 ± 348.9 ng.h/mL
AUC_{0-inf}	196.3 ± 68.5 ng.h/mL	745.2 ± 374.7 ng.h/mL
Plasma C_{max}	8.1 ± 5.9 ng/mL	19.4 ± 9.3 ng/mL
Plasma T_{max} (h)	11.0 ± 6.4	4.0 ± 6.5
Plasma $t_{1/2}$ (h)	36.7 ± 20.8	79.0 ± 38.1
K_{el} (h^{-1})	0.024 ± 0.010	0.011 ± 0.004
CL/F (L/h)	244.7 ± 84.7[1]	--

[1]Apparent total body clearance

Absorption

Diclofenac systemic exposure from diclofenac sodium topical solution application (4 times daily for 1 week) was approximately 1/3 of the diclofenac systemic exposure from the Solaraze (diclofenac topical gel) application (twice daily for 4 weeks).

Distribution

Diclofenac is more than 99% bound to human serum proteins, primarily to albumin.

Diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

Metabolism

Five diclofenac metabolites have been identified in human plasma and urine. The metabolites include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy diclofenac. The major diclofenac metabolite, 4'-hydroxy-diclofenac, has very weak pharmacologic activity. The formation of 4'-hydroxy diclofenac is primarily mediated by CPY2C9. Both diclofenac and its oxidative metabolites undergo glucuronidation or sulfation followed by biliary excretion. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CPY2C8 may also play a role in diclofenac metabolism. CYP3A4 is responsible for the formation of minor metabolites, 5-hydroxy and 3'-hydroxy-diclofenac.

Excretion

Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites.

Little or no free unchanged diclofenac is excreted in the urine.

Special Populations

Pediatric: The pharmacokinetics of diclofenac sodium topical solution has not been investigated in pediatric patients.

Race: Pharmacokinetic differences due to race have not been studied.

12.4 Platelets

The effect of diclofenac sodium topical solution on platelet function was evaluated in 10 healthy human volunteers as a sub-study of a multiple-dose pharmacokinetic study *[see Clinical Pharmacology (12.3)]*. Average (range) platelet aggregation time following stimulation with adenosine diphosphate, collagen, epinephrine and arachidonic acid was 101.3% (73.3 to 128.1), 99.8% (69.6 to 112.9), 109.9% (66.2 to 178.1) and 99.0% (15.5 to 126.6) of baseline value, respectively. These results indicate that there was no effect on platelet aggregation after application of the maximum clinical dose for 7 days *[see Clinical Pharmacology (12.3)]*.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies in mice and rats administered diclofenac sodium as a dietary constituent for 2 years resulted in no significant increases in tumor incidence at doses up to 2 mg/kg/day corresponding to approximately 0.35- and 0.7-fold (mouse and rat, respectively) of the maximum recommended human topical dose (MRHD) of diclofenac sodium topical solution (based on apparent bioavailability and body surface area comparison).

In a dermal carcinogenicity study conducted in albino mice, daily topical applications of diclofenac sodium for two years at concentrations up to 0.035% diclofenac sodium (a 43-fold lower diclofenac sodium concentration than present in diclofenac sodium topical solution) did not increase neoplasm incidence.

In a photococarcinogenicity study conducted in hairless mice, topical application of diclofenac sodium at doses up to 0.035% diclofenac sodium (a 43-fold lower diclofenac sodium concentration than present in diclofenac sodium topical solution) resulted in an earlier median time of onset of tumors.

Mutagenesis: Diclofenac was not mutagenic or clastogenic in a battery of genotoxicity tests that included the bacterial reverse mutation assay, in vitro mouse lymphoma point mutation assay, chromosomal aberration studies in Chinese hamster ovarian cells in vitro, and in vivo rat chromosomal aberration assay of bone marrow cells.

Impairment of Fertility: Fertility studies have not been conducted with diclofenac sodium topical solution. Diclofenac sodium administered to male and female rats at doses up to 4 mg/kg/day (1.4-fold of the MRHD of diclofenac sodium topical solution based on apparent bioavailability and body surface area comparison) did not affect fertility. Studies have not been conducted to determine the safety of DMSO on fertility.

13 2 Animal Toxicology and/or Pharmacology

Ocular Effects

No adverse effects were observed using indirect ophthalmoscopy after multiple-daily dermal application to rats for 26 weeks and minipigs for 52 weeks of DMSO at twice the concentration found in diclofenac sodium topical solution. Published studies of dermal or oral administration of DMSO to rabbits, dogs and pigs described refractive changes of lens curvature and cortical fibers indicative of myopic changes and/or incidences of lens opacity or discoloration when evaluated using slit-lamp biomicroscopy examination, although no ocular abnormalities were observed in rhesus monkeys during daily oral or dermal treatment with DMSO for 9 to 18 months.

14. CLINICAL STUDIES

14.1 Pivotal Studies in Osteoarthritis of the Knee

The use of diclofenac sodium topical solution for the treatment of the signs and symptoms of osteoarthritis of the knee was evaluated in two double-blind controlled trials conducted in the US and Canada, involving patients treated with diclofenac sodium topical solution at a dose of 40 drops four times a day for 12 weeks. Diclofenac sodium topical solution was compared to topical placebo (2.3% DMSO with other excipients) and/or topical vehicle solution (45.5% w/w DMSO with other excipients), applied directly to the study knee. In both trials, diclofenac sodium topical solution treatment resulted in statistically significant clinical improvement compared to placebo and/or vehicle, in all three primary efficacy variables - pain, physical function (Western Ontario and McMaster Universities LK3.1 OA Index (WOMAC) pain and physical function dimensions) and Patient Overall Health Assessment (POHA)/ Patient Global Assessment (PGA). Numerical results are summarized in Tables 3 and 4.

Table 3: Change in treatment outcomes after 12 weeks of treatment in one study of efficacy of diclofenac sodium topical solution

Efficacy Variable	Study I Mean baseline score and mean change in efficacy variables after 12 weeks of treatment			
	Mean Baseline score	Diclofenac sodium topical solution N=154	Topical placebo[1] N=155	Topical vehicle[2] N=161
WOMAC pain score (Likert 3.1, 0–20)	13	-6.0	-4.7	-4.7
WOMAC physical function (Likert 3.1, 0–68)	42	-15.7	-12.3	-12.1
POHA (0–4)	2.3	-1.0	-0.4	-0.6

[1] placebo formulation included 2.3 % DMSO
[2] vehicle formulation included 45.5 % DMSO

Table 4: Change in treatment outcomes after 12 weeks of treatment in one study of efficacy of diclofenac sodium topical solution

Efficacy Variable	Study II Mean baseline score and mean change in efficacy variables after 12 weeks of treatment		
	Mean Baseline score	Diclofenac sodium topical solution N=164	Topical vehicle[1] N=162
WOMAC pain score (Likert 3.1, 0–20)	13	-5.9	-4.4
WOMAC physical function (Likert 3.1, 0–68)	42	-15.3	-10.3
PGA (0–4)	3.1	-1.3	-1.0

[1]vehicle formulation included 45.5% DMSO

16. HOW SUPPLIED/STORAGE AND HANDLING

Diclofenac sodium topical solution is supplied as a clear, colorless to faintly pink-orange solution containing 16.05 mg of diclofenac sodium per mL of solution, in a white high density polyethylene bottle with a white low-density dropper cap.

NDC Number & Size

150 mL bottle NDC # 40032-016-61

Storage

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

17. PATIENT COUNSELING INFORMATION

See FDA-Approved patient labeling (Medication Guide and Instructions for Use).

17.1 Patient/Caregiver Instructions

Inform patients of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Encourage patients to read the NSAID Medication Guide that accompanies each prescription dispensed prior to using diclofenac sodium topical solution *[see Medication Guide and Instructions for Use]*.

17.2 Cardiovascular Effects

Diclofenac sodium topical solution, like other NSAIDs, may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, instruct patients to be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and to ask for medical advice when observing any indicative sign or symptoms. Inform patients of the importance of this follow-up *[see Warnings and Precautions (5.1)]*.

17.3 Gastrointestinal Effects

Diclofenac sodium topical solution, like other NSAIDs, may cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, inform patients to be alert for the signs and symptoms of ulceration and bleeding, and to ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Instruct patients of the importance of this follow-up *[see Warnings and Precautions (5.2)]*.

17.4 Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop therapy with diclofenac sodium topical solution and seek immediate medical therapy *[see Warnings and Precautions (5.3)]*.

17.5 Adverse Skin Reactions

Diclofenac sodium topical solution, like other NSAIDs, can cause serious systemic skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious systemic skin reactions may occur without warning, instruct patients to be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and to ask for medical advice when observing any indicative signs or symptoms *[see Warnings and Precautions (5.8)]*.

Advise patients to stop diclofenac sodium topical solution immediately if they develop any type of generalized rash and contact their physicians as soon as possible.

Diclofenac sodium topical solution can cause a localized skin reaction at the application site. Advise patients to contact their physicians as soon as possible if they develop any type of localized application site rash.

Instruct patients not to apply diclofenac sodium topical solution to open skin wounds, infections, inflammations, or exfoliative dermatitis, as it may affect absorption and reduce tolerability of the drug.

Instruct patients to wait until the area treated with diclofenac sodium topical solution is completely dry before applying sunscreen, insect repellant, lotion, moisturizer, cosmetics, or other topical medication.

Instruct patients to minimize or avoid exposure of treated knee(s) to natural or artificial sunlight.

17.6 Weight Gain and Edema

Instruct patients to promptly report to their physician signs or symptoms of unexplained weight gain or edema following treatment with diclofenac sodium topical solution *[see Warnings and Precautions (5.5)]*.

17.7 Anaphylactoid Reactions

Inform patients of the signs of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). If these occur, instruct patients to seek immediate emergency help *[see Warnings and Precautions (5.7)]*.

17.8 Effects During Pregnancy

Instruct patients who are pregnant or intending to become pregnant not to use diclofenac sodium topical solution *[see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.1)]*.

17.9 Eye Exposure

Instruct patients to avoid contact of diclofenac sodium topical solution with the eyes and mucosa. Advise patients that if eye contact occurs, immediately wash out the eye with water or saline and consult a physician if irritation persists for more than an hour.

17.10 Prevention of Secondary Exposure

Instruct patients to avoid skin-to-skin contact between other people and the knee(s) to which diclofenac sodium topical solution was applied until the knee(s) is completely dry.

Manufactured by:
Novel Laboratories, Inc.
Somerset, NJ 08873
PI0166100101
Rev. 01/2015

Medication Guide For Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

(See the end of this Medication Guide for a list of prescription NSAID medicines.)

What is the most important information I should know about medicines called Non-Steroidal Anti- Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death.

This chance increases:
- with longer use of NSAID medicines
- in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:
- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:
- taking medicines called "corticosteroids" and "anticoagulants"
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:
- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:
- different types of arthritis
- menstrual cramps and other types of short-term pain

Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?

Do not take an NSAID medicine:
- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

Tell your healthcare provider:
- about all of your medical conditions.
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**
- if you are pregnant. **NSAID medicines should not be used by pregnant women late in their pregnancy.**
- if you are breastfeeding. **Talk to your doctor.**

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

Serious side effects include:	Other side effects include:
• heart attack • stroke • high blood pressure • heart failure from body swelling (fluid retention) • kidney problems including kidney failure • bleeding and ulcers in the stomach and intestine • low red blood cells (anemia) • life-threatening skin reactions • life-threatening allergic reactions • liver problems including liver failure • asthma attacks in people who have asthma	• stomach pain • constipation • diarrhea • gas • heartburn • nausea • vomiting • dizziness

Get emergency help right away if you have any of the following symptoms:
- shortness of breath or trouble breathing
- chest pain
- slurred speech
- weakness in one part or side of your body
- swelling of the face or throat

Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:
- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms and legs, hands and feet

These are not all the side effects with NSAID medicines.
Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about Non-Steroidal Anti- Inflammatory Drugs (NSAIDs):
- Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some of these NSAID medicines are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the- counter NSAIDs for more than 10 days.

NSAID medicines that need a prescription

Generic Name	Tradename
Celecoxib	Celebrex®
Diclofenac	Flector, Cataflam®, Voltaren®, Arthrotec™ (combined with misoprostol), Diclofenac sodium topical solution
Diflunisal	Dolobid®
Etodolac	Lodine®, Lodine® XL
Fenoprofen	Nalfon®, Nalfon® 200
Flurbirofen	Ansaid®
Ibuprofen	Motrin®, Tab-Profen®, Vicoprofen®* (combined with hydrocodone), Combunox™ (combined with oxycodone)
Indomethacin	Indocin®, Indocin® SR, Indo-Lemmon™, Indomethagan™
Ketoprofen	Oruvail®
Ketorolac	Toradol®
Mefenamic Acid	Ponstel®
Meloxicam	Mobic®
Nabumetone	Relafen®
Naproxen	Naprosyn®, Anaprox®, Anaprox® DS, EC-Naproxyn®, Naprelan®, Naprapac® (copackaged with lansoprazole)
Oxaprozin	Daypro®
Piroxicam	Feldene®
Sulindac	Clinoril®
Tolmetin	Tolectin®, Tolectin DS®, Tolectin® 600

*Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAID, and is usually used for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may increase the risk of heart attack or stroke.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Instructions for Use
Diclofenac Sodium (dye kloe' fen ak soe' dee um) Topical Solution

Read the Medication Guide that comes with diclofenac sodium topical solution first. Be sure that you read, understand and follow these Instructions for Use before you use diclofenac sodium topical solution for the first time.

Important: For use on the skin only (topical). Do not get diclofenac sodium topical solution in your eyes, nose or mouth.

Before you use diclofenac sodium topical solution:
- Apply diclofenac sodium topical solution exactly as your healthcare provider tells you. Talk with your healthcare provider or pharmacist if you are not sure.
- Only use diclofenac sodium topical solution to treat pain from osteoarthritis in your knee or knees.
- Apply diclofenac sodium topical solution on clean, dry skin that does not have any cuts, infections or rashes.
- Use diclofenac sodium topical solution 4 times each day on your knee or knees as prescribed.
- Your total dose for each knee is 40 drops of diclofenac sodium topical solution, each time you use it.
- If you get diclofenac sodium topical solution in your eyes, rinse your eyes right away with water or saline. Call your healthcare provider if your eyes are irritated for more than one hour.

Steps for using diclofenac sodium topical solution:

Step 1. Wash your hands with soap and water before applying diclofenac sodium topical solution.

Step 2. Put 10 drops of diclofenac sodium topical solution **either** on your hand **or** directly on your knee (see **Figure A**).

Figure A or

Step 3. Spread diclofenac sodium topical solution evenly on the front, back and sides of your knee (see **Figures B** and **C**). Repeat steps 2 and 3, three times so that your knee is completely covered with a **total** of 40 drops of diclofenac sodium topical solution.

Figure B **Figure C**

Step 4. If your healthcare provider has prescribed diclofenac sodium topical solution for both knees, repeat steps 2 and 3 for the other knee.

After you use diclofenac sodium topical solution:

- Wash your hands with soap and water right away after applying diclofenac sodium topical solution.

Do not
- touch the treated knee or allow another person to touch the knee treated with diclofenac sodium topical solution until your knee is completely dry.
- cover your knee with clothing until your knee is completely dry
- put sunscreen, insect repellant, lotion, moisturizer, cosmetics, or other topical medicines on your knee until it is completely dry
- take a shower or a bath for at least 30 minutes after you put diclofenac sodium topical solution on your knee.
- use heating pads or cover the treated area with bandages where you have applied diclofenac sodium topical solution
- use sunlamps and tanning beds. Protect your treated knee from sunlight. Wear clothes that cover your skin if you have to be in sunlight.

How should I store diclofenac sodium topical solution?

- Store diclofenac sodium topical solution at room temperature between 68°F to 77°F (20°C to 25°C).

Keep diclofenac sodium topical solution and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Novel Laboratories, Inc.
Somerset, NJ 08873
PI0166100101
Rev. 01/2015

Medication Guide For
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

(See the end of this Medication Guide for a list of prescription NSAID medicines.)

What is the most important information I should know about medicines called Non-Steroidal Anti- Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death.

This chance increases:
- with longer use of NSAID medicines
- in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:
- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:
- taking medicines called "corticosteroids" and "anticoagulants"
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:
- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:
- different types of arthritis
- menstrual cramps and other types of short-term pain

Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?

Do not take an NSAID medicine:
- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

Tell your healthcare provider:
- about all of your medical conditions.
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**
- if you are pregnant. **NSAID medicines should not be used by pregnant women late in their pregnancy.**
- if you are breastfeeding. **Talk to your doctor.**

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

Serious side effects include:	**Other side effects include:**
• heart attack • stroke • high blood pressure • heart failure from body swelling (fluid retention) • kidney problems including kidney failure • bleeding and ulcers in the stomach and intestine • low red blood cells (anemia) • life-threatening skin reactions • life-threatening allergic reactions • liver problems including liver failure • asthma attacks in people who have asthma	• stomach pain • constipation • diarrhea • gas • heartburn • nausea • vomiting • dizziness

Get emergency help right away if you have any of the following symptoms:
- shortness of breath or trouble breathing
- chest pain
- slurred speech
- weakness in one part or side of your body
- swelling of the face or throat

Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:
- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms and legs, hands and feet

These are not all the side effects with NSAID medicines.
Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about Non-Steroidal Anti- Inflammatory Drugs (NSAIDs):
- Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some of these NSAID medicines are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the- counter NSAIDs for more than 10 days.

NSAID medicines that need a prescription

Generic Name	**Tradename**
Celecoxib	Celebrex®
Diclofenac	Flector, Cataflam®, Voltaren®, Arthrotec™ (combined with misoprostol), Diclofenac sodium topical solution
Diflunisal	Dolobid®
Etodolac	Lodine®, Lodine® XL

(b) (4)

Fenoprofen	Nalfon®, Nalfon® 200
Flurbirofen	Ansaid®
Ibuprofen	Motrin®, Tab-Profen®, Vicoprofen®* (combined with hydrocodone), Combunox™ (combined with oxycodone)
Indomethacin	Indocin®, Indocin® SR, Indo-Lemmon™, Indomethagan™
Ketoprofen	Oruvail®
Ketorolac	Toradol®
Mefenamic Acid	Ponstel®
Meloxicam	Mobic®
Nabumetone	Relafen®
Naproxen	Naprosyn®, Anaprox®, Anaprox® DS, EC-Naproxyn®, Naprelan®, Naprapac® (copackaged with lansoprazole)
Oxaprozin	Daypro®
Piroxicam	Feldene®
Sulindac	Clinoril®
Tolmetin	Tolectin®, Tolectin DS®, Tolectin® 600

*Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAID, and is usually used for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may increase the risk of heart attack or stroke.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Instructions for Use
Diclofenac Sodium (dye kloe' fen ak soe' dee um) Topical Solution

Read the Medication Guide that comes with diclofenac sodium topical solution first. Be sure that you read, understand and follow these Instructions for Use before you use diclofenac sodium topical solution for the first time.

Important: For use on the skin only (topical). Do not get diclofenac sodium topical solution in your eyes, nose or mouth.

Before you use diclofenac sodium topical solution:

- Apply diclofenac sodium topical solution exactly as your healthcare provider tells you. Talk with your healthcare provider or pharmacist if you are not sure.
- Only use diclofenac sodium topical solution to treat pain from osteoarthritis in your knee or knees.
- Apply diclofenac sodium topical solution on clean, dry skin that does not have any cuts, infections or rashes.
- Use diclofenac sodium topical solution 4 times each day on your knee or knees as prescribed.
- Your total dose for each knee is 40 drops of diclofenac sodium topical solution, each time you use it.
- If you get diclofenac sodium topical solution in your eyes, rinse your eyes right away with water or saline. Call your healthcare provider if your eyes are irritated for more than one hour.

Steps for using diclofenac sodium topical solution:

Step 1. Wash your hands with soap and water before applying diclofenac sodium topical solution.

Step 2. Put 10 drops of diclofenac sodium topical solution **either** on your hand **or** directly on your knee (see **Figure A**).

Figure A or

Step 3. Spread diclofenac sodium topical solution evenly on the front, back and sides of your knee (see **Figures B** and **C**). Repeat steps 2 and 3, three times so that your knee is completely covered with a **total** of 40 drops of diclofenac sodium topical solution.

Figure B **Figure C**

Step 4. If your healthcare provider has prescribed diclofenac sodium topical solution for both knees, repeat steps 2 and 3 for the other knee.

After you use diclofenac sodium topical solution:

- Wash your hands with soap and water right away after applying diclofenac sodium topical solution.

Do not

- touch the treated knee or allow another person to touch the knee treated with diclofenac sodium topical solution until your knee is completely dry.
- cover your knee with clothing until your knee is completely dry
- put sunscreen, insect repellant, lotion, moisturizer, cosmetics, or other topical medicines on your knee until it is completely dry
- take a shower or a bath for at least 30 minutes after you put diclofenac sodium topical solution on your knee.
- use heating pads or cover the treated area with bandages where you have applied diclofenac sodium topical solution
- use sunlamps and tanning beds. Protect your treated knee from sunlight. Wear clothes that cover your skin if you have to be in sunlight.

How should I store diclofenac sodium topical solution?

- Store diclofenac sodium topical solution at room temperature between 68°F to 77°F (20°C to 25°C).

Keep diclofenac sodium topical solution and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Novel Laboratories, Inc.
Somerset, NJ 08873
PI0166100101
Rev. 01/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 205878

LABELING REVIEW(S)

LABELING REVIEW

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

Date of This Review	09/15/2015
ANDA Number(s)	205878
Review Number	2
Applicant Name	Novel Laboratories, Inc.
Established Name & Strength(s)	Diclofenac Sodium Topical Solution 1.5% w/w
Proposed Proprietary Name	None
Submission Received Date	06/05/2015
Labeling Reviewer	Hyun Lee Hong, Pharm.D
Labeling Team Leader	Ellen Hwang, Pharm.D

Review Conclusion

☐ ACCEPTABLE – No Comments.

☒ ACCEPTABLE – Include Post Approval Comments

☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

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

☐ On Policy Alert List

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

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

NA

Submit your revised labeling electronically in final print format.

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.

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

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

NA

1.3 POST APPROVAL REVISIONS

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

1. PRESCRIBING INFORMATION
   In the HIGHLIGHTS OF PRESCRIBING INFORMATION, revise the Highlights Limitation Statement and the title line as follows:

   > These highlights do not include all the information needed to use DICLOFENAC SODIUM TOPICAL SOLUTION safely and effectively. See Full Prescribing Information for DICLOFENAC SODIUM TOPICAL SOLUTION.
   >
   > DICLOFENAC SODIUM topical solution.
   > Initial U.S. Approval:1988

2. MEDICATION GUIDE
   In the Instructions for Use, “Do Not” section: Ensure the formatting is same as the RLD, including placement of punctuation marks.

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"].

The below comments are from the labeling review C1 based on the submission dated 06/24/2013.

1. GENERAL COMMENT

Please address the patent number 8741956 that is listed in the Orange Book.

Response:

We are providing paragraph III certification for the patent number 8741956 in this amendment.
Please refer to amended patent certification enclosed in section and exclusivity statement in section for further details.

2. CONTAINER

a. Increase the prominence of the established drug name and the strength as they compete with the NDC number and net quantity.

Response:

We revised as per the Agency's comment.

b. We encourage to use a title case for the established drug name to increase readability as shown below: Diclofenac Sodium Topical Solution

Response:

We revised as per the Agency's comment.

c. There should be no space between "1.5" and "%".

Response:

We revised as per the Agency's comment.

d. Storage: Revise "excursion" to read "excursions".

Response:

We revised as per the Agency's comment.
Please refer to revised container labels enclosed in section

[m1-14-2-12-final-carton-or-container-labels] **for further details.**

Carton:

Additionally, based on marketing requirement, we are proposing carton as a secondary packaging component and have included carton labeling in Final Printed Format for Agency's review.

3. PRESCRIBING INFORMATION

a. Update your labeling to be in accord with the most recently approved Reference Listed Drug (RLD) labeling, NDA 020947/S-008, approved on October 21, 2013.

Response:

We revised as per the Agency's comment.

b. HIGHLIGHTS OF PRESCRIBING INFORMATION: The product title, immediately above the initial U.S. approval date, should be revised as below to comply with the PLR format requirements.
DICLOFENAC sodium topical solution, 1.5% w/w

Response:

We revised as per the Agency's comment.
Please refer to revised package insert in and enclosed in section *[m1-14-2-2-final-Package-Insert]* for further details.

4. MEDICATION GUIDE

a. Submit a copy of the stand-alone Medication Guide in final printed format for our review.

Response:

We are submitting stand-alone Medication Guide in final printed format for review.

b. Comment how you would provide a sufficient number of Medication Guides.

Response:

In line with Reference Listed Drug Product, Novel will provide one medication guide contained within the Prescribing information with each 150 mL Bottle.

Submit your revised labeling electronically in final print format.

Response:

We are submitting revised Labeling electronically in final print format.
Please refer to revised , and enclosed in section 1.14.2 of Module 1.
To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.
Response:
Please refer to the side-by-side comparison of our proposed labeling with the reference listed drug labeling with all differences annotated and explained.

Reviewer Comments:

The applicant's response to C1 review comments are acceptable except for the revised title line in the HIGHLIGHTS OF PRESCRIBING INFORMATION. We will ask for the title line to be further revised.

Note, the firm provided PIII certification for the patent number 8741956 initially; the firm then submitted patent amendment to convert all PIII certifications to PIV certifications in 06/05/2015 (Sequence 0003) submission.

Also, Carton Label, which was not included in the original submission dated 06/24/2013, is included in this submission and is reviewed.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
YES

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

- New labeling (carton label) included: "… based on marketing requirement, we are proposing carton as a secondary packaging component and have included carton labeling in Final Printed Format for Agency's review.


(b) (4)

Currently Proposed	
Assessment	**Container and carton labels are acceptable.**

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:
None

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's Repository files? 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.

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient 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, also enter ANDA model labeling information.)

NDA# /Supplement# (S-000 if original): 020947/S-008

Supplement Approval Date: 10/21/2013

Proprietary Name: Pennsaid®

Established Name: Diclofenac Sodium topical solution

Description of Supplement: This "Prior Approval" supplemental new drug application proposes labeling revisions intended to minimize medication errors and ensure that Pennsaid labeling provides adequate information for its safe and effective use.

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

ANDA#/Supplement# (S-000 if original): NA

Supplement Approval Date: NA

Proprietary Name: NA

Established Name: NA

Description of Supplement: NA

☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** NA

☐ **OTHER (Describe):** NA

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**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

1. PRESCRIBING INFORMATION
   In the HIGHLIGHTS OF PRESCRIBING INFORMATION, revise the Highlights Limitation Statement and the title line as follows:

   These highlights do not include all the information needed to use DICLOFENAC SODIUM TOPICAL

SOLUTION safely and effectively. See Full Prescribing Information for DICLOFENAC SODIUM TOPICAL SOLUTION.

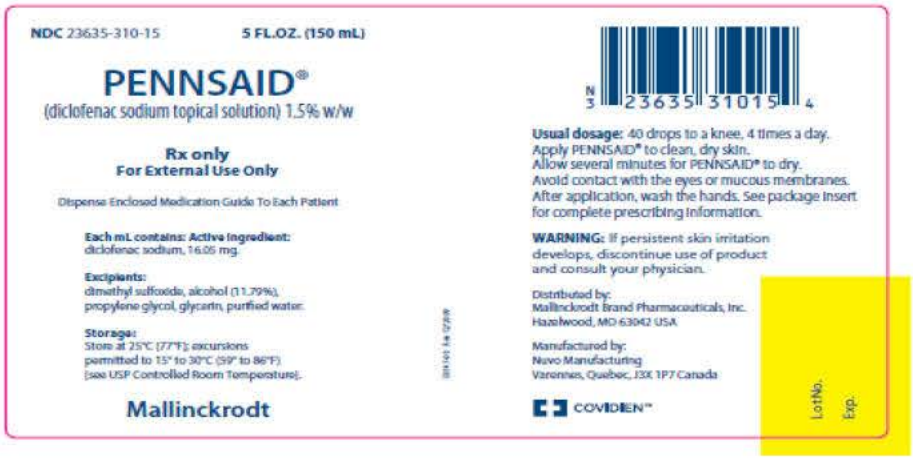
DICLOFENAC SODIUM topical solution.
Initial U.S. Approval:1988

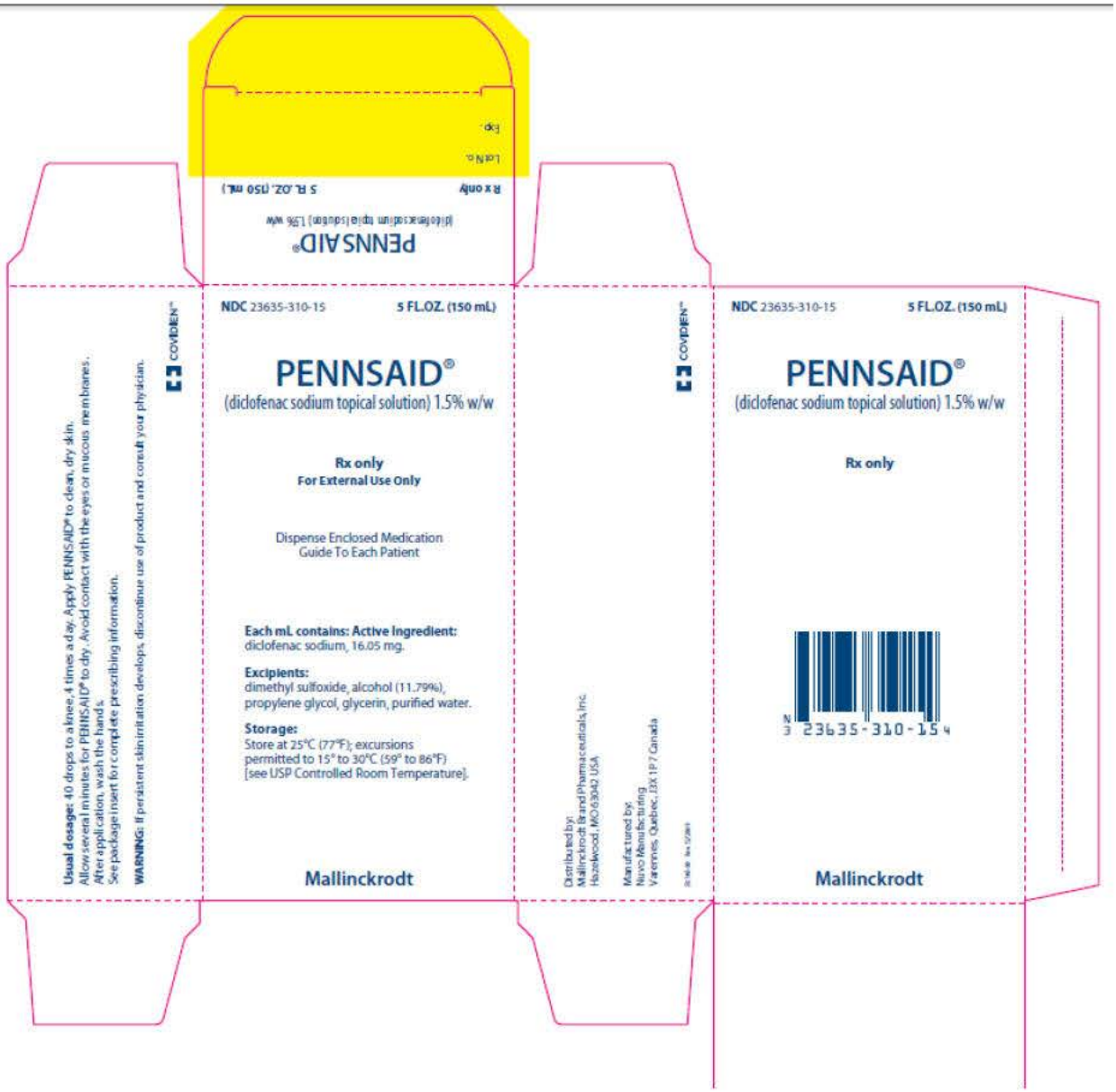
2. MEDICATION GUIDE

In the Instructions for Use, "Do Not" section: Ensure the formatting is same as the RLD, including placement of punctuation marks.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: Penssaid NDA 020947 AR-4, 02/26/2014]





3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results

	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	9/15/2015	No	NA	NA
PF	9/15/2015	No	NA	NA

Reviewer Comments:

NA

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 9/15/2015.

Table 3 provides Orange Book patents for the Model Labeling 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
8217078	07/10/2029	U-1248	USE OF TOPICAL DICLOFENAC ON THE KNEE AND A SECOND TOPICAL MEDICATION ON THE SAME KNEE	PIV	06/05/2015	None
8546450	08/09/2030	U-1436	USE OF TOPICAL DICLOFENAC ON THE KNEE AND A SECOND TOPICAL AGENT SELECTED FROM SUNSCREEN AND INSECT REPELLANT	PIV	06/05/2015	None
8546450	08/09/2030	U-1435	COMBINATION USE OF TOPICAL DICLOFENAC ON THE KNEE AN DADMINISTRATION OF AN ORAL NSAID.	PIV	06/05/2015	None
8618164	07/10/2029	U-1477	USE OF TOPICAL DICLOFENAC ON THE KNEE AND A SECOND TOPICAL PRESCRIPTION MEDICATION ON THE SAME KNEE	PIV	06/05/2015	None
8741956	07/10/2029	U-1435	COMBINATION USE OF TOPICAL DICLOFENAC ON THE KNEE AN DADMINISTRATION OF AN ORAL NSAID.	PIV	06/05/2015	None

Reviewer Assessment:

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

Reviewer Comments:

The firm first submitted PIII patent certifications for all patents in 06/05/2015 submission (Sequence # 0002). Patent amendment to convert all PIII certifications to PIV certifications were submitted on 06/05/2015 (Sequence # 0003).

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
NA					

Reviewer Assessment:

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

Reviewer Comments:

NA

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? **YES**
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 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Diclofenac sodium topical solution is supplied as a clear, colorless to faintly pink-orange solution containing 16.05 mg of diclofenac sodium per mL of solution, in a white high density polyethylene bottle with a white low-density dropper cap. **NDC Number & Size** 150 mL bottle (b) (4)	Diclofenac sodium topical solution is supplied as a clear, colorless to faintly pink-orange solution containing 16.05 mg of diclofenac sodium per mL of solution, in a white high density polyethylene bottle with a white low-density dropper cap. NDC Number & Size 150 mL bottle NDC # 40032-016-61	NDC number has been changed. Acceptable.

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**

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:

None

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

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

Reviewer Comments:
None

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.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	Bottles of 150 mL	06/05/2015	Satisfactory
Blister	NA	NA	NA	NA
Carton	Final	1 x 150 mL	06/05/2015	Satisfactory
(Other – specify)	NA	NA	NA	NA
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	Final	01/2015	06/05/2015	Satisfactory
Medication Guide	Final	01/2015	06/05/2015	Satisfactory
Patient Information	NA	NA	NA	NA
SPL Data Elements		04/2015	06/05/2015	Satisfactory

***** This document contains proprietary information that cannot be released to the public*****

LABELING REVIEW

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

Date of This Review	11/19/14
ANDA Application Number	205878
Review Cycle Number	1
Applicant Name	Novel Laboratories, Inc.
Established Name	Diclofenac Sodium Topical Solution
Strength(s)	1.5% w/w
Proposed Proprietary Name	NA
DARRTS Received Date	6/24/13 2/3/14
Labeling Reviewer	Ellen Hwang
Labeling Team Leader	John Grace

Review Conclusion

☐ No Comments – The Labels and Labeling are ready for : NA

☒ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for the Letter to Applicant

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

LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

1. GENERAL COMMENT
   Please address the patent number 8741956 that is listed in the Orange Book.

2. CONTAINER
   a. Increase the prominence of the established drug name and the strength as they compete with the NDC number and net quantity.
   b. We encourage you to use a title case for the established drug name to increase readability as shown below:

      Diclofenac Sodium Topical Solution

   c. There should be no space between "1.5" and "%".
   d. Storage: Revise "excursion" to read "excursions".

3. PRESCRIBING INFORMATION
   a. Update your labeling to be in accord with the most recently approved Reference Listed Drug (RLD) labeling, NDA 020947/S-008, approved on October 21, 2013.
   b. HIGHLIGHTS OF PRESCRIBING INFORMATION: The product title, immediately above the initial U.S. approval date, should be revised as below to comply with the PLR format requirements.

      DICLOFENAC sodium topical solution, 1.5% w/w

4. MEDICATION GUIDE
   a. Submit a copy of the stand-alone Medication Guide in final printed format for our review.
   b. Comment how you would provide a sufficient number of Medication Guides.

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug's labeling with all differences annotated and explained.

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

1. MODEL LABELING FOR ANDA

1.1 MODEL CONTAINER LABELS FOR ANDA
1.2 PRESCRIBING INFORMATION MODEL LABELING

2. MATERIAL ANALYSIS

2.1 GENERAL

2.1.1 Established Name Assessment
2.1.2 United States Pharmacopeia (USP) & Pharmacopeia Forum (PF)

2.2 CONTAINER LABEL

2.2.1 Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors
2.2.2 Other Container Label Considerations
2.2.3 Container Label for Small Volume Parenteral Solutions:
2.2.4 Container Label for Sterile Solid Injectable:
2.2.5 Container Label for Pharmacy Bulk Package:
2.2.6 Unit Dose Blister Labels
2.2.7 Over The Counter (OTC) Label
2.2.8 Presentation of Manufacturer/Distributor/Packer on Labeling
2.2.9 Description of the Container/Closure
2.2.10 Storage and Dispensing Recommendations
2.2.11 Related Applications Containing the Same Active Ingredient
2.2.12 Comparison of ANDA Inactive Ingredients that Require Special Labeling Statements to Model

2.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING
2.4 PRESCRIBING INFORMATION

2.4.1 Patents and Exclusivities
2.4.2 Comparison of ANDA Inactive Ingredients to Model Labeling (Topical And Oral Products Only)
2.4.3 Comparison of ANDA Inactive Ingredients to Model Labeling (Ophthalmic, Injectable, And Otic Products Only)
2.4.4 How Supplied Section
2.4.5 Previous Labeling Reviews for ANDA and/or Related Correspondence

2.5 MEDICATION GUIDE
2.6 OTHER PATIENT LABELING
2.7 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

3.1 ANDA LABELS AND LABELING SUBMITTED

4. QUESTIONS AND COMMENTS FOR CLICK HERE TO ENTER TEXT.
5. SPECIAL CONSIDERATIONS
6. POST APPROVAL REVISIONS

1. MODEL LABELING FOR ANDA

Our review is based on the following model labels and labeling used for comparison to the submitted ANDA labeling.

1.1 MODEL CONTAINER LABELS FOR ANDA

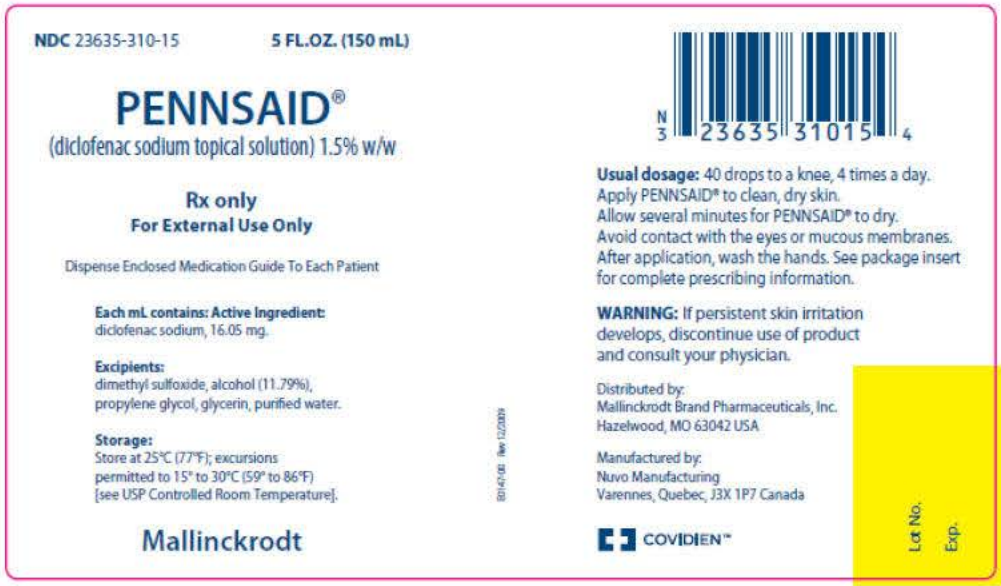
In Table 1 below, check all sources for Model container labels and carton labeling (secondary packaging) that applies.

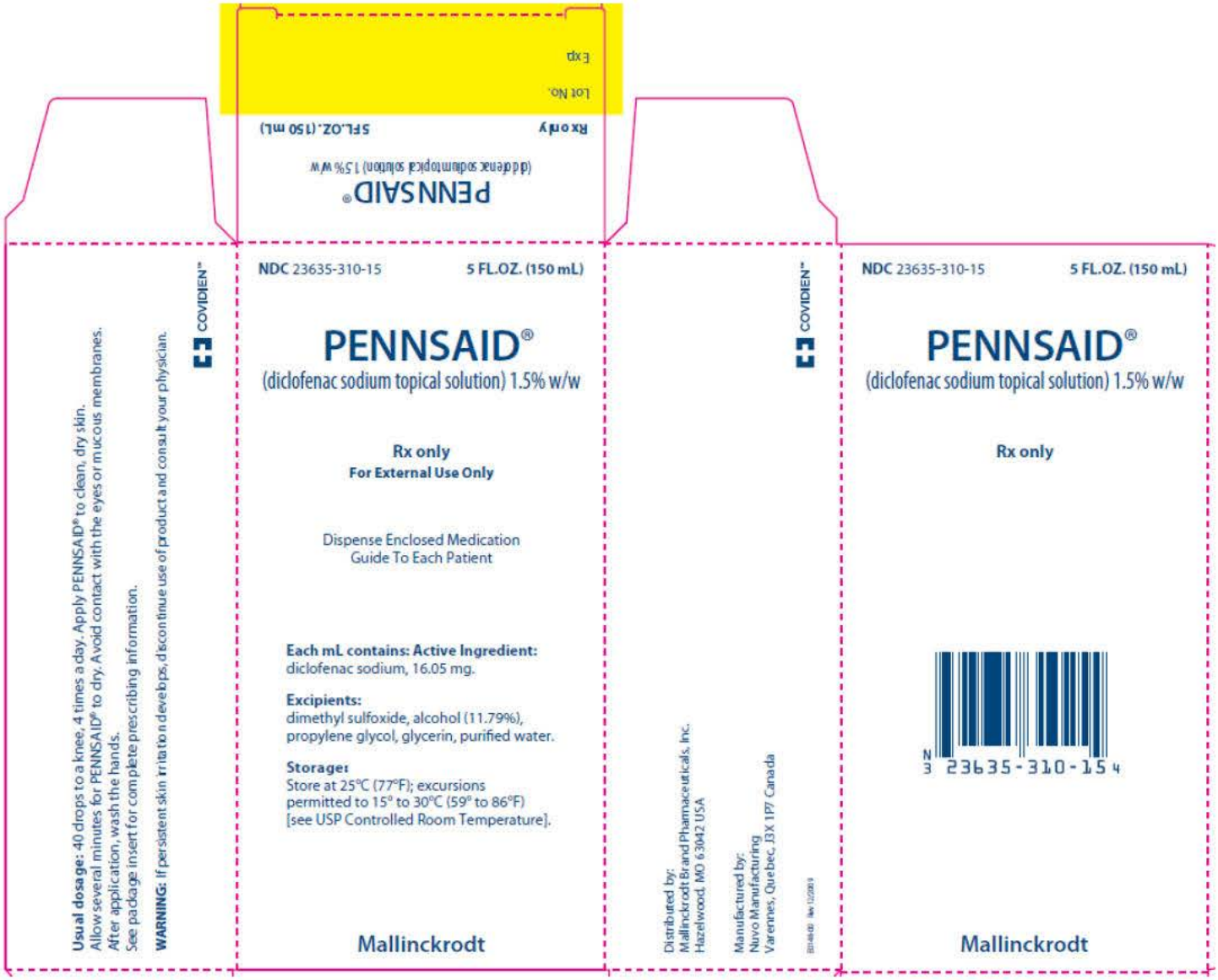
Container labels are assessed in section 2.2.

Carton labeling (outer or secondary packaging) is assessed in section 2.3.

Table 1: Review Model Labeling for Container Label and Carton Labeling (Check all sources that apply)	
Source	**Date of source document (i.e. supplement approval date, annual report date)**
☐ **drugs@fda** Click here to enter text.	Click here to enter text.
☐ **DARRTS** Click here to enter text.	Click here to enter text.
☐ **DailyMed** Click here to enter text.	Click here to enter text.
☒ **Annual Report -4**	**2/26/14**
☐ **Other** Click here to enter text.	Click here to enter text.

Model labels and carton labeling. [Insert or paste images below]





1.2 PRESCRIBING INFORMATION MODEL LABELING

The review model labels and labeling used for comparison to the submitted ANDA labeling are described in Table 2.

Prescribing information is assessed in section 2.4.

Table 2: Review Model Labeling for Prescribing Information and Patient Labeling(Check all that apply)		
☐ MOST RECENTLY APPROVED REFERENCE LISTED DRUG		
NDA 020947	Proprietary Name: PENNSAID	Approval date: 3/25/10
S- 001 & 002	Description of Supplement: S-001 provides for editorial changes to the package insert and Medication Guide including changes to reflect the Transfer of Ownership of NDA 020947 that was effective November 10, 2010. S-002 provides for the modifications of the approved REMS to change the company name and logo on the REMS, REMS Supporting Document, and Medication Guide to reflect the Transfer of Ownership of NDA 020947, that was effective on November 10, 2009.	

Table 2: Review Model Labeling for Prescribing Information and Patient Labeling(Check all that apply)
☐ BPCA or PREA TEMPLATE
☐ OTHER (Describe): Click here to enter text.

2. MATERIAL ANALYSIS

The results for each material reviewed in this section provide the basis for the labeling comments to the applicant (Page 2).

2.1 GENERAL

2.1.1 Established Name Assessment

We compared the established names of this ANDA, the Model Labeling and the USP to determine if the established name presented on the labeling is acceptable.

Table 3: Comparison of Established Names

Model Labeling: **diclofenac sodium topical solution**
ANDA: **Diclofenac sodium topical solution**
USP: NA

Reviewer Assessment:

Is the established name for ANDA acceptable? **YES**
Is the established (and proprietary name) displayed in a manner consistent 21 CFR 201.10? **YES**
Is title case used in established name? **NO**
Is established name on list of name pairs that use Tall Man lettering found on FDA webpage? **NO**

- If yes does labeling comply with Tall Man lettering recommendations? **NA**

Reviewer Comments: Title case should be used for the container label.

2.1.2 United States Pharmacopeia (USP) & Pharmacopeia Forum (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph and determined how the monograph impacts the ANDA labeling with respect to packaging and storage. The results of this search are provided in Table 4.

Table 4: USP and PF Search Results

	Date Searched	Monograph? YES or NO	Labeling statements found NA if no monograph
USP	11/19/2014	**NO**	NA
PF	11/19/2014	**NO**	NA

Reviewer Assessment:

Does the ANDA labeling require revision or is clarification needed from other review disciplines based on the comparison of USP or PF label/labeling requirements? **NA**
Do required labeling statements appear on/in the ANDA labeling? **NA**
Are the USP packaging and storage recommendations reflected in the labels and labeling? **NA**

Reviewer Comments: none

2.2 CONTAINER LABEL

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

2.2.1 Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors

We used the draft Guidance for Industry titled Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors for the following assessment.

Reviewer Assessment:

Does the following information appear as the most prominent information on the Principal Display Panel?
- Proprietary name? **NA**
- Established name? **YES**
- Product strength? **YES**
- Route(s) of administration (other than oral)? **YES**
- Warnings (if any) or cautionary statements (if any)? **YES**

Does the following information appear of lesser prominence on the Principal Display Panel?
- Rx-only statement? **YES**
- Net quantity statement? **NO**
- Manufacturer logo? **YES**

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: The NDC and net quantity statement appears equally prominent as the strength.

2.2.2 Other Container Label Considerations

Reviewer Assessment:

Does this container meet the "too small" exemption found in 21 CFR 201.10(i)? **NO**
Are all abbreviations acceptable? (i.e., mg, mcg, HCl)? **YES**
Are multiple strengths differentiated by use of different color or other acceptable means? **NA**
Does the net quantity statement appear separate from and less prominent than the statement of strength (e.g., not highlighted, boxed, or bolded)? **NO**
Are the rules governing leading and terminal zeroes, decimals, and commas followed? **YES**
If other than oral use, is the route of administration correctly described? **YES**
Are all required warning statements that appear on Model Label properly displayed? **YES**
Is space provided to display expiration date properly? **YES**
Is bar code properly displayed per 21 CFR 201.25(c)(2)? **YES**
Is NDC properly displayed? **YES**
Is controlled substance symbol properly displayed? **NA**
Is the "Usual Dosage" on side panel and is it acceptable? **YES**
Is a product strength equivalency statement on side panel? **YES**
Are the Medication Guide Pharmacist instructions included per 208.24(d)? **YES**

Reviewer Comments: Some editorial changes should be made. See comments.

2.2.3 Container Label for Small Volume Parenteral Solutions:

Is container for small volume parenteral solution? **NO**
If YES go to Reviewer Assessment below, if NO go to section 2.2.4.

Reviewer Assessment:

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP, General Chapter <1> Injection? **NA**
If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength?**NA**
Are inactive ingredients listed on label as required by regulations? **NA**

Reviewer Comments: none

2.2.4 Container Label for Sterile Solid Injectable:

Is container for sterile solid injectable? **NO**
If YES go to Reviewer Assessment below, if NO go to section 2.2.5.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **NA**
Are instructions for reconstituting the product and the resultant concentration if space permits? **NA**
Are inactive ingredients listed on label as required by regulations? **NA**

Reviewer Comments: none

2.2.5 Container Label for Pharmacy Bulk Package:

Is container a Pharmacy Bulk Package? **NO**
If YES go to Reviewer Assessment below, if NO go to section 2.2.6.

Reviewer Assessment:

Is there a prominent, boxed declaration reading "Pharmacy Bulk Package – Not for Direct Infusion" on the principal display panel following the expression of strength? **NA**
Does the container label include graduation marks? **NA**
Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **NA**
Are inactive ingredients listed on label as required by regulations? **NA**

Reviewer Comments: none

2.2.6 Unit Dose Blister Labels

Is container a Unit Dose Blister Pack? **NO**
If YES go to Reviewer Assessment below, if NO go to section 2.2.7

Reviewer Assessment:

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **NA**
Do proprietary name, established name, strength, lot number, expiration date, bar code, and manufacturer appear on each blister cell? **NA**
Does the established name describe only one unit (e.g. "tablet" rather than "tablets")? **NA**

Reviewer Comments: none

2.2.7 Over The Counter (OTC) Label

Is this label for an OTC product? **NO**
If YES go to Reviewer Assessment below, if NO go to section 2.2.8

Reviewer Assessment:

Is Drug Facts Labeling format acceptable per 21 CFR 201.66? **NA**
Does packaging meet the requirements for Special Packaging under the Poison Prevention Act and defined per 16 CFR 1700? **NA**
Does packaging meet the tamper-evident requirements 21 CFR 211.132? **NA**
Does "Questions?" have a toll-free number no less than size 6 pt. font per 21 CFR 201.66(c)(9) or "1-800-FDA-1088" [21 CFR 201.66 (c)(5)(vii)]? **NA**
Did firm submit a Labeling Format Information Table to evaluate the font size? **NA**

Reviewer Comments: none

2.2.8 Presentation of Manufacturer/Distributor/Packer on Labeling

We compared the name and address of the manufacturer of this product to the name and address listed on the labels and labeling to determine if the labeling statements are consistent with the regulations (21 CFR 201.1). Table 5 provides a description of this comparison. [NOTE: This presentation/assessment may apply to other labeling submitted].

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements	
Name and Address of Facility ANDA Manufactured	Novel Laboratories, Inc. 400 Campus Drive Somerset NJ 08873
Name and Address on ANDA Labels	Manufactured By: Novel Laboratories, Inc. Somerset, NJ 08873 USA
Name and Address on ANDA Labeling	Manufactured by: Novel Laboratories, Inc. Somerset, NJ 08873

Reviewer Assessment:

Does the labeling have the required qualifiers per 21 CFR 201.1? **YES**
For Foreign manufacturers, does the labeling have the country of origin? **NA**
For Foreign manufacturers, does the labeling have a US contact/distributor? **NA**

Reviewer Comments: Acceptable

2.2.9 Description of the Container/Closure

We evaluated the container/closure system of this product to determine if special child-resistant packaging is required based on packaging configuration. Additionally, we evaluated other aspects of the container closure that relate to the dosage form, product formulation, and product class. Below is a description of the container/closure for the ANDA product.

Reviewer Assessment:

Does the container require a child-resistant closure (CRC) as described in the Poison Prevention Act and regulations? **NO**
Describe container closure in **Reviewer Comments** text box (e.g. 30s CRC, 100s non-CRC)
If the closure is not child-resistant, does the container or carton require a labeling statement warning the product is not child-resistant? **NO**
Are the tamper evident requirements met for OTC and Controlled Substances? **NA**
Does this ophthalmic products cap color match the American Academy of Ophthalmology (AAO) packaging color-coding scheme? **NA**
For parenteral products:
Is there text on the cap/ferrule overseal of this injectable product? **NA**
If YES, does text comply with the recommendations in USP General Chapter <1>? **NA**
What is the cap and ferrule color? Click here to enter text.
NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Comment This product is non-CRC.

2.2.10 Storage and Dispensing Recommendations

We compared the storage and dispensing statements that appear on the ANDA labels to the model labeling and USP to confirm the statements do not conflict and the format is consistent with USP and OGD standards (see Table 6). [NOTE: This assessment may apply to other labeling submitted]

Table 6: Model Labeling and ANDA Storage/Dispensing Recommendations
Model Labeling
Insert – Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].
Container – Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Carton – Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].
ANDA
Insert - Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].
Container - Store at 25°C (77°F); excursion permitted to 15° – 30° C (59° – 86°F) [See USP Controlled Room Temperature].
USP
NA

Reviewer Assessment:

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**
Are the storage temperature recommendations acceptable? **YES**
Does the temperature statement conform to the OGD format for controlled room temperature?**YES**

Reviewer Comments: Acceptable

2.2.11 Related Applications Containing the Same Active Ingredient

We evaluated the following applications that contain the same active ingredient from the same applicant to determine if the labels and labeling are adequately differentiated from one another.

Reviewer Assessment:

Are the labels and labeling of these products differentiated to avoid selection errors? **YES**

Reviewer Comments: There is a pending ANDA 207282 for Diclofenac Sodium Delayed Release Tablet and Misoprostol Tablet, 75 mg and 200 mcg. It does not appear to cause medication selection errors.

2.2.12 Comparison of ANDA Inactive Ingredients that Require Special Labeling Statements to Model

We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling. Specific inactive ingredients that require special warnings, precautions, or label/labeling statements are in Table 7.

NOTE: This section is for assessing required statements on container labels only for both prescription and OTC drug products. Required statements for prescribing information is assessed for Prescription drug products in Sections 2.4.2 and 2.4.3

Table 7: Inactive Ingredients contained in Model Product and ANDA that require special labeling statements	
Model Labeling	**ANDA**
none	none

Reviewer Assessment:

Do any of the inactive ingredients need a label statement required by regulations? **NO**
If the labeling includes "Does not contain …" statements – Has this statement been verified by chemistry? **NA**

Reviewer Comments: none

2.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Reviewer Assessment:

Do all required label statements and safety considerations assessed above for CONTAINER labels appear on the carton? NA
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**
For unit dose blister that are not child-resistant is there a statement indicating the package is not child-resistant. For example, "This package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be used"? **NA**
If country of origin is not on Container, does appear on outer packaging labeling? **NA**

Reviewer Comments: none

2.4 PRESCRIBING INFORMATION

Reviewer Assessment:

Are the labeling contained in the submission the same as the review model labeling? **NA**
Are the differences allowed under 21 CFR 314.94(a)(8)? **NA**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **NO**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments: The RLD model labeling used is outdated. The firm needs to update the labeling.

2.4.1 Patents and Exclusivities

Are there any unexpired patents or marketing exclusivities for Model Labeling? **YES**

If YES go to the table and assessments below.
If NO go to section 2.4.2.
Table 8 describes how the applicant certified to the Orange Book patent(s) for the Model Labeling and how this certification impacts the ANDA labels and labeling. For applications that have no patents N/A is entered in the patent number column.

Table 8: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	How Applicant Filed	Labeling Impact
8217078	Jul 10, 2029	U-1248	USE OF TOPICAL DICLOFENAC ON THE KNEE AND A SECOND TOPICAL MEDICATION ON THE SAME KNEE	PIII	none
8546450	Aug 9, 2030	U-1436	USE OF TOPICAL DICLOFENAC ON THE KNEE AND A SECOND TOPICAL AGENT SELECTED FROM SUNSCREEN AND INSECT REPELLANT	PIII	none
8546450	Aug 9, 2030	U-1435	COMBINATION USE OF TOPICAL DICLOFENAC ON THE KNEE AN DADMINISTRATION OF AN ORAL NSAID.	PIII	none
8618164	Jul 10, 2029	U-1477	USE OF TOPICAL DICLOFENAC ON THE KNEE AND A SECOND TOPICAL PRESCRIPTION MEDICATION ON THE SAME KNEE	PIII	none
8741956	Jul 10, 2029	U-1435	Refer above	not filed	unknown

Reviewer Assessment:

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

Reviewer Comments: Patent number 8741956 has not been addressed by the firm.

Table 9 describes how the expiration of the Orange Book exclusivities for the Model Labeling impacts the ANDA labels and labeling. For applications that have no exclusivities N/A is entered in the Exclusivity Code column.

Table 9: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling			
Exclusivity Code	**Exclusivity Code Definition**	**Exclusivity Expiration**	**Labeling Impact**
NA	Click here to enter text.	Click here to enter text.	Click here to enter text.

Reviewer Assessment:

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

Reviewer Comments: none

2.4.2 Comparison of ANDA Inactive Ingredients to Model Labeling (Topical And Oral Products Only)

Is submitted labeling for a topical or oral product? **YES**

If YES, complete tables 10a, 10b, and 10c along with assessment below.
If NO, go to section 2.4.3.
We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

In Table 10a we compared the lists of inactive ingredients in the DESCRIPTION sections of the Model labeling and the ANDA labeling.

Table 10a: Inactive Ingredients contained in Model Product and ANDA from Description section

Model Labeling Inactive Ingredients	ANDA Inactive Ingredients
dimethyl sulfoxide USP (DMSO, 45.5% w/w), propylene glycol, alcohol, glycerin and purified water.	dimethyl sulfoxide USP (DMSO, 45.5% w/w), propylene glycol, alcohol, glycerin and purified water.

In Table 10b we compared the lists of inactive ingredients in the DESCRIPTION section and Components and Components statements in ANDA.

Table 10b: Comparison Inactive Ingredients contained in ANDA Description section and Components and Composition

Description Section	Components and Composition			
	Item #	Ingredients	Qty in % (w/w)	Function
dimethyl sulfoxide USP (DMSO, 45.5% w/w), propylene glycol, alcohol, glycerin and purified water.	1.	Diclofenac Sodium, USP	1.5%	Active
	2.	Dimethyl Sulfoxide, USP	45.50 %	(b) (4)
	3.	Ethyl Alcohol (b) (4) (b) (4)	(b) (4)	
	4.	Propylene Glycol, USP		
	5.	Glycerin (b) (4)		
	6.	Purified Water, USP		
		Total	100.00 %	

We noted any specific inactive ingredients that require special warnings, precautions, or label/labeling statements are listed in Table 10c.for Model and ANDA

Table 10c Specific inactive ingredients that require special warnings, precautions

Model Labeling Inactive Ingredients	ANDA Inactive Ingredients
none	none

Reviewer Assessment:

Is the DESCRIPTION section of the labeling consistent with the component and composition statement contained in the ANDA? **YES**
Are the required labeling statements present in the ANDA labeling? **NA**

Reviewer Comments: Acceptable

2.4.3 Comparison of ANDA Inactive Ingredients to Model Labeling (Ophthalmic, Injectable, And Otic Products Only)

Is submitted labeling for an ophthalmic, injectable, or an otic product? **NO**

If YES, complete tables 11a, 11b, and 11c along with the assessment below.
If NO go to section 2.4.4.

We compared the list of inactive ingredients and the amount of the inactive ingredient contained in this product as to those contained in the Model Labeling to determine if all components and composition are the same and if they are listed accurately in the labeling.

In Table 11a we compared the lists of inactive ingredients in the DESCRIPTION sections of the Model labeling and the ANDA labeling.

Table 11a: Inactive Ingredients contained in Model Product and ANDA from Description section

Model Labeling Inactive Ingredients	ANDA Inactive Ingredients
Click here to enter text.	Click here to enter text.

In Table 11b we compared the lists of inactive ingredients in the DESCRIPTION section and Components and Components statements in ANDA.

Table 11b: Comparison Inactive Ingredients contained in ANDA Description section and Components and Composition

Description Section	Components and Composition
Click here to enter text.	Click here to enter text.

We noted any specific inactive ingredients that require special warnings, precautions, or label/labeling statements are listed in Table 11c.for Model and ANDA

Table 11c Specific inactive ingredients that require special warnings, precautions

Model Labeling Inactive Ingredients	ANDA Inactive Ingredients
Click here to enter text.	Click here to enter text.

Reviewer Assessment:

Is the DESCRIPTION section of the labeling consistent with the component and composition statement contained in the application? **NA**
Are the required labeling statements present in the ANDA labeling? **NA**
If the labeling includes "Does not contain …" statements – Has this statement been verified by chemistry? **NA**

Reviewer Comments: none

2.4.4 How Supplied Section

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as coring configuration, are highlighted in Table 12 and will be referred to the appropriate review discipline for evaluation. Additionally, we evaluated if the text contained in the HOW SUPPLIED section is accurate based

on the ANDA finished product description.

Table 12: Comparison of Model Labeling to ANDA finished product	
Model Labeling	**PENNSAID is supplied as a clear, colorless to faintly pink-orange solution containing 16.05 mg of diclofenac sodium per mL of solution, in a white high density polyethylene bottle with a white low-density dropper cap.** **NDC Number & Size** **15 mL bottle (physician sample) NDC # 23635-310-11** **150 mL bottle NDC # 23635-310-15**
ANDA	**Quality: How supplied: Diclofenac sodium topical solution is supplied as a clear, colorless to faintly pink-orange solution containing 16.05 mg of diclofenac sodium per mL of solution, in a white high density polyethylene bottle with a white low-density dropper cap. NDC Number & Size** **150 mL bottle NDC #** (b) (4)

Reviewer Assessment:

Is the description (scoring, color, and imprint) of the finished product accurate in the HOW SUPPLIED section of the insert? **YES**
Are the packaging sizes acceptable as compared to the Model Labeling? **YES**
Does the packaging configuration require the addition or deletion of labeling statements based on the comparison to Model Labeling and/or stability data? **NO**

Reviewer Comments: Acceptable

2.4.5 Previous Labeling Reviews for ANDA and/or Related Correspondence

Table 13 contains a listing of previously completed OGD labeling reviews and other correspondence relating to this application from DARRTS. We reviewed this information to determine if previous labeling comments were addressed by the applicant or if there is new information that may impact the labeling.

Table 13: Completed Labeling Reviews or Other Correspondence for Application Under Review		
Search Date	**Finalized Date of DARRTS Document**	**Were Previous Comments Addressed? (Yes/No/Explain)**
11/19/14	**NA**	**NA: This is the 1st cycle.**

2.5 MEDICATION GUIDE

We evaluated the medication guide to ensure the text is the same as the model labeling. We also ensured the directive appears on the container and carton labeling.

Reviewer Assessment:

Does the format meet the requirements of 21 CFR 208.20? **YES**
Are the dispensing and distributions requirements of 21 CFR 208.24 met? **NO**
Has the Applicant committed to provide a sufficient number of medication guides? **NO**
Is the phonetic spelling of the proprietary or established name present? **NO**
Is the dispensing directive present on the container and carton labeling? **YES**
Is FDA 1-800-FDA-1088 phone number included? **YES**

Reviewer Comments: There is no phonetic spelling of the drug name since the tile is for "Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)" which is consistent with the RLD. The firm should submit information on how to provide a sufficient number of MGs.

2.6 OTHER PATIENT LABELING

None

2.7 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

We evaluated the SPL data elements to ensure they are consistent with the information submitted in the ANDA. Additionally, we compared the size of the model and ANDA tablet/capsule size to determine if the size of the ANDA tablet/capsule poses a safety risk or require a labeling statement (see Table 14).

Table 14: Comparison of Model and ANDA Tablet/Capsule Size

Model Labeling	Click here to enter text.
ANDA Labeling	Click here to enter text.

Reviewer Assessment:

Are the data elements consistent with the information submitted in the ANDA? **YES**
Is the tablet/capsule size similar to the RLD? **NA**

Reviewer Comments: Acceptable

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 15 and 16 provide a summary of recommendations for each material analyzed in this review.

Table 15: Review Summary of Container Label and Carton Labeling			
	Packaging Sizes	Submission Date	Recommendation
Container ☒ Draft ☐ FPL	150 mL bottle	6/24/13	☐ Satisfactory ☒ Revise
Table 16 Review Summary of Prescribing Information and Patient Labeling			
	Revision Date and/or code	Submission Date	Recommendation
Prescribing Info ☒ Draft ☐ FPL	6/13	6/24/13	☐ Satisfactory ☒ Revise
Medication Guide ☒ Draft ☐ FPL	6/13	6/24/13	☒ Satisfactory ☐ Revise
SPL ☒	5/13	6/24/13	☒ Satisfactory ☐ Revise

3.1 ANDA LABELS AND LABELING SUBMITTED

Please see "205878 Labeling.pdf" for the submitted labeling on 6/24/13.

4. QUESTIONS AND COMMENTS FOR : NA

During the course of this review, we sought clarification on the following issues to determine if a label or labeling revision is necessary.

Reviewer Assessment:

Does the response(s) received require a label and/or labeling revision? **NA**
Reviewer Comments: none

Appears This Way On Original

5. SPECIAL CONSIDERATIONS

None

6. POST APPROVAL REVISIONS

NA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 205878

CHEMISTRY REVIEW(S)

CMC Approvable as of 30-Nov-2015

ANDA 205878

(Review #2)

Diclofenac Sodium Topical Solution, 1.5% w/w

Novel Laboratories, Inc.

Andrei Ponta, Ph.D.
OPS ANDA Review Squad

Table of Contents

Table of Contents i

Chemistry Review Data Sheet 1

1. ANDA #: 205878 1
2. REVIEW #: 2 1
3. REVIEW DATE: 25-Oct-2015 1
4. REVIEWER: Andrei Ponta, Ph.D. 1
5. PREVIOUS DOCUMENTS: 1
6. SUBMISSION(S) BEING REVIEWED: 1
7. NAME & ADDRESS OF APPLICANT: 1
8. DRUG PRODUCT NAME/CODE/TYPE: 1
9. LEGAL BASIS FOR SUBMISSION: 1
10. PHARMACOL. CATEGORY: 2
11. DOSAGE FORM: Solution 2
12. STRENGTH/POTENCY: 1.5% w/w 2
13. ROUTE OF ADMINISTRATION: Topical 2
14. Rx/OTC DISPENSED: X Rx OTC 2

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): 2

15b. NANOTECHNOLOGY PRODUCT TRACKING: 2

15c. PRECEDENT: 2

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: 2
17. RELATED/SUPPORTING DOCUMENTS: 3
18. STATUS as of 15-Oct-2015 4
19. ORDER OF REVIEW 4
20. EES INFORMATION – Adequate as of 25-Nov-2015 4

I. Recommendations 5

A. Recommendation and Conclusion on Approvability 5

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 5

II. Summary of Chemistry Assessments 5

A. Description of the Drug Product(s) and Drug Substance(s) 5

B. Description of How the Drug Product is Intended to be Used 5
C. Basis for Approvability or Not-Approval Recommendation 6
I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2 7
2.3 Introduction to the Quality Overall Summary 7
2.3.S DRUG SUBSTANCE [Diclofenac Sodium, (b) (4) (b) (4) 7
2.3.S.1 General Information 7
2.3.S.2 Manufacture 8
2.3.S.3 Characterization 8
2.3.S.4 Control of Drug Substance 9
2.3.S.5 Reference Standards or Materials 16
2.3.S.6 Container Closure System 17
2.3.S.7 Stability 17
2.3.P DRUG PRODUCT [Diclofenac Sodium, Topical Solution, 1.5% w/w] 19
2.3.P.1 Description and Composition of the Drug Product 19
2.3.P.2 Pharmaceutical Development 20
2.3.P.3 Manufacture 31
2.3.P.4 Control of Excipients 38
2.3.P.5 Control of Drug Product 39
2.3.P.6 Reference Standards or Materials 50
2.3.P.7 Container Closure System 51
2.3.P.8 Stability 52
A APPENDICES 59
A.1 Facilities and Equipment (biotech only): N/A 59
A.2 Adventitious Agents Safety Evaluation: N/A 59
A.3 Novel Excipients: N/A 59
A.4 Nanotechnology Product Information: N/A 59
A.5 Precedent Setting Information: N/A 59
R REGIONAL INFORMATION 59
R.1 Executed Batch Records (Refer to Sections S.4 and P.5): 59
R.2 Comparability Protocols: N/A 59
R.3 Methods Validation Package (Refer to Sections S.4 and P.5): 59
II. Review of Common Technical Document-Quality (Ctd-Q) Module 1 60
Administrative 61

Chemistry Review Data Sheet

1. **ANDA #:** 205878

2. **REVIEW #:** 2

3. **REVIEW DATE:** 25-Oct-2015

4. **REVIEWER:** Andrei Ponta, Ph.D.

5. **PREVIOUS DOCUMENTS:**

Previous Document(s)	Document Date
N/A	N/A

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Supporting Document #1 (eCTD sequence #0000)	24-Jun-2013
Supporting Document #2 (eCTD sequence #0001)	3-Feb-2014
Supporting Document #3 (eCTD sequence #0002)	5-Jun-2015
Supporting Document #7 (eCTD sequence #0006)	24-Nov-2015

7. **NAME & ADDRESS OF APPLICANT:**

Name:	Novel Laboratories, Inc.
Address:	400 Campus Drive Somerset, NJ 08873
Representative:	Scott Talbot
Telephone:	(b) (6)

8. **DRUG PRODUCT NAME/CODE/TYPE:**

Proprietary Name: N/A
Non-Proprietary Name (USAN): Diclofenac Sodium Topical Solution

9. **LEGAL BASIS FOR SUBMISSION:**

- Reference listed drug (RLD): PENNSAID (Diclofenac Sodium Topical Solution 1.5% w/w)
- NDA#: 020947
- RLD's Firm's name: Mallinckrodt
- Patent (S):

Product #	Patent #	Patent Expiration	Patent Use Code
001	8217078	10-Jul-2029	U-1248
001	8546450	9-Aug-2030	U-1436

001	8618164	10-Jul-2029	U-1477
001	8741956	10-Jul-2029	U-1435

- Exclusivity: There is no unexpired exclusivity for Diclofenac Sodium Topical Solution, 1.5% w/w listed in the Electronic Orange Book.

10. PHARMACOL. CATEGORY:

Diclofenac Sodium Topical Solution, 1.5% w/w is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of signs and symptoms of osteoarthritis of the knee(s).

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 1.5% w/w

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: X Rx _ OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed
☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

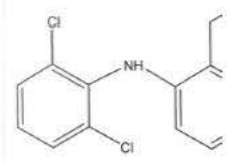
☐ NANO product – Form Completed (See Appendix A.4)
☒ Not a NANO product

15c. PRECEDENT:

☐ The review of this ANDA establishes a precedent – TL concurrence
☒ Not a Precedent

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Diclofenac Sodium
Chemical Name: Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, monosodium salt
Molecular Formula: $C_{14}H_{10}Cl_2NNaO_2$
Molecular Weight: 318.13 g/mole (b) (4)
Structure Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMF(s):

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	Reviewer
(b) (4)	II	(b) (4)		Adequate	08-03-2015	D. Skanchy
	III			N/A		
	III			N/A		
	III			N/A		
	III			N/A		
	III			N/A		
	III			N/A		
	III			N/A		

[1] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Pennsaid (Diclofenac Sodium Topical Solution 1.5% w/w) held by Mallinckodt, Inc.	NDA 020947	RLD

18. STATUS as of 15-Oct-2015

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
Methods Validation	N/A		
Labeling	Adequate	22-Sep-2015	Danielle Russel
Bioequivalence	Adequate	03-Dec-2014	Amanda Maniscalo
Toxicology/Clinical	NA		
EA	Categorical Exclusion	12-Jun-2013	

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No

20. EES INFORMATION – Adequate as of 25-Nov-2015

Overall Recommendation:
Drug Substance
(b) (4)

Executive Summary Section

Chemistry Review for ANDA 205878

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This ANDA is approvable in its current state.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

I Drug Substance

The drug substance is a white to slightly yellowish-white crystalline powder of Diclofenac Sodium. Diclofenac Sodium, a benzeacetic acid derivative, has a molecular weight of 318.14 g/mol and an empirical formula of $C_{14}H_{10}Cl_2NNaO_2$. Diclofenac Sodium is hygroscopic and sparingly soluble in water but soluble in ethanol (10-30 mg/mL). The Diclofenac Sodium synthesis is described in DMF (b) (4). Diclofenac Sodium is a compendial drug substance.

II Drug Product

The proposed drug product, Diclofenac Sodium Topical Solution, 1.5% w/w is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of signs and symptoms of osteoarthritis of the knee(s). The drug product is by prescription only. It is a clear, colorless to faint pink-orange solution. The drug product contains 16.05 mg/mL Diclofenac Sodium as the active ingredient and dimethyl sulfoxide (DMSO), ethyl alcohol, propylene glycol, glycerin, and purified water. The drug product is contained in a 150 mL oval white HDPE bottle with a dropper cap to be stored at room temperature. There is no USP monograph for Diclofenac Sodium Topical Solution, 1.5% w/w.

B. Description of How the Drug Product is Intended to be Used

Route of Administration	Topical
Proposed Indication(s)	NSAID for treatment of signs and symptoms of osteoarthritis of the knee(s).
Dosing Regime	The recommended does is 40 drops on each painful knee, 4 times a day.

The dosing regimen consists of 40 drops on each knee, four times a day. Forty drops contain approximately 1.2 mL, with each mL containing 16.05 mg of Diclofenac Sodium. Therefore, the maximum daily does is 154.08 mg, as shown below.

2 knees x 4 times daily x 1.2 mL (40 drops) x 16.05 mg/mL = 154.08 mg

The following ICH Q3A and Q3B limits apply:

Maximum Daily Dose (MDD):

	Identification Threshold (IT)	**Qualification Threshold (QT)**
Drug Substance	0.10%	0.15%
Drug Product	0.2%	0.2%

C. Basis for Approvability or Not-Approval Recommendation

ANDA 205878 is approvable per this review. Prior chemistry deficiencies were addressed in the applicant's response on 24-Nov-2015. Refer to the review for details.

The labeling and bioequivalence reviews are complete with an adequate status. The toxicology/clinical, and microbiology reviews are pending.

Chemistry Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product	N/A
Non-Proprietary Name of Drug Product	Diclofenac Sodium Topical Solution
Non-Proprietary Name of Drug Substance	Diclofenac Sodium, USP
Company Name	Novel Laboratories, Inc.
Dosage Form	Solution
Strength(s)	1.5% w/w
Route of Administration	Topical
Proposed Indication(s)	Indicated for the treatment of signs and symptoms of osteoarthritis of the knee(s).

(b) (4)

[redacted]

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula, and molecular weight? ***-Same as Item 16 above-***

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, partition coefficient?

Item	Description
Physical Form	A white to slightly yellowish-white crystalline powder.
pKa	4.0 ± 0.2 at 25°C in water
pH	2.5% w/v suspension is between 3.5 and 4.5
Polymorphism	None
Hygroscopicity	Hygroscopic in nature
Melting point	284 C
Solubility	Sparingly soluble in water (30 - 100 g/mL) Freely soluble in methanol (1 - 10 g/mL) Soluble in ethanol (10 - 30 g/mL) Slightly soluble in acetone (100 - 1000 g/mL)

	Practically insoluble in ether (>10,000 g/mL)
Partition Coefficient	13.4 at pH 7.4 and 1545 at pH 5.2

Reviewer's Assessment (Review #2): Satisfactory

The applicant provides adequate information regarding the drug substance nomenclature, molecular formula, molecular weight, and molecular structure.

The physicochemical properties information included is satisfactory.

2.3.S.2 Manufacture

Who manufactures the drug substance? ***-Refer to Item 20 Above-***
How do the manufacturing processes and controls ensure consistent production of drug substance? ***-Reference can be made to the DMF-***

Please refer to DMF (b) (4) for information regarding chemistry manufacturing and controls used in the production of Diclofenac Sodium, USP.

Reviewer's Assessment (Review #2): Satisfactory

(b) (4)

2.3.S.3 Characterization

How was the drug substance structure elucidated and characterized? How were potential impurities identified and characterized?

Information Provided:

The drug substance is elucidated and characterized based (b) (4)

(b) (4)

(b) (4).

(b) (4)

(b) (4)

Reviewer's Assessment (Review #2): Adequate After Response

(b) (4)

IR Response: Acceptable

The applicant has acknowledged the Agency's request.

2.3.S.4 Control of Drug Substance

(b) (4)

49 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

A APPENDICES

A.1 Facilities and Equipment (biotech only): N/A

A.2 Adventitious Agents Safety Evaluation: N/A

A.3 Novel Excipients: N/A

A.4 Nanotechnology Product Information: N/A

A.5 Precedent Setting Information: N/A

R REGIONAL INFORMATION

R.1 Executed Batch Records (Refer to Sections S.4 and P.5):

The executed batch records are provided.

R.2 Comparability Protocols: N/A

R.3 Methods Validation Package (Refer to Sections S.4 and P.5):

Method validation packages were provided for the drug substance in module 3 under section **3.2.R** and for the drug product in module 3 under section **3.2.R**. Further details are provided in the method validation section of the drug substance and drug product review.

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Documents

Patent Certification Provided: ☒ Yes ☐ No

Exclusivity Provided: ☒ Yes ☐ No

Debarment Certification Provided: ☒ Yes ☐ No

cGMP Statement Provided: ☒ Yes ☐ No

Reprocessing Statement Provided: ☒ Yes ☐ No

Letters of Authorization Provided: ☒ Yes ☐ No

Request for Bio-waiver Provided: ☒ Yes ☐ No

Citizen Petition and/or Control Request Linked to the Application: N/A

Environmental Impact Considerations/Categorical Exclusions Provided:
☒ Yes ☐ No

A. Labeling & Package Insert

a) DESCRIPTION section

i) Is the information accurate? ☒ Yes ☐ No

ii) Is the drug product subject of a USP monograph? ☐ Yes ☒ No

b) HOW SUPPLIED section

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

ii) Are the storage conditions acceptable? ☒ Yes ☐ No
If "No," explain.

c) 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.

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

Administrative

Endorsement Block

Chemist Name/Date: Andrei Ponta 25-Nov-15
Secondary Reviewer Name/Date: LChristensen 30-Nov-2015
Project Manager Name/Date:

TYPE OF LETTER: Approvable

Not Approvable – MAJOR Deficiencies

ANDA 205878

(Review #1)

Diclofenac Sodium Topical Solution, 1.5% w/w

Novel Laboratories, Inc.

Andrei Ponta, Ph.D.
OPS ANDA Review Squad

Table of Contents

Table of Contents i

Chemistry Review Data Sheet 1

1. ANDA #: 205878 1
2. REVIEW #: 1 1
3. REVIEW DATE: 31-Dec-2014 1
4. REVIEWER: Andrei Ponta, Ph.D. 1
5. PREVIOUS DOCUMENTS: 1
6. SUBMISSION(S) BEING REVIEWED: 1
7. NAME & ADDRESS OF APPLICANT: 1
8. DRUG PRODUCT NAME/CODE/TYPE: 1
9. LEGAL BASIS FOR SUBMISSION: 2
10. PHARMACOL. CATEGORY: 2
11. DOSAGE FORM: Solution 2
12. STRENGTH/POTENCY: 1.5% w/w 2
13. ROUTE OF ADMINISTRATION: Topical 2
14. Rx/OTC DISPENSED: X Rx OTC 2

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): 2

15b. NANOTECHNOLOGY PRODUCT TRACKING: 3

15c. PRECEDENT: 3

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: 3
17. RELATED/SUPPORTING DOCUMENTS: 4
18. STATUS as of 27-Dec-2014 5
19. ORDER OF REVIEW 5
20. EES INFORMATION – Adequate as of 1-Dec-2014 5

I. Recommendations 6

A. Recommendation and Conclusion on Approvability 6

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 6

II. Summary of Chemistry Assessments 6

A. Description of the Drug Product(s) and Drug Substance(s) 6

B. Description of How the Drug Product is Intended to be Used 6

C. Basis for Approvability or Not-Approval Recommendation 7

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2 8

2.3 Introduction to the Quality Overall Summary 8

2.3.S DRUG SUBSTANCE [Diclofenac Sodium, (b) (4) (b) (4) 8

2.3.S.1 General Information 8
2.3.S.2 Manufacture 9
2.3.S.3 Characterization 9
2.3.S.4 Control of Drug Substance 10
2.3.S.5 Reference Standards or Materials 17
2.3.S.6 Container Closure System 18
2.3.S.7 Stability 18

2.3.P DRUG PRODUCT [Diclofenac Sodium, Topical Solution, 1.5% w/w] 20

2.3.P.1 Description and Composition of the Drug Product 20
2.3.P.2 Pharmaceutical Development 21
2.3.P.3 Manufacture 30
2.3.P.4 Control of Excipients 37
2.3.P.5 Control of Drug Product 38
2.3.P.6 Reference Standards or Materials 48
2.3.P.7 Container Closure System 48
2.3.P.8 Stability 49

A APPENDICES 55

A.1 Facilities and Equipment (biotech only): N/A 55
A.2 Adventitious Agents Safety Evaluation: N/A 55
A.3 Novel Excipients: N/A 55
A.4 Nanotechnology Product Information: N/A 55
A.5 Precedent Setting Information: N/A 55

R REGIONAL INFORMATION 55

R.1 Executed Batch Records (Refer to Sections S.4 and P.5): 55
R.2 Comparability Protocols: N/A 55
R.3 Methods Validation Package (Refer to Sections S.4 and P.5): 55

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1 56

III. List of Deficiencies To Be Communicated 58

A. Deficiencies 58

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response: 61

Chemistry Review Data Sheet

1. ANDA #: 205878

2. REVIEW #: 1

3. REVIEW DATE: 31-Dec-2014

4. REVIEWER: Andrei Ponta, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
N/A	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Supporting Document #1 (eCTD sequence #0000)	24-Jun-2013
Supporting Document #2 (eCTD sequence #0001)	3-Feb-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Novel Laboratories, Inc.
Address:	400 Campus Drive Somerset, NJ 08873
Representative:	Scott Talbot
Telephone:	(b) (6)

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A
Non-Proprietary Name (USAN): Diclofenac Sodium Topical Solution

9. LEGAL BASIS FOR SUBMISSION:

- Reference listed drug (RLD): PENNSAID (Diclofenac Sodium Topical Solution 1.5% w/w)
- NDA#: 020947
- RLD's Firm's name: Mallinckrodt
- Patent (S):

Product #	Patent #	Patent Expiration	Patent Use Code
001	8217078	10-Jul-2029	U-1248
001	8546450	9-Aug-2030	U-1436
001	8618164	10-Jul-2029	U-1477
001	8741956	10-Jul-2029	U-1435

- Exclusivity: There is no unexpired exclusivity for Diclofenac Sodium Topical Solution, 1.5% w/w listed in the Electronic Orange Book.

10. PHARMACOL. CATEGORY:

Diclofenac Sodium Topical Solution, 1.5% w/w is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of signs and symptoms of osteoarthritis of the knee(s).

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 1.5% w/w

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: X Rx _ OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ NANO product – Form Completed (See Appendix A.4)

☒ Not a NANO product

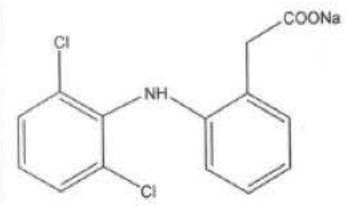
15c. PRECEDENT:

☐ The review of this ANDA establishes a precedent – TL concurrence

☒ Not a Precedent

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Diclofenac Sodium
Chemical Name: Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, monosodium salt
Molecular Formula: $C_{14}H_{10}Cl_2NNaO_2$
Molecular Weight: 318.13 g/mole (b) (4)
Structure Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMF(s):

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	Reviewer
(b) (4)	II		(b) (4)	Adequate	03-Oct-2011	Yusuf Amin
	III			N/A		
	III			N/A		
	III			N/A		
	III			N/A		
	III			N/A		
	III			N/A		
	III			N/A		

[1] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Pennsaid (Diclofenac Sodium Topical Solution 1.5% w/w) held by Mallinckodt, Inc.	NDA 020947	RLD

18. STATUS as of 27-Dec-2014

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
Methods Validation	N/A		
Labeling	Inadequate	20-Nov-2014	Ellen Hwang
Bioequivalence	Adequate	03-Dec-2014	Amanda Maniscalo
Toxicology/Clinical	Pending		
EA	Categorical Exclusion	12-Jun-2013	

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No

20. EES INFORMATION – Adequate as of 1-Dec-2014

(b) (4)

Executive Summary Section

Chemistry Review for ANDA 205878

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This ANDA is not approvable in its current state.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

I Drug Substance

The drug substance is a white to slightly yellowish-white crystalline powder of Diclofenac Sodium. Diclofenac Sodium, a benzeacetic acid derivative, has a molecular weight of 318.14 g/mol and an empirical formula of $C_{14}H_{10}Cl_2NNaO_2$. Diclofenac Sodium is hygroscopic and sparingly soluble in water but soluble in ethanol (10-30 mg/mL). The Diclofenac Sodium synthesis is described in DMF (b) (4). Diclofenac Sodium is a compendial drug substance.

II Drug Product

The proposed drug product, Diclofenac Sodium Topical Solution, 1.5% w/w is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of signs and symptoms of osteoarthritis of the knee(s). The drug product is by prescription only. It is a clear, colorless to faint pink-orange solution. The drug product contains 16.05 mg/mL Diclofenac Sodium as the active ingredient and dimethyl sulfoxide (DMSO), ethyl alcohol, propylene glycol, glycerin, and purified water. The drug product is contained in a 150 mL oval white HDPE bottle with a dropper cap to be stored at room temperature. There is no USP monograph for Diclofenac Sodium Topical Solution, 1.5% w/w.

B. Description of How the Drug Product is Intended to be Used

Route of Administration	Topical
Proposed Indication(s)	NSAID for treatment of signs and symptoms of osteoarthritis of the knee(s).
Dosing Regime	The recommended does is 40 drops on each painful knee, 4 times a day.

The dosing regimen consists of 40 drops on each knee, four times a day. Forty drops contain approximately 1.2 mL, with each mL containing 16.05 mg of Diclofenac Sodium. Therefore, the maximum daily does is 154.08 mg, as shown below.

2 knees x 4 times daily x 1.2 mL (40 drops) x 16.05 mg/mL = 154.08 mg

The following ICH Q3A and Q3B limits apply:

Maximum Daily Dose (MDD):

	Identification Threshold (IT)	**Qualification Threshold (QT)**
Drug Substance	0.10%	0.15%
Drug Product	0.2%	0.2%

C. Basis for Approvability or Not-Approval Recommendation

ANDA 205878 is not approvable per this review and a major deficiency is recommended. Chemistry deficiencies were identified in various areas. Refer to the review for details.

The labeling review is complete and currently has an inadequate status. The bioequivalence review is complete with an adequate status. The toxicology/clinical, and microbiology reviews are pending.

Chemistry Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product	N/A
Non-Proprietary Name of Drug Product	Diclofenac Sodium Topical Solution
Non-Proprietary Name of Drug Substance	Diclofenac Sodium, USP
Company Name	Novel Laboratories, Inc.
Dosage Form	Solution
Strength(s)	1.5% w/w
Route of Administration	Topical
Proposed Indication(s)	Indicated for the treatment of signs and symptoms of osteoarthritis of the knee(s).

(b) (4)

[redacted]

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula, and molecular weight? ***-Same as Item 16 above-***

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, partition coefficient?

Item	Description
Physical Form	A white to slightly yellowish-white crystalline powder.
pKa	4.0 ± 0.2 at 25°C in water
pH	2.5% w/v suspension is between 3.5 and 4.5
Polymorphism	None
Hygroscopicity	Hygroscopic in nature
Melting point	284 C
Solubility	Sparingly soluble in water (30 - 100 g/mL) Freely soluble in methanol (1 - 10 g/mL) Soluble in ethanol (10 - 30 g/mL) Slightly soluble in acetone (100 - 1000 g/mL)

	Practically insoluble in ether (>10,000 g/mL)
Partition Coefficient	13.4 at pH 7.4 and 1545 at pH 5.2

Reviewer's Assessment (Review #1): Satisfactory

The applicant provides adequate information regarding the drug substance nomenclature, molecular formula, molecular weight, and molecular structure.

The physicochemical properties information included is satisfactory.

2.3.S.2 Manufacture

Who manufactures the drug substance? ***-Refer to Item 20 Above-***
How do the manufacturing processes and controls ensure consistent production of drug substance? ***-Reference can be made to the DMF-***

Please refer to [redacted] (b) (4) for information regarding chemistry manufacturing and controls used in the production of Diclofenac Sodium, USP.

Reviewer's Assessment (Review #1): Satisfactory

[redacted] (b) (4)

45 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

A APPENDICES

A.1 ***Facilities and Equipment (biotech only): N/A***

A.2 ***Adventitious Agents Safety Evaluation: N/A***

A.3 ***Novel Excipients: N/A***

A.4 ***Nanotechnology Product Information: N/A***

A.5 ***Precedent Setting Information: N/A***

R REGIONAL INFORMATION

R.1 ***Executed Batch Records (Refer to Sections S.4 and P.5):***
The executed batch records are provided.

R.2 ***Comparability Protocols: N/A***

R.3 ***Methods Validation Package (Refer to Sections S.4 and P.5):***
Method validation packages were provided for the drug substance in module 3 under section **3.2.R** and for the drug product in module 3 under section **3.2.R**. Further details are provided in the method validation section of the drug substance and drug product review.

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Documents

Patent Certification Provided: ☒ Yes ☐ No

Exclusivity Provided: ☒ Yes ☐ No

Debarment Certification Provided: ☒ Yes ☐ No

cGMP Statement Provided: ☒ Yes ☐ No

Reprocessing Statement Provided: ☒ Yes ☐ No

Letters of Authorization Provided: ☒ Yes ☐ No

Request for Bio-waiver Provided: ☒ Yes ☐ No

Citizen Petition and/or Control Request Linked to the Application: N/A

Environmental Impact Considerations/Categorical Exclusions Provided:
☒ Yes ☐ No

A. Labeling & Package Insert

a) DESCRIPTION section

i) Is the information accurate? ☒ Yes ☐ No

ii) Is the drug product subject of a USP monograph? ☐ Yes ☒ No

b) HOW SUPPLIED section

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

ii) Are the storage conditions acceptable? ☒ Yes ☐ No
If "No," explain.

c) 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.

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

III. List of Deficiencies To Be Communicated

Chemistry Comments to be Provided to the Applicant

ANDA: 205878 APPLICANT: Novel Laboratories, Inc.

DRUG PRODUCT: Diclofenac Sodium Topical Solution, 1.5% w/w

The deficiencies presented below represent **MAJOR** deficiencies.

The following deficiencies listed below may be delivered via the easily correctable deficiency method (10 day firm response expected) if the situation allows ☐ YES ☒ NO

A. Deficiencies

Drug Substance

(b) (4)

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

ADMINISTRATIVE

Endorsement Block

Chemist Name/Date: Andrei Ponta 26-Nov-2014, 31-Dec-2014
Secondary Reviewer Name/Date: LChristensen/ 12/27/2014
Project Manager Name/Date:

TYPE OF LETTER: Major Deficiency

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 205878

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 205878 **FIRM NAME** Novel Laboratories, Inc.

DRUG NAME Diclofenac Sodium Topical Solution

DOSAGE FORM Topical Solution, 1.5% w/w
SUBJ: Request for Waiver of In vivo Bioequivalence Requirements

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☐	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☒	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____ Date: _____
Zenghui Mi, Ph.D.
Reviewer

_____ Date: _____
Parthapratim Chandaroy, Ph.D.
Team Leader

_____ Date: _____
Ethan M. Stier, Ph.D., R.Ph.
Acting Director, Division of Bioequivalence II

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	205878		
Drug Product Name	Diclofenac Sodium Topical Solution		
Strength(s)	1.5% (w/w)		
Applicant Name	Novel Laboratories, Inc.		
Applicant Address	400 Campus Drive Somerset, NJ 08873		
Contact Name	Scott Talbot, Vice President, Quality Assurance and Regulatory Affairs		
Contact's Telephone Number	(b) (6)		
Contact's Fax Number	908-603-6060		
Original Submission Date(s)	24 Jun 2013		
Submission Date(s) of Amendment(s) Under Review	N/A		
First Generic	No		
Reviewer	Amanda Maniscalco, Ph.D.		
OVERALL REVIEW RESULT	**ADEQUATE**		
REVISED/NEW DRAFT GUIDANCE INCLUDED	**No**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**Waiver**	**1.5%**	**ADEQUATE**

1 EXECUTIVE SUMMARY

The firm, Novel Laboratories, Inc., requested a waiver of *in vivo* bioequivalence (BE) testing for its test product, Diclofenac Sodium Topical Solution, 1.5%, under Section 21 CFR § 320.22 (b)(3). The Reference Listed Drug (RLD) product used in this application is PENNSAID® (diclofenac sodium topical solution), 1.5%, manufactured by Mallinckrodt, Inc. (NDA 020947) approved 04 Nov 2009[1].

The test product is qualitatively (Q1) and quantitatively (Q2) the same as the reference product. The dosage form, route of administration, indications and usage, dosage, active ingredients for Novel Laboratories' Diclofenac Sodium Topical Solution, 1.5% is the same as those for RLD Mallinckrodt's PENNSAID® (diclofenac sodium topical solution), 1.5%.

Based on the information provided, the Division of Bioequivalence I (DBI) grants the waiver of *in vivo* BE study requirements for Diclofenac Sodium Topical Solution, 1.5%, per criteria set forth in Section 21 CFR § 320.22 (b) (3).

The application is acceptable with no deficiencies.

[1] Electronic Orange Book; Search Term: Diclofenac Sodium; Last Access: 01 Dec 2014

2 TABLE OF CONTENTS

1 Executive Summary 2
2 Table of Contents 3
3 Submission Summary 4
3.1 Drug Product Information 4
3.2 PK/PD Information[2,] 4
3.3 OGD Recommendations for Drug Product 5
3.4 Contents of Submission 6
3.5 Formulation 6
3.6 Waiver Request(s) For Immediate Release Dosage Forms 7
3.7 Deficiency Comments 7
3.8 Recommendations 7
3.9 Comments for Other OGD Disciplines 8
3.10 Comments for Other OGD Disciplines 8
4 Appendix 9
4.1 Comparative Formulation Data 9
4.2 Additional Attachments 10

3 SUBMISSION SUMMARY

3.1 Drug Product Information[2]

Test Product	Diclofenac Sodium Topical Solution, 1.5%
Reference Product	PENNSAID® (diclofenac sodium topical solution), 1.5%
RLD Manufacturer	Mallinckrodt, Inc.
ANDA No.	020947
RLD Approval Date	04 Nov 2009
Indication	For the relief of signs and symptoms of osteoarthritis of the knee(s).

3.2 PK/PD Information[3]

Bioavailability	Diclofenac systemic exposure from PENNSAID® application (4 times daily for 1 week) was approximately 1/3 of the diclofenac systemic exposure from the Solaraze (diclofenac topical gel) application (twice daily for 4 weeks).
Food Effect	N/A
Tmax	11.0 ± 6.4 hours (single dose) and 4.0 ± 6.5 hours (multiple dose of 4-times daily for 7 days)
Metabolism	Five diclofenac metabolites have been identified in human plasma and urine, which include 4'-hydroxy-, 5-hydroxy-, 3'-hydroxy-, 4',5-dihydroxy- and 3'-hydroxy-4'-methoxy diclofenac. The major diclofenac metabolite, 4'-hydroxy-diclofenac, has very weak pharmacologic activity. The formation of 4'-hydroxy diclofenac is primarily mediated by CPY2C9. Both diclofenac and its oxidative metabolites undergo glucuronidation or sulfation followed by biliary excretion. Acylglucuronidation mediated by UGT2B7 and oxidation mediated by CPY2C8 may also play a role in diclofenac metabolism. CYP3A4 is responsible for the formation of minor metabolites, 5-hydroxy and 3'-hydroxy-diclofenac.
Excretion	Diclofenac is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates.
Half-life	36.7 ± 20.8 hours (single dose) and 79.0 ± 38.1 hours (multiple dose of 4-times daily for 7 days)
Dosage and Administration	40 drops per knee, 4 times daily Application of PENNSAID® in an amount exceeding or less than the recommended dose has not been studied and is therefore not recommended.
Drug Specific Issues (if any)	WARNING: CARDIOVASCULAR AND GASTROINTESTINAL RISK Cardiovascular Risk • Nonsteroidal anti-inflammatory drugs (NSAIDs) may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular

[2] Electronic Orange Book; Last Access: 01 Dec 2014
[3] DailyMed; Search Term: Diclofenac Sodium; Last Access: 01 Dec 2014

	disease or risk factors for cardiovascular disease may be at greater risk. • PENNSAID® is contraindicated in the perioperative setting of coronary artery bypass graft surgery. Gastrointestinal Risk • NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

3.3 OGD Recommendations for Drug Product

I. Waiver option

Number of studies recommended:	N/A-Waiver Request

Analytes to measure (in plasma/serum/blood):	N/A
Bioequivalence based on:	a. To qualify for a waiver of the in vivo bioequivalence study requirement under 21 CFR 320.22(b)(3), generic versions must contain the same active drug ingredient in the same concentration and dosage form as the RLD and contain no inactive ingredient or other change in formulation from the RLD that may significantly affect systemic or local availability of the active ingredient. b. For a topical drug product that differs from the RLD in inactive ingredients [as permitted by the chemistry, manufacturing and controls regulations for abbreviated new drug applications, 21CFR 314.94(a)(9)(v)], the regulation specifies that the applicant must identify and characterize the differences and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product. If the generic version has different inactive ingredients compared to the RLD or differences in the amounts of the same inactive ingredients that are proportionally more than +/- 5% compared to the RLD, then the Office of Generic Drugs (OGD) may request a bioequivalence study with clinical endpoints and/or a bioequivalence study with pharmacokinetic endpoints and/or a skin irritation and sensitization study to determine bioequivalence between the products, especially if the differences involve potential penetration enhancers.
Waiver request of in-vivo testing:	Yes
Source of most recent recommendations:	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM252729.pdf (recommended Apr 2011; revised Jun 2011)
Summary of OGD or DB History	As of December 2014, per Online-Orange Book (http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm) OGD has approved ANDAs: • 202027 by Apotex, Inc. (approved 27 May 2014) • 202393 by Paddock LLC (approved 24 Nov 2014) • 202852 by Watson Labs, Inc. (approved 24 Nov 2014) Per DARRTS, the OGD has received several applications for this drug product under review.

II. In vivo option

Number of studies recommended:	2

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	1.5%
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	None

2.	**Type of study:**	Bioequivalence study with clinical endpoint
	Design:	Randomized, double blind, parallel, placebo-controlled in vivo
	Strength:	1.5%
	Subjects:	Healthy males and females with osteoarthritis of the knee
	Additional Comments:	FDA recommends submitting a protocol for review and comment prior to conducting the study.

Analytes to measure (in plasma/serum/blood):	Diclofenac in plasma (in vivo option, study 1)
Bioequivalence based on:	Diclofenac in plasma (in vivo option, study 1); clinical endpoint (in vivo option, study 2)
Waiver request of in-vivo testing:	N/A

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	--
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	No	--
Waiver requests	Yes	1
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	No	--

3.5 Formulation

Location in appendix	Appendix 4.1
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	N/A

3.6 Waiver Request(s) For Immediate Release Dosage Forms

Strengths for which waivers are requested	1.5%
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A (for a solution formulation)
Waivers granted?	**WAIVER GRANTED**
If not then why?	N/A

3.7 Deficiency Comments

None

3.8 Recommendations

The Division of Bioequivalence I (DBI) agrees that the information submitted by Novel Laboratories, Inc. demonstrated that its test product, Diclofenac Sodium Topical Solution, 1.5%, meets the requirements of Section 21 CFR § 320.22(b)(3). The DBI recommends granting the waiver of *in vivo* bioequivalence testing for test product.

3.9 Comments for Other OGD Disciplines

Discipline	Comment
None.	

3.10 Comments for Other OGD Disciplines

Discipline	Comment
None.	

4 APPENDIX

4.1 Comparative Formulation Data

Comparative compositions of test drug product Diclofenac Sodium Topical Solution, 1.5%, and reference listed drug (RLD) product PENNSAID® (diclofenac sodium topical solution), 1.5% are as follows:

Table 1A. Comparative Compositions of Test Product and the RLD Product

Ingredients	Functions	Test Formulation[4] Quantity (%, w/w)	RLD Formulation[5] Quantity (% w/w)	Percentage Difference ((T-R)/R x 100%)
Diclofenac Sodium, USP	Active Ingredient	1.5	1.5	(b) (4)
Dimethyl Sulfoxide, USP	(b) (4)	45.50	45.50	
Ethyl Alcohol (b) (4)			(b) (4)	
(b) (4)				
Propylene Glycol, USP				
Glycerin, USP				
Purified Water, USP				
Total		100	100	

Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Are the amounts of all inactive ingredients based on Maximum Daily Dose (MDD) within IIG (per unit) limits?	N/A

Reviewer's Comments:

- The test drug product contains the same active ingredient in the same dosage form as the reference product and is intended for the same indications, dosage regimen and route of administration.
- (b) (4)
- Based on the BE review, the firm meets the criteria for waiver of the in vivo bioequivalence study requirement for its test product per Section 21 CFR § 320.22 (b)(3). The test product formulation is acceptable.

[4] EDR; ANDA 205878; Section 3.2.P.1; Submit Date 24 Jun 2013
[5] DARRTS; NDA 020947: REV-QUALITY-03(General Review) dated 06/22/2009

4.2 Additional Attachments

None.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 205878

APPLICANT: Novel Laboratories, Inc.

DRUG PRODUCT: Diclofenac Sodium Topical Solution, 1.5% (w/w)

The Division of Bioequivalence I (DB1) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Wayne DeHaven, Ph.D.
Acting Director
Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

Item Verified:		YES	NO	Comments
Individual Product BE Recommendations		☒	☐	Recommended April, 2011; Revised June 2011 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM252729.pdf
RLD Product Appropriateness		☒	☐	Mallinckrodt Inc.'s Pennsaid® (diclofenac sodium) Topical Solution, 1.5% (NDA #020947)
16 Biosummary Tables	Fast	☐	☒	N/A
	Fed	☐	☒	N/A
	Other	☐	☒	N/A
Formulation (All Studies)		☒	☐	Module 2.3.: Quality Overall Summary: Introduction: diclofenac-qos.pdf, page 15/43 Module 3.2.P.1.:unit-composition.pdf
Individual Dissolution Data and Report		☐	☒	N/A
Multimedia Dissolution Data and Report for ER Products (where applicable)		☐	☒	N/A
Alcohol Dose Dumping Dissolution Data and Report (where applicable)		☐	☒	N/A
Half-Tablet Dissolution Data and Report for Scored ER Tablets (where applicable)		☐	☒	N/A
Certificate of Analysis of Test Product (Potency, Assay, Content Uniformity, Date of Manufacture, Lot Number)		☒	☐	Module 3.2.P.5.4.:Batch Analysis: fp-coa.pdf
Certificate of Analysis of Reference Product (Potency, Assay, Content Uniformity, Date of Expiry, Lot Number)		☒	☐	Module 3.2.P.5.4.:Batch Analysis: rld-coa.pdf
Bio Batch Size		☒	☐	Module 2.3.: Quality Overall Summary: Introduction: diclofenac-qos.pdf, page 23/43

BE Study Protocol	Fast	☐	☒	N/A
	Fed	☐	☒	
	Other	☐	☒	
Non Standard Meal Menu	Fed	☐	☒	N/A
Clinical Report	Fast	☐	☒	N/A
	Fed	☐	☒	N/A
	Other	☐	☒	N/A
IRB Approval	Fast	☐	☒	N/A
	Fed	☐	☒	
	Other	☐	☒	
Pre-Screening of Patients	Fast	☐	☒	N/A
	Fed	☐	☒	
	Other	☐	☒	
Consent Form	Fast	☐	☒	N/A
	Fed	☐	☒	
	Other	☐	☒	
Randomization Schedule	Fast	☐	☒	N/A
	Fed	☐	☒	
	Other	☐	☒	
Test Article Inventory	Fast	☐	☒	N/A
	Fed	☐	☒	
	Other	☐	☒	
Individual Adverse Event Report	Fast	☐	☒	N/A
	Fed	☐	☒	
	Other	☐	☒	

Protocol Deviations	Fast	☐	☒	N/A
	Fed	☐	☒	
	Other	☐	☒	
Individual and Mean Data & Graphs, Linear & Ln	Fast	☐	☒	N/A
	Fed	☐	☒	
	Other	☐	☒	

SAS Datasets	Fast	☐	☒	N/A
	Fed	☐	☒	
	Other	☐	☒	
Statistical Report (Including SAS Output)	Fast	☐	☒	N/A
	Fed	☐	☒	
	Other	☐	☒	
Analytical SOP (Procedural SOP, Reanalysis SOP and Method Validation SOP)	Fast	☐	☒	N/A
	Fed	☐	☒	
	Other	☐	☒	
Pre-Study Validation Report	Fast	☐	☒	N/A
	Fed	☐	☒	
	Other	☐	☒	
Within Study Analytical Report	Fast	☐	☒	N/A
	Fed	☐	☒	
	Other	☐	☒	
Individual Samples Repeat Analysis Results (Include original and repeat values)	Fast	☐	☒	N/A
	Fed	☐	☒	
	Other	☐	☒	
Chromatograms, 20%	Fast	☐	☒	N/A

	Fed	☐	☒	
	Other	☐	☒	
Raw Numerical Data, 100%	Fast	☐	☒	N/A
	Fed	☐	☒	
	Other	☐	☒	

Summary results provided by the firm indicate studies pass BE criteria	☐	☒	N/A
Waiver requests for other strengths / supporting data	☐	☒	Waiver request was submitted for the 1.5% (w/w) strength

Additional Comments regarding the ANDA:

Novel Laboratories, Inc.is requesting a waiver of the in vivo bioequivalence testing requirements for its Diclofenac Sodium Topical Solution, 1.5% w/w as per 21 CFR 320.22(b)(3). The reference listed drug (RLD) is Mallinckrodt's Pennsaid® (diclofenac sodium) Topical Solution, 1.5% w/w, NDA #020947 (approved November 4, 2009).

The firm submitted a controlled correspondence# 12-1111A on November 15, 2012 (date of control document: 3/21/2013), in which the firm proposed a test formulation (formula 1, see additional attachment) that was confirmed to be considered Q1/Q2 the same as the RLD by FDA regulatory reviewer, Shannon Hill, on 05/06/2013 (\\cdsnas\ogds6\CONTROLS\2012-docs\12-1111A.pdf, page 11 of 12). The firm submitted the same formulation (formulation 1) data as in controlled correspondence# 12-1111A, for the waiver request for its Diclofenac Sodium Topical Solution, 1.5% w/w, in the current application (see additional attachments).

Currently, the draft guidance on Diclofenac Sodium Topical Solution[1] recommends two options (waiver or in vivo) for bioequivalence. To qualify for a waiver, the generic version of the solution must contain the same active ingredients in the same concentration and dosage form as the reference listed drug (RLD) and contain no inactive ingredients or other change in formulation from the RLD that may significantly affect systemic or local availability of the active ingredient. For a topical product that differs from the RLD in inactive ingredients, the regulation specifies that the applicant must identify and characterize that the differences do not affect the safety or efficacy of the proposed drug product. If the generic version has different inactive ingredients compared to the RLD or differences in the amounts of the same inactive ingredients that are proportionally more than ±5% compared to the RLD, then the Office of Generic Drugs (OGD) may request a BE study with clinical endpoints and/or a BE study with pharmacokinetic endpoints and/or a skin irritation and sensitization study. The in vivo option recommends 2 studies: a fasting single-dose, two-way crossover in vivo BE study and a randomized, double-blind, parallel, placebo-controlled in vivo BE study with clinical endpoint.

[1] Draft Guidance on Diclofenac Sodium Topical Solution, Recommended April 2011; Revised June 2011. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM252729.pdf

Bio-management meeting minutes on a related ANDA is attached in this review (please refer to additional attachments).

Additional Attachments

1. **Formulations Proposed in Controlled Correspondence# 12-1111A on November 15, 2012 (Date of Control Document: 3/21/2013)**

Ingredients	Formula 1		Formula 2		Formula 3	
	(% weight/weight)	mg/g	(% weight/weight)	mg/g	(% weight/weight)	mg/g
Diclofenac Sodium, USP	1.50*	15.00	1.50*	15.00	1.50*	15.00
Dimethyl Sulfoxide, USP	45.50	455.00	45.50	455.00	45.50	455.00
Alcohol (b) (4) USP						
Propylene Glycol, USP						
Glycerin (b) (4) USP						
Purified Water, USP						
Total	100.00	1000.00	100.00	1000.00	100.00	1000.00

(b) (4)

(*each mL contains 16.05 mg Diclofenac Sodium active ingredient as in the RLD)

2. **Telephone Memo (Control Correspondence)**

(b) (4)

(b) (6)

3. Formulation Submitted in this current ANDA (#205878)

1. Diclofenac sodium topical solution, 1.5 % w/w:

Item #	Ingredients	Qty in % (w/w)	Function
1.	Diclofenac Sodium, USP	1.5%	Active
2..	Dimethyl Sulfoxide, USP	45.50 %	(b) (4)
3.	Ethyl Alcohol (b) (4) (b) (4)	(b) (4)	
4.	Propylene Glycol, USP		
5.	Glycerin (b) (4)		
6.	Purified Water, USP		
	Total	100.00 %	

RLD Formulation[2] for Pennsaid® (Diclofenac Sodium) Topical Solution, 1.5% w/w (NDA #020947)

Quantitative Formula for PENNSAID® Topical Solution

Ingredients	mg/g	% w/w	(b) (4)
Diclofenac Sodium USP	15	1.5	
Dimethyl Sulfoxide (DMSO) USP	455	45.5	
Glycerin (b) (4)	(b) (4)		
Propylene Glycol USP			
Ethanol (b) (4)			
Purified Water USP			
Total Weight mg/g and Percent w/w	1000 mg/g	100.00% w/w	

4. DBII Biomanagement Meeting Minutes

Note: Only biomanagement meeting minutes related to this dug product are copied below:

DBII Bio Management Meeting Minutes[3]
Meeting Date: 03/27/2012

[2] In DARRTS, NDA020947, REV-QUALITY-03(General Review), final date: 6/22/2009, page 23/43
[3] V:\DIVISION\BIO\BIO2\BIO Management Meeting Minutes\2012 Meeting Minutes\ 03-27-12.doc

Attendees: Barbara Davit, Ethan Stier, Aaron Sigler, Yi Zhang, Kimberly Raines, Parthapratim Chandaroy, Moheb Makary, Chandra Chaurasia, Xiaojian Jiang, Kuldeep Dhariwal and Zhuojun Zhao

Chandra Chaurasia (Team 5)

Question: Could we accept the ANDA for filing?

Management decision:
Yes. Based on the presented information, the application meets the filling requirements for waiver option.

Reviewer's Comments:
The application is acceptable for filing.

Productivity Data:

Completed Assignment for 205878 ID: 20766

Reviewer: Mi, Zenghui **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: Diclofenac Sodium Topical Solution, 1.5% w/w

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
20766	6/24/2013	Filing Checklist (REGULAR)	ANDA Filing Checklist	1	1
				Total:	1

DB II Review Complexity Summary
ANDA 205878

First Generic Check List	
Paragraph 4	1
Checklist Review Total	**1**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZENGHUI MI
09/30/2013

Parthapratim CHANDAROY
09/30/2013

ETHAN M STIER
10/01/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 205878

ADMINISTRATIVE and CORRESPONDENCE DOCUMENT(S)

Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	**Author:** Heather Strandberg	

Approval Type: ☒ **FULL APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)**

RPM: Gwen Murphy Team: Mandy Kwong **Approval Date: 12/9/2015**

☐ **PI** ☐ **PII** ☐ **PIII** ☒ **PIV** (*eligible for 180 day exclusivity* ☐ **Yes** ☒ **No)** ☐ **MOU** ☒ **RX or** ☐ **OTC**

ANDA #: 205878 Applicant: Novel Laboratories, Inc. Established Product Name: Diclofenac Sodium Topical Solution, 1.5% w/w

Basis of Submission (RLD): Pennsaid 1.5% (NDA 020947)
(Is ANDA based on an approved Suitability Petition? ☐ *Yes* ☒ *No)*

Does the ANDA contain REMS? ☐ **Yes** ☒ **No** *(If YES, initiate approval action 6 weeks prior to target action date)*

Regulatory Project Manager Evaluation: **Date: 12/3/2015**

☒ Date last Complete Response (CR) letter was issued -- Date 1/7/2015
☐ Previously reviewed and tentatively approved (if applicable) --- Date N/A

Date of Application 6/24/2013	Original Received Date 6/24/2013	Date Acceptable for Filing 6/24/2013

YES	NO		
☒	☐	All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A)	
		Date of Acceptable Quality 11/30/2015 Date of Acceptable Dissolution N/A Date of Acceptable Bioequivalence 6/10/2015 Date of Acceptable Labeling 9/22/2015	If applicable: Date of Acceptable Microbiology N/A Date of Acceptable Clinical Review N/A Date of Acceptable REMS N/A
☐	☒	Are consults pending for any discipline?	
☐	☒	Has there been an amendment providing for a major change in formulation or new strength since filing? If YES→Verify a second filing review was completed and that all disciplines completed new reviews ☐	
☐	☒	Is there a pending Citizen Petition (CP)?	
☒	☐	Overall OC Recommendation is acceptable (EES is acceptable) Date Acceptable: 10/15/2015 Re-evaluation Date: N/A	
☒	☐	OSI Clinical Endpoint and Bioequivalence Site Inspections are acceptable	
☐	☒	Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)? If YES → Email OGD Communications Staff (OGDREQUEST) 30 to 60 days prior to approval, Date emailed _____	
Draft Approval/Tentative Approval Letter			
☒	☐	Approval/Tentative Approval letter is drafted and uploaded to the Final Decision task	
Review Discipline/Division Endorsements			
☒	☐	Division of Legal and Regulatory Support Endorsement completed, Date 12/4/2015	
☒	☐	Paragraph IV Evaluation completed (if applicable), Date 12/7/2015	
☒	☐	Quality Endorsement completed, Date 12/3/2015	
☒	☐	Bioequivalence Endorsement completed, Date 12/3/2015	
☒	☐	Labeling Endorsement completed, Date 12/4/2015	
☐	☒	REMS Endorsement (if applicable), Date N/A	
RPM Team Leader Endorsement and Action Package Verification			
☒	☐	RPM Team Leader Endorsement completed, Date 12/8/2015	
Final Decision and Letter Sign-off			
☒	☐	Final Decision recommending approval/tentative approval completed, Date 12/9/2015	
☒	☐	Approval/Tentative Approval letter electronically signed, Date: 12/9/2015	
Project Close-Out			
☒	☐	Notify applicant of approval and provide a courtesy copy of the electronically signed letter	
☐	☒	Is there a Post Marketing Agreement (PMA)? IF YES → Send email to PMA coordinator, Date emailed _____	
☒	☐	Email OGD Approval distribution list (CDER-OGDAPPROVALS) with approval information	

Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

This page to be completed by the RPM

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 12/3/2015
Name/Title: RTP

Contains GDEA certification: Yes ☐ No ☐	
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD = Pennsaid NDA# 20947 Date Checked _____ Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☐ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☐ No ☐ Was applicant sued w/in 45 days: Yes ☐ No ☐ Has case been settled: Yes ☐ No ☐ Date settled: Is applicant eligible for 180 day Is a forfeiture memo needed: Yes ☐ No ☐ If yes, has it been completed	
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐	
Date of latest Labeling Review/Approval Summary	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☐☐	
Type of Letter: ☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER:	
Comments:	
BOS=Pennsaid NDA 20947ANDA submitted on 06/24/2013 ANDA ack. for filing on 06/24/2013 (LO dated 02/18/2014) with PIII certification to '078 (expires 07/10/2029) Patent Amendment rec'd 2/03/2014-PIII cert. to '450 (08/9/2030) and '164 (07/10/2029), newly listed patents prior to ACK for filing. Patent Amendment rec'd 06/5/2015; Revised PIV → PIII for '078, '450, '164, '956. Patent Amendment rec'd on 06/18/2015: Patent Amendment rec'd 08/11/2015: FDA that an action for patent infringement was not filed by the patent/NDA holder within the statutory 45 day period. Apotex's ANDA 202027 180 day exclusivity expired on 11/23/2014. Application is eligible for Full Approval due to no suit.	

2. ***Paragraph IV Evaluation (for ANDAs with PIV certifications or other controversial regulatory issues)***
   Date: _____Name/Title: _____ Comments:

   Or see corresponding endorsement task under the ANDA project within the platform

3. ***Quality Endorsement by the Office of Pharmaceutical Science***
   Date: _____Name/Title: _____ Comments:

   Or see corresponding endorsement task under the ANDA project within the platform

4. ***Bioequivalence Endorsement***
   Date: _____Name/Title: _____ Comments:

   Or see corresponding endorsement task under the ANDA project within the platform

5. ***Labeling Endorsement***
   Date: _____Name/Title: _____ Comments:

   Or see corresponding endorsement task under the ANDA project within the platform

6. ***REMS Endorsement***
   Date: _____Name/Title: _____ Comments:

   Or see corresponding endorsement task under the ANDA project within the platform

7. ***RPM Team Leader Endorsement***
   Date: _____Name/Title: _____ Comments:

   Or see corresponding endorsement task under the ANDA project within the platform

8. Final Decision

Date: 12/9/2015
Name/Title: wpr

Para.IV Patent Cert: Yes ☒ No ☐
Pending Legal Action: Yes ☐ No ☒
Petition: Yes ☐ No ☒
Entered to APTrack database ☒
GDUFA User Fee Obligation Status Met ☒ Unmet ☐
Press Release Acceptable ☐
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg. Issue ☐

Date PETS checked for first generic drug _____

Comments:
BOS=Pennsaid NDA 20947. The applicant provided a PIV certs for the '078, '450, '164, '956 patents. They complied with the notification requirements and were not sued within the 45 day period. Apotex's ANDA 202027 180 day exclusivity expired on 11/23/2014. Chemistry acceptable 11/30/2015. QE 12/3/2015. Bio acceptable 12/2/2014 (waiver granted). Labeling acceptable 9/22/2015. Inspection report acceptable with e-mail confirmation. This ANDA is eligible for Full Approval.

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

To: Murphy, Gwendolyn; OPF Facilities Questions
Subject: RE: ANDA-205878-ORIG-1-AMEND-3

Confirmed.

Regards,
Quallyna

From: Murphy, Gwendolyn
Sent: Monday, December 07, 2015 1:41 PM
To: OPF Facilities Questions
Subject: ANDA-205878-ORIG-1-AMEND-3

Good afternoon,

In preparation for approval, may I please ask for confirmation that the facilities Overall Rec of "Approve" still stands for ANDA-205878-O-1-A-3, as of today?

Thank you,
Gwen

Application History:

Click here to enter text.

Orange Book Report:

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

FDA Home › Drug Databases › Orange Book

Patent and Exclusivity Search Results from query on Appl No 020947 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020947	001	8217078	Jul 10, 2029			U - 1248	
N020947	001	8546450	Aug 9, 2030			U - 1436	
N020947	001	8546450	Aug 9, 2030			U - 1435	
N020947	001	8618164	Jul 10, 2029			U - 1477	
N020947	001	8741956	Jul 10, 2029			U - 1435	

Exclusivity Data

There is no unexpired exclusivity for this product.

Additional information:

REFERENCES / ASSOCIATED DOCUMENTS

4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Version	Effective date	Name	Role	Summary of changes
01	10/1/2014	Heather Strandberg	Author	New Form

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 205878

INFORMATION REQUEST

Novel Laboratories, Inc.
Attention: Scott Talbot
Vice President, Quality Assurance and Regulatory Affairs
400 Campus Drive
Somerset, NJ 08873

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 24, 2013, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Diclofenac Sodium Topical Solution, 1.5 % w/w.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than 10 days, November 23, 2015 in order to continue our evaluation of your ANDA.

Please note, submitting unsolicited information in your response to this Information Request may have an impact on your Target Action Date.

Chemistry deficiencies:

1. (b) (4)
2.
3.

If you do not submit a complete response by November 23, 2015, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
Chemistry
REFERENCE # 186763

If you have any questions, please contact Ankara N. Yokum, Regulatory Business Process Manager, at (240) 402-8838.

Sincerely,

Ankara Yokum -A

Digitally signed by Anka a Yokum -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Anka a Yokum -A, 0.9.2342.19200300.100.1.1=2001305863
Date: 2015.11.12 13:55:29 -05'00'

Ankara N. Yokum
Regulatory Business Process Manager
Office of Program and Regulatory Operations Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 205878

COMPLETE RESPONSE

Novel Laboratories, Inc.
Attention: Scott Talbot
Vice President, Quality Assurance and Regulatory Affairs
400 Campus Drive
Somerset, NJ 08873

Dear Sir:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 24, 2013, received June 24, 2013, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Diclofenac Sodium Topical Solution, 1.5% w/w.

We acknowledge receipt of your amendment dated February 3, 2014.

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.

PRODUCT QUALITY

The deficiencies presented below represent **MAJOR** deficiencies.

A. Deficiencies

(b) (4)

[redacted]

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

BIOEQUIVALENCE

The Division of Bioequivalence has completed its review and has no further questions at this time. The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

LABELING

1. GENERAL COMMENT
   Please address the patent number 8741956 that is listed in the Orange Book.

2. CONTAINER
   a. Increase the prominence of the established drug name and the strength as they compete with the NDC number and net quantity.
   b. We encourage you to use a title case for the established drug name to increase readability as shown below:
      Diclofenac Sodium Topical Solution

c. There should be no space between “1.5” and “%”.
d. Storage: Revise “excursion” to read “excursions”.

3. PRESCRIBING INFORMATION
   a. Update your labeling to be in accord with the most recently approved Reference Listed Drug (RLD) labeling, NDA 020947/S-008, approved on October 21, 2013.
   b. HIGHLIGHTS OF PRESCRIBING INFORMATION: The product title, immediately above the initial U.S. approval date, should be revised as below to comply with the PLR format requirements.

      DICLOFENAC sodium topical solution, 1.5% w/w

4. MEDICATION GUIDE
   a. Submit a copy of the stand-alone Medication Guide in final printed format for our review.
   b. Comment how you would provide a sufficient number of Medication Guides.

Submit your revised labeling electronically in final print format.
To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug’s labeling with all differences annotated and explained.
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

FACILITY INSPECTIONS

Office of Compliance has no further questions at this time. The compliance status of each facility named in the application may be re-evaluated upon re-submission.

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

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
CHEMISTRY/LABELING

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions 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 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 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.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug 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 fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a 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 payment.

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 goal dates to apply to that application.

If you have any questions, call Gwendolyn Murphy, Regulatory Project Manager, at (240) 402-9624.

Sincerely yours,

William P. Rickman -S

Digitally signed by William P Rickman -S
DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=1300043242 cn=William P Rickman -S
Date: 2015 01 07 09:31:49 05'00'

For Denise P. Toyer McKan, Pharm.D.
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs