CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 90-495

Name: Sumatriptan Injection USP, 6 mg/0.5 mL

Sponsor: Dr. Reddy's Laboratories, Inc.

Approval Date: January 29, 2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-495

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-495

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 090495

Dr. Reddy's Laboratories, Inc.
U.S. Agent for: Dr. Reddy's Laboratories Limited
Attention: Srinivasa Rao
200 Somerset Corporate Boulevard, 7th Floor
Bridgewater, NJ 08807

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated April 28, 2008, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Sumatriptan Injection USP, 6 mg/0.5 mL, packaged in a Single-dose Prefilled Syringe with Autoinjector).

Reference is also made to the Complete Response letter issued by this office on September 3, 2013; and your amendment dated October 24, 2013.

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 Division of Bioequivalence has determined your Sumatriptan Injection USP, 6 mg/0.5 mL, packaged in a Single-dose Prefilled Syringe with Autoinjector to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug product (RLD), Imitrex STATdose System, 6 mg/0.5 mL, of GlaxoSmithKline.

Under section 506A of the 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 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 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 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,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

ROBERT L WEST

01/29/2014

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

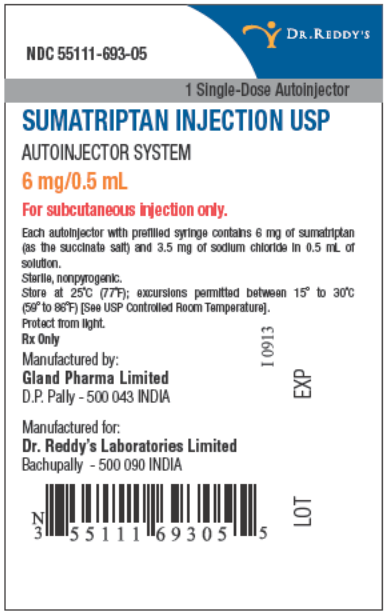
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

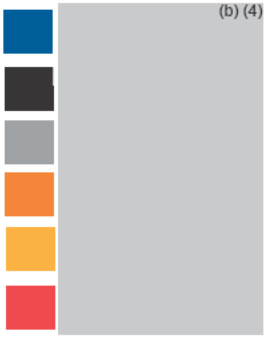
ANDA 90-495

LABELING

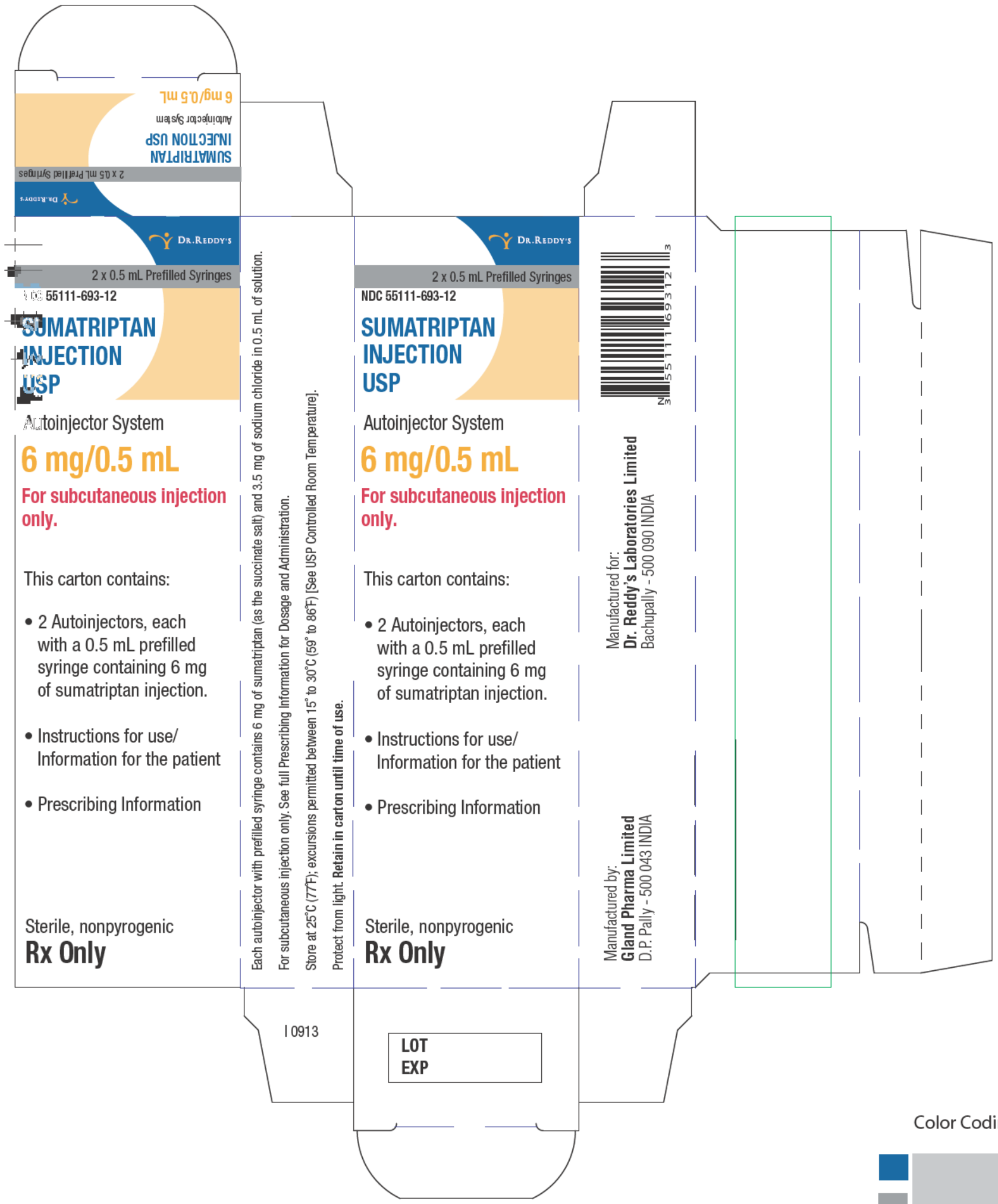
Final Autoinjector Container Label for Sumatriptan Injection USP, 6 mg/0.5 mL



Color Coding:



Final Autoinjector Carton Label for Sumatriptan Injection USP, 6 mg/0.5 mL



Color Coding:

(b) (4)

Reference ID: 3399267

Sumatriptan Injection USP
6 mg/0.5 mL
Rx Only
I 0913
55111-693-05

Sumatriptan Injection USP
6 mg/0.5 mL
Rx Only
I 0913
55111-693-05

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use sumatriptan injection safely and effectively. See full prescribing information for sumatriptan injection USP.

SUMATRIPTAN Injection, USP
For Subcutaneous Use
Initial U.S. Approval: 1992

----------------INDICATIONS AND USAGE----------------
Sumatriptan injection is a serotonin (5-HT$_{1B/1D}$) receptor agonist (triptan) indicated for:
- Acute treatment of migraine with or without aura in adults (1)
- Acute treatment of cluster headache in adults (1)

Limitations of Use:
- Use only if a clear diagnosis of migraine or cluster headache has been established. (1)
- Not indicated for the prevention of migraine attacks. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- For subcutaneous use only. (2.1)
- Acute treatment of migraine: 1 to 6 mg single dose. (2.1)
- Acute treatment of cluster headache: 6 mg single dose. (2.1)
- Maximum dose in a 24-hour period: 12 mg, Separate doses by at least 1 hour. (2.1)
- Patients receiving doses other than 6 mg: Use the 6 mg single-dose vial. (2.3)

----------DOSAGE FORMS AND STRENGTHS--------
- Injection: 6 mg single-dose prefilled syringe assembled in an autoinjector (3)

----------------CONTRAINDICATIONS----------------
- Coronary artery disease or coronary vasospasm (4)
- Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders (4)
- History of stroke, transient ischemic attack, or hemiplegic or basilar migraine (4)
- Peripheral vascular disease (4)
- Ischemic bowel disease (4)
- Uncontrolled hypertension (4)
- Recent (within 24 hours) use of another 5-HT$_1$ agonist (e.g., another triptan) or of an ergotamine-containing medication (4)
- Concurrent or recent (past 2 weeks) use of monoamine oxidase-A inhibitor (4)
- Known hypersensitivity to sumatriptan (4)
- Severe hepatic impairment (4)

-----------WARNINGS AND PRECAUTIONS -----------
- Myocardial ischemia/infarction and Prinzmetal's angina: Perform cardiac evaluation in patients with multiple cardiovascular risk factors. (5.1)
- Arrhythmias: Discontinue sumatriptan injection if occurs. (5.2)
- Chest/throat/neck/jaw pain, tightness, pressure, or heaviness: Generally not associated with myocardial ischemia; evaluate for coronary artery disease in patients at high risk. (5.3)
- Cerebral hemorrhage, subarachnoid hemorrhage, and stroke: Discontinue sumatriptan injection if occurs. (5.4)
- Gastrointestinal ischemia and infarction events, peripheral vasospastic reactions: Discontinue sumatriptan injection if occurs. (5.5)
- Medication overuse headache: Detoxification may be necessary. (5.6)
- Serotonin syndrome: Discontinue sumatriptan injection if occurs. (5.7)
- Increase in blood pressure: Monitor blood pressure. (5.8)
- Anaphylactic/anaphylactoid reactions: Discontinue sumatriptan injection if occurs (5.9)
- Seizures: Use with caution in patients with epilepsy or a lowered seizure threshold. (5.10)

-------------- ADVERSE REACTIONS ----------------
Most common adverse reactions (≥5% and >placebo) were injection site reactions, tingling, dizziness/vertigo, warm/hot sensation, burning sensation, feeling of heaviness, pressure sensation, flushing, feeling of tightness, and numbness (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Dr. Reddy's Laboratories Inc. at 1-888-375-3784 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------USE IN SPECIFIC POPULATIONS ----------
- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Geriatric use: A cardiovascular evaluation is recommended in those who have other cardiovascular risk factors prior to receiving sumatriptan injection. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA- approved patient labeling.

Revised: 09/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
Sumatriptan injection is indicated in adults for (1) the acute treatment of migraine, with or without aura, and (2) the acute treatment of cluster headache.

Limitations of Use:
- Use only if a clear diagnosis of migraine or cluster headache has been established.
- If a patient has no response to the first migraine attack treated with sumatriptan injection, reconsider the diagnosis of migraine before sumatriptan injection is administered to treat any subsequent attacks.
- Sumatriptan injection is not indicated for the prevention of migraine attacks.

2 DOSAGE AND ADMINISTRATION
2.1 Dosing Information
The maximum single recommended adult dose of sumatriptan injection for the acute treatment of migraine or cluster headache is 6 mg injected subcutaneously. For the treatment of migraine, if side effects are dose limiting, lower doses (1 to 5 mg) may be used [see **Clinical Studies (14.1)**]. For the treatment of cluster headache, the efficacy of lower doses has not been established.

The maximum cumulative dose that may be given in 24 hours is 12 mg, two 6 mg injections separated by at least 1 hour. A second 6 mg dose should only be considered if some response to a first injection was observed.

2.2 Administration Using the Autoinjector
An autoinjector device is available for use with a 6 mg prefilled syringe to facilitate self-administration in patients using the 6 mg dose. With this device, the needle penetrates approximately 1/4 inch (5 to 6 mm). The injection is intended to be given subcutaneously, and intramuscular or intravascular delivery should be avoided. Instruct patients on the proper use of the sumatriptan autoinjector and direct them to use injection sites with an adequate skin and subcutaneous thickness to accommodate the length of the needle.

2.3 Administration of Doses of Sumatriptan Injection Other Than 6 mg
In patients receiving doses other than 6 mg, use the 6 mg single-dose vial; do not use the Sumatriptan Autoinjector Pen. Visually inspect the vial for particulate matter and discoloration before administration. Do not use if particulates and discolorations are noted.

3 DOSAGE FORMS AND STRENGTHS
- Injection: 6 mg prefilled syringe assembled in an autoinjector

4 CONTRAINDICATIONS
Sumatriptan injection is contraindicated in patients with:
- Ischemic coronary artery disease (CAD) (angina pectoris, history of myocardial infarction, or documented silent ischemia) or coronary artery vasospasm, including Prinzmetal's angina [see **Warnings and Precautions (5.1)**].
- Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders [see **Warnings and Precautions (5.2)**].
- History of stroke or transient ischemic attack (TIA) because these patients are at a higher risk of stroke [see **Warnings and Precautions (5.4)**].
- History of hemiplegic or basilar migraine.
- Peripheral vascular disease [see **Warnings and Precautions (5.5)**].
- Ischemic bowel disease [see **Warnings and Precautions (5.5)**].
- Uncontrolled hypertension [see **Warnings and Precautions (5.8)**].
- Recent (i.e., within 24 hours) use of ergotamine-containing medication, ergot-type medication (such as dihydroergotamine or methysergide), or another 5-hydroxytryptamine$_1$ (5-HT$_1$) agonist [see **Drug Interactions (7.1, 7.3)**].
- Concurrent administration of an MAO-A inhibitor or recent (within 2 weeks) use of an MAO-A inhibitor [see **Drug Interactions (7.2) and Clinical Pharmacology (12.3)**].
- Known hypersensitivity to sumatriptan [see **Warnings and Precautions (5.9) and Adverse Reactions (6.2)**].
- Severe hepatic impairment [see **Clinical Pharmacology (12.3)**].

5 WARNINGS AND PRECAUTIONS
5.1 Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina
The use of sumatriptan injection is contraindicated in patients with ischemic or vasospastic CAD. There have been rare reports of serious cardiac adverse reactions, including acute myocardial infarction, occurring within a few hours following administration of sumatriptan injection. Some of these reactions occurred in patients without known CAD. 5-HT$_1$ agonists, including sumatriptan injection, may cause coronary artery vasospasm (Prinzmetal's angina), even in patients without a history of CAD.

Perform a cardiovascular evaluation in triptan-naive patients who have multiple cardiovascular risk factors (e.g., increased age, diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving sumatriptan injection. If there is evidence of CAD or coronary artery vasospasm, sumatriptan injection is contraindicated. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administering the first dose of sumatriptan injection in a medically supervised setting and performing an electrocardiogram (ECG) immediately following sumatriptan injection. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of sumatriptan injection.

Evaluate patients with signs or symptoms suggestive of angina following sumatriptan injection for the presence of CAD or Prinzmetal's angina before receiving additional doses of sumatriptan injection.

5.2 Arrhythmias
Life-threatening disturbances of cardiac rhythm, including ventricular tachycardia and ventricular fibrillation leading to death, have been reported within a few hours following the administration of 5-HT$_1$ agonists. Discontinue sumatriptan injection if these disturbances occur. Sumatriptan injection is contraindicated in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders.

5.3 Chest, Throat, Neck, and/or Jaw Pain/Tightness/Pressure
As with other 5-HT$_1$ agonists, sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck, and jaw commonly occur after treatment with sumatriptan injection and are usually non-cardiac in origin. However, perform a cardiac evaluation if these patients are at high cardiac risk. The use of sumatriptan injection is contraindicated in patients shown to have CAD and those with Prinzmetal's variant angina.

5.4 Cerebrovascular Events
Cerebral hemorrhage, subarachnoid hemorrhage, and stroke have occurred in patients treated with 5-HT$_1$ agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the 5-HT$_1$ agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. Also, patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, TIA). Discontinue sumatriptan injection if a cerebrovascular event occurs.

As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, exclude other potentially serious neurological conditions. Sumatriptan injection is contraindicated in patients with a history of stroke or TIA.

5.5 Other Vasospasm Reactions
5-HT$_1$ agonists, including sumatriptan injection, may cause non-coronary vasospastic reactions, such as peripheral vascular ischemia, gastrointestinal vascular ischemia and infarction (presenting with abdominal pain and bloody diarrhea), splenic infarction, and Raynaud's syndrome. Until further evaluation, sumatriptan injection is contraindicated in patients who experience symptoms or signs suggestive of non-coronary vasospasm reaction following the use of any 5-HT$_1$ agonist.

Reports of transient and permanent blindness and significant partial vision loss have been reported with the use of 5-HT$_1$ agonists. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT$_1$ agonists have not been clearly established.

5.6 Medication Overuse Headache
Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, combination of drugs for 10 or more days per month) may lead to exacerbation of headache (medication overuse headache). Medication overuse headache may present as migraine-like daily headaches or as a marked increase in frequency of migraine attacks. Detoxification of patients, including withdrawal of the overused drugs, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

5.7 Serotonin Syndrome
Serotonin syndrome may occur with triptans, including sumatriptan injection, particularly during coadministration with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and MAO inhibitors [see **Drug Interactions (7.4)**]. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms usually occurs within minutes to hours of receiving a new or a greater dose of a serotonergic medication. Discontinue sumatriptan injection if serotonin syndrome is suspected.

5.8 Increase in Blood Pressure
Significant elevation in blood pressure, including hypertensive crisis with acute impairment of organ systems, has been reported on rare occasions in patients treated with 5-HT$_1$ agonists, including patients without a history of hypertension. Monitor blood pressure in patients treated with sumatriptan. Sumatriptan injection is contraindicated in patients with uncontrolled hypertension.

5.9 Anaphylactic/Anaphylactoid Reactions
Anaphylactic/anaphylactoid reactions have occurred in patients receiving sumatriptan. Such reactions can be life threatening or fatal. In general, anaphylactic reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens. Sumatriptan injection is contraindicated in patients with prior serious anaphylactic reaction.

5.10 Seizures
Seizures have been reported following administration of sumatriptan. Some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures. There are also reports in patients where no such predisposing factors are apparent. Sumatriptan injection should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in more detail in other sections of the labeling:
- Myocardial ischemia, myocardial infarction, and Prinzmetal's angina [see **Warnings and Precautions (5.1)**]
- Arrhythmias [see **Warnings and Precautions (5.2)**]
- Chest, throat, neck, and/or jaw pain/tightness/pressure [see **Warnings and Precautions (5.3)**]
- Cerebrovascular events [see **Warnings and Precautions (5.4)**]
- Other vasospasm reactions [see **Warnings and Precautions (5.5)**]
- Medication overuse headache [see **Warnings and Precautions (5.6)**]
- Serotonin syndrome [see **Warnings and Precautions (5.7)**]
- Increase in blood pressure [see **Warnings and Precautions (5.8)**]
- Anaphylactic/anaphylactoid reactions [see **Warnings and Precautions (5.9)**]
- Seizures [see **Warnings and Precautions (5.10)**]

6.1 Clinical Trials 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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Migraine Headache: Table 1 lists adverse reactions that occurred in 2 U.S. placebo-controlled clinical trials in migraine subjects [**Studies 2 and 3, see Clinical Studies (14.1)**] following either a single 6 mg dose of sumatriptan injection or placebo. Only reactions that occurred at a frequency of 2% or more in groups treated with sumatriptan injection 6 mg and that occurred at a frequency greater than the placebo group are included in Table 1.

Table 1. Adverse Reactions Reported by at Least 2% of Subjects and at a Greater Frequency Than Placebo in 2 Placebo-Controlled Migraine Clinical Trials (Studies 2 and 3)[a]

Adverse Reaction	Percent of Subjects Reporting	
	Sumatriptan Injection 6 mg Subcutaneous (n = 547)	Placebo (n = 370)
Atypical sensations	42	9
Tingling	14	3
Warm/hot sensation	11	4
Burning sensation	7	<1
Feeling of heaviness	7	1
Pressure sensation	7	2
Feeling of tightness	5	<1
Numbness	5	2
Feeling strange	2	<1
Tight feeling in head	2	<1
Cardiovascular		
Flushing	7	2
Chest discomfort	5	1
Tightness in chest	3	<1
Pressure in chest	2	<1
Ear, nose, and throat		
Throat discomfort	3	<1
Discomfort: nasal cavity/sinuses	2	<1
Injection site reaction[b]	59	24
Miscellaneous		
Jaw discomfort	2	0
Musculoskeletal		
Weakness	5	<1
Neck pain/stiffness	5	<1
Myalgia	2	<1
Neurological		
Dizziness/vertigo	12	4
Drowsiness/sedation	3	2
Headache	2	<1
Skin		
Sweating	2	1

[a] The sum of the percentages cited is greater than 100% because subjects may have experienced more than 1 type of adverse reaction. Only reactions that occurred at a frequency of 2% or more in groups treated with sumatriptan injection and occurred at a frequency greater than the placebo groups are included.
[b] Includes injection site pain, stinging/burning, swelling, erythema, bruising, bleeding.

The incidence of adverse reactions in controlled clinical trials was not affected by gender or age of the subjects. There were insufficient data to assess the impact of race on the incidence of adverse reactions.

Cluster Headache: In the controlled clinical trials assessing the efficacy of sumatriptan injection as a treatment for cluster headache [**Studies 4 and 5, see Clinical Studies (14.2)**], no new significant adverse reactions were detected that had not already been identified in trials of sumatriptan injection in subjects with migraine.

Overall, the frequency of adverse reactions reported in the trials of cluster headache was generally lower than in the migraine trials. Exceptions include reports of paresthesia (5% sumatriptan injection, 0% placebo), nausea and vomiting (4% sumatriptan injection, 0% placebo), and bronchospasm (1% sumatriptan injection, 0% placebo).

Other Adverse Reactions: In the paragraphs that follow, the frequencies of less commonly reported adverse reactions are presented. Reaction frequencies were calculated as the number of subjects reporting a reaction divided by the total number of subjects (N = 6,218) exposed to subcutaneous sumatriptan injection. All reported reactions are included except those already listed in the previous table. Reactions are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent are defined as those occurring in at least 1/100 subjects, infrequent are those occurring in 1/100 to 1/1,000 subjects, and rare are those occurring in fewer than 1/1,000 subjects.

Cardiovascular: *Infrequent* were hypertension, hypotension, bradycardia, tachycardia, palpitations, and syncope. *Rare* was arrhythmia.

Gastrointestinal: *Frequent* was abdominal discomfort.

Musculoskeletal: *Frequent* were muscle cramps.

Neurological: *Frequent* was anxiety. *Infrequent* were mental confusion, euphoria, agitation, tremor. *Rare* were myoclonia, sleep disturbance, and dystonia.

Respiratory: *Infrequent* was dyspnea.

Skin: *Infrequent* were erythema, pruritus, and skin rashes.

Miscellaneous: *Infrequent* was "serotonin agonist effect".

Adverse Events Observed With Other Formulations of Sumatriptan: The following adverse events occurred in clinical trials with sumatriptan tablets and sumatriptan nasal spray.

Because the reports include events observed in open and uncontrolled trials, the role of sumatriptan in their causation cannot be reliably determined. All reported events are included except those already listed, those too general to be informative, and those not reasonably associated with the use of the drug.

Cardiovascular: Angina, cerebrovascular lesion, heart block, peripheral cyanosis, phlebitis, thrombosis.

Gastrointestinal: Abdominal distention and colitis.

Neurological: Convulsions, hallucinations, syncope, suicide, and twitching.

Miscellaneous: Edema, hypersensitivity, swelling of extremities, and swelling of face.

6.2 Postmarketing Experience
The following adverse reactions have been identified during postapproval use of sumatriptan tablets, sumatriptan nasal spray, and sumatriptan injection. 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. These reactions have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to sumatriptan or a combination of these factors.

Blood: Hemolytic anemia, pancytopenia, thrombocytopenia.

Ear, Nose, and Throat: Deafness.

Eye: Ischemic optic neuropathy, retinal artery occlusion, retinal vein thrombosis.

Neurological: Central nervous system vasculitis, cerebrovascular accident, serotonin syndrome, subarachnoid hemorrhage.

Non-Site Specific: Angioedema, cyanosis, temporal arteritis.

Skin: Exacerbation of sunburn, hypersensitivity reactions (allergic vasculitis, erythema, pruritus, rash, shortness of breath, urticaria), photosensitivity. Following subcutaneous administration of sumatriptan injection, pain, redness, stinging, induration, swelling, contusion, subcutaneous bleeding, and, on rare occasions, lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) have been reported.

Urogenital: Acute renal failure.

7 DRUG INTERACTIONS
7.1 Ergot-Containing Drugs
Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and sumatriptan injection within 24 hours of each other is contraindicated.

7.2 Monoamine Oxidase-A Inhibitors
MAO-A inhibitors increase systemic exposure by 2-fold. Therefore, the use of sumatriptan injection in patients receiving MAO-A inhibitors is contraindicated [see **Clinical Pharmacology (12.3)**].

7.3 Other 5-HT$_1$ Agonists
Because their vasospastic effects may be additive, coadministration of sumatriptan injection and other 5-HT$_1$ agonists (e.g., triptans) within 24 hours of each other is contraindicated.

7.4 Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome
Cases of serotonin syndrome have been reported during coadministration of triptans and SSRIs, or SNRIs, TCAs, and MAO inhibitors [see **Warnings and Precautions (5.7)**].

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C: There are no adequate and well-controlled trials of sumatriptan injection in pregnant women. Sumatriptan injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When sumatriptan was administered intravenously to pregnant rabbits daily throughout the period of organogenesis, embryolethality was observed at doses at or close to those producing maternal toxicity. These doses were less than the maximum recommended human dose (MRHD) of 12 mg/day on a mg/m^2 basis. Oral administration of sumatriptan to rabbits during organogenesis was associated with increased incidences of fetal vascular and skeletal abnormalities. The highest no-effect dose for these effects was 15 mg/kg/day. The intravenous administration of sumatriptan to pregnant rats throughout organogenesis at doses that are approximately 10 times the MRHD on a mg/m^2 basis, did not produce evidence of embryolethality. The subcutaneous administration of sumatriptan to pregnant rats prior to and throughout pregnancy did not produce evidence of embryolethality or teratogenicity.

8.3 Nursing Mothers
It is not known whether sumatriptan is excreted in human breast milk following subcutaneous administration. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from sumatriptan injection, 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 of sumatriptan injection in pediatric patients under 18 years of age have not been established; therefore, sumatriptan injection is not recommended for use in patients under 18 years of age.

Two controlled clinical trials evaluated sumatriptan nasal spray (5 to 20 mg) in 1,248 adolescent migraineurs aged 12 to 17 years who treated a single attack. The trials did not establish the efficacy of sumatriptan nasal spray compared with placebo in the treatment of migraine in adolescents. Adverse reactions observed in these clinical trials were similar in nature to those reported in clinical trials in adults.

Five controlled clinical trials (2 single-attack trials, 3 multiple-attack trials) evaluating oral sumatriptan (25 to 100 mg) in pediatric subjects aged 12 to 17 years enrolled a total of 701 adolescent migraineurs. These trials did not establish the efficacy of oral sumatriptan compared with placebo in the treatment of migraine in adolescents. Adverse reactions observed in these clinical trials were similar in nature to those reported in clinical trials in adults. The frequency of all adverse reactions in these subjects appeared to be both dose- and age-dependent, with younger subjects reporting reactions more commonly than older adolescents.

Postmarketing experience documents that serious adverse reactions have occurred in the pediatric population after use of subcutaneous, oral, and/or intranasal sumatriptan. These reports include reactions similar in nature to those reported rarely in adults, including stroke, visual loss, and death. A myocardial infarction has been reported in a 14-year-old male following the use of oral sumatriptan; clinical signs occurred within 1 day of drug administration. Since clinical data to determine the frequency of serious adverse reactions in pediatric patients who might receive subcutaneous, oral, or intranasal sumatriptan are not presently available, the use of sumatriptan in patients under 18 years of age is not recommended.

8.5 Geriatric Use
Clinical trials of sumatriptan injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

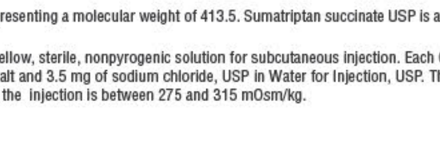
A cardiovascular evaluation is recommended for geriatric patients who have other cardiovascular risk factors (e.g., diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving sumatriptan injection [see **Warnings and Precautions (5.1)**].

10 OVERDOSAGE
No gross overdoses in clinical practice have been reported. Coronary vasospasm was observed after intravenous administration of sumatriptan injection [see **Contraindications (4)**]. Overdoses would be expected from animal data (dogs at 0.1 g/kg, rats at 2 g/kg) to possibly cause convulsions, tremor, inactivity, erythema of the extremities, reduced respiratory rate, cyanosis, ataxia, mydriasis, injection site reactions (desquamation, hair loss, and scab formation), and paralysis.

The elimination half-life of sumatriptan is about 2 hours [see **Clinical Pharmacology (12.3)**], and therefore monitoring of patients after overdose with sumatriptan injection should continue for at least 10 hours or while symptoms or signs persist.

It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of sumatriptan.

11 DESCRIPTION
Sumatriptan injection USP contains sumatriptan succinate, a selective 5-HT$_{1B/1D}$ receptor agonist. Sumatriptan succinate is chemically designated as 3-[2-(dimethylamino)ethyl]-N methyl-indole-5-methanesulfonamide succinate (1:1), and it has the following structure:



The molecular formula is $C_{14}H_{21}N_3O_2S \cdot C_4H_6O_4$, representing a molecular weight of 413.5. Sumatriptan succinate USP is a white to off-white powder that is readily soluble in water and in saline.

Sumatriptan injection USP is a clear, colorless to pale yellow, sterile, nonpyrogenic solution for subcutaneous injection. Each 0.5 mL of solution contains 6 mg of sumatriptan (base) as the succinate salt and 3.5 mg of sodium chloride, USP in Water for Injection, USP. The pH range of the solutions is approximately 4.2 to 5.3. The osmolality of the injection is between 275 and 315 mOsm/kg.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Sumatriptan binds with high affinity to human cloned 5-HT$_{1B/1D}$ receptors. Sumatriptan presumably exerts its therapeutic effects in the treatment of migraine headache by binding to 5-HT$_{1B/1D}$ receptors located on intracranial blood vessels and sensory nerves of the trigeminal system.

Current theories proposed to explain the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of sensory neuropeptides (including substance P and calcitonin gene-related peptide) through nerve endings in the trigeminal system. The therapeutic activity of sumatriptan for the treatment of migraine and cluster headaches is thought to be due to the agonist effects at the 5-HT$_{1B/1D}$ receptors on intracranial blood vessels (including the arterio-venous anastomoses) and sensory nerves of the trigeminal system, which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.

12.2 Pharmacodynamics
Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported in patients with and without a history of hypertension [see **Warnings and Precautions (5.8)**].

Peripheral (Small) Arteries: In healthy volunteers (N = 18), a trial evaluating the effects of sumatriptan on peripheral (small vessel) arterial reactivity failed to detect a clinically significant increase in peripheral resistance.

Heart Rate: Transient increases in blood pressure observed in some subjects in clinical trials carried out during sumatriptan's development as a treatment for migraine were not accompanied by any clinically significant changes in heart rate.

12.3 Pharmacokinetics
Absorption and Bioavailability: The bioavailability of sumatriptan via subcutaneous site injection to 18 healthy male subjects was 97% ± 16% of that obtained following intravenous injection.

After a single 6 mg subcutaneous manual injection into the deltoid area of the arm in 18 healthy males (age: 24 ± 6 years, weight: 70 kg), the maximum serum concentration (C_{max}) of sumatriptan was (mean ± standard deviation) 74 ± 15 ng/mL and the time to peak concentration (T_{max}) was 12 minutes after injection (range: 5 to 20 minutes). In this trial, the same dose injected subcutaneously in the thigh gave a C_{max} of 61 ± 15 ng/mL by manual injection versus 52 ±15 ng/mL by autoinjector techniques. The T_{max} or amount absorbed was not significantly altered by either the site or technique of injection.

Distribution: Protein binding, determined by equilibrium dialysis over the concentration range of 10 to 1,000 ng/mL, is low, approximately 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated.

Following a 6 mg subcutaneous injection into the deltoid area of the arm in 9 males (mean age: 33 years, mean weight: 77 kg) the volume of distribution central compartment of sumatriptan was 50 ± 8 liters and the distribution half-life was 15± 2 minutes.

Metabolism: *In vitro* studies with human microsomes suggest that sumatriptan is metabolized by MAO, predominantly the A isoenzyme. Most of a radiolabeled dose of sumatriptan excreted in the urine is the major metabolite indole acetic acid (IAA) or the IAA glucuronide, both of which are inactive.

Elimination: After a single 6 mg subcutaneous dose, 22% ± 4% was excreted in the urine as unchanged sumatriptan and 38% ± 7% as the IAA metabolite.

Following a 6 mg subcutaneous injection into the deltoid area of the arm, the systemic clearance of sumatriptan was 1,194 ± 149 mL/min and the terminal half-life was 115 ± 19 minutes.

Special Populations: Age: The pharmacokinetics of sumatriptan in the elderly (mean age: 72 years, 2 males and 4 females) and in subjects with migraine (mean age: 38 years, 25 males and 155 females) were similar to that in healthy male subjects (mean age: 30 years).

Renal Impairment: The effect of renal impairment on the pharmacokinetics of sumatriptan has not been examined.

Hepatic Impairment: The effect of mild to moderate hepatic disease on the pharmacokinetics of subcutaneously administered sumatriptan has been evaluated. There were no significant differences in the pharmacokinetics of subcutaneously administered sumatriptan in moderately hepatically impaired subjects compared with healthy controls. The pharmacokinetics of subcutaneously administered sumatriptan in patients with severe hepatic impairment has not been studied. The use of sumatriptan injection in this population is contraindicated [see **Contraindications (4)**].

Race: The systemic clearance and C_{max} of sumatriptan were similar in black (n = 34) and Caucasian (n = 38) healthy male subjects.

Drug Interaction Studies: Monoamine Oxidase-A Inhibitors: In a trial of 14 healthy females, pretreatment with an MAO-A inhibitor decreased the clearance of sumatriptan, resulting in a 2-fold increase in the area under the sumatriptan plasma concentration-time curve (AUC), corresponding to a 40% increase in elimination half-life.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: In carcinogenicity studies, rats and mice were given sumatriptan by oral gavage. Mice were dosed for 78 weeks and rats were dosed for 104 weeks. Average exposures achieved in mice receiving the highest dose were approximately 110 times the exposure attained in humans after the maximum recommended single dose of 6 mg. The highest dose to rats was approximately 260 times the maximum single dose of 6 mg on a mg/m^2 basis. There was no evidence of an increase in tumors in either species related to sumatriptan administration.

Mutagenesis: Sumatriptan was not mutagenic in the presence or absence of metabolic activation when tested in 2 gene mutation assays (the Ames test and the *in vitro* mammalian Chinese hamster V79/HGPRT assay). It was not clastogenic in 2 cytogenetics assays (the *in vitro* human lymphocyte assay and the *in vivo* rat micronucleus assay).

Impairment of Fertility: A fertility study (Segment I) by the subcutaneous route, during which male and female rats were dosed daily with sumatriptan prior to and throughout the mating period, has shown no evidence of impaired fertility at doses equivalent to approximately 100 times the maximum recommended single human dose of 6 mg on a mg/m^2 basis. However, following oral administration, a treatment-related decrease in fertility, secondary to a decrease in mating, was seen for rats treated with 50 and 500 mg/kg/day. The no-effect dose for this finding was approximately 8 times the maximum recommended single human dose of 6 mg on a mg/m^2 basis. It is not clear whether the problem is associated with the treatment of males or females or both.

13.2 Animal Toxicology and/or Pharmacology
Corneal Opacities: Dogs receiving oral sumatriptan developed corneal opacities and defects in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg/day, and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a 60 week study. Earlier examinations for these toxicities were not conducted and no-effect doses were not established; however, the relative exposure at the lowest dose tested was approximately 5 times the human exposure after a 100 mg oral dose or 3 times the human exposure after a 6 mg subcutaneous dose.

Melanin Binding: In rats with a single subcutaneous dose (0.5 mg/kg) of radiolabeled sumatriptan, the elimination half-life of radioactivity from the eye was 15 days, suggesting that sumatriptan and its metabolites bind to the melanin of the eye. The clinical significance of this binding is unknown.

14 CLINICAL STUDIES
14.1 Migraine
In controlled clinical trials enrolling more than 1,000 subjects during migraine attacks who were experiencing moderate or severe pain and 1 or more of the symptoms enumerated in Table 3, onset of relief began as early as 10 minutes following a 6 mg sumatriptan injection. Lower doses of sumatriptan injection may also prove effective, although the proportion of subjects obtaining adequate relief was decreased and the latency to that relief is greater with lower doses.

In Study 1, 6 different doses of sumatriptan injection (n = 30 each group) were compared with placebo (n = 62), in a single-attack, parallel-group design, the dose response relationship was found to be as shown in Table 2.

Table 2. Proportion of Subjects With Migraine Relief and Incidence of Adverse Events by Time and by Sumatriptan Dose in Study 1

Dose of Sumatriptan Injection	Percent Subjects With Relief[a]				Adverse Events Incidence (%)
	at 10 Minutes	at 30 Minutes	at 1 Hour	at 2 Hours	
Placebo	5	15	24	21	55
1 mg	10	40	43	40	63
2 mg	7	23	57	43	63
3 mg	17	47	57	60	77
4 mg	13	37	50	57	80
6 mg	10	63	73	70	83
8 mg	23	57	80	83	93

[a] Relief is defined as the reduction of moderate or severe pain to no or mild pain after dosing without use of rescue medication.

In 2 randomized, placebo-controlled clinical trials of sumatriptan injection 6 mg in 1,104 subjects with moderate or severe migraine pain (Studies 2 and 3), the onset of relief was less than 10 minutes. Headache relief, as defined by a reduction in pain from severe or moderately severe to mild or no headache, was achieved in 70% of the subjects within 1 hour of a single 6 mg subcutaneous dose of sumatriptan injection. Approximately 82% and 65% of subjects treated with sumatriptan injection 6 mg had headache relief and were pain free within 2 hours, respectively.

Table 3 shows the 1- and 2-hour efficacy results for sumatriptan injection 6 mg in Studies 2 and 3.

Table 3. Proportion of Subjects With Pain Relief and Relief of Migraine Symptoms After 1 and 2 Hours of Treatment in Studies 2 and 3

1-Hour Data	Study 2		Study 3	
	Placebo (n = 190)	Sumatriptan Injection 6 mg (n = 384)	Placebo (n = 180)	Sumatriptan Injection 6 mg (n = 350)
Subjects with pain relief (grade 0/1)	18%	70%[a]	26%	70%[a]
Subjects with no pain	5%	48%[a]	13%	49%[a]
Subjects without nausea	48%	73%[a]	50%	73%[a]
Subjects without photophobia	23%	56%[a]	25%	58%[a]
Subjects with little or no clinical disability[b]	34%	76%[a]	34%	76%[a]
2-Hour Data	**Study 2**		**Study 3**	
	Placebo[c]	Sumatriptan Injection 6 mg[d]	Placebo[c]	Sumatriptan Injection 6 mg[d]
Subjects with pain relief (grade 0/1)	31%	81%[a]	39%	82%[a]
Subjects with no pain	11%	63%[a]	19%	65%[a]
Subjects without nausea	56%	82%[a]	63%	81%[a]
Subjects without photophobia	31%	72%[a]	35%	71%[a]
Subjects with little or no clinical disability[b]	42%	85%[a]	49%	84%[a]

[a] P<0.05 versus placebo.
[b] A successful outcome in terms of clinical disability was defined prospectively as ability to work mildly impaired or ability to work and function normally.
[c] Includes subjects that may have received an additional placebo injection 1 hour after the initial injection.
[d] Includes subjects that may have received an additional 6 mg of sumatriptan injection 1 hour after the initial injection.

Sumatriptan injection also relieved photophobia, phonophobia (sound sensitivity), nausea, and vomiting associated with migraine attacks. Similar efficacy was seen when subjects self-administered sumatriptan injection using an autoinjector.

The efficacy of sumatriptan injection was unaffected by whether or not the migraine was associated with aura, duration of attack, gender or age of the subject, or concomitant use of common migraine prophylactic drugs (e.g., beta-blockers).

14.2 Cluster Headache
The efficacy of sumatriptan injection in the acute treatment of cluster headache was demonstrated in 2 randomized, double-blind, placebo-controlled, 2-period crossover trials (Studies 4 and 5). Subjects aged 21 to 65 years were enrolled and were instructed to treat a moderate to very severe headache within 10 minutes of onset. Headache relief was defined as a reduction in headache severity to mild or no pain. In both trials, the proportion of individuals gaining relief at 10 or 15 minutes was significantly greater among subjects receiving 6 mg of sumatriptan injection compared with those who received placebo (see Table 4).

PHARMACIST - DETACH FROM HERE

PATIENT INFORMATION
Sumatriptan Injection USP

Read this Patient Information before you start taking sumatriptan and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about sumatriptan injection?

Sumatriptan can cause serious side effects, including:

Heart attack and other heart problems. Heart problems may lead to death.

Stop taking sumatriptan and get emergency medical help right away if you have any of the following symptoms of a heart attack:
- discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
- severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
- pain or discomfort in your arms, back, neck, jaw, or stomach
- shortness of breath with or without chest discomfort
- breaking out in a cold sweat
- nausea or vomiting
- feeling lightheaded

Sumatriptan is not for people with risk factors for heart disease unless a heart exam is done and shows no problem. You have a higher risk for heart disease if you:
- have high blood pressure
- have high cholesterol levels
- smoke
- are overweight
- have diabetes
- have a family history of heart disease

What is sumatriptan?

Sumatriptan is a prescription medicine used to treat acute migraine headaches with or without aura and acute cluster headaches in adults who have been diagnosed with migraine or cluster headaches.

Sumatriptan is not used to treat other types of headaches such as hemiplegic (that make you unable to move on one side of your body) or basilar (rare form of migraine with aura) migraines.

Sumatriptan is not used to prevent or decrease the number of migraine or cluster headaches you have.

It is not known if sumatriptan is safe and effective in children under 18 years of age.

Who should not take sumatriptan injection?

Do not take sumatriptan injection if you have:
- heart problems or a history of heart problems
- narrowing of blood vessels to your legs, arms, stomach, or kidney (peripheral vascular disease)
- uncontrolled high blood pressure
- hemiplegic migraines or basilar migraines. If you are not sure if you have these types of migraines, ask your healthcare provider.
- had a stroke, transient ischemic attacks (TIAs), or problems with your blood circulation
- taken any of the following medicines in the last 24 hours:
  - almotriptan (AXERT®)
  - eletriptan (RELPAX®)
  - frovatriptan (FROVA®)
  - naratriptan (AMERGE®)
  - rizatriptan (MAXALT®, MAXALT-MLT®)
  - sumatriptan and naproxen (TREXIMET®)
  - ergotamines (CAFERGOT®, ERGOMAR®, MIGERGOT®)
  - dihydroergotamine (D.H.E. 45®, MIGRANAL®)

Ask your healthcare provider if you are not sure if your medicine is listed above.
- an allergy to sumatriptan or any of the ingredients in sumatriptan injection. See the end of this leaflet for a complete list of ingredients in sumatriptan injection.

What should I tell my healthcare provider before taking sumatriptan injection?

Before you take sumatriptan, tell your healthcare provider about all of your medical conditions, including if you:
- have high blood pressure
- have high cholesterol
- have diabetes
- smoke
- are overweight
- have heart problems or family history of heart problems or stroke
- have liver problems
- have had epilepsy or seizures
- are not using effective birth control
- become pregnant while taking sumatriptan
- are breastfeeding or plan to breastfeed. Sumatriptan passes into your breast milk and may harm your baby. Talk with your healthcare provider about the best way to feed your baby if you take sumatriptan.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Using sumatriptan with certain other medicines can affect each other, causing serious side effects.

Especially tell your healthcare provider if you take antidepressant medicines called:
- selective serotonin reuptake inhibitors (SSRIs)
- serotonin norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants (TCAs)
- monoamine oxidase inhibitors (MAOIs)

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take sumatriptan injection?
- Certain people should take their first dose of sumatriptan injection in their healthcare provider's office or in another medical setting. Ask your healthcare provider if you should take your first dose in a medical setting.
- Use sumatriptan injection exactly as your healthcare provider tells you to use it.
- Your healthcare provider may change your dose. Do not change your dose without first talking with your healthcare provider.
- For adults, the usual dose is a single injection given just below the skin.
- You should give an injection as soon as the symptoms of your headache start, but it may be given at any time during a migraine attack.
- If you did not get any relief after the first injection, do not give a second injection without first talking with your healthcare provider.
- You can take a second injection 1 hour after the first injection, but not sooner, if your headache came back after your first injection.
- Do not take more than 12 mg in a 24 hour period.
- If you use too much sumatriptan injection, call your healthcare provider or go to the nearest hospital emergency room right away.
- You should write down when you have headaches and when you take sumatriptan injection so you can talk with your healthcare provider about how sumatriptan injection is working for you.

What should I avoid while taking sumatriptan injection?

Sumatriptan can cause dizziness, weakness, or drowsiness. If you have these symptoms, do not drive a car, use machinery, or do anything where you need to be alert.

What are the possible side effects of sumatriptan injection?

Sumatriptan may cause serious side effects. See "**What is the most important information I should know about sumatriptan injection?**"

These serious side effects include:
- changes in color or sensation in your fingers and toes (Raynaud's syndrome)
- stomach and intestinal problems (gastrointestinal and colonic ischemic events). Symptoms of gastrointestinal and colonic ischemic events include:
  - sudden or severe stomach pain
  - stomach pain after meals
  - weight loss
  - nausea or vomiting
  - constipation or diarrhea
  - bloody diarrhea
  - fever
- problems with blood circulation to your legs and feet (peripheral vascular ischemia). Symptoms of peripheral vascular ischemia include:
  - cramping and pain in your legs or hips
  - feeling of heaviness or tightness in your leg muscles
  - burning or aching pain in your feet or toes while resting
  - numbness, tingling, or weakness in your legs
  - cold feeling or color changes in 1 or both legs or feet
- medication overuse headaches. Some people who use too many sumatriptan injections may have worse headaches (medication overuse headache). If your headaches get worse, your healthcare provider may decide to stop your treatment with sumatriptan.
- serotonin syndrome. Serotonin syndrome is a rare but serious problem that can happen in people using sumatriptan injection, especially if sumatriptan injection is used with antidepressant medicines called SSRIs or SNRIs.

Call your healthcare provider right away if you have any of the following symptoms of serotonin syndrome:
  - mental changes such as seeing things that are not there (hallucinations), agitation, or coma
  - fast heartbeat
  - changes in blood pressure
  - high body temperature
  - tight muscles
  - trouble walking
- seizures. Seizures have happened in people taking sumatriptan injection who have never had seizures before. Talk with your healthcare provider about your chance of having seizures while you take sumatriptan injection.

The most common side effects of sumatriptan injection include:
- pain or redness at your injection site
- tingling or numbness in your fingers or toes
- dizziness
- warm, hot, burning feeling to your face (flushing)
- discomfort or stiffness in your neck
- feeling weak, drowsy, or tired

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of sumatriptan injection. For more information, ask your healthcare provider or pharmacist.

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

How should I store sumatriptan injection?
- Store at 25°C (77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
- Store your medicine away from light.
- Keep your medicine in the packaging or carrying case provided with it.

Keep sumatriptan injection and all medicines out of the reach of children.

General information about the safe and effective use of sumatriptan injection

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use sumatriptan injection for a condition for which it was not prescribed. Do not give sumatriptan injection to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about sumatriptan injection. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about sumatriptan injection that is written for healthcare professionals.

For more information, call 1-888-375-3784.

What are the ingredients in sumatriptan succinate injection?

Active ingredient: sumatriptan succinate USP

Inactive ingredients: sodium chloride, water for injection.

The other brands listed are trademarks of their respective owners and are not trademarks of Dr. Reddy's Laboratories Limited. The makers of these brands are not affiliated with and do not endorse Dr. Reddy's Laboratories Limited or its products.

(Continued on other side)

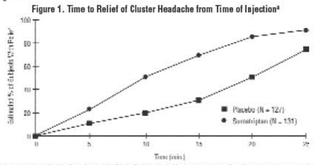
(b) (4)

Table 4. Proportion of Subjects With Cluster Headache Relief by Time is Studies 4 and 5

	Study 4		Study 5	
	Placebo (n = 39)	Sumatriptan Injection 6 mg (n = 39)	Placebo (n = 88)	Sumatriptan Injection 6 mg (n = 92)
Subjects with pain relief (no/mild)				
5 Minutes post-injection	8%	21%	7%	23%[a]
10 Minutes post-injection	10%	49%	25%	49%[a]
15 Minutes post-injection	26%	74%	35%	75%[a]

[a] P<0.05.
(n = Number of headaches treated.)
An estimate of the cumulative probability of a subject with a cluster headache obtaining relief after being treated with either sumatriptan injection or placebo is presented in Figure 1.

Figure 1. Time to Relief of Cluster Headache from Time of Injection[a]



[a] The figure uses Kaplan-Meier (product limit) Survivorship Plot. Subjects taking rescue medication were censored at 15 minutes.
The plot was constructed with data from subjects who either experienced relief or did not require (request) rescue medication within a period of 2 hours following treatment. As a consequence, the data in the plot are derived from only a subset of the 258 headaches treated (rescue medication was required in 52 of the 127 placebo-treated headaches and 18 of the 131 headaches treated with sumatriptan injection).

Other data suggest that treatment with sumatriptan injection is not associated with an increase in early recurrence of headache and has little effect on the incidence of later-occurring headaches (i.e., those occurring after 2, but before 18 or 24 hours).

16 HOW SUPPLIED/STORAGE AND HANDLING

Sumatriptan injection USP contains sumatriptan (base) as the succinate salt and is supplied as a clear, colorless to pale yellow, sterile, nonpyrogenic solution as follows:

NDC 55111-693-12 Sumatriptan Injection USP Autoinjector System includes 2 Autoinjectors, each with an associated single-dose prefilled syringe which contains 6 mg of sumatriptan (as the succinate salt) and 3.5 mg of sodium chloride in 0.5 mL of solution.

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use).

17.1 Risk of Myocardial Ischemia and/or Infarction, Prinzmetal's Angina, Other Vasospasm-Related Events, Arrhythmias, and Cerebrovascular Events

Inform patients that sumatriptan injection may cause serious cardiovascular side effects such as myocardial infarction or stroke. Although serious cardiovascular events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, irregular heartbeat, significant rise in blood pressure, weakness, and slurring of speech and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up [see **Warnings and Precautions (5.1, 5.2, 5.4, 5.5, and 5.8)**].

17.2 Anaphylactic/Anaphylactoid Reactions

Inform patients that anaphylactic/anaphylactoid reactions have occurred in patients receiving sumatriptan injection. Such reactions can be life threatening or fatal. In general, anaphylactic reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens [see **Warnings and Precautions (5.9)**].

17.3 Medication Overuse Headache

Inform patients that use of acute migraine drugs for 10 or more days per month may lead to an exacerbation of headache and encourage patients to record headache frequency and drug use (e.g., by keeping a headache diary) [see **Warnings and Precautions (5.6)**].

17.4 Pregnancy

Inform patients that sumatriptan injection should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus [see **Use in Specific Populations (8.1)**].

17.5 Nursing Mothers

Advise patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed [see **Use in Specific Populations (8.3)**].

17.6 Ability To Perform Complex Tasks

Since migraines or treatment with sumatriptan injection may cause somnolence and dizziness, instruct patients to evaluate their ability to perform complex tasks during migraine attacks and after administration of sumatriptan injection.

17.7 Serotonin Syndrome

Patients should be cautioned about the risk of serotonin syndrome with the use of sumatriptan injection or other triptans, particularly during combined use with SSRIs, SNRIs, TCAs, and MAO inhibitors [see **Warnings and Precautions (5.7) and Drug Interactions (7.4)**].

17.8 How to Use Sumatriptan Injection

Provide patients instruction on the proper use of sumatriptan injection if they are able to self-administer sumatriptan injection in medically unsupervised situation.

Inform patients that the needle in the autoinjector penetrates approximately 1/4 of an inch (5 to 6 mm). Inform patients that the injection is intended to be given subcutaneously and intramuscular or intravascular delivery should be avoided. Instruct patients to use injection sites with an adequate skin and subcutaneous thickness to accommodate the length of the needle.

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PATIENT INFORMATION
Sumatriptan Injection USP

Read this Patient Information before you start taking sumatriptan and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about sumatriptan injection?

Sumatriptan can cause serious side effects, including:

Heart attack and other heart problems. Heart problems may lead to death.

Stop taking sumatriptan and get emergency medical help right away if you have any of the following symptoms of a heart attack:
- discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
- severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
- pain or discomfort in your arms, back, neck, jaw, or stomach
- shortness of breath with or without chest discomfort
- breaking out in a cold sweat
- nausea or vomiting
- feeling lightheaded

Sumatriptan is not for people with risk factors for heart disease unless a heart exam is done and shows no problem. You have a higher risk for heart disease if you:
- have high blood pressure
- have high cholesterol levels
- smoke
- are overweight
- have diabetes
- have a family history of heart disease

What is sumatriptan?

Sumatriptan is a prescription medicine used to treat acute migraine headaches with or without aura and acute cluster headaches in adults who have been diagnosed with migraine or cluster headaches.

Sumatriptan is not used to treat other types of headaches such as hemiplegic (that make you unable to move on one side of your body) or basilar (rare form of migraine with aura) migraines.

Sumatriptan is not used to prevent or decrease the number of migraine or cluster headaches you have.
It is not known if sumatriptan is safe and effective in children under 18 years of age.

Who should not take sumatriptan injection?

Do not take sumatriptan injection if you have:
- heart problems or a history of heart problems
- narrowing of blood vessels to your legs, arms, stomach, or kidney (peripheral vascular disease)
- uncontrolled high blood pressure
- hemiplegic migraines or basilar migraines. If you are not sure if you have these types of migraines, ask your healthcare provider.
- had a stroke, transient ischemic attacks (TIAs), or problems with your blood circulation
- taken any of the following medicines in the last 24 hours:
  - almotriptan (AXERT®)
  - eletriptan (RELPAX®)
  - frovatriptan (FROVA®)
  - naratriptan (AMERGE®)
  - rizatriptan (MAXALT®, MAXALT-MLT®)
  - sumatriptan and naproxen (TREXIMET®)
  - ergotamines (CAFERGOT®, ERGOMAR®, MIGERGOT®)
  - dihydroergotamine (D.H.E. 45®, MIGRANAL®)

Ask your healthcare provider if you are not sure if your medicine is listed above.
- an allergy to sumatriptan or any of the ingredients in sumatriptan injection. See the end of this leaflet for a complete list of ingredients in sumatriptan injection.

What should I tell my healthcare provider before taking sumatriptan injection?

Before you take sumatriptan, tell your healthcare provider about all of your medical conditions, including if you:
- have high blood pressure
- have high cholesterol
- have diabetes
- smoke
- are overweight
- have heart problems or family history of heart problems or stroke
- have liver problems
- have had epilepsy or seizures
- are not using effective birth control
- become pregnant while taking sumatriptan
- are breastfeeding or plan to breastfeed. Sumatriptan passes into your breast milk and may harm your baby. Talk with your healthcare provider about the best way to feed your baby if you take sumatriptan.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Using sumatriptan with certain other medicines can affect each other, causing serious side effects.

Especially tell your healthcare provider if you take antidepressant medicines called:
- selective serotonin reuptake inhibitors (SSRIs)
- serotonin norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants (TCAs)
- monoamine oxidase inhibitors (MAOIs)

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take sumatriptan injection?
- Certain people should take their first dose of sumatriptan injection in their healthcare provider's office or in another medical setting. Ask your healthcare provider if you should take your first dose in a medical setting.
- Use sumatriptan injection exactly as your healthcare provider tells you to use it.
- Your healthcare provider may change your dose. Do not change your dose without first talking with your healthcare provider
- For adults, the usual dose is a single injection given just below the skin.
- You should give an injection as soon as the symptoms of your headache start, but it may be given at any time during a migraine attack.
- If you did not get any relief after the first injection, do not give a second injection without first talking with your healthcare provider.
- You can take a second injection 1 hour after the first injection, but not sooner, if your headache came back after your first injection.
- Do not take more than 12 mg in a 24 hour period.
- If you use too much sumatriptan injection, call your healthcare provider or go to the nearest hospital emergency room right away.
- You should write down when you have headaches and when you take sumatriptan injection so you can talk with your healthcare provider about how sumatriptan injection is working for you.

What should I avoid while taking sumatriptan injection?

Sumatriptan can cause dizziness, weakness, or drowsiness. If you have these symptoms, do not drive a car, use machinery, or do anything where you need to be alert.

What are the possible side effects of sumatriptan injection?

Sumatriptan may cause serious side effects. See **"What is the most important information I should know about sumatriptan injection?"**

These serious side effects include:
- changes in color or sensation in your fingers and toes (Raynaud's syndrome)
- stomach and intestinal problems (gastrointestinal and colonic ischemic events). Symptoms of gastrointestinal and colonic ischemic events include:
  - sudden or severe stomach pain
  - stomach pain after meals
  - weight loss
  - nausea or vomiting
  - constipation or diarrhea
  - bloody diarrhea
  - fever
- problems with blood circulation to your legs and feet (peripheral vascular ischemia). Symptoms of peripheral vascular ischemia include:
  - cramping and pain in your legs or hips
  - feeling of heaviness or tightness in your leg muscles
  - burning or aching pain in your feet or toes while resting
  - numbness, tingling, or weakness in your legs
  - cold feeling or color changes in 1 or both legs or feet
- medication overuse headaches. Some people who use too many sumatriptan injections may have worse headaches (medication overuse headache). If your headaches get worse, your healthcare provider may decide to stop your treatment with sumatriptan.
- serotonin syndrome. Serotonin syndrome is a rare but serious problem that can happen in people using sumatriptan injection, especially if sumatriptan injection is used with antidepressant medicines called SSRIs or SNRIs.

Call your healthcare provider right away if you have any of the following symptoms of serotonin syndrome:
- mental changes such as seeing things that are not there (hallucinations), agitation, or coma
- fast heartbeat
- changes in blood pressure
- high body temperature
- tight muscles
- trouble walking
- seizures. Seizures have happened in people taking sumatriptan injection who have never had seizures before. Talk with your healthcare provider about your chance of having seizures while you take sumatriptan injection.

The most common side effects of sumatriptan injection include:
- pain or redness at your injection site
- tingling or numbness in your fingers or toes
- dizziness
- warm, hot, burning feeling to your face (flushing)
- discomfort or stiffness in your neck
- feeling weak, drowsy, or tired

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of sumatriptan injection. For more information, ask your healthcare provider or pharmacist.

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

How should I store sumatriptan injection?
- Store at 25°C (77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
- Store your medicine away from light.
- Keep your medicine in the packaging or carrying case provided with it.

Keep sumatriptan injection and all medicines out of the reach of children.

General information about the safe and effective use of sumatriptan injection

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use sumatriptan injection for a condition for which it was not prescribed. Do not give sumatriptan injection to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about sumatriptan injection. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about sumatriptan injection that is written for healthcare professionals.

For more information, call 1-888-375-3784.

What are the ingredients in sumatriptan injection?

Active ingredient: sumatriptan succinate USP

Inactive ingredients: sodium chloride, water for injection

The other brands listed are trademarks of their respective owners and are not trademarks of Dr. Reddy's Laboratories Limited. The makers of these brands are not affiliated with and do not endorse Dr. Reddy's Laboratories Limited or its products.

SUMATRIPTAN INJECTION
INSTRUCTIONS FOR USE OF DISPOSABLE SUMATRIPTAN AUTOINJECTOR SYSTEM

Read this Patient Instructions for Use before you start to use Sumatriptan Autoinjector System. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment. You and your healthcare provider should talk about sumatriptan injection when you start taking it and at regular checkups.

- **Use the device immediately once the cap has been removed; it is advised not to postpone the injection.**
- **Keep the Sumatriptan Autoinjector System out of the reach of children.**

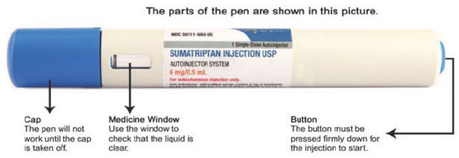
Instructions for Use of Autoinjector Pen
Important things that you need to know

This device is called an Autoinjector pen. Here we use the shorter name 'pen'.
1. Read all of the Instructions carefully before using this pen.
2. Follow these step-by-step instructions every time you use the pen.
3. Only use each pen once - do not try to use more than once.

If you have any further questions, ask your doctor or pharmacist

A. ABOUT THE AUTOINJECTOR PEN

The parts of the pen are shown in this picture.



Cap
The pen will not work until the cap is taken off.

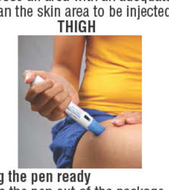
Medicine Window
Use the window to check that the liquid is clear.

Button
The button must be pressed firmly down for the injection to start.

B. GETTING READY
Getting ready for the injection

1. Wash your hands.
2. Choose an area with an adequate fatty tissue layer.
3. Clean the skin area to be injected with alcohol or a new sterile swab

THIGH

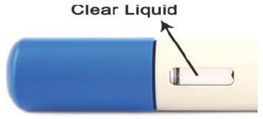


ARM

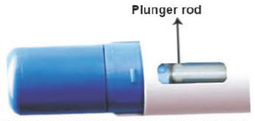
Getting the pen ready

4. Take the pen out of the package.
5. Look in the medicine window on the pen.
   - Before injection, to check that the liquid is clear.
   - If it is difficult to see what is in the window, hold the pen upto the light and check.
   - After injection, the plunger rod completely fills the medicine window.

Before Injection
Clear Liquid



After Injection
Plunger rod



If the plunger rod can be seen through the medicine window, the device is spent and cannot be used again.

6. **Pull the cap off the pen**
   - Do not twist the cap.
   - Pull it straight off.
   - Keep the cap for step 7.

7. **Look inside the cap, check that the gray needle cover is inside.**
   - Do not use the pen if the gray needle cover is not inside the cap.

8. **Do not try to put the cap back**
   - If you try to put it back, this will damage the needle.

You are now ready to inject the medicine, go to step 9.

C. INJECTING THE MEDICINE

9. **Without pressing the blue button, push the pen firmly against your skin.**
   - You will now see a small blue projection in the medicine window.
   - **As long as the blue circle is visible in the medicine window, the safety lock is de-activated; the pen could fire unintentionally if the blue button is pressed by accident.**

Keep the pen pressed against your skin for the next steps

10. **Do not attempt to re-engage the safety lock at any time.**
11. **Firmly press down the blue button on the top of the pen until it will not go further.**
    - You will hear a loud click (this indicates that the injection has started)
    - Keep pushing the pen against your skin

12. **Do not take the pen off your skin**
    - Wait for about 5 seconds until you hear the second click.
    - The second click indicates you that the injection has finished.

If you take the pen off before the second click, not all the medicine will be injected.

13. **Carefully take the pen off your skin.**

D. WHAT TO DO AFTER THE INJECTION

14. **Replace the cap right away**

If you notice a spot of blood at the injection site, dab away with a cotton ball or tissue paper. Do not rub the injection site. If needed, you may cover the injection site with a bandage.

15. **Discard the whole sumatriptan injection autoinjector after use.**
    Do not try to reuse the autoinjector pen

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

To reorder additional Patient information sheets contact Dr. Reddy's Customer Service at 1-866-733-3952.

Rx Only

Manufactured by:
Gland Pharma Limited
D.P. Pally – 500 043 INDIA

Manufactured for:
Dr. Reddy's Laboratories Limited
Bachupally – 500 090 INDIA

Issued: 0913

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PHARMACIST - DETACH FROM HERE

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SUMATRIPTAN INJECTION
INSTRUCTIONS FOR USE OF DISPOSABLE SUMATRIPTAN AUTOINJECTOR SYSTEM

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- **Use the device immediately once the cap has been removed; it is advised not to postpone the injection.**
- **Keep the Sumatriptan Autoinjector System out of the reach of children.**

Instructions for Use of Autoinjector Pen
Important things that you need to know

This device is called an Autoinjector pen. Here we use the shorter name 'pen'.
1. Read all of the Instructions carefully before using this pen.
2. Follow these step-by-step instructions every time you use the pen.
3. Only use each pen once - do not try to use more than once.

If you have any further questions, ask your doctor or pharmacist

A. ABOUT THE AUTOINJECTOR PEN

B. GETTING READY
Getting ready for the injection

1. Wash your hands.
2. Choose an area with an adequate fatty tissue layer.
3. Clean the skin area to be injected with alcohol or a new sterile swab

THIGH

ARM

Getting the pen ready

4. Take the pen out of the package.
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   - Before injection, to check that the liquid is clear.
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   - After injection, the plunger rod completely fills the medicine window.

Before Injection
Clear Liquid

After Injection
Plunger rod

If the plunger rod can be seen through the medicine window, the device is spent and cannot be used again.

6. **Pull the cap off the pen**
   - Do not twist the cap.
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C. INJECTING THE MEDICINE

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15. **Discard the whole sumatriptan injection autoinjector after use.**
    Do not try to reuse the autoinjector pen

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PATIENT INFORMATION
Sumatriptan Injection USP

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Sumatriptan can cause serious side effects, including:

Heart attack and other heart problems. Heart problems may lead to death.

Stop taking sumatriptan and get emergency medical help right away if you have any of the following symptoms of a heart attack:

- discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
- severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
- pain or discomfort in your arms, back, neck, jaw, or stomach
- shortness of breath with or without chest discomfort
- breaking out in a cold sweat
- nausea or vomiting
- feeling lightheaded

Sumatriptan is not for people with risk factors for heart disease unless a heart exam is done and shows no problem. You have a higher risk for heart disease if you:

- have high blood pressure
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- smoke
- are overweight
- have diabetes
- have a family history of heart disease

What is sumatriptan?

Sumatriptan is a prescription medicine used to treat acute migraine headaches with or without aura and acute cluster headaches in adults who have been diagnosed with migraine or cluster headaches.

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Who should not take sumatriptan injection?

Do not take sumatriptan injection if you have:

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- narrowing of blood vessels to your legs, arms, stomach, or kidney (peripheral vascular disease)
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- hemiplegic migraines or basilar migraines. If you are not sure if you have these types of migraines, ask your healthcare provider.
- had a stroke, transient ischemic attacks (TIAs), or problems with your blood circulation
- taken any of the following medicines in the last 24 hours:
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  - eletriptan (RELPAX®)
  - frovatriptan (FROVA®)
  - naratriptan (AMERGE®)
  - rizatriptan (MAXALT®, MAXALT-MLT®)
  - sumatriptan and naproxen (TREXIMET®)
  - ergotamines (CAFERGOT®, ERGOMAR®, MIGERGOT®)
  - dihydroergotamine (D.H.E. 45®, MIGRANAL®)

Ask your healthcare provider if you are not sure if your medicine is listed above.

- an allergy to sumatriptan or any of the ingredients in sumatriptan injection. See the end of this leaflet for a complete list of ingredients in sumatriptan injection.

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Before you take sumatriptan, tell your healthcare provider about all of your medical conditions, including if you:

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- have high cholesterol
- have diabetes
- smoke
- are overweight
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- have liver problems
- have had epilepsy or seizures
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- are breastfeeding or plan to breastfeed. Sumatriptan passes into your breast milk and may harm your baby. Talk with your healthcare provider about the best way to feed your baby if you take sumatriptan.

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- You can take a second injection 1 hour after the first injection, but not sooner, if your headache came back after your first injection.
- Do not take more than 12 mg in a 24 hour period.
- If you use too much sumatriptan injection, call your healthcare provider or go to the nearest hospital emergency room right away.
- You should write down when you have headaches and when you take sumatriptan injection so you can talk with your healthcare provider about how sumatriptan injection is working for you.

What should I avoid while taking sumatriptan injection?

Sumatriptan can cause dizziness, weakness, or drowsiness. If you have these symptoms, do not drive a car, use machinery, or do anything where you need to be alert.

What are the possible side effects of sumatriptan injection?

Sumatriptan may cause serious side effects. See **"What is the most important information I should know about sumatriptan injection?"**

These serious side effects include:

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  - weight loss
  - nausea or vomiting
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  - bloody diarrhea
  - fever
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  - cramping and pain in your legs or hips
  - feeling of heaviness or tightness in your leg muscles
  - burning or aching pain in your feet or toes while resting
  - numbness, tingling, or weakness in your legs
  - cold feeling or color changes in 1 or both legs or feet
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Call your healthcare provider right away if you have any of the following symptoms of serotonin syndrome:

- mental changes such as seeing things that are not there (hallucinations), agitation, or coma
- fast heartbeat
- changes in blood pressure
- high body temperature
- tight muscles
- trouble walking

- seizures. Seizures have happened in people taking sumatriptan injection who have never had seizures before. Talk with your healthcare provider about your chance of having seizures while you take sumatriptan injection.

The most common side effects of sumatriptan injection include:

- pain or redness at your injection site
- tingling or numbness in your fingers or toes
- dizziness
- warm, hot, burning feeling to your face (flushing)
- discomfort or stiffness in your neck
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Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of sumatriptan injection. For more information, ask your healthcare provider or pharmacist.

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- Store your medicine away from light.
- Keep your medicine in the packaging or carrying case provided with it.

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This Patient Information leaflet summarizes the most important information about sumatriptan injection. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about sumatriptan injection that is written for healthcare professionals.

For more information, call 1-888-375-3784.

What are the ingredients in sumatriptan succinate injection?

Active ingredient: sumatriptan succinate USP

Inactive ingredients: sodium chloride, water for injection.

The other brands listed are trademarks of their respective owners and are not trademarks of Dr. Reddy's Laboratories Limited. The makers of these brands are not affiliated with and do not endorse Dr. Reddy's Laboratories Limited or its products.

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SUMATRIPTAN INJECTION
INSTRUCTIONS FOR USE OF DISPOSABLE SUMATRIPTAN AUTOINJECTOR SYSTEM

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- **Use the device immediately once the cap has been removed; it is advised not to postpone the injection.**
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Important things that you need to know

This device is called an Autoinjector pen. Here we use the shorter name 'pen'.

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   If you have any further questions, ask your doctor or pharmacist

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B. GETTING READY
Getting ready for the injection

1. Wash your hands.
2. Choose an area with an adequate fatty tissue layer.
3. Clean the skin area to be injected with alcohol or a new sterile swab

THIGH

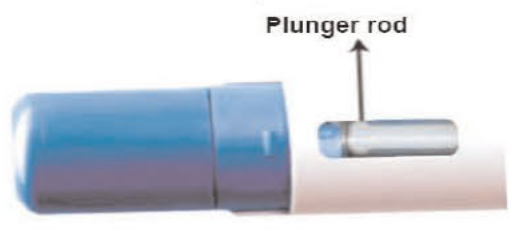
ARM

Getting the pen ready

4. Take the pen out of the package.
5. Look in the medicine window on the pen.
   - Before injection, to check that the liquid is clear.
   - If it is difficult to see what is in the window, hold the pen upto the light and check.
   - After injection, the plunger rod completely fills the medicine window.

Before Injection

After Injection



If the plunger rod can be seen through the medicine window, the device is spent and cannot be used again.

6. **Pull the cap off the pen**
   - Do not twist the cap.
   - Pull it straight off.
   - Keep the cap for step 7.

7. **Look inside the cap, check that the gray needle cover is inside.**
   - Do not use the pen if the gray needle cover is not inside the cap.

8. **Do not try to put the cap back**
   - If you try to put it back, this will damage the needle.

You are now ready to inject the medicine, go to step 9.

C. INJECTING THE MEDICINE

9. **Without pressing the blue button, push the pen firmly against your skin.**
   - You will now see a small blue projection in the medicine window.
   - **As long as the blue circle is visible in the medicine window, the safety lock is de-activated; the pen could fire unintentionally if the blue button is pressed by accident.**

Keep the pen pressed against your skin for the next steps

10. **Do not attempt to re-engage the safety lock at any time**

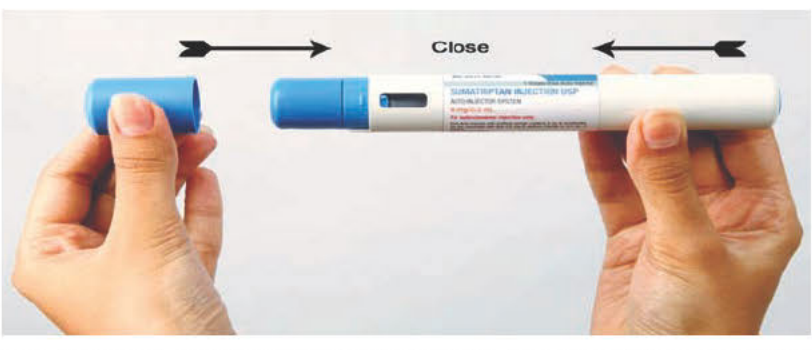
11. **Firmly press down the blue button on the top of the pen until it will not go further.**
    - You will hear a loud click (this indicates that the injection has started)
    - Keep pushing the pen against your skin

12. **Do not take the pen off your skin**
    - Wait for about 5 seconds until you hear the second click.
    - The second click indicates you that the injection has finished.
      If you take the pen off before the second click, not all the medicine will be injected.

13. **Carefully take the pen off your skin.**

D. WHAT TO DO AFTER THE INJECTION

14. **Replace the cap right away**



If you notice a spot of blood at the injection site, dab away with a cotton ball or tissue paper. Do not rub the injection site. If needed, you may cover the injection site with a bandage.

15. **Discard the whole sumatriptan injection autoinjector after use. Do not try to reuse the autoinjector pen**

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

To reorder additional Patient information sheets contact Dr. Reddy's Customer Service at 1-866-733-3952.

Rx Only

Manufactured by:
Gland Pharma Limited
D.P. Pally – 500 043 INDIA

Manufactured for:
Dr. Reddy's Laboratories Limited
Bachupally – 500 090 INDIA

Issued: 0913

DR. REDDY'S

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-495

LABELING REVIEWS

APPROVAL SUMMARY

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING (Third Cycle)

ANDA Number:	**090495**
Date of Submission:	**October 24, 2013**
Applicant:	**Dr Reddy's Laboratories, Limited**
Established Name and Strength:	**Sumatriptan Injection USP, 0.6 mg/0.5 mL (Prefilled Syringe)**
Proposed Proprietary Name:	**None**

Labeling Comments below are considered:

☒ No Comments **(**Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated October 24, 2013.

Please continue to monitor available labeling resources such as 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.

Note RPM - Labeling comments end here

REVISIONS NEEDED POST APPROVAL? Place net quantity statement on container label

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER: none

Review Summary

Labeling Submitted	Date submitted	Final or Draft	Recommendation
CONTAINER	10-24-13	FINAL	APPROVE
CARTON	10-24-13	FINAL	APPROVE
INSERT	10-24-13	FINAL	APPROVE
PATIENT INFORMATION	10-24-13	FINAL	APPROVE
INSTRUCTIONS FOR USE	10-24-13	FINAL	APPROVE
REMS PLAN	NONE	N/A	N/A
SPL	10-24-13	FINAL	APPROVE

REMS required? NO			
PPIs (505-1(e))	☒ Yes	☐ No	
Communication plan (505-1(e))	☐ Yes	☒ No	
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☒ No	
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☒ No	
Timetable for assessment (505-1(d))	☐ Yes	☒ No	
ANDA REMS acceptable?	☐ Yes	☐ No	☒ N/A

FOR THE RECORD:

1. **MODEL LABELING**

Review based on the labeling of Imitrex® Injection (NDA 20-080/S-039/S-040/S-041/S-045; approved 10-2-12.

2. **USP & PF -- Drug Product has a USP monograph.**

PACKAGING AND STORAGE: Preserve in single-dose containers, preferably of Type 1 glass. Store between 2° and 30°, protected from light

3. **PATENT AND EXCLUSIVITY**

Patent Data – 20-080

No	Expiration	Use Code	Use	Labeling Impact	File
None					

Exclusivity Data – 20-080

Code/sup	Expiration	Use Code	Description		Labeling Impact
None					NONE

4. **INACTIVE INGREDIENTS**
RLD - Sodium Chloride, Water for Injection
ANDA - Sodium Chloride, Water for Injection

5. **MANUFACTURING FACILITY** - Gland Pharma Limited - INDIA

6. **FINISHED PRODUCT DESCRIPTION**

RLD and ANDA: **Clear, colorless to pale yellow, sterile, non-pyrogenic solution**

7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD - Store between 2° and 30°C (36° and 86°F). Protect from light.
ANDA - Store at 25° C (77°F); excursions permiteed between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].. Protect from light. Retain in carton until time of use.

8. **PRODUCT LINE**

RLD

- Imitrex STAT dose System®, 4 mg, containing 2 prefilled syringe cartridge (Imitrex STAT dose pen®), and instruction for use.
- Imitrex STAT dose System®, 6 mg, containing 2 prefilled syringe cartridge (Imitrex STAT dose pen®), and instruction for use.
- Imitrex two 4 mg single-dose prefilled syringe cartridges for use with Imitrex STATdose System.
- Imitrex two 6 mg single-dose prefilled syringe cartridges for use with Imitrex STATdose System.
- Imitrex Injection Single-dose Vials (6 mg/0.5 mL) in carton of 5 vials.

ANDA

Sumatriptan Succinate Injection, 6 mg/0.5 mL is proposed to be supplied as follows:

0.5 mL single-dose prefilled syringe. - One prefilled syringe shall be packed in a trade pack with 2 prefilled syringes and 2 autoinjectors packed in the firm's trade carton along with a PIL (Patient Information Leaflet, an IFU (Instructions For Use) and an insert labeling.

9. **CONTAINER/CLOSURE –** 1 mL clear glass pre-filled syringe USP Type I plugged with 13 mm black (b) (4) plunger stopper

10. **MEDICATION GUIDES/PATIENT PACKAGE INSERT**
Patient Information Sheet and Patient Instructions for Use

11. **RELATED APPLICATIONS -** NONE

12. **SPL DATA ELEMENTS – SPL ACCEPTABLE**

13. **CITIZENS PETITION/PROPRIETARY NAME/CONSULTS –** NONE

14. Consults were requested from CDRH and CLINICAL – everything complete (though deficient) except for labeling. Labeling comments from the most recent CLINICAL CONSULT review will be included in the CR letter. All of CLINICAL'S concerns were adequately addressed in the 10-24-13 submission.

Date of Review: October 30, 2013

Primary Reviewer: Adolph Vezza

Team Leader: Captain Koung Lee

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

/s/

ADOLPH E VEZZA
10/31/2013

KOUNG U LEE
11/07/2013
Consults from CDRH and Clinical were found to be deficient.

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **090495**

Dates of Submission: **August 31, 2009; January 22, 2010; May 26, 2011; May 18, 2012 and April 30, 2013**

Applicant's Name: **Dr Reddy's Laboratories, Limited**

Established Name and Strength: **Sumatriptan Injection USP, 0.6 mg/0.5 mL (Prefilled Syringe)**

Proposed Proprietary Name: **None**

Labeling Comments below are considered:

☐ NOT easily correctable (applicant cannot respond within 10 business days)

☐ Easily correctable (respond within 10 business days)

☐ No Comments **(**Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

Labeling Deficiencies determined on 8-8-13 based on your submission dated 4-30-13:

AUTOINJECTOR CARTON

1. Include a net quantity statement.

2. 2 Auto-injectors, each with a 0.5 mL prefilled syringe containing 6 mg of sumatriptan injection

INSERT

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

   a. TITLE - "**SUMATRIPTAN Injection, USP**"

b. CONTRAINDICATIONS – Eighth bullet

"Concurrent or recent …"

c. Place a solid horizontal line at the end of this section to separate it from the "FULL PRESCRIBING INFORMATION – CONTENTS*" section.

2. FULL PRESCRIBING INFORMATION

a. 1 INDICATIONS AND USAGE

Limitations of Use, second bullet – Delete the second comma.

b. 2.2 Administration Using the Autoinjector

i. We note that the needle penetration range for the innovator has "(5 to 6 mm)" while your labeling indicates (b) (4) Please comment.

ii. Revise the last sentence to read as follows:

"Instruct patients on the proper use of the sumatriptan autoinjector and direct them to use …"

c. 4 CONTRAINDICATIONS

Eighth bullet – "5-hydroxytryptamine$_1$" [subscript]

d. **5.8 Increase in Blood Pressure**

Revise the title of the subsection to read as shown above.

First sentence – "5-HT$_1$" [subscript]

e. 6.1 Clinical Trials Experience - Migraine Headache

i. First paragraph, first sentence - "U.S." rather than "US"

ii. Table 1 – The data presented in the "Neurological" row is not aligned correctly.

f. 6.2 Postmarketing Experience – First paragraph, last sentence

Delete "injection".

g. 7.4 Selective Serotonin Reuptake Inhibitors/Serotonin …

Delete the second occurrence of "SNRIs".

h. 11 DESCRIPTION – Last sentence – "injection" rather than "injections"

i. 12.1 Mechanism of Action

i. First paragraph, last sentence

A. Delete "injection".

B. Place "5-" and $HT_{1B/1D}$" on the same line of text.

ii. Last paragraph, last sentence

j. 14.1 Migraine – Table 3

Please note that the data has not been entered properly under the "1-Hour Data" rows. Please correct.

k. 14.2 Cluster Headache – Table 4, footnotes

Place "(n = Number of headaches treated.)" immediately under the footnote so it appears on its own line of text.

l 16 HOW SUPPLIED/STORAGE AND HANDLING

"… each with an associated single-dose prefilled syringe which contains 6 mg of sumatriptan (as the succinate salt) and 3.5 mg of sodium chloride in 0.5 mL of solution."

m. 17.8 How to Use Sumatriptan Injection

We note that the needle penetration range for the innovator has "(5 to 6 mm)" while your labeling indicates (b) (4) Please comment.

3. PATIENT INFORMATION

a. "**What should I tell** …",

i. "**Especially tell** …" - "antidepressant medicines" [delete hyphen – add "s"]

ii. "Keep a list …" – "pharmacist" [lower case "p"]

b. "How should I take …", fifth bullet – Delete the excess space between the

words “be” and “given”.

c. “**What are the possible** …”

i. Delete the “●” before “Symptoms of peripheral …”

ii. serotonin syndrome

A). “…using sumatriptan injection.” [delete “s”]

B). “antidepressant” [delete hyphen]

iii. “Call your healthcare …”, seizures – “injection” rather than “injections” [three instances]

iv. “These are not all …” - “injection” rather than “injections”

v. Bold the last two sentences [“**Call your doctor … effects. You may report …**”]

d. “**How should I** …” – **Keep sumatriptan injection and** …” [“injection” rather than “injections”]

e. Place trade name disclaimers at the end of this labeling piece

INFORMATION FOR THE PATIENT

See comments under INSERT – (3) PATIENT INFORMATION

INSTRUCTIONS FOR USE

1. TITLE

Reformat the title to read as shown below:

SUMATRIPTAN INJECTION
INSTRUCTIONS FOR USE OF DISPOSABLE SUMATRIPTAN AUTOINJECTOR SYSTEM

2. See further comments under Division of CLINICAL REVIEW.

Revise your labeling, as instructed above, and submit electronically.

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 **or** your last submitted 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

Note RPM - Labeling comments end here
REMS required? NO **(OTC do NOT require)**

MedGuides and/or PPIs (505-1(e))	☒ Yes	☐ No
Communication plan (505-1(e))	☐ Yes	☒ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☒ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☒ No
Timetable for assessment (505-1(d))	☐ Yes	☒ No

ANDA REMS acceptable?
☐ Yes ☐ No ☒ n/a

	Date submitted	Final or Draft	Recommendation
CARTON	4-30-13	FINAL	REVISE
AUTOINJECTOR PEN LABEL	4-30-13	FINAL	APPROVE
INSERT	4-30-13	FINAL	REVISE
PATIENT INFORMATION	4-30-13	FINAL	REVISE
INSTRUCTIONS FOR USE	4-30-13	FINAL	REVISE
REMS PLAN	NONE	N/A	N/A
SPL	4-30-13	FINAL	REVISE

REVISIONS NEEDED POST APPROVAL?

NOTES/QUESTIONS TO THE CHEMIST REVIEWER: - NONE

FOR THE RECORD:

1. **MODEL LABELING**

Review based on the labeling of Imitrex® Injection (NDA 20-080/S-039/S-040/S-041/S-045; approved 10-2-12.

2. **USP & PF -- Drug Product has a USP monograph.**

PACKAGING AND STORAGE: Preserve in single-dose containers, preferably of Type 1 glass. Store between 2° and 30°, protected from light

3. **PATENT AND EXCLUSIVITY**

Patent Data – 20-080

No	Expiration	Use Code	Use	Labeling Impact	File
None					

Exclusivity Data – 20-080

Code/sup	Expiration	Use Code	Description		Labeling Impact
None					NONE

4. **INACTIVE INGREDIENTS**

RLD - Sodium Chloride, Water for Injection
ANDA - Sodium Chloride, Water for Injection

5. **MANUFACTURING FACILITY -** Gland Pharma Limited - INDIA

6. **FINISHED PRODUCT DESCRIPTION**

RLD and ANDA: **Clear, colorless to pale yellow, sterile, non-pyrogenic solution**

7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD - Store between 2° and 30°C (36° and 86°F). Protect from light.
ANDA - Store at 25° C (77°F); excursions permiteed between 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].. Protect from light. Retain in carton until time of use.

8. **PRODUCT LINE**

RLD

- Imitrex STAT dose System®, 4 mg, containing 2 prefilled syringe cartridge (Imitrex STAT dose pen®), and instruction for use.
- Imitrex STAT dose System®, 6 mg, containing 2 prefilled syringe cartridge (Imitrex STAT dose pen®), and instruction for use.
- Imitrex two 4 mg single-dose prefilled syringe cartridges for use with Imitrex STATdose System.

- Imitrex two 6 mg single-dose prefilled syringe cartridges for use with Imitrex STATdose System.
- Imitrex Injection Single-dose Vials (6 mg/0.5 mL) in carton of 5 vials.

ANDA
Sumatriptan Succinate Injection, 6 mg/0.5 mL is proposed to be supplied as follows:

0.5 mL single-dose prefilled syringe. - One prefilled syringe shall be packed in a trade pack with 2 prefilled syringes and 2 autoinjectors packed in the firm's trade carton along with a PIL (Patient Information Leaflet, an IFU (Instructions For Use) and an insert labeling.

9. **CONTAINER/CLOSURE –** 1 mL clear glass pre-filled syringe USP Type I plugged with 13 mm black (b) (4) plunger stopper

10. **MEDICATION GUIDES/PATIENT PACKAGE INSERT**
Patient Information Sheet and Patient Instructions for Use

11. **RELATED APPLICATIONS -** NONE

12. **SPL DATA ELEMENTS – SPL needs revision**

13. **CITIZENS PETITION/PROPRIETARY NAME/CONSULTS –** NONE

14. Consults were requested from CDRH and CLINICAL – everything complete (though deficient) except for labeling. Labeling comments from the most recent CLINICAL CONSULT review will be included in the CR letter.

Date of Review: 8-8-13

Primary Reviewer: Adolph Vezza

Team Leader: Captain Koung Lee

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

/s/

ADOLPH E VEZZA
08/09/2013

KOUNG U LEE
08/14/2013

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 90-495 Date of Submission: April 28, 2008

Applicant's Name: Dr. Reddy's Laboratories, Limited

Established Name: Sumatriptan Succinate Injection, (b) (4) 6 mg (base)/0.5 mL

Labeling Deficiencies:

1. (b) (4)

2. CONTAINER LABEL FOR AUTO-INJECTION SYSTEM

   Please explain what this proposed label is for. Will it be placed on the auto-injector containing the prefilled syringe? We believe that this label should not be on the auto-injector as it will interfere with the proper use of the auto-injector. Please comment.

3. (b) (4)

4. CARTON - 2 Auto-Injectors with Prefilled Syringe

   a. Relocate the route of administration. See comment 3(b) above.

   b. Add an asterisk (*) to read "*Each Auto-Injector with prefilled syringe…".

   c. See comment 3(f) above.

   d. Include the terms "Sterile, nonpyrogenic".

   e. Include the text (b) (4)

h. Revise to read as follows:

This carton contains:

- 2 Auto-injectors, [redacted] (b) (4)
- Instructions for use/Information for the patient
- Prescribing Information

5. INSERT

a. WARNINGS

Please include the following subsection to appear immediately after the "Other Vasospasm-Related Events" subsection.

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome may occur with triptans, including treatment with sumatriptan, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram) or SNRI (e.g., venlafaxine, duloxetine) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

b. PRECAUTIONS

i. Information for Patients

A) Please verify that your statement "With the autoinjector, the needle penetrates approximately 1/4 of an inch (5 to 6mm)." is accurate.

B) Include the following text as the new last paragraph:

Patients should be cautioned about the risk of serotonin syndrome with the use of sumatriptan or other triptans, especially during combined use with SSRIs or SNRIs.

ii. Drug Interactions - Revise this subsection to red as follows:

Drug Interactions: ***Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome:*** Cases of life-threatening serotonin syndrome have been reported during combined use of SSRIs or SNRIs and triptans (see WARNINGS).

Migraine Prophylactic Medications: There is no evidence that concomitant use of migraine prophylactic medications has any effect on the efficacy of sumatriptan. In 2 Phase III trials in the US, a retrospective analysis of 282 patients who had been using prophylactic drugs (verapamil n = 63, amitriptyline n = 57, propranolol n = 94, for 45 other drugs n = 123) were compared to those who had not used prophylaxis (N = 452). There were no differences in relief rates at 60 minutes postdose for sumatriptan injection, whether or not prophylactic medications were used.

Ergot-Containing Drugs: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and sumatriptan within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

Monoamine Oxidase-A Inhibitors: MAO-A inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure. Therefore, the use of sumatriptan in patients receiving MAO-A inhibitors is not ordinarily recommended. If the clinical situation warrants the combined use of sumatriptan and an MAOI, the dose of sumatriptan employed should be reduced (see CLINICAL PHARMACOLOGY: Drug Interactions: *Monoamine Oxidase Inhibitors* and WARNINGS: Concomitant Drug Use).

c. DOSAGE AND ADMINISTRATION

i. Penultimate paragraph:

See 5(b)(i)(A) above.

ii. Last paragraph:

(b) (4)

d. HOW SUPPLIED

i. 2nd paragraph - Revise to read:

… single-dose prefilled syringe 6 mg(base)/0.5 mL and…

ii. 3rd paragraph - Revise to read:

(b) (4) …

6. INFORMATION FOR THE PATIENT

Please revise the patient information to be the same as the one posted at the DailyMeds website except the following:

Talk to your healthcare…injection (2. Important questions … injection) - Revise the 9th bullet to read as follows and include the disclaimer statements at the end of the labeling.

- Are you taking any medicine for depression or other health problems such as a monoamine oxidase inhibitor, selective serotonin reuptake inhibitor (SSRI), or serotonin norepinephrine reuptake inhibitor (SNRI)? Common SSRIs are citalopram HBr (CELEXA®), escitalopram oxalate (LEXAPRO®), paroxetine (PAXIL®), fluoxetine (PROZAC®/SARAFEM®), olanzapine/fluoxetine (SYMBYAX®), sertraline (ZOLOFT®), and fluvoxamine. Common SNRIs are duloxetine (CYMBALTA®) and venlafaxine (EFFEXOR®).

7. INSTRUCTIONS FOR USE LEAFLET

i. We note that your proposed instructions are incomplete missing the pictorial illustrations for the figures. Please complete these in your next submission.

ii. Your proposed autoinjector is under review. We will defer the comment for the instructions for the autoinjector pending the acceptance of your proposed device. We will not request the final printed labeling until all issues associated with your proposed device is resolved.

Revise the labeling as described above and submit final printed labeling electronically. Please provide the labeling in the Structured Product Labeling (SPL) as well as pdf. format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. 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

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

If you have any questions, please call Dr. Chan Park at 240-276-8951 or send e-mail to chan.park@fda.hhs.gov

{See appended electronic signature page}

_____

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

FOR THE RECORD:

1. MODEL LABELING - Imitrex® Injection was last approved 2/1/06. (NDA 20-080/S-036). However, the innovator's labeling in effect (submitted on 4/11/07, NDA 20-830/S-038) was used as a model.

   a. **MedWatch** contains the following safety information:

   FDA ALERT [7/2006] – Possible Life-Threatening Serotonin Syndrome When Used With SSRI or SNRI Medicines

   A life-threatening condition called serotonin syndrome can happen when medicines called 5-hydroxytryptamine receptor agonists (triptans), such as Imitrex, and medicines used to treat depression and mood disorders called selective serotonin reuptake inhibitors (SSRIs) or selective serotonin/norepinephrine reuptake inhibitors (SNRIs), are used together.

   b. NDA 20-080/S-038 is the last labeling supplement in effect, containing additional information specific to the safety alert posted on the MedWatch website aforementioned.

   c. NDA 20-080/S-040 contains some additional information not directly associated with this safety information. Thus, it was not used as a model for review.

   d. The patient information leaflet submitted in S-038 is identical to the one posted on the website for DailyMeds, except the comment (4) above. We will have the sponsor model after the S-038.

   e. The language on the interaction of sumatriptan and SSRI/SNRIs on the package insert labeling posted on the DailyMeds is slightly different from the one proposed in the S-038. We will go by S-038.

   f. There is neither AE letter nor review on the pending labeling supplements in the DFS.

2. This drug product is not the subject of a USP monograph. Only drug substance is subject to USP monograph.

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition. (section 3.2.p.1) In addition, the inactive ingredients are identical to those for the RLD.

4. The sponsor's proposed labeling includes references to the sumatriptan succinate tablets and nasal spray throughout the labeling. Since the insert labeling specific to the Imitrex® injection contains these references, we find this acceptable. This is the decision made at the time of review ANDA 77-332.

5. PATENTS/EXCLUSIVITIES

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Patent Use Code	Patent certification	Labeling Impact
020080	001	5037845	Aug 6, 2008	U-72	III	None
020080		5037845*PED	Feb 6, 2009			

Exclusivity Data
There is no unexpired exclusivity for this product.
U-72 TREATMENT OF MIGRAINE

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD - Store between 2o and 30oC (36o and 86oF). Protect from light.
ANDA - Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]
Sumatriptan - Preserve in tight, light resistant containers. Protect from freezing, and store below 30°.

7. PACKAGING CONFIGURATIONS
RLD
• Imitrex STAT dose System®, 4 mg, containing 2 prefilled syringe cartridge (Imitrex STAT dose pen®), and instruction for use.
• Imitrex STAT dose System®, 6 mg, containing 2 prefilled syringe cartridge (Imitrex STAT dose pen®), and instruction for use.
• Imitrex two 4 mg single-dose prefilled syringe cartridges for use with Imitrex STATdose System.
• Imitrex two 6 mg single-dose prefilled syringe cartridges for use with Imitrex STATdose System.
• Imitrex Injection Single-dose Vials (6 mg/0.5 mL) in carton of 5 vials.

ANDA
(b) (4)

• 2 Auto-injectors each filled with 6 mg/0.5 mL Single-dose prefilled syringe, Instructions for use

8. Manufacturer - (b) (4)
(b) (4)

9. Container/Closure system - (b) (4)

(b) (4) 1 mL long
Type I glass syringe barrel

with [redacted] needle

Plunger Stopper for 1 mL
long syringe barrel

10. The following e-mail is to/from the division regarding labeling issue:

I am reviewing labeling for one generic application for this drug product and have one question. In the Patient Information Leaflet, it reads [redacted] " section. What is this statement exactly referring to? Is there an instruction sheet inside the carton as to how to use the autoinjector device containing this information? [redacted]. Your feedback on this question would be appreciated. Thanks,

Answer from Lana on 3/15/06 via en e-mail

Chan,
Yes I believe that statement refers to the Imitrex Statdose autoinjector.
Hope this helps. Feel free to contact me if you have further questions.
Thanks, Lana

Date of Review: 11/13/08 Date of Submission: 4/28/08

Primary Reviewer: Chan Park Date:

Team Leader: Lillie Golson Date:

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cc:

ANDA: 90-495
DUP/DIVISION FILE
HFD-613/CPark/LGolson (no cc)

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Review

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

/s/

Chan Park
11/17/2008 12:53:28 PM
LABELING REVIEWER

Lillie Golson
11/17/2008 06:51:00 PM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-495

MEDICAL REVIEWS

Clinical Consultation

Sumatriptan Succinate Injection

Drug Product:	Sumatriptan pre-filled autoinjector
Drug Class:	Drug device combination product Therapeutic Code: Migraine (2011110)
Chemical Name:	Sumatriptan Succinate
ANDA:	090495
ANDA Sponsor:	Dr. Reddy's Laboratories
Reference Listed Drug:	Imitrex Statdose
RLD Sponsor:	Glaxo Smith Kline
Reviewer:	Deborah Seibel, M.D. Medical Officer, Division of Clinical Review (DCR), Office of Generic Drugs
Secondary Reviewer:	John Peters, M.D. Director, Division of Clinical Review (DCR) Office of Generic Drugs
To:	Sukhamaya Bain, Product Quality Reviewer Division of Chemistry II, Office of Generic Drugs Steven Yang, Senior Regulatory Chemist, Consult Coordinator Division of Chemistry I, II, III, Office of Generic Drugs
Reason for Consult:	Please see the quality amendment (SD-23) dated 24-OCT-2013, submitted in response to DCR comments dated 09-JAN-2013 (DARRTS), which were incorporated in the CR letter dated 03-SEP-2013 (DARRTS).
Materials Reviewed:	Sponsor's amendment (SD-23) dated 10/24/2013 ANDA 090495 Complete Response Letter dated 9/3/2013
Date of Submission:	Document date 10/24/2013
Consult Request Date:	11/07/2013
Assignment Date	11/15/2013
Date of Completion:	12/23/2013
Conclusion:	The DCR has evaluated the Sponsor's response to DCR comments dated 1/9/2013 that were incorporated in the CR letter dated 9/3/2013. We find the labeling changes and the Sponsor's clarifications adequately address clinical safety deficiencies. We defer to DBII the decision regarding the Sponsor's BE study and bioequivalence requirements related to device specifications.

1 Executive Summary:

Dr. Reddy first submitted ANDA 90495 to the Division of Bioequivalence II (DBII) April 30, 2008. On March 20, 2009 DCII informed the Sponsor that the application was Not Approvable (NA) because the triggering mechanism for the proposed autoinjector device differed significantly from that employed by the Reference Listed Drug. The major amendment dated August 31, 2009 attempted to correct the deficiencies. The OGD Division of Clinical Review (DCR) consultation dated December 14, 2011 evaluated the proposed sumatriptan auto-injector product for any potential concerns with respect to safety or therapeutic equivalence. Clinical Deficiencies were communicated to the Sponsor by DBII on December 21, 2011. The Sponsor addressed these deficiencies in the Quality/Response to Information Request dated May 18, 2012. The DCR consultation dated 1/9/2013 evaluated the May 18, 2012 Quality/Response to Information Request. DCR's recommendations were incorporated in the CR letter dated 9/3/2013. The clinical deficiencies were primarily related to clarification of the instructions for use (IFU) or other labeling clarifications. The Sponsor's response to the deficiencies cited in the CR letter is contained in the Quality Amendment dated 10/24/2013. This consultation is the DCR evaluation of the Sponsor's response to the DCR recommendations that were included in the CR letter.

We find the labeling changes and the Sponsor's clarifications adequately address clinical safety deficiencies. We defer to DBII the decision regarding the Sponsor's BE study and bioequivalence requirements related to device specifications.

2 Recommendation:

The DCR has evaluated the Sponsor's response to DCR comments dated 1/9/2013 which were incorporated in the CR letter dated 9/3/2013. We find the labeling changes and the Sponsor's clarifications adequately address clinical safety deficiencies. We defer to DBII the decision regarding the Sponsor's BE study and bioequivalence requirements related to device specifications.

3 Regulatory Background:

Dr. Reddy first submitted ANDA 90495 to the Division of Bioequivalence II (DBII) April 30, 2008. On March 20, 2009 DCII informed the Sponsor that the application was Not Approvable (NA) because the triggering mechanism for the proposed autoinjector device differed significantly from that employed by the Reference Listed Drug. In response to the NA letter, the Sponsor submitted a major amendment to correct deficiencies, and also requested an expedited review on August 31, 2009. In this amendment the device design was changed from a (b) (4) to a push & button design, closer to that of the RLD. DBII sent a request to the OGD Division of Clinical Review (DCR) to evaluate the proposed sumatriptan auto-injector product for any potential concerns with respect to safety or therapeutic equivalence; this consultation was finalized in DARRTS on December 14, 2011. Clinical Deficiencies were communicated to the Sponsor by DBII on December 21, 2011. The Sponsor addressed these deficiencies in the Quality/Response to Information Request dated May 18, 2012.

At the request of DBII, the DCR consultation dated 1/9/2013 evaluated the May 18, 2012 Quality/Response to Information Request. DCR's recommendations were incorporated in the CR letter dated 9/3/2013. The Sponsor's response to the deficiencies cited in the CR letter is contained in the Quality Amendment dated 10/24/2013. DBII requested DCR evaluate the Sponsor's response to the DCR recommendations that were included in the CR letter.

4 Review of Quality Amendment Responses to DCR Comments

4.1 Response to deficiencies

DCR review dated 1/9/2013 was the source of clinical deficiencies that were communicated to the Sponsor in the CR letter dated 9/3/2013. The Sponsor responded with a Quality Amendment dated 10/24/2013. Below are the deficiencies in *italics*, followed by the Sponsor's attempt to address those deficiencies.

1. *It is acceptable that the safety remains disengaged if the tip is pressed and then released without initiating an injection. This allows a user to change injection site if, for example, the first site does not feel to have enough fat. The device could be repositioned and the injection given.*

Response: We acknowledge and agree with the agency's comment.

Reviewer Comment: ***The Sponsor's response is acceptable.***

2. *Since the safety remains disengaged if the device is pressed and then released without initiating an injection, the current wording, stating that the device* (b) (4) *, is incorrect and potentially misleading. A user should be warned that as long as the blue circle is visible in the medicine window, the safety catch is in the off position; the pen could fire unintentionally if the blue button is pressed by accident.*

Response: As recommended by the Agency, the following instruction is included in the IFU: "As long as the blue circle is visible in the medicine window, the safety lock is de-activated; the pen could fire unintentionally if the blue button is pressed by accident".

Reviewer Comment: ***The Sponsor's revised labeling was reviewed. The instructions for use contain the recommended language. The response is acceptable.***

3. (b) (4)

Response: (b) (4)

The IFU (instructions for use) is revised accordingly to instruct the user as, "Use the device immediately once the cap has been removed; it is advised not to postpone the injection" at the beginning of IFU. The following statement is also included as point 10 in the IFU:
"Do not attempt to re-engage the safety lock at any time".

Reviewer Comment: ***The Sponsor's revised labeling was reviewed. The instructions for use contain the direction to use the device immediately and caution against any attempt to re-engage the safety lock. The response is acceptable.***

4. *The following recommendations pertain to the instructions for use: Rather than running together in normal text, the warning* (b) (4) *and the second warning to keep out of the reach of children, should be bulleted, and/or separated, and/or bolded for clarity.*
   - (b) (4)
   - *Keep the Sumatriptan Succinate Auto-Injector System out of the reach of children.*

Response: As recommended by the Agency, the warnings (b) (4) and to keep out of reach of children are listed as two separated bullet points in bold text:

- Use the device immediately once the cap has been removed; it is advised not to postpone the injection.
- Keep the Sumatriptan Autoinjector System out of the reach of children.

Reviewer Comment: ***The Sponsor's revised labeling was reviewed. The instructions for use contain the recommended bold bulleted points. The response is acceptable.***

5. *The figure in Step* (b) (4) *of the instructions for use attempts to demonstrate the plunger rod that can be seen through the window after injection, or in a spent device. Inspection of the viewing window prior to injection should ensure that there is clear liquid present, and also ensure that the device is not spent.*
   - The "after injection" figure currently in Step (b) (4) should be moved to "before injection" Step 5 in order to show what should and what should not be visible through the window of an unspent device.
   - In both "before injection" and "after injection" figures, the important features are not clearly visible. Even with the arrow pointing to the plunger rod, it is difficult to see the plunger in the figure, as it is in the device itself. This reviewer was only able to see the plunger by holding the pen up to the light.
   - Since it is important to be certain that the liquid is clear, and that the plunger is not present, Step 5 should instruct users that if they have difficulty seeing what is in the window, they may hold the pen up to the light.

   Response: Step 5 in the IFU (instructions for use) guides the user to look into the medicine window and ensure that there is clear liquid present. Presence of clear liquid gives assurance to the user that the device is not spent.
   As recommended by the Agency, the "after injection" figure in step (b) (4) is moved to "before injection" step 5 to show how an unspent device differs from a spent device. The medicine window is filled with clear liquid before injection and the same is filled with plunger rod after injection. The "before injection" and "after injection" figures are replaced with figures

which are clearly visible. In order to be certain that the liquid is clear and the plunger rod is not present in the medicine window before injection, an instruction is added in Step 5 as, "If it is difficult to see what is in the window, hold the pen up to the light and check."

Reviewer Comment: ***The Sponsor's revised labeling was reviewed. The instructions for use contain the recommended changes. The response is acceptable.***

6. *Although needle position cannot be used to differentiate between a spent injector and one that has not been injected, you should provide information so that users can tell the difference. For example, users could be informed that if the plunger rod can be seen through the window, the device is spent and cannot be used again.*

Response: As recommended by the Agency, a note is incorporated in Step 5 to inform the user that the device is spent and cannot be used, if the plunger rod can be seen through the medicine window.

Reviewer Comment: ***The Sponsor's revised labeling was reviewed. The instructions for use contain the recommended changes. The response is acceptable.***

7. *The current instruction in Step (b) (4) does not adequately emphasize that the entire dosage delivery system is intended to be a disposable device and disposed of in its entirety. The instruction should include the word "whole" or "entire" as in, "After you have used the pen, throw away the entire pen in a special container"*

Response: As recommended by the Agency, the instruction to discard the pen after use is modified as "Discard the whole Sumatriptan injection autoinjector after use".

Reviewer Comment: ***The Sponsor's revised labeling was reviewed. The instructions for use contain the recommended changes. The response is acceptable.***

8. *The inconsistencies between the 2 "final" versions of the IFU raise some concern as to which device this sponsor is intending to be reviewed.*

- *The Sponsor should clarify whether the to-be-marketed presentation will have (b) (4) (b) (4)*
- *The final package insert and instructions for use should be consistent, and show only images identical to the to-be-marketed device.*
- *The Sponsor should clarify the color of images and text for the final labeling. The (b) (4) background of the Annotated IFU makes the text difficult to read.*

Response: We would like to confirm that the to-be-marketed device has (b) (4)
The final package inserts and instructions for use show images identical to the to-be-marketed device. To avoid difficulty while reading, the (b) (4) background of the Annotated IFU (Instructions for use) has been removed. We clarify that the color of the images provided in the IFU (Instructions for use) resembles the to-be-marketed device.
Dr. Reddy's also brings to the Agency's notice that the above concerns were already addressed in the last gratuitous amendment submitted on April 30, 2013. However, we request the Agency to consider the proposed IFU (instructions for use) submitted along with this submission as it addresses all the concerns raised in this complete response letter.

Reviewer Comment: ***The Sponsor's revised labeling was reviewed. The instructions for use contain the recommended changes. The response is acceptable.***

9. *In your most recent submissions, you have not defined all abbreviations. For example, there are multiple references to the PIL but no definition for this abbreviation. This is especially important since PIL closely resembles the commonly used abbreviation PI that has been used to mean prescribing information, package insert, or patient information. The term PIL does not actually appear in your labeling, but in future communications with the Agency you should clearly define all abbreviations.*

Response: We acknowledge the Agency's comments.

Reviewer Comment: ***The response is acceptable.***

4.2 Additional device recommendations

DCR review dated 1/9/2013 contained additional comments regarding the device.

1. Some concerns were not communicated to the Sponsor in the CR letter dated 9/3/2013 and therefore were not addressed in the 10/24/2013 Quality Amendment. Below is the DCR comment that has not been addressed.
   - (b) (4)

Reviewer Comment: ***Although the CR letter did not advise the Sponsor of this concern and the Sponsor did not address it, the issue of accidental needle stick by probing the device opening is hypothetical and not considered to be a likely occurrence. Therefore, no further action is indicated.***

2. Prior to the DCR review dated 1/9/2013, the Sponsor had submitted performance and specification data (e.g. needle gauge, injection cycle time, force to displacement distance profile) to illustrate similarities to the RLD. However the submitted data did not address how the differences in the specified parameters would affect PK.
   - *The Division of Clinical Review agrees with DBII that a clinical bioequivalence study is needed for this product because of this. As recommended by DBII, you should conduct a*

single-dose, two-way crossover, fasting bioequivalence study in healthy volunteers where the subjects inject themselves with both the test and reference products using the respective device.

Subsequent to the 1/9/2013 DCR review, the Sponsor conducted a fasting bioequivalence study that was reviewed by DBII.

Per the CR letter, the BE study was incomplete with the following reasons:

- Subject Nos. 1, 8 and 34 revealed no clinical abnormalities. Excluding these subjects from the statistical analysis of the study is not justified. After including all subjects in the study, the confidence intervals for AUCt, AUCi and Cmax do not fall within the acceptable 80-125% range. Therefore, the study is unacceptable.
- The DB II does not accept results of statistical outlier tests to justify dropping subjects from a BE study. To re-evaluate the pharmacokinetic performance of subject Nos. 1, 8 and 34, you may re-dose these three subjects along with several other subjects (control group) chosen at random from the same study. Additionally, the study procedures and study drug lot numbers should be identical to Study # 71912 (original study).
  Alternatively, you may conduct a new fasting bioequivalence study.

Response to CR: The Sponsor's CR response cover letter included a 3 page (pages 7-9) argument for acceptance of the BE study data concluding:
"Based on the above information and the in-vitro comparative data provided in the ANDA, Dr. Reddy's believes that the exclusion of the anomalous data for subjects 1, 8 and 34 from the final study data is justified. Since the BE study was conducted to evaluate if minor differences that are present between the test device and the reference device in performance and specifications (e.g. needle gauge, injection cycle time, force to displacement distance profile) have any impact on the PK as pointed by the OGD Clinical consult, Dr Reddy's believes that the available data demonstrated equivalency of the test product device and the reference product device."

Reviewer Comment: ***As the DCR did not evaluate the BE study protocol or the BE study results, the DCR defers to DBII regarding the validity of the Sponsor's argument and the acceptability of the BE study results to adequately demonstrate a comparison of the Test product with the RLD.***

5 Discussion:

Dr. Reddy first submitted ANDA 90495 to the Division of Bioequivalence II (DBII) April 30, 2008. On March 20, 2009 DCII informed the Sponsor that the application was Not Approvable (NA) because the triggering mechanism for the proposed autoinjector device differed significantly from that employed by the Reference Listed Drug. Since then, there have been several exchanges related to deficiencies communicated to the Sponsor, and amendments from the Sponsor attempting to address those deficiencies. The most recent DCR consultation dated 1/9/2013 evaluated the May 18, 2012 Quality/Response to Information Request. DCR's recommendations were incorporated in the CR letter dated 9/3/2013. The clinical deficiencies were primarily related to clarification of the instructions for use (IFU) or other labeling clarifications. The Sponsor's response to the deficiencies cited in the CR letter is contained in the Quality Amendment dated 10/24/2013 that is reviewed here.

The 10/24/213 amendment contains the Sponsor's response to the DCR recommendations included in the 9/3/2013 CR letter. The Sponsor complied with all DCR recommendations in the CR letter. The labeling changes and the Sponsor's clarifications adequately address clinical safety deficiencies. We defer to DBII the decision regarding the Sponsor's BE study and bioequivalence requirements related to device specifications.

6 Conclusions and Recommendations:

Dr. Reddy first submitted ANDA 90495 to the Division of Bioequivalence II (DBII) April 30, 2008. On March 20, 2009 DCII informed the Sponsor that the application was Not Approvable (NA) because the triggering mechanism for the proposed autoinjector device differed significantly from that employed by the Reference Listed Drug. The major amendment dated August 31, 2009 attempted to correct the deficiencies. The OGD Division of Clinical Review (DCR) consultation dated December 14, 2011 evaluated the proposed sumatriptan auto-injector product for any potential concerns with respect to safety or therapeutic equivalence. Clinical Deficiencies were communicated to the Sponsor by DBII on December 21, 2011. The Sponsor addressed these clinical deficiencies in the Quality/Response to Information Request dated May 18, 2012. The DCR consultation dated 1/9/2013 evaluated the May 18, 2012 Quality/Response to Information Request. DCR's recommendations were incorporated in the CR letter dated 9/3/2013. The clinical deficiencies were primarily related to clarification of the instructions for use (IFU) or other labeling clarifications. The Sponsor's response to the deficiencies cited in the CR letter is contained in the Quality Amendment dated 10/24/2013.

This consultation represents the DCR evaluation of the Sponsor's response to the DCR recommendations that were included in the 9/3/2013 CR letter. We find the labeling changes and the Sponsor's clarifications adequately address clinical safety deficiencies. We defer to DBII the decision regarding the Sponsor's BE study and bioequivalence requirements related to device specifications.

7 Appendix: Excerpt of 1/9/2013 DCR Clinical Consultation for ANDA 090495

7.1 Executive Summary

Dr. Reddy's Laboratories submitted ANDA 90495 for Sumatriptan Succinate Injection, Prefilled Single Dose Syringes, 6 mg/0.5 mL to the Division of Bioequivalence II (DBII) on April 30, 2008. The application was reviewed and judged to be Not Approvable because the triggering mechanism for the proposed autoinjector device differed from that employed by the Reference Listed Drug (RLD). An amendment dated August 31, 2009 proposed a push & button device design, closer to that of the RLD. On December 14, 2011, the Division of Clinical Review (DCR) provided a consult response to DBII citing deficiencies of both the new device and instructions for use. The Sponsor responded with modifications to the device and labeling in a submission dated May 18, 2012. These modifications are the subject of this consult.

Deficiencies noted in the previous DCR consult include:

- instructions for use (IFU) that differ from the RLD
- confusing descriptions, illustrations, and instructions
- device specifications (e.g. needle gauge, injection volume, injection speed) that could affect PK.

The DCR also reiterated additional concerns noted by CDRH including:

- inadequate labeling (submitted May 26, 2011) that does not include any reference to a rubber needle shield, although a rubber needle shield contained in the cap is evident in the sample device
- the IFU description of the clicks audible during injection does not include information regarding the significance of each click
- the color of the device in the previous IFU illustrations differed from that on the sample device.
- inadequate safety locking mechanism (b) (4) (b) (4)
- difficultly identifying if a device is used or unused
- and critically, difficultly knowing the device is activated such that it could be fired accidentally.

The repeat Human Factors Study demonstrated that 100% of participants, including representative users, could perform a successful injection on the 2nd and 3rd try, but 16% (8 of 48) users failed on the first try, not due to device malfunction or to safety issues, but due to unfamiliarity with the device and/or failure to read/follow the instructions for use.

After reviewing sample devices along with proposed instructions for use, some of the previous deficiencies have been addressed; others remain, and are detailed below in Recommendations. These deficiencies relate to:

- further clarification of the instructions for use,
- improved safety features

- a clinical PK study is now required by DBII because the Sponsor has not addressed how PK would be affected by differences in performance and specifications of this device compared to the RLD.

7.2 Recommendations

The following recommendations pertain to the device.

- (b) (4)

- Data regarding differences in performance and specifications (e.g. needle gauge, injection cycle time, force to displacement distance profile) submitted by the Sponsor illustrate similarities to the RLD but do not address how the differences in the specified parameters would affect PK. The Division of Clinical Review agrees with DBII that a clinical bioequivalence study is needed for this product because of this. As recommended by DBII, you should conduct a single-dose, two-way crossover, fasting bioequivalence study in healthy volunteers where the subjects inject themselves with both the test and reference products using the respective device.

- Regarding the safety locking mechanism and instructions for using the safety mechanism:
  - It is acceptable that the safety remains disengaged if the tip is pressed and then released without initiating an injection. This allows a user to change injection site if, for example, the first site does not feel to have enough fat. The device could be repositioned and the injection given.
  - Since the safety remains disengaged if the device is pressed and then released without initiating an injection, the current wording, stating that the device (b) (4) (b) (4) is incorrect and potentially misleading. A user should be warned that **as long as the blue circle is visible in the medicine window, the safety catch is in the off position; the pen could fire unintentionally if the blue button is pressed by accident**.
  - (b) (4)

(b) (4)

The following recommendations pertain to the instructions for use.

- Rather than running together in normal text, the warning (b) (4) and the second warning to keep out of the reach of children, should be bulleted, and/or separated, and/or bolded for clarity:
  - (b) (4)
  - Keep the Sumatriptan Succinate Auto-Injector System out of the reach of children.

- The figure in Step (b) (4) of the instructions for use attempts to demonstrate the plunger rod that can be seen through the window after injection, or in a spent device. Inspection of the viewing window prior to injection should ensure that there is clear liquid present, and also ensure that the device is not spent.
  - The "after injection" figure currently in Step (b) (4) should be moved to "before injection" Step 5 in order to show what should and what should not be visible through the window of an unspent device.
  - In both "before injection" and "after injection" figures, the important features are not clearly visible. Even with the arrow pointing to the plunger rod, it is difficult to see the plunger in the figure, as it is in the device itself. This reviewer was only able to see the plunger by holding the pen up to the light.
  - Since it is important to be certain that the liquid is clear, and that the plunger is not present, Step 5 should instruct users that if they have difficulty seeing what is in the window, they may hold the pen up to the light.

- Although needle position cannot be used to differentiate between a spent injector and one that has not been injected, you should provide information so that users can tell the difference. For example, users could be informed that if the plunger rod can be seen through the window, the device is spent and cannot be used again.

- The current instruction in Step (b) (4) does not adequately emphasize that the entire dosage delivery system is intended to be a disposable device and disposed of in its entirety. The instruction should include the word "whole" or "entire" as in, "After you have used the pen, throw away the entire pen in a special container"

- The inconsistencies between the 2 "final" versions of the IFU raise some concern as to which device this sponsor is intending to be reviewed.
  - The Sponsor should clarify whether the to-be-marketed presentation will have (b) (4) (b) (4)
  - The final package insert and instructions for use should be consistent, and show only images identical to the to-be-marketed device.
  - The Sponsor should clarify the color of images and text for the final labeling. The (b) (4) background of the Annotated IFU makes the text difficult to read.

- In your most recent submissions, you have not defined all abbreviations. For example, there are multiple references to the PIL but no definition for this abbreviation. This is especially important since PIL closely resembles the commonly used abbreviation PI that has been used to mean prescribing information, package insert, or patient information. The term PIL does not actually appear in your labeling, but in future communications with the Agency you should clearly define all abbreviations.

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

/s/

DEBORAH J SEIBEL
12/23/2013

DAIVA SHETTY on behalf of JOHN R PETERS
12/23/2013

Clinical Consultation

Sumatriptan Succinate Injection

Drug Product:	Sumatriptan pre-filled autoinjector
Drug Class:	Drug device combination product Therapeutic Code: Migraine (2011110)
Chemical Name:	Sumatriptan Succinate
ANDA:	090495
ANDA Sponsor:	Dr. Reddy's Laboratories
Reference Listed Drug:	Imitrex Statdose
RLD Sponsor:	Glaxo Smith Kline
Reviewer:	Deborah Seibel, M.D. Medical Officer, Division of Clinical Review (DCR), Office of Generic Drugs
Secondary Reviewer:	John Peters, M.D. Director, Division of Clinical Review (DCR) Office of Generic Drugs
To:	Andrew Langowski, OMPT/CDER/OPS/OGD Peter Capella, OMPT/CDER/OPS/OGD/DCII Trang Q. Tran, OMPT/CDER/OPS/OGD/DLPS/RSB
Consult Request Date:	10/23/2012
Reason for Consult:	Please see the quality amendment (SD 17) dated 5/18/2012 submitted in response to our deficiency communication issued by the Agency on 12/21/2011.
Materials Reviewed:	6/18/2012 Bioequivalence Review 5/18/2012 Quality/Response To Information Request 5/18/2012 Bioequivalence/Response to Information Request 4/10/2012 CDRH Consult Response: Human Factors Testing 2/19/2012 CDRH Consult Response: Device Review 12/14/2011 Clinical Review
Date of Submission:	Document date 5/18/2012
Date of Completion:	1/9/2013
Conclusion:	The DCR has evaluated the autoinjector device samples provided by this sponsor and compared them to the RLD device. We find that this device can be used as easily as the RLD, but still has safety deficiencies. There are also bioequivalence requirements that must be addressed for the device to be acceptable.

1 Executive Summary

Dr. Reddy's Laboratories submitted ANDA 90495 for Sumatriptan Succinate Injection, Prefilled Single Dose Syringes, 6 mg/0.5 mL to the Division of Bioequivalence II (DBII) on April 30, 2008. The application was reviewed and judged to be Not Approvable because the triggering mechanism for the proposed autoinjector device differed from that employed by the Reference Listed Drug (RLD). An amendment dated August 31, 2009 proposed a push & button device design, closer to that of the RLD. On December 14, 2011, the Division of Clinical Review (DCR) provided a consult response to DBII citing deficiencies of both the new device and instructions for use. The Sponsor responded with modifications to the device and labeling in a submission dated May 18, 2012. These modifications are the subject of this consult.

Deficiencies noted in the previous DCR consult include:

- instructions for use (IFU) that differ from the RLD
- confusing descriptions, illustrations, and instructions
- device specifications (e.g. needle gauge, injection volume, injection speed) that could affect PK.

The DCR also reiterated additional concerns noted by CDRH including:

- inadequate labeling (submitted May 26, 2011) that does not include any reference to a rubber needle shield, although a rubber needle shield contained in the cap is evident in the sample device
- the IFU description of the clicks audible during injection does not include information regarding the significance of each click
- the color of the device in the previous IFU illustrations differed from that on the sample device.
- inadequate safety locking mechanism ((b) (4) (b) (4))
- difficultly identifying if a device is used or unused
- and critically, difficultly knowing the device is activated such that it could be fired accidentally.

The repeat Human Factors Study demonstrated that 100% of participants, including representative users, could perform a successful injection on the 2nd and 3rd try, but 16% (8 of 48) users failed on the first try, not due to device malfunction or to safety issues, but due to unfamiliarity with the device and/or failure to read/follow the instructions for use.

After reviewing sample devices along with proposed instructions for use, some of the previous deficiencies have been addressed; others remain, and are detailed below in Recommendations. These deficiencies relate to:

- further clarification of the instructions for use,
- improved safety features
- a clinical PK study is now required by DBII because the Sponsor has not addressed how PK would be affected by differences in performance and specifications of this device compared to the RLD.

2 Recommendations

The following recommendations pertain to the device.

- (b) (4)

- Data regarding differences in performance and specifications (e.g. needle gauge, injection cycle time, force to displacement distance profile) submitted by the Sponsor illustrate similarities to the RLD but do not address how the differences in the specified parameters would affect PK. The Division of Clinical Review agrees with DBII that a clinical bioequivalence study is needed for this product because of this. As recommended by DBII, you should conduct a single-dose, two-way crossover, fasting bioequivalence study in healthy volunteers where the subjects inject themselves with both the test and reference products using the respective device.

- Regarding the safety locking mechanism and instructions for using the safety mechanism:
  - It is acceptable that the safety remains disengaged if the tip is pressed and then released without initiating an injection. This allows a user to change injection site if, for example, the first site does not feel to have enough fat. The device could be repositioned and the injection given.
  - Since the safety remains disengaged if the device is pressed and then released without initiating an injection, the current wording, stating that the device (b) (4) (b) (4), is incorrect and potentially misleading. A user should be warned that **as long as the blue circle is visible in the medicine window, the safety catch is in the off position; the pen could fire unintentionally if the blue button is pressed by accident**.
  - (b) (4)

The following recommendations pertain to the instructions for use.

- Rather than running together in normal text, the warning (b) (4) and the second warning to keep out of the reach of children, should be bulleted, and/or separated, and/or bolded for clarity:
  - (b) (4)
  - Keep the Sumatriptan Succinate Auto-Injector System out of the reach of children.

- The figure in Step (b) (4) of the instructions for use attempts to demonstrate the plunger rod that can be seen through the window after injection, or in a spent device. Inspection of the viewing window prior to injection should ensure that there is clear liquid present, and also ensure that the device is not spent.
  - The "after injection" figure currently in Step (b) (4) should be moved to "before injection" Step 5 in order to show what should and what should not be visible through the window of an unspent device.
  - In both "before injection" and "after injection" figures, the important features are not clearly visible. Even with the arrow pointing to the plunger rod, it is difficult to see the plunger in the figure, as it is in the device itself. This reviewer was only able to see the plunger by holding the pen up to the light.
  - Since it is important to be certain that the liquid is clear, and that the plunger is not present, Step 5 should instruct users that if they have difficulty seeing what is in the window, they may hold the pen up to the light.

- Although needle position cannot be used to differentiate between a spent injector and one that has not been injected, you should provide information so that users can tell the difference. For example, users could be informed that if the plunger rod can be seen through the window, the device is spent and cannot be used again.

- The current instruction in Step (b) (4) does not adequately emphasize that the entire dosage delivery system is intended to be a disposable device and disposed of in its entirety. The instruction should include the word "whole" or "entire" as in, "After you have used the pen, throw away the entire pen in a special container"

- The inconsistencies between the 2 "final" versions of the IFU raise some concern as to which device this sponsor is intending to be reviewed.
  - The Sponsor should clarify whether the to-be-marketed presentation will have (b) (4) (b) (4)
  - The final package insert and instructions for use should be consistent, and show only images identical to the to-be-marketed device.
  - The Sponsor should clarify the color of images and text for the final labeling. The (b) (4) background of the Annotated IFU makes the text difficult to read.

- In your most recent submissions, you have not defined all abbreviations. For example, there are multiple references to the PIL but no definition for this abbreviation. This is especially important since PIL closely resembles the commonly used abbreviation PI that

has been used to mean prescribing information, package insert, or patient information. The term PIL does not actually appear in your labeling, but in future communications with the Agency you should clearly define all abbreviations.

3 Regulatory Background

Dr. Reddy first submitted ANDA 90495 to the Division of Bioequivalence II (DBII) April 30, 2008. On March 20, 2009 DCII informed the Sponsor that the application was Not Approvable (NA) because the triggering mechanism for the proposed autoinjector device differed significantly from that employed by the Reference Listed Drug. In response to the NA letter, the Sponsor submitted a major amendment to correct deficiencies, and also requested an expedited review on August 31, 2009. In this amendment the device design was changed from a (b) (4) to a push & button design, closer to that of the RLD. DBII sent a request to the OGD Division of Clinical Review (DCR) to evaluate the proposed sumatriptan auto-injector product for any potential concerns with respect to safety or therapeutic equivalence. This consultation was finalized in DARRTS on December 14, 2011. Clinical Deficiencies were communicated to the Sponsor by DBII on December 21, 2011. The Sponsor addressed these deficiencies in the Quality/Response To Information Request dated May 18, 2012. DBII requested DCR evaluate the response on October 23, 2012. This document addresses primarily the Quality/Response To Information Request, with input from both the June 18, 2012 Bioequivalence review, and consult responses from CDRH, February 19, 2012, and April 10, 2012.

4 Review of Minor Amendment, Quality

DCR review dated 12/14/2011 was the source of deficiencies that were communicated to the Sponsor in the deficiencies letter dated 12/22/2011. The Sponsor responded with a quality amendment dated 5/18/2012. Below are the *deficiencies in italics,* followed by the Sponsor's attempt to address those deficiencies.

1. *Additional sample units are required to allow for full evaluation. The units do not have to contain active drug, but they should be fully functional.*

   The Sponsor sent an additional 10 injector units for evaluation.

Reviewer Comment: This is acceptable. This review is based on 4 of the 10 units the Sponsor sent for evaluation.

2. *The position of the needle after injection should be clarified and justified from the standpoint of safe handling and disposal after injection.*

   The needle remains inside the device before injection and retracts back after the completion of the injection. The position of the needle before and after injection is shown below:

The needle remains inside the device before injection and retracts back after the completion of the injection. The position of the needle before and after injection is shown:

(b) (4)

(b) (4)

A total of 382 devices were assessed for needle retraction depth and confirms to the specification. The data of the needle retraction depth is given:

Specification: (b) (4)	Results (mm) (b) (4)
Minimum	
Maximum	
Mean	7.64
Median	7.64
Standard Deviation	0.24

(b) (4)

Based on the above design and operation of the device and the retraction depth data of the test device, the device allows the safe handling and disposal after injection.

Reviewer Comment: (b) (4)

(b) (4)

This cannot be compared to the RLD (Imitrex) where the needle does not retract back, but remains entirely exposed after use. However, immediately after use of the RLD, the needle containing portion of the injector is detached back into the carrying case where the needle is securely protected from any possible contact with probing fingers.

3. [redacted] (b) (4)

Usability of the test device [redacted] (b) (4) was evaluated in several Human Factors studies during 2011. Evaluation of the [redacted] (b) (4) in its final presentation, including the provision of instructions for use and video/ demonstration of the use of the device is resulted in 100% successful use. Evaluation of risks associated with not pushing the Button far enough to actuate the device are discussed in the Human Factors Validation report (Section 12) of Device Master File (MAF)- [redacted] (b) (4)

Reviewer Comment: ***(see also section 5 below for additional information on Usability testing)***

- ***The first click provides audible confirmation that the device has started the injection process and the second click, that the injection process is complete.***
- ***The IFU adequately describes the depth at which the button needs to be depressed (until the first click is heard. At the same depth, a second click is heard. The IFU provides information that "If you take the pen off before the second click, not all the medicine will be injected."***

4. *The button on the sample unit and the actuation force data for the device suggest that the device may be difficult to fire for some individuals. Evaluation of additional samples will be helpful in this regard, but the sponsor should also provide information to support the ease of firing and operating this device in a diverse population.*

   The current range of actuation force is (b) (4). The latest usability testing of the test device (b) (4), demonstrated successful actuations by 83.33% of the study group, involving mixed population, on the first attempt at using the device and 100% by second and subsequent attempts. The details of the participant type/profile/gender details are provided in Table 1, below.

   The report on actuation force data and on Usability/Human Factors Validation is found in Master File (MAF)-(b) (4). Based on the above, we conclude that the concern of difficult to fire the device by some individuals is mitigated.

Reviewer Comment: Refer to the section 5 below for additional information on Usability testing. Failures appear to have been related to not pressing the button, at all, (i.e. omission of the step) rather than inability to press the button. This reviewer found the button firm, but acceptable. A button requiring less force would be more likely to fire accidentally. Therefore, this is not considered to be a problem.

5. *It is known that differences in injection technique and site of injection can affect the pharmacokinetics of Sumatriptan. Therefore, while the performance and specifications of the proposed device are generally similar to those of the RLD, the small differences in performance and specifications that are present (e.g. needle gauge, injection cycle time, force to displacement distance profile) have the theoretical potential to affect PK. DCR defers to DBE the decision of whether or not a BE study should be required for this product.*

   We acknowledge the agency's comment and would like to confirm that a bioequivalence amendment to address the comments received from DBE is also submitted on May 18, 2012. A comparative in-vitro data of the test device and reference listed drug device (STATdose) for the following parameters is given below:

   1. Injection cycle time
   2. Dose delivery volume
   3. Needle protrusion depth
   4. Button/Actuation Force

Results for the requested parameters were included in the May 18, 2012 Quality/Response To Information Request. Following is a summary of the results:

Table 1 Summary of Performance and Specification Parameters

		(b) (4)		STATdose
Injection Cycle Time	Number Samples	431	31	31
Injection Time (seconds)	Median (SD)	1.36 (9.32%)	1.33 (13.64%)	1.22 (13.33%)

Dose Delivery Volume	Number Samples	381	31	31
Volume Delivered (mL)	Median (SD)	0.538 (0.006)	0.537 (0.007)	0.499 (0.028)
Needle Protrusion Depth	Number Samples	61	31	31
Needle Protrusion (mm)	Median (SD)	5.917 (0.097)	5.928 (0.112)	6.240 (0.377)
Button Actuation Force	Number Samples	382	50	50
Actuation Force (N)	Median (SD)	19.82 (1.33)	18.66 (1.47)	14.46 (2.87)
Source: ANDA 90495 Quality Amendment (SD 17) dated 5/18/2012, pages 6-7				

The above data pertaining to performance and specifications (e.g. needle gauge, injection cycle time, force to displacement distance profile) comes from the May 18, 2012 Quality/Response to Information Request that is the subject of the consult. The same information is included with other bioequivalence data in the Sponsor's Bioequivalence/Response to Information Request received May 18, 2012. On June 18, 2012 the Division of Bioequivalence II (DBII) review was finalized in DARRTS. On June 19, 2012 DB II sent following deficiency to the Sponsor:

> "The DB II does not agree that the information you submitted supports bioequivalence of your test product, Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL, pre-filled syringe with auto-injector, to the RLD, Imitrex® STATDOSE Injectable, EQ 6 mg base/0.5 mL, manufactured by GlaxoSmithKline. Consequently, the DB II recommends that you conduct a single-dose, two-way crossover, fasting bioequivalence study in healthy volunteers where the subjects inject themselves with both the test and reference products using the respective device."

<u>Reviewer Comment</u>: The data submitted by the Sponsor illustrates similarities to the RLD but does not address how the differences in the specified parameters would affect PK. DCR concurs with DBII the decision that a BE study is required for this product. As recommended by DBII, you should conduct a single-dose, two-way crossover, fasting bioequivalence study in healthy volunteers where the subjects inject themselves with both the test and reference products using the respective device.

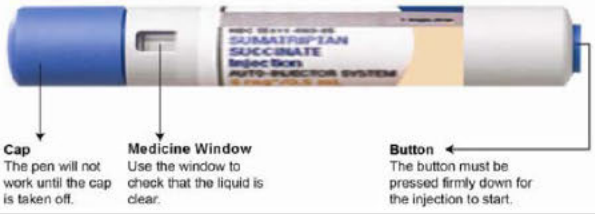
6. *The following additional comments to pertain to the proposed patient labeling insert:*
   [In some cases the Sponsor's responses to the have been shortened or paraphrased, especially when the response was satisfactory compliance with the Agency's recommendation.]

a) *Wherever possible and appropriate, the proposed labeling should mirror that for the RLD. For example, the RLD labeling instructs the user to read the leaflet several times. Unless there is justification for doing otherwise, the generic labeling should also instruct the user to read several times, and not* (b) (4) *as currently proposed.*

The instruction has been revised to instruct the user to read the leaflet several times to make in line with RLD labeling.

***Reviewer Comment*: The change is acceptable.**

b) *As is done in the RLD (Imitrex) labeling, the labeling for the generic should contain a section describing the parts of the injector, including figures in which relevant parts of the injector are clearly labeled.*

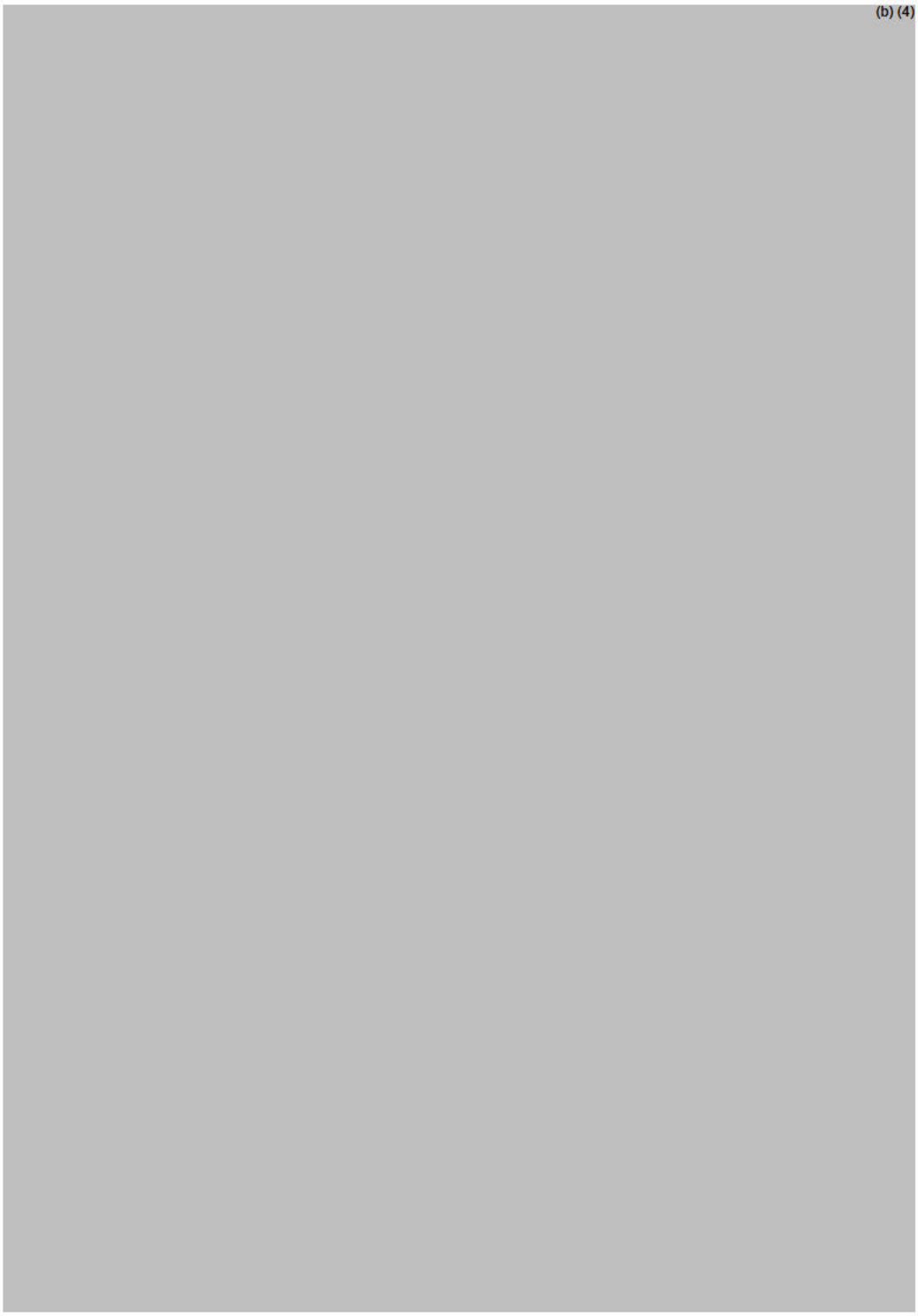
The test product labeling has been revised to include a photograph of the test device describing the parts of the injector. Shown to the right is the reference photograph from the proposed instructions for use under Section A: About the Auto-injector Pen.	**A. ABOUT THE AUTO-INJECTOR PEN** **The parts of the pen are shown in this picture.**  **Cap** The pen will not work until the cap is taken off. **Medicine Window** Use the window to check that the liquid is clear. **Button** The button must be pressed firmly down for the injection to start.

***Reviewer Comment*: The illustration is adequate for patient instruction. Additionally, more specific close ups of injector parts are provided in relevant sections of the instructions for use. However, the above illustration is not consistent with the sample devices that were provided.** (b) (4)

For a side by side comparison of the different devices refer to the Proposed Instructions for Use section, below, where this inconsistency is discussed further.

c) *The color configuration of the product needs to be clarified: the sample provided has a different color configuration than described in the proposed labeling.*

The correct color configuration has been provided in the section 8 of MAF- (b) (4). The Sponsor also provided a table with the color configuration of the components:



***Reviewer Comment*: The colors in the proposed labeling appear consistent with the samples of test product.**

d) *The statement and accompanying figure state that the device* (b) (4) *needs to be clarified. It is difficult to understand what sections are being referred to and how the user can ascertain that the injector is* (b) (4)

Based on the results of Human Factors/Usability studies, the instructions for use have been revised and additional photographs have been added to provide better clarity to the user. The (b) (4) section of the PIL has been revised. The relevant section is shown to the right.	(b) (4)

Reviewer Comment: Presumably PIL refers to patient information label. The instructions are easy to follow and the window makes it clear that the injector is in the activated position. Additionally, the user is able to feel the shift when the mechanism slides into position, allowing the blue circle to be visible.

e) *The safety catch mechanism needs to be clarified. It appears that the mechanism* (b) (4) (b) (4) *. The sponsor needs to clarify whether or not the safety catch mechanism remains disengaged if the tip is pressed and then released without initiating an injection. If the safety lock does remain disengaged, instruction should be provided on whether or not it is safe to reengage the safety lock, and how to do so.*

(b) (4)

Reviewer Comment: The device functions as described above by the Sponsor. Since the potential for contamination of the needle increases with time after removal of the cover, it is preferable that the device be used as soon as possible after the device cap is removed. Pressing against the injection site disengages the safety, allowing the blue button to be pressed, completing the injection.

- ***It is acceptable that the safety remains disengaged if the tip is pressed and then released without initiating an injection. This allows a user to change injection site if, for example,***

the first site does not feel to have enough fat. The device could be repositioned and the injection given.

- ***However, since the safety remains disengaged if the device is pressed and then released without initiating an injection, the current wording, stating that the device*** (b) (4) ***is incorrect and potentially misleading. A user should be warned that as long as the blue circle is visible in the medicine window, the safety catch is off, and the pen could fire unintentionally if the blue button is pressed by accident.***
- (b) (4)

f) The user should be clearly instructed not to disengage the safety feature until just before the injection is to be initiated.

As recommended by the agency, the following instruction has been included in (b) (4) section of the PIL: (b) (4)

Reviewer Comment: This instruction is not clearly a warning in the IFU. For more emphasis, the warning (b) (4) ***and the second warning to keep out of the reach of children, should be bulleted, and/or separated, and/or bolded. Following is the current text:*** (b) (4)

This should be changed to:

- (b) (4)
- ***Keep the Sumatriptan Succinate Auto-Injector System out of the reach of children.***

g) The labeling should provide a figure and description of the viewing window with instructions on its use and the expected appearance of the window before and after injection.

As recommended by the agency, the figure and description of the viewing window appearance before and after injection is included as **Step5** in the (b) (4) **section** of the PIL for better clarity. However, there is no functional requirement to check the window following injection.

Reviewer Comment: ***refer to Reviewer Comment for h) just following.***

h) The sponsor should also clarify whether or not the stopper should be inspected through the viewing window and what the appropriate position should be both before and after injection.

We would like to clarify that the stopper is not inspected through the viewing window. As recommended by the agency, the figure and description of the viewing window appearance before and after injection are included as **Step 5** (for before injection) and **Step** (b) (4) (for after injection) in the (b) (4) **section** of the PIL (Patient Information Leaflet) for better clarity. However, there is no functional requirement to check the window following injection.

Reviewer Comments: ***(refer to Appendixfor sample text and figures from the proposed IFU)***

- ***The figure in Step*** (b) (4) ***attempts to demonstrate the plunger rod that can be seen through the window after injection, or in a spent device.***
  Inspection of the viewing window prior to injection should ensure that there is clear liquid present, and also ensure that the device is not spent.
- ***The "after injection" figure currently in Step*** (b) (4) ***should be moved to "before injection" Step 5 in order to show what should and what should not be visible through the window of an unspent device.***
- ***In both "before injection" and "after injection" figures, the important features are not clearly visible. Even with the arrow pointing to the plunger rod, it is difficult to see the plunger in the figure, as it is in the device itself. This reviewer was only able to see the plunger by holding the pen up to the light.***
- ***Since it is important to be certain that the liquid is clear, and that the plunger is not present, Step 5 should instruct users that if they have difficulty seeing what is in the window, they may hold the pen up to the light.***

i) The instruction to "firmly press against the skin…" should be prefaced with "without pressing the blue button", as in the RLD (Imitrex) label.

As recommended by the agency, we have revised the instruction *"firmly press against the skin…"*with a preface *"without pressing the blue button"* in the (b) (4) **section** of the PIL. (Reference: Step 9).

Reviewer Comment: ***The revised instruction is acceptable.***

j) The instructions and post-injection photo should describe clearly the needle position after injection and also provide information so that users can tell the difference between a spent injector and one that has not been injected.

As explained in the response to point #2 of this deficiency and as shown in the cross-sectional figures, the position of the needle before injection remains inside the device and retracted back to its original position after the injection. The user will not be able to differentiate the position of the needle before and after injection in the photographs. Hence these photographs have not been included in the PIL to clarify the needle position.

Reviewer Comment: ***Also refer to Reviewer Comment for h).***

- ***Although needle position cannot be used to differentiate between a spent injector and one that has not been injected, you should provide information so that users can tell the***

difference. Users should be informed that if the plunger rod can be seen through the window, the device is spent and cannot be used again.

k) Instruction should be provided about proper handling and disposal procedures after injection and these instructions should provide clarification that the entire dosage delivery system is intended to be a disposable device and disposed of in its entirety. This clarification is necessary because this device differs significantly from the RLD in this respect.

As recommended by the agency, the PIL has been revised for better clarity on the disposal of the device after the injection.

Reviewer Comment:

- ***The current instruction in Step*** (b) (4) ***does not adequately emphasize that the entire dosage delivery system is intended to be a disposable device and disposed of in its entirety. The instruction should include the word "whole" or "entire" as in, "After you have used the pen, throw away the entire pen in a special container"***

l) Some versions of labeling have included a directive to pull the blue cap straight off ensuring that the rubber needle shield has been removed. The sponsor should clarify whether or not this instruction is necessary and to provide justification.

This instructions regarding the straight off pulling the blue cap and ensuring the needle shield removal is required to be part of the (b) (4) **section** of the PIL.

6. Pull the cap off the pen • Do not twist the cap • Pull it straight off • Keep the cap for step 7	**7. Look inside the cap, check that the gray needle cover is inside.** • Do not use the pen if the gray needle cover is not inside the cap

Reviewer Comment: The sponsor did not explicitly state that it is necessary to pull the blue cap straight off and did not justify this direction with the reason (in order to ensure that the rubber needle shield has been removed). However, the instructions are now adequately clear especially with the relevant figures, placing emphasis on the correct steps, and are acceptable.

m) Versions of labeling have differed with respect to when clicks will be heard upon operating the device. The sponsor should clarify at which point(s) clicks will be heard and reflect this information appropriately in the labeling.

Based on the Human Factors Validation Study, the (b) (4) section of the PIL has been revised reflecting the information about the audile clicks. In response to point # 3 of this deficiency, a detailed explanation about the audible clicks is provided.

Reviewer Comment: Refer to the comment for number 3, above. The IFU adequately describes that the button needs to be depressed until the first click is heard, and continue to press until the second click is heard. This signifies that a full dose of medicine has been injected

5 Brief Review of Human Factors (HF)/ Usability Testing

The Sponsor modified the design of the device and its instructions for use as a result of prior HF testing, and conducted a re-validation study. This re-validation study utilized the same test protocol as the initial study, with 48 participants (16 self-injectors, 16 home caregivers, and 16 healthcare professionals as shown in Table 1, Participants in Usability Testing. Test participants injected three times. For the first injection, participants were provided with a copy of the instructions and a dummy device. Participants were requested to read the IFU and perform an injection. For the 2nd and 3rd injections, half of participants also had an instructor demonstration or watched a video.

Table 1: Participants in Usability Testing

Participants Age

Participant Type/Profile	18-28	29-39	40-50	51-61	62-72
Overall	4	5	18	18	3
Self Injectors (Total)	2	3	4	5	2
Naive	1	2	2	3	0
Experienced	1	1	2	2	2
Health Professionals (Total)	1	2	7	5	1
Registered Nurses	1	1	2	2	1
Licensed Vocational Nurses	0	1	5	3	0
Home Health Care Aides (Total)	1	0	7	8	0
Naïve	1	0	4	3	0
Experienced	0	0	3	5	0

Participant Gender

Participant Type/Profile	Males	Females
Overall	10	38
Self Injectors (Total)	7	9
Naive	3	5
Experienced	4	4
Health Professionals (Total)	2	14
Registered Nurses	2	6
Licensed Vocational Nurses	0	8
Home Health Care Aides (Total)	1	15
Naïve	1	7
Experienced	0	8

The results showed that for the 1st try, 8 of the 48 participants failed to complete a successful injection. Failures were not associated with the depth at which the button needs to be depressed or pressing to the wrong stop. 3 participants did not apply sufficient force to release the safety mechanism, 3 failed to press the blue button, and 2 released pressure to the injection site when they pressed the blue button. However, on the 2nd and 3rd try, all 48 participants were able to complete a successful injection. Thus, failures appear to be due to unfamiliarity with the device and/or failure to read/follow the IFU.

The April 10, 2012 CDRH review found the results of the revalidation study acceptable, and had no further questions.

***Reviewer Comment:* The Human Factors testing is acceptable and supports the Sponsor's responses in points 3 and 4 above.**

6 Proposed Instructions for Use

INSTRUCTIONS FOR USE were included with the labeling submission May 18, 2012. This submission contains the proposed Final Labeling Text (section 1.14.2.2) and an Annotated Side

by Side Comparison of Package Insert Labeling with differences from the previous version (section 1.14.2.3). (b) (4)

(b) (4)

Reviewer Comments: The inconsistencies between the 2 "final" versions of the IFU raise some concern as to which device this sponsor is intending to be reviewed.

- ***The Sponsor should clarify whether the to-be-marketed presentation will have*** (b) (4) (b) (4)
- ***The final package insert and instructions for use should be consistent, and show only images identical to the to-be-marketed device.***
- ***The Sponsor should clarify the color of images and text for the final labeling. The*** (b) (4) ***background of the Annotated IFU makes the text difficult to read.***

7 RLD Label:

Current RLD product labeling (Imitrex) was approved on October 2, 2012.
There is not a Black Box warning.

7.1 Indications:

IMITREX is a serotonin (5-HT1B/1D) receptor agonist (triptan) indicated for:

- Acute treatment of migraine with or without aura in adults
- Acute treatment of cluster headache in adults

7.2 Usual dosage:

The maximum single recommended adult dose of IMITREX Injection for the acute treatment of migraine or cluster headache is 6 mg injected subcutaneously. For the treatment of migraine, if

side effects are dose limiting, lower doses (1 to 5 mg) may be used. For the treatment of cluster headache, the efficacy of lower doses has not been established. The maximum cumulative dose that may be given in 24 hours is 12 mg, two 6-mg injections separated by at least 1 hour. A second 6-mg dose should only be considered if some response to a first injection was observed.

7.3 Maximum dose:

Refer to 7.2

7.4 Initial dosage:

Refer to 7.2

7.5 Maintenance dosage:

Refer to 7.2

7.6 Contraindications:

- Coronary artery disease or coronary vasospasm
- Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders
- History of stroke, transient ischemic attack, or hemiplegic or basilar migraine
- Peripheral vascular disease
- Ischemic bowel disease
- Uncontrolled hypertension
- Recent (within 24 hours) use of another 5-HT1 agonist (e.g., another triptan) or of an ergotamine-containing medication

7.7 Significant Warnings and Precautions:

- Myocardial ischemia/infarction and Prinzmetal's angina: Perform cardiac evaluation in patients with multiple cardiovascular risk factors.
- Arrhythmias: Discontinue IMITREX if occurs.
- Chest/throat/neck/jaw pain, tightness, pressure, or heaviness: Generally not associated with myocardial ischemia; evaluate for coronary artery disease in patients at high risk
- Cerebral hemorrhage, subarachnoid hemorrhage, and stroke: Discontinue IMITREX if occurs.
- Gastrointestinal ischemia and infarction events, peripheral vasospastic reactions: Discontinue IMITREX if occurs.
- Medication overuse headache: Detoxification may be necessary.
- Serotonin syndrome: Discontinue IMITREX if occurs.
- Increase in blood pressure: Monitor blood pressure.
- Anaphylactic/anaphylactoid reactions: Discontinue IMITREX if occurs
- Seizures: Use with caution in patients with epilepsy or a lowered seizure threshold.

7.8 Adverse Reactions:

The most commonly reported adverse reactions (≥5% and > placebo) were injection site reactions, tingling, dizziness/vertigo, warm/hot sensation, burning sensation, feeling of heaviness, pressure sensation, flushing, feeling of tightness, and numbness.

7.9 Pregnancy Category: C

Sumatriptan has been shown to be embryolethal in rabbits when given daily at a dose approximately equivalent to the maximum recommended single human subcutaneous dose of 6 mg on a mg/m2 basis. There is no evidence that establishes that sumatriptan is a human teratogen; however, there are no adequate and well-controlled studies in pregnant women. IMITREX Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

7.10 Off-Label Uses:

Drug Facts and Comparisons indicate all 3 dosage forms of sumatriptan (oral, intranasal, subcutaneous injection) have been studied for treatment of:

- Migraine headaches in children and adolescents
- Post dural puncture headache

The dose for off label use has not been determined.

7.11 Pharmacokinetics:

Absorption and Bioavailability: The bioavailability of sumatriptan via subcutaneous site injection to 18 healthy male subjects was 97% ± 6% of that obtained following intravenous injection. After a single 6-mg subcutaneous manual injection into the deltoid area of the arm in 18 healthy males (age: 24 ± 6 years, weight: 70 kg), the maximum serum concentration (Cmax) of sumatriptan was (mean ± standard deviation) 74 ± 15 ng/mL and the time to peak concentration (Tmax) was 12 minutes after injection (range: 5 to 20 minutes). In this trial, the same dose injected subcutaneously in the thigh gave a Cmax of 61 ± 15 ng/mL by manual injection versus 52 ± 15 ng/mL by autoinjector techniques. The Tmax or amount absorbed was not significantly altered by either the site or technique of injection.

Distribution: Protein binding, determined by equilibrium dialysis over the concentration range of 10 to 1,000 ng/mL, is low, approximately 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated. Following a 6-mg subcutaneous injection into the deltoid area of the arm in 9 males (mean age: 33 years, mean weight: 77 kg) the volume of distribution central compartment of sumatriptan was 50 ± 8 liters and the distribution half-life was 15 ± 2 minutes.

Metabolism: In vitro studies with human microsomes suggest that sumatriptan is metabolized by MAO, predominantly the A isoenzyme. Most of a radiolabeled dose of sumatriptan excreted in the urine is the major metabolite indole acetic acid (IAA) or the IAA glucuronide, both of which are inactive.

Elimination: After a single 6-mg subcutaneous dose, 22% ± 4% was excreted in the urine as unchanged sumatriptan and 38% ± 7% as the IAA metabolite. Following a 6-mg subcutaneous

injection into the deltoid area of the arm, the systemic clearance of sumatriptan was 1,194 ± 149 mL/min and the terminal half-life was 115 ± 19 minutes.

7.12 Mechanism of Action:

Sumatriptan binds with high affinity to human cloned 5-HT1B/1D receptors. IMITREX presumably exerts its therapeutic effects in the treatment of migraine headache by binding to 5-HT1B/1D receptors located on intracranial blood vessels and sensory nerves of the trigeminal system. Current theories proposed to explain the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of sensory neuropeptides (including substance P and calcitonin gene-related peptide) through nerve endings in the trigeminal system. The therapeutic activity of IMITREX for the treatment of migraine and cluster headaches is thought to be due to the agonist effects at the 5-HT1B/1D receptors on intracranial blood vessels (including the arterio-venous anastomoses) and sensory nerves of the trigeminal system, which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.

8 Discussion

According to the International Headache Society (http://www.i-h-s.org) all triptans are effective and relatively safe for the acute treatment of moderate to severe migraine headaches. Available triptans include sumatriptan (Imitrex®), rizatriptan (Maxalt®), eletriptan (Relpax®), almotriptan (Axert®) and zolmitriptan (Zomig®). Triptans can be administered via three routes of administration, oral, nasal inhalation, and subcutaneous (SC) injection, but only sumatriptan is available for SC administration.

Several open label studies of sumatriptan treatment for migraines found that autoinjectors provide convenient, effective treatment and that patients found the devices easy to use, preferring them to previous treatment options. In one study, 376 migraine patients were given an in office explanation and practice session, then patients were given a Glaxo sumatriptan autoinjector pen for treating their own migraine attacks. The patients used a headache diary to document administration outside the practice session. 80% of the patients rated the Glaxo-Pen "very easy" or "easy" to use. [1] Another study was an open-label, phase 3 trial in 63 migraine patients. The patients assessed their own ability to self-inject a single dose of sumatriptan using the Alsuma® sumatriptan auto-injector, and evaluated the safety, tolerability, and effectiveness of this sumatriptan auto-injector during an acute migraine attack. 100% of patients found the instructions clear and easy to follow; 95.2% of patients found the auto-injector was easy to use.[2]

The prefilled autoinjector seems a reasonable way to treat severe migraines, as well as other acute conditions, such as anaphylaxis. Although convenient, prefilled autoinjectors are not without concerns. For example, autoinjector use for anaphylaxis is increasing, but so is the occurrence of unintentional injection of epinephrine from autoinjectors. A review of these

[1] Göbel, H. Practicability and acceptance of subcutaneous self-administration of the selective serotonin agonist sumatriptan. Headache. 1998 Apr;38(4):267-9.
[2] Landy, S.H. et al. An Open-Label Trial of a Sumatriptan Auto-Injector for Migraine in Patients Currently Treated With Subcutaneous Sumatriptan. Headache. 2012 Nov 13.

occurrences[3] concludes that the efficacy and safety of autoinjectors strongly depend on their proper use. The authors suggested that unintentional injection could be prevented by both coaching of potential device users, and by improved autoinjector design[4]. An acceptable autoinjector would be reliable, user friendly[5] and self-contained so that it can be available in a pocket or handbag. This is consistent with the history of use of the device provided with the RLD.

9 Conclusions and Recommendations

Dr. Reddy's Laboratories submitted ANDA 90495 for Sumatriptan Succinate Injection, Prefilled Single Dose Syringes, 6 mg/0.5 mL to the Division of Bioequivalence II (DBII) on April 30, 2008. The application was reviewed and judged to be Not Approvable because the triggering mechanism for the proposed autoinjector device differed from that employed by the Reference Listed Drug (RLD). An amendment dated August 31, 2009 proposed a push & button device design, closer to that of the RLD. On December 14, 2011, the Division of Clinical Review (DCR) provided a consult response to DBII citing deficiencies of both the new device and instructions for use. The Sponsor responded with modifications to the device and labeling in a submission dated May 18, 2012. These modifications are the subject of this consult.

The repeat Human Factors Study demonstrated that 100% of participants, including representative users, could perform a successful injection on the 2nd and 3rd try, but 16% (8 of 48) users failed on the first try, not due to device malfunction or to safety issues, but due to unfamiliarity with the device and/or failure to read/follow the instructions for use.

After reviewing sample devices along with proposed instructions for use, some of the previous deficiencies have been addressed; others remain, and are detailed below in Recommendations. These deficiencies relate to:

- further clarification of the instructions for use,
- improved safety features
- a clinical PK study now required by DBII because the Sponsor has not addressed how PK would be affected by differences in performance and specifications of this device compared to the RLD.

The following recommendations pertain to the device.

- (b) (4)

[3] Simons FE, Voluntarily reported unintentional injections from epinephrine auto-injectors. J Allergy Clin Immunol. 2010 Feb;125(2):419-423

[4] Kranke, et al. How to improve the safety of adrenaline (epinephrine) autoinjectors Journal of Allergy and Clinical Immunology, Volume 127, Issue 6, June 2011, Page 1645

[5] Frew A.J. What are the 'ideal' features of an adrenaline (epinephrine) auto-injector in the treatment of anaphylaxis? Allergy 2011; 66: 15–24.

(b) (4)

- Data regarding differences in performance and specifications (e.g. needle gauge, injection cycle time, force to displacement distance profile) submitted by the Sponsor illustrate similarities to the RLD but do not address how the differences in the specified parameters would affect PK. The Division of Clinical Review agrees that a clinical bioequivalence study is needed for this product. As recommended by DBII, you should conduct a single-dose, two-way crossover, fasting bioequivalence study in healthy volunteers where the subjects inject themselves with both the test and reference products using the respective device.

- Regarding the safety locking mechanism and instructions for using the safety mechanism:
  - It is acceptable that the safety remains disengaged if the tip is pressed and then released without initiating an injection. This allows a user to change injection site if, for example, the first site does not feel to have enough fat. The device could be repositioned and the injection given.
  - Since the safety remains disengaged if the device is pressed and then released without initiating an injection, the current wording, stating that the device (b) (4) (b) (4) is incorrect and potentially misleading. A user should be warned that as long as the blue circle is visible in the medicine window, the safety catch is in the off position, the pen could fire unintentionally if the blue button is pressed by accident.
  - (b) (4)

The following recommendations pertain to the instructions for use.

- Rather than running together in normal text, the warning (b) (4) and the second warning to keep out of the reach of children, should be bulleted, and/or separated, and/or bolded for clarity:
  - (b) (4)
  - Keep the Sumatriptan Succinate Auto-Injector System out of the reach of children.

- The figure in Step (b) (4) of the instructions for use attempts to demonstrate the plunger rod that can be seen through the window after injection, or in a spent device. Inspection of the viewing window prior to injection should ensure that there is clear liquid present, and also ensure that the device is not spent.
    - The "after injection" figure currently in Step (b) (4) should be moved to "before injection" Step 5 in order to show what should and what should not be visible through the window of an unspent device.
    - In both "before injection" and "after injection" figures, the important features are not clearly visible. Even with the arrow pointing to the plunger rod, it is difficult to see the plunger in the figure, as it is in the device itself. This reviewer was only able to see the plunger by holding the pen up to the light.
    - Since it is important to be certain that the liquid is clear, and that the plunger is not present, Step 5 should instruct users that if they have difficulty seeing what is in the window, they may hold the pen up to the light.

- Although needle position cannot be used to differentiate between a spent injector and one that has not been injected, you should provide information so that users can tell the difference. For example, users could be informed that if the plunger rod can be seen through the window, the device is spent and cannot be used again.

- The current instruction in Step (b) (4) does not adequately emphasize that the entire dosage delivery system is intended to be a disposable device and disposed of in its entirety. The instruction should include the word "whole" or "entire" as in, "After you have used the pen, throw away the entire pen in a special container"

- The inconsistencies between the 2 "final" versions of the IFU raise some concern as to which device this sponsor is intending to be reviewed.
    - The Sponsor should clarify whether the to-be-marketed presentation will have (b) (4) (b) (4).
    - The final package insert and instructions for use should be consistent, and show only images identical to the to-be-marketed device.
    - The Sponsor should clarify the color of images and text for the final labeling. The (b) (4) background of the Annotated IFU makes the text difficult to read.

- In your most recent submissions, you have not defined all abbreviations. For example, there are multiple references to the PIL but no definition for this abbreviation. This is especially important since PIL closely resembles the commonly used abbreviation PI that has been used to mean prescribing information, package insert, or patient information. The term PIL does not actually appear in your labeling, but in future communications with the Agency you should clearly define all abbreviations.

References:

1. Frew A.J. What are the 'ideal' features of an adrenaline (epinephrine) auto-injector in the treatment of anaphylaxis? Allergy 2011; 66: 15–24.
2. Göbel, H. Practicability and acceptance of subcutaneous self-administration of the selective serotonin agonist sumatriptan. Headache. 1998 Apr;38(4):267-9.
3. Kranke, et al. How to improve the safety of adrenaline (epinephrine) autoinjectors. Journal of Allergy and Clinical Immunology, Volume 127, Issue 6, June 2011, Page 1645
4. Landy, SH et al. An Open-Label Trial of a Sumatriptan Auto-Injector for Migraine in Patients Currently Treated With Subcutaneous Sumatriptan. Headache. 2012 Nov 13.
5. Simons FE, Voluntarily reported unintentional injections from epinephrine auto-injectors. J Allergy Clin Immunol. 2010 Feb;125(2):419-423

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/s/

DEBORAH J SEIBEL
01/09/2013

JOHN R PETERS
01/09/2013

MEDICAL CONSULTATION

To:	**Glen Smith** **Director, DCI, OGD**
Re:	**ANDA 90-495**
Drug Product:	**Sumatriptan Succinate Injection** **6 mg/0.5 ml with autoinjector**
Sponsor:	**Dr. Reddy's Laboratories, Ltd**
RLD:	**Imitrex STATdose** **N20080** **GlaxoSmithKline**
Date of Review:	**December 14, 2011**
Consultant:	**Nancy Chang, M.D.** **Medical Officer, Office of Generic Drugs**
Through:	**John Peters, M.D.** **Acting Director, DCR, OGD**

Reason for Consult

DCII has requested that the clinical group evaluate this proposed sumatriptan autoinjector product for any potential concerns with respect to safety or therapeutic equivalence.

Labeling of the RLD

The Imitrex STATdose System is a sumatriptan autoinjector indicated for the acute treatment of migraine attacks and the acute treatment of cluster headache episodes in adults.

Sumatriptan is a 5HT1 agonist intended for subcutaneous injection. Distribution and terminal half-life were approximately 15 minutes and 115 minutes after 6-mg subcutaneous injection into the deltoid, with a Tmax of approximately 12 minutes.

Cmax after 6 mg of sumatriptan varied somewhat depending on site of injection and injection technique:

1) manual subcutaneous injection into the deltoid: 74 ± 15 ng/ml
2) manual subcutaneous injection into the thigh: 61 ± 15 ng/ml
3) autoinjector injection into the thigh: 52 ± 15 ng/ml

Imitrex has the following contraindications:

Intravenous injection

History, symptoms or signs of ischemic cardiac, cerebrovascular or peripheral vascular syndromes
Uncontrolled hypertension
Administration within 24 hours of any ergot-type medication
Hemiplegic or basilar migraine
Severe hepatic impairment

The Warnings section has an extensive discussion of the potential for vasospasm-related events associated with this drug.

Patients are instructed that the injection is intended for subcutaneous use, and that intramuscular or intravascular delivery should be avoided. Injection sites should have an adequate skin and subcutaneous thickness to accommodate the length of the needle.

Review

Comparative Instructions for Use

The Imitrex STATdose includes a patient insert describing the operation of the device. Dr. Reddy proposes a similar section in their patient insert. A side by side comparison with the RLD labeling was not provided, so the proposed Dr. Reddy instructions are presented below with reviewer comments. This labeling is taken from the 5/26/11 submission to the ANDA. For reference, the corresponding section of the Imitrex RLD labeling is provided in the appendix to this review.

(b) (4)

(b) (4)

(b) (4)

Keep the Sumatriptan Succinate Auto-Injector System out of the reach of children.

Reviewer comments:

The Imitrex labeling instructs patients to "read the leaflet carefully several times before

you start to use the …system." The statement that the product [redacted] also differs from the Imitrex labeling, which describes use of a 4-mg strength in addition to a 6-mg strength.

Recommendations:

Unless the sponsor has reasonable justification for doing so, labeling should conform to that of the RLD as much as possible. Therefore, the generic should instruct patients to read several times. The wording regarding the 6-mg strength is appropriate.

[redacted]

Reviewer comments:

Prior to presenting syringe preparation steps, the Imitrex labeling contains a section describing the parts of the injector, including a figure in which parts of the autoinjector device are clearly labeled. A section describing the autoinjector parts and a labeled diagram are not present in the Dr. Reddy labeling.

The injector appears to have a viewing window, but no instructions or descriptions are provided in labeling about this window.

The sample provided for review has a different color configuration (i.e. [redacted] cap, [redacted] body) than is described in these directions.

The statement and accompanying figure stating that the device [redacted] are not clear. It is difficult to understand what the sections are being referred to, and how the user can ascertain that the injector is [redacted]

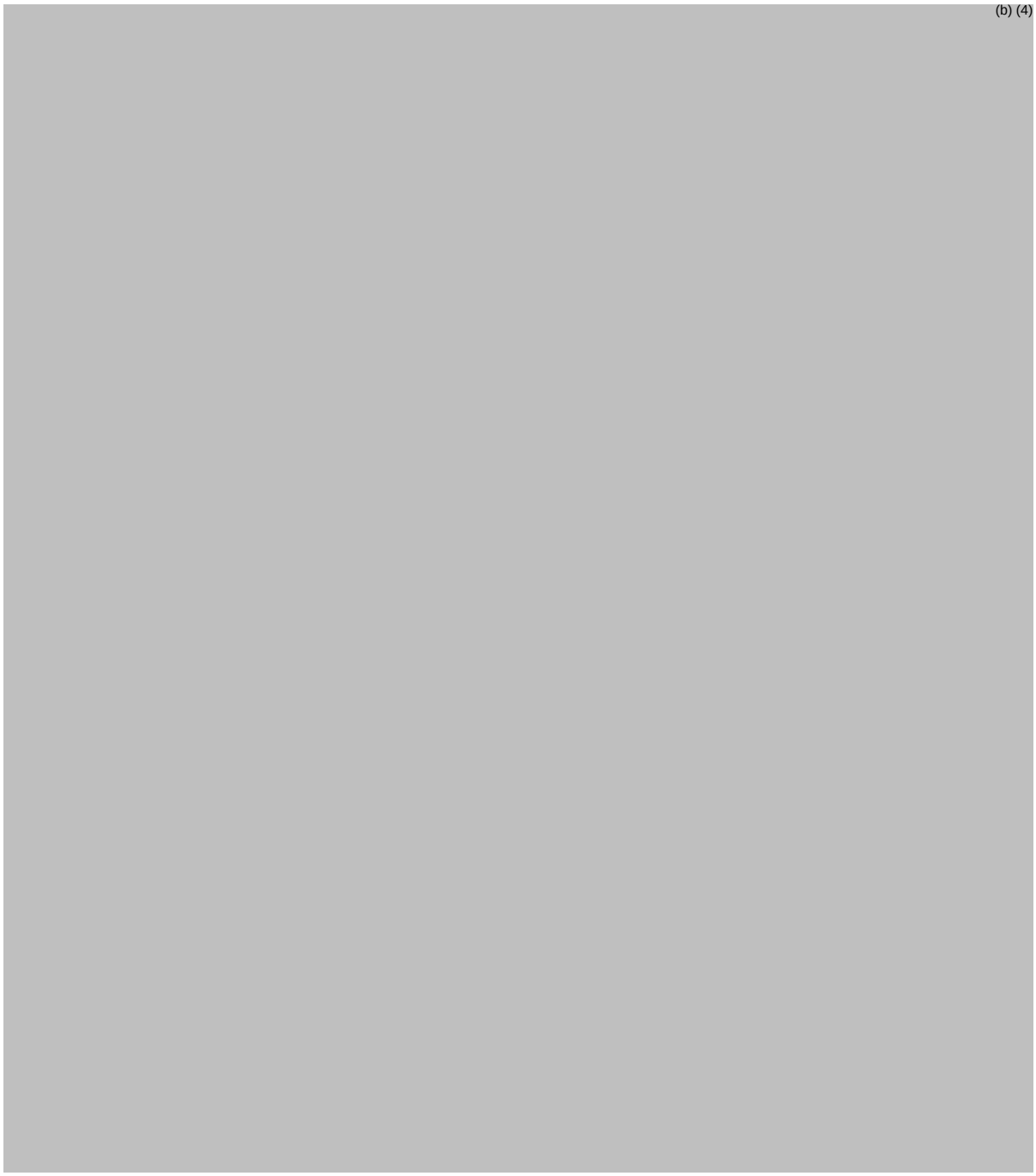
It appears that, unlike the Imitrex injector, the Dr. Reddy [redacted] As such, the current wording, stating that the device [redacted] may be incorrect and potentially misleading.

Based on the provided sample, it does not appear possible to disengage the safety lock before removal of the blue cap. This is an appropriate design feature.

Recommendations:
A section describing the parts of the injector and a labeled figure should be included. Parts that would be particularly helpful to see identified include the blue device cap, the body, [redacted], the blue button, the white section and the [redacted] section. A clearer description and illustration of what it means to have the [redacted], and how the device looks different before and after [redacted] should also be included. The user should be able to clearly determine whether or not the safety feature is active. The instructions should also clarify for the user if the safety feature, once disengaged, will stay disengaged, even if the autoinjector is no longer pressed against the skin. In addition, the user should also be clearly instructed not to disengage the safety feature until initiation of the injection. If the safety lock is disengaged before the user intends to inject, instruction should be provided on whether or not it is safe to re-engage the safety lock, and if so, how it may be safely re-engaged.

This injector is not intended for re-use, and the user will be starting with a brand new locked device with each subsequent injection. Therefore, even if the proposed product differs from the RLD in that the safety lock does not automatically re-engage, this difference would be acceptable from a clinical safety standpoint with appropriate labeling to warn users not to disengage the safety lock until just before injection. This is in distinction from [redacted]

The labeling should provide a description of the viewing window and instructions to the user on its use and on the expected appearance of the drug/device through the window. The labeling should also inform the user on how to determine if a device has already been injected.



Reviewer comments:
The supplied sample unit did not appear to be operational (i.e. it did not fire); therefore, the clinical evaluation of the autoinjector was limited.

[redacted] (b) (4)

Unlike the Imitrex label, Dr. Reddy does not preface the step "Firmly press… against the skin…" with "Without pressing the blue button".

Unlike the Imitrex labeling, Dr. Reddy's instructions [redacted] (b) (4)

Recommendations:
Dr. Reddy's labeling should include the language found in the Imitrex labeling as described above. This language is important to the safe operation of the device, and it is particularly important if there should be cases in which users have inadvertently disengaged the safety lock prior to this step.

The sponsor should provide exact information on the position of the needle tip relative to the end of the injector housing after injection as well as justification for that needle position in the context of safe handling and disposal of the product after use. Information should also be provided in the labeling on the position of the needle after injection. If the end of the needle will extend beyond the autoinjector housing, or if it will be close enough to the end that it could pose a risk of an inadvertent needle stick, the sponsor will also need to ensure that the device incorporates safety features to allow safe isolation and disposal of the exposed needle.

The Imitrex product has both reusable and disposable components. Although Dr. Reddy's labeling does state that the auto-injector pen should not be reused, the label should describe disposal procedures and further clarify that the entire dosage delivery unit is intended to be a disposable device and should be disposed of in its entirety.

Functional sample units should be provided for review, and Dr. Reddy should clarify how deeply the button needs to be depressed to inject. [redacted] (b) (4) *the directions for use should be clarified and the sponsor should also provide information and specifications to ensure that the button can easily be operated.*

The Dr. Reddy device presents an audible click [redacted] (b) (4) *and at the end of injection, unlike the Imitrex injector. From a clinical standpoint, these are helpful aids to the user and are acceptable differences from the RLD.*

CMC review
The CMC review by Dr. Langowski (DARRTS entry date 1/28/10) was reviewed, along

with a consult from the OGD CMC division to CDRH (DARRTS entry date 10/27/11), for any additional design or specifications issues that would be relevant to clinical safety. CDRH will also be assessing the device design and specifications of this device as part of their consultation review.

The following additional potential concerns were identified on review of these documents. The instructions for use referenced in the CMC review and CDRH consult are included in the appendix of this review:

The instructions for use referenced in the CMC review include a directive to pull the blue cap straight off ensuring that the rubber needle shield has been removed. The labeling submitted 5/26/11 does not include any reference to a rubber needle shield, although a rubber needle shield contained in the cap is evident in the sample device. The sponsor should clarify whether or not this instruction is intended to be omitted, and if so, to provide justification.

The instructions for use referenced in the CMC review indicate that a click will be heard upon pushing the button which initiates injection. The 5/26/11 labeling describes (b) (4) (b) (4) The sponsor should clarify when the clicks will occur.

The instructions referenced in the CMC review state that the user should inspect the stopper position through the viewing window to confirm the dose is fully delivered. The sponsor should include this instruction in labeling with clear descriptions of how to assess proper stopper position or they should explain why this instruction is omitted in the current labeling.

The following comparative specifications were available between the Dr. Reddy (b) (4) (b) (4) device and the Imitrex (STATdose) device.

Table 1: Cap/Needle Shield Removal Force

	(b) (4) Results (N)	STATdose Results (N)
Min	(b) (4)	
Max		
Mean	20 (19.53)	22 (21.70)
Median	19 (19.00)	20 (19.80)
Standard Deviation	7 (7.09)	7 (7.02)

Table 2: Dose Delivery Volume

	Specification	(b) (4) Results (ml)	STATdose Results (ml)
Min		(b) (4)	
Max			
Mean	N/A	0.526	0.499
Median	N/A	0.526	0.501
Standard Deviation	N/A	0.014	0.028

Table 3: Injection Cycle Time

	Specification	(b) (4) Results (sec)	STATdose Results (sec)
Min		(b) (4)	
Max			
Mean	N/A	1.42	1.21
Median	N/A	1.40	1.20
Standard Deviation	N/A	0.19	0.16

Table 4: Actuation Force

	(b) (4) Results All Conditions(N)	STATdose Results (N)
Min	(b) (4)	
Max		
Mean	26.98	14.83
Median	26.42	14.59
Standard Deviation	2.19	2.87

Table 5: Needle Protrusion Depth

	(b) (4) Result (mm)	STATdose Result (mm)
Min	(b) (4)	
Max		
Mean	6.24	6.24
Median	6.23	6.34

Spring rate

The sponsor states that the spring rate (average force over the displacement distance) was the same, although it is also noted that the STATdose spring doesn't have a straight line graph, suggesting that the force at each point in time during injection may differ between the RLD and Dr. Reddy device.

Needle Gauge

The proposed device has a (b) (4) gauge needle. Based on information submitted to ANDA 78319 in 2007, the Imitrex device has a 26 gauge needle.

Conclusions/Recommendations

Dr. Reddy is proposing a disposable, single-use sumatriptan injector referencing Imitrex. While the basic design principles appear to be appropriate from a clinical safety standpoint, the following issues should first be addressed and/or clarified before DCR can make a final recommendation:

1. Additional sample units are required to allow for full evaluation. The units do not have to contain active drug, but they should be fully functional.
2. The position of the needle after injection should be clarified and justified from the standpoint of safe handling and disposal after injection.
3. (b) (4)

(b) (4)

4. The button on the sample unit and the actuation force data for the device suggest that the device may be difficult to fire for some individuals. Evaluation of additional samples will be helpful in this regard, but the sponsor should also provide information to support the ease of firing and operating this device in a diverse population.
5. It is known that differences in injection technique and site of injection can affect the pharmacokinetics of sumatriptan. Therefore, while the performance and specifications of the proposed device are generally similar to those of the RLD, the small differences in performance and specifications that are present (e.g. needle gauge, injection cycle time, force to displacement distance profile) have the theoretical potential to affect PK. DCR defers to DBE the decision of whether or not a BE study should be required for this product.
6. The following additional comments pertain to the proposed patient insert:
    a. Wherever possible and appropriate, the proposed labeling for the generic product should mirror that for the RLD. For example, the RLD labeling instructs the user to read the leaflet several times. Unless there is justification for doing otherwise, the generic labeling should also instruct the user to read several times, and not (b) (4) as currently proposed.
    b. As is done in the Imitrex labeling, the labeling for the generic should contain a section describing the parts of the injector, including figures in which relevant parts of the autoinjector device are clearly labeled.
    c. The color configuration of the product needs to be clarified: the sample provided has a different color configuration than described in the proposed labeling.
    d. The statement and accompanying figure stating that the device (b) (4) need to be clarified. It is difficult to understand what the sections are being referred to and how the user can ascertain that the injector is (b) (4)
    e. The use of the safety catch mechanism needs to be clarified. It appears that the mechanism (b) (4) The sponsor needs to clarify whether or not the safety catch mechanism remains disengaged if the tip is pressed and then released without initiating an injection. If the safety lock does remain disengaged, instruction should be provided on whether or not it is safe to re-engage the safety lock, and how to do so.
    f. The user should be clearly instructed not to disengage the safety feature until just before the injection is to be initiated.
    g. The labeling should provide a figure and description of the viewing window with instructions on its use and on the expected appearance of the window before and after injection.
    h. The sponsor should also clarify whether or not the stopper position should

be inspected through the viewing window and what the appropriate position should be both before and after injection.

i. The instruction to "firmly press…against the skin" should be prefaced with "without pressing the blue button", as in the Imitrex label.

j. The instructions and the post-injection photo should describe clearly the needle position after injection and also provide information so that users can tell the difference between a spent injector unit and one that has not been injected.

k. Instruction should be provided about proper handling and disposal procedures after injection and these instructions should provide further clarification that the entire dosage delivery system is intended to be a disposable device and should be disposed of in its entirety. This clarification is necessary because this device differs significantly from the RLD device in this respect.

l. Some versions of labeling have included a directive to pull the blue cap straight off ensuring that the rubber needle shield has been removed. The sponsor should clarify whether or not this instruction is necessary and to provide justification.

m. Versions of labeling have differed with respect to when clicks will be heard upon operating the device. The sponsor should clarify at which point(s) clicks will be heard and reflect this information appropriately in labeling (e.g. (b) (4), upon pushing the button to initiate injection, upon completion of injection).

Appendix 1

Imitrex labeling

PATIENT INFORMATION

The following wording is contained in a separate leaflet provided for patients.

Read this leaflet carefully several times before you start to use the IMITREX STATdose System.

If you have any questions, ask your healthcare provider.

Keep the IMITREX STATdose System out of the reach of children.

Before you use the IMITREX STATdose System

When you first open the IMITREX STATdose System box, the Cartridge Pack and the IMITREX STATdose Pen® are already in the Carrying Case for your convenience.

The grey and blue **Carrying Case** is used for storing the unloaded Pen and the Cartridge Pack when they are not being used.

The **Cartridge Pack** holds 2 individually sealed **Syringe Cartridges**. Each Syringe Cartridge holds 1 dose of IMITREX® (sumatriptan succinate) Injection. The Cartridge Pack for the 4-mg strength of this medicine is yellow, and the Cartridge Pack for the 6-mg strength is blue (as shown). Refill Cartridge Packs are available.

The grey and blue **Pen** is used to automatically inject 1 dose of medicine from a Syringe Cartridge. Do not touch the **Blue Button** until you have pressed the Pen against your skin to give a dose. If you press it at any other time, you might lose a dose. The **Safety Catch** keeps the Pen from accidentally firing until you are ready. The Pen will only work when you slide the grey part of the barrel down to the blue part. Always check to make sure that the white Priming Rod is not

sticking out from the end of the Pen (as shown in Figure 2) before you load a new Syringe Cartridge. If it is sticking out, you will lose that dose.

How to load the IMITREX STATdose Pen

Do not load the Pen until you are ready to give yourself an injection. Do not touch the Blue Button on top of the Pen (see Figure 1) while you are loading the Pen.

Figure 1

Figure 2

1. Open the lid of the Carrying Case.

The tamper-evident seals over the 2 Syringe Cartridges are labeled " A" and " B" (see Figure 1 inset). Always use the Syringe Cartridge marked " A" before the one marked " B" to help you keep track of your doses. **Do not use if either seal is broken or missing when you first open the Carrying Case.**

2. Tear off one of the tamper-evident seals (see Figure 1). Throw away the seal. Open the lid over the Syringe Cartridge.

3. Hold the Pen by the ridges at the top. Take it out of the Carrying Case (see Figure 2).

Check to make sure the white Priming Rod is not sticking out from the lower end of the Pen (see Figure 2 inset). If it is sticking out, put the Pen back into the Carrying Case and press down firmly until you feel it click. Then take the Pen out of the Carrying Case.

4. Put the Pen in the Cartridge Pack. Turn it to the right (clockwise) until it will not turn any more (about half a turn) (see Figure 3).

Figure 3

Figure 4

5. Hold the loaded Pen by the ridges and pull it **straight out** (see Figure 4). You may need to pull hard on the Pen, but this is normal. Do not press the Blue Button yet.

The Pen is now ready to use. Do not put the loaded Pen back into the Carrying Case because that will damage the needle.

How to use the IMITREX STATdose Pen to take your medicine

Before injecting your medicine, choose an area with a fatty tissue layer (see Figure 5a **or** Figure 5b). Ask your healthcare provider if you have a question about where to inject. Clean the skin around this area.

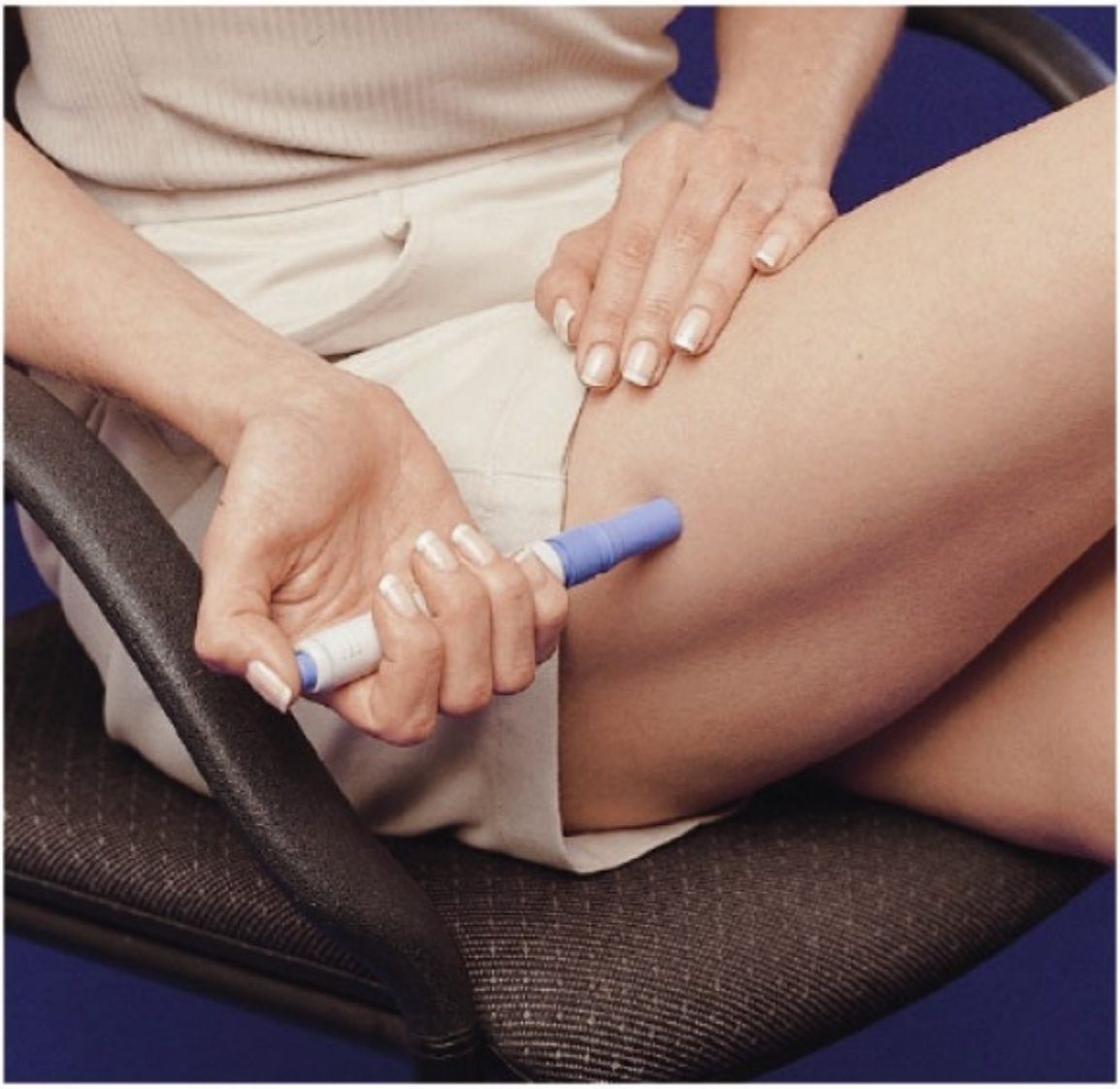


Figure 5a

or

Figure 5b

Figure 6

1. Without pushing the Blue Button, press the loaded Pen firmly against the skin so that the grey barrel slides down toward the blue section that holds the Syringe Cartridge (see Figure 4). (This releases the Safety Catch that keeps the Pen from firing by mistake until you are ready.)
2. Push the Blue Button. Hold the Pen still for **at least 5 seconds**. If the Pen is taken away from the skin too soon, not all the medicine will come out.
3. **After 5 seconds,** carefully take the Pen away from your skin. The needle will be showing (see Figure 6). **Do not touch the needle.**

How to unload the IMITREX STATdose Pen after taking your medicine

Right after you take a dose with the Pen, you need to return the used Syringe Cartridge to the Cartridge Pack.

Figure 7

Figure 8

Figure 9

1. Push the Pen down into the empty side of the Cartridge Pack as far as it will go (see Figure 7).
2. Turn the Pen to the left (counterclockwise) about half a turn until it is released from the Syringe Cartridge (see Figure 8).
3. Pull the empty Pen out of the Cartridge Pack (see Figure 9).

Because the Pen has now been used, the white Priming Rod will stick out from the lower end of the Pen.

4. Close the Cartridge Pack lid over the used Syringe Cartridge. When the used Syringe Cartridges are inserted correctly, the Cartridge Pack is a disposable, protective case to help you avoid needle sticks and use the syringes correctly.
5. Put the Pen back into the Carrying Case and press it down firmly until you feel it click. Close the Carrying Case lid. This gets the Pen ready for the next use.

If the lid will not close, push the Pen down until you feel it click. Then close the lid.

How to take out a used Cartridge Pack

After both Syringe Cartridges have been used, take the Cartridge Pack out of the Carrying Case and throw it away. **Never reuse a Syringe Cartridge.**

Figure 10

Figure 11

1. Open the Carrying Case lid.
2. Hold the Carrying Case with one hand and press the 2 buttons on either side of the Carrying Case (see Figure 10).
3. Gently pull out the Cartridge Pack with the other hand (see Figure 11).

(continued on other side)

How to insert a new Cartridge Pack

Figure 12

Figure 13

Figure 14

1. Take the new Cartridge Pack out of its box. **Do not take off the tamper-evident seals** (see Figure 12).
2. Put the Cartridge Pack in the Carrying Case. Slide it down smoothly (see Figure 13).
3. The Cartridge Pack will click into place when the 2 buttons show through the holes in the Carrying Case (see Figure 14). Close the lid.

February 2008

Appendix 2

Chart comparing use of Dr. Reddy device compared to Imitrex
Taken from 10/25/11 OGD consult to CDRH

Following this page, 3 Pages Withheld in Full as (b)(4)

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

/s/

NANCY S CHANG
12/14/2011

JOHN R PETERS
12/14/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-495

CHEMISTRY REVIEWS

ANDA 090495

Sumatriptan Succinate Injection 6 mg (base)/0.5 mL

Dr. Reddy's Laboratories, Ltd

Sukhamaya (Sam) Bain, Ph.D.
Office of Generic Drugs
Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. **ANDA:** 090495

2. **REVIEW #:** 5

3. **REVIEW DATE:** 08-JAN-2014

4. **REVIEWER:** Sukhamaya (Sam) Bain, Ph.D.

5. **PREVIOUS DOCUMENTS:**

Previous Document	Document Date/Status	Location
Review #4	15-APR-2013/Not Approvable	DARRTS

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

Submission(s) Reviewed	Date of Submission
Amendment	24-OCT-2013

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

Name:	Dr. Reddy's Laboratories, Ltd
Address:	FTO-Unit 3, Survey No 41 Bachupally Village, Qutubullapur Mandal Ranga Reddy District Andhra Pradesh 500 090 India
US Agent:	Dr. Reddy's Laboratories, Inc. Attn: Srinivasa Rao 200 Somerset Corporate Boulevard, 7th Floor Bridgewater, NJ 08807
Telephone:	908-203-7022
Fax:	908-203-4980

8. DRUG PRODUCT NAME/CODE/TYPE: Sumatriptan Succinate Injection

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Sumatriptan Succinate Injection

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Imitrex Injection 6 mg(base)/0.5 mL; 12mg/mL.

10. PHARMACOL. CATEGORY: Anti-hypertensive

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY:6 mg(base)/0.5 mL; 12 mg/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

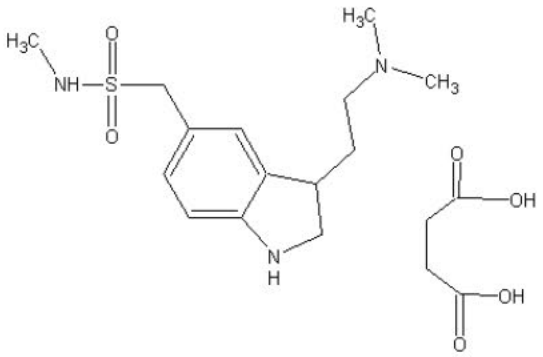
__x___Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

___x__Not a NANO product

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



Molecular Formula: $C_{18}H_{27}N_3O_6S$

Molecular Weight: 413.40 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	REVIEWER REVIEW DATE
16534	II	Dr. Reddy's	Sumatriptan Succinate	1	Adequate-IR	S. Bain 07-JAN-2013
(b) (4)	III	(b) (4)		4		
	III			4		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

18. STATUS:

Consults/CMC Related Reviews	Recommendation	Reviewer	Date
Microbiology	N/A		
EES	Acceptable	T. Sharp	12-FEB-2013
Methods Validation	Satisfactory	A. Langowski	15-APR-2013
Labeling	Satisfactory	A. E. Vezza	07-NOV-2013
Bioequivalence	Satisfactory	C. H. Lee	03-DEC-2013
DCR Consult	Satisfactory	D. J. Seibel	23-DEC-2013
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 090495

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend Approval.

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) (From CR4)

Sumatriptan succinate is chemically designated as 3-[2-(dimethyl-amino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate (1:1). The empirical formula is C 14 H 21 N 3 O 2 S·C 4 H 6 O 4 , representing a molecular weight of 413.5. Sumatriptan succinate is a white to off-white powder that is readily soluble in water and in saline.

The drug product consists of a solution of the drug substance contained in a prefilled syringe which is placed in an autoinjector.

The drug substance is an article of the USP. The drug product is not.

B. Description of How the Drug Product is Intended to be Used (From CR4)

Subcutaneous injection (is used) for relief of migraine headache. A maximum of two 6 mg injections within 24 hours is the recommend maximum daily dose.

C. Basis for Approvability or Not-Approval Recommendation

No CMC deficiency.

Following this page, 7 Pages Withheld in Full as (b)(4)

III. List of Deficiencies/Comments to Be Communicated to the Applicant

ANDA: 090495 APPLICANT: Dr. Reddy's Laboratories, Ltd

DRUG PRODUCT: Sumatriptan Succinate Injection 6 mg (base)/0.5 mL

No Chemistry deficiency.

Sincerely yours,

Glen J. Smith
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Endorsements:

Reviewer/Date: S. Bain/08-JAN-2014
Team Leader/Date: P. Capella/P. Simamora for P.C./8-Jan-2014
Division Director/Date: G. Smith/11-Jan-2014
Project Manager/Date: S. Khanna/January 12, 2014

TYPE OF LETTER: APPROVABLE

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

/s/

SUKHAMAYA BAIN
01/13/2014

SAVAN N KHANNA
01/13/2014

PAHALA SIMAMORA` on behalf of PETER CAPELLA
01/13/2014

GLEN J SMITH
01/14/2014

ANDA 90495

Sumatriptan Succinate Injection 6 mg(base)/0.5 mL

Dr. Reddy's Laboratories, Ltd

Andrew J. Langowski
OGD Chemistry Division II

Not Approvable

Review # 4.

3/12/13

Table of Contents

Chemistry Review Data Sheet

1. **ANDA 90-495**

2. **REVIEW #: 4**

3. **REVIEW DATE: Jul 10, 2012**

4. **REVIEWER: Andrew J. Langowski**

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date
Amendment	March 12, 2010

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

Submission(s) Reviewed	Document Date
Amendment	5/26/2011
Amendment	9/8/2011
Amendment	10/18/2011
Amendment	10/21/2011
Amendment	12/15/2011
Amendment	5/18/2012

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

Name:	Dr.Reddy's Laboratories, Ltd
Address:	200 Somerset Corporate Blvd(7th fl) Bridgewater NJ 08807
Representative:	Kumara Sekar, Ph.D.

8. DRUG PRODUCT NAME/CODE/TYPE: Sumatriptan Succinate Injection

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN): Sumatriptan Succinate

c) Code Name/# N/A

9. LEGAL BASIS FOR SUBMISSION: The RLD is Imitrex Injection 6 mg(base)/0.5 mL; 12mg/mL.

10. PHARMACOL. CATEGORY: Anti-hypertensive

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 6 mg(base)/0.5 mL; 12 mg/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED: _x__Rx ___OTC

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

_____SPOTS product – Form Completed

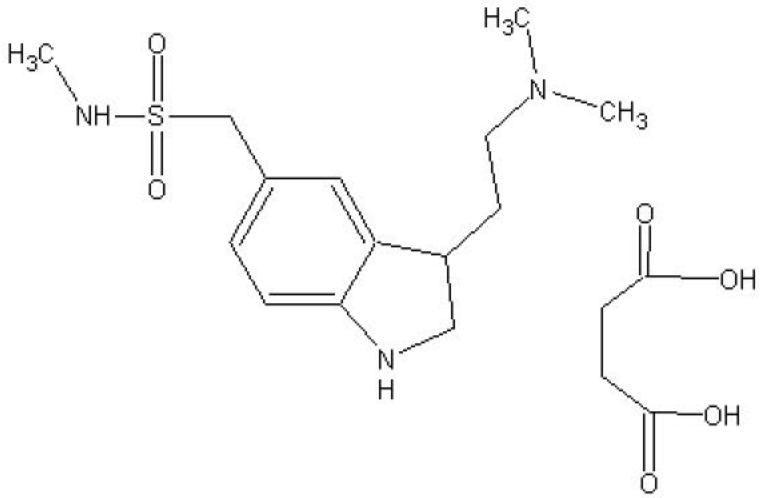
__x___Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

___x___Not a NANO product

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



Molecular Formula: $C_{18}H_{27}N_3O_6S$

Molecular Weight: 413.40 g/mol

17. RELATED/SUPPORTING DOCUMENTS: none

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
16534	II	Dr.Reddy	Sumatriptan Succinate	1	A	08/28/12	Adequate, A. Langowski
(b) (4)	III	(b) (4)		4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review

4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

18. STATUS:

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	5/5/2010	
EES	Acceptable	6/12/2012	
Methods Validation	Acceptable		
Labeling	Pending		
Bioequivalence	Deficient	06/19/2012	C.Lee
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 90-495

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval pending BIO, Clinical and Label

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)

Sumatriptan succinate is chemically designated as 3-[2-(dimethyl-amino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate (1:1). The empirical formula is C 14 H 21 N 3 O 2 S·C 4 H 6 O 4 , representing a molecular weight of 413.5. Sumatriptan succinate is a white to off-white powder that is readily soluble in water and in saline.

The drug product consists of a solution of the drug substance contained in a prefilled syringe which is placed in an autoinjector.

The drug substance is an article of the USP. The drug product is not.

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

Subcutaneous injection for relief of migraine headache. A maximum of two 6 mg injections within 24 hours is the recommend maximum daily dose.

C. Basis for Approvability or Not-Approval Recommendation

Approval pending BIO, Clinical and Labeling

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

A.Langowski/
P.Capella/ 11-Jan-2013
S. Rosencrance/
T.Nhu/

C. CC Block

Administrative

A. Reviewer's Signature

B. Endorsement Block

A.Langowski/
P.Capella/11-Jan-2013, 11-Mar-2013
S. Rosencrance/
T.Nhu/

III. List Of Deficiencies To Be Communicated

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-495 APPLICANT: Dr. Reddy's Laboratories

DRUG PRODUCT: Sumatriptan Succinate Injection 0.6 mg (base)/0.5 mL

Deficiencies:

The following comments are from the OGD Division of Clinical Review:

Regarding the safety locking mechanism and instructions for using the safety mechanism:

- It is acceptable that the safety remains disengaged if the tip is pressed and then released without initiating an injection. This allows a user to change injection site if, for example, the first site does not feel to have enough fat. The device could be repositioned and the injection given.

- Since the safety remains disengaged if the device is pressed and then released without initiating an injection, the current wording, stating that the device [redacted] (b) (4) is incorrect and potentially misleading.
  A user should be warned that **as long as the blue circle is visible in the medicine window, the safety catch is in the off position; the pen could fire unintentionally if the blue button is pressed by accident**.

- [redacted] (b) (4)

(b) (4)

The following recommendations pertain to the instructions for use.

- Rather than running together in normal text, the warning (b) (4) and the second warning to keep out of the reach of children, should be bulleted, and/or separated, and/or bolded for clarity:
  - (b) (4)
  - Keep the Sumatriptan Succinate Auto-Injector System out of the reach of children.

- The figure in Step (b) (4) of the instructions for use attempts to demonstrate the plunger rod that can be seen through the window after injection, or in a spent device. Inspection of the viewing window prior to injection should ensure that there is clear liquid present, and also ensure that the device is not spent.
  - The "after injection" figure currently in Step (b) (4) should be moved to "before injection" Step 5 in order to show what should and what should not be visible through the window of an unspent device.
  - In both "before injection" and "after injection" figures, the important features are not clearly visible. Even with the arrow pointing to the plunger rod, it is difficult to see the plunger in the figure, as it is in the device itself. This reviewer was only able to see the plunger by holding the pen up to the light.
  - Since it is important to be certain that the liquid is clear, and that the plunger is not present, Step 5 should instruct users that if they have difficulty seeing what is in the window, they may hold the pen up to the light.

- Although needle position cannot be used to differentiate between a spent injector and one that has not been injected, you should provide information so that users can tell the difference. For example, users could be informed that if the plunger rod can be seen through the window, the device is spent and cannot be used again.

- The current instruction in Step (b) (4) does not adequately emphasize that the entire dosage delivery system is intended to be a disposable device and disposed of in

its entirety. The instruction should include the word "whole" or "entire" as in, "After you have used the pen, throw away the entire pen in a special container"

- The inconsistencies between the 2 "final" versions of the IFU raise some concern as to which device this sponsor is intending to be reviewed.
  - The Sponsor should clarify whether the to-be-marketed presentation will have (b) (4)
  - The final package insert and instructions for use should be consistent, and show only images identical to the to-be-marketed device.
  - The Sponsor should clarify the color of images and text for the final labeling. The (b) (4) background of the Annotated IFU makes the text difficult to read.

• In your most recent submissions, you have not defined all abbreviations. For example, there are multiple references to the PIL but no definition for this abbreviation. This is especially important since PIL closely resembles the commonly used abbreviation PI that has been used to mean prescribing information, package insert, or patient information. The term PIL does not actually appear in your labeling, but in future communications with the Agency you should clearly define all abbreviations.

TYPE OF LETTER: Complete Response

– **Note** DBE deficiencies were sent out on 06/19/2012 and Labeling review is pending. (OGD DCR review has labeling-related recommendations.) Based on consult responses CDRH has no further questions at this time.

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

/s/

ANDREW J LANGOWSKI
04/03/2013

PETER CAPELLA
04/03/2013

SUSAN M ROSENCRANCE
04/15/2013

TINA T NHU
04/15/2013

ANDA 90-495

Sumatriptan Succinate Injection 6 mg(base)/0.5 mL

Dr. Reddy's Laboratories, Ltd

Andrew J. Langowski
OGD Chemistry Division II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 90-495

2. REVIEW #: 3

3. REVIEW DATE: Jul 20, 2010

4. REVIEWER: Andrew J. Langowski

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	4/28/09
Amendment(micro)	10/15/09
Amendment(micro)	12/2/09
Amendment (cmc)	8/31/09

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (CMC)	3/12/2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Dr.Reddy's Laboratories, Ltd
Address:	200 Somerset Corporate Blvd(7th fl) Bridgewater NJ 08807
Representative:	Kumara Sekar, Ph.D.

Telephone: 908-203-4937

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Sumatriptan Succinate
c) Code Name/# N/A

9. LEGAL BASIS FOR SUBMISSION: The RLD is Imitrex Injection 6 mg(base)/0.5 mL; 12mg/mL.

10. PHARMACOL. CATEGORY: Anti-hypertensive

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 6 mg(base)/0.5 mL; 12 mg/mL

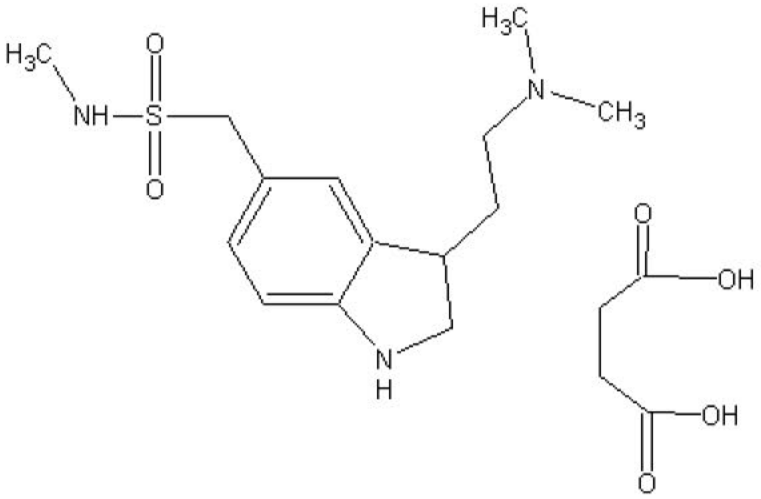
13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x___Not a SPOTS product

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



Molecular Formula: $C_{18}H_{27}N_3O_6S$

Molecular Weight: 413.40 g/mol

17. RELATED/SUPPORTING DOCUMENTS: none

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
16534	II	Dr.Reddy	Sumatriptan Succinate	1	A	Jan 2009	
(b) (4)	III		(b) (4)	4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
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5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] 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

18. STATUS:

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	5/5/2010	
EES	Pending		
Methods Validation	Acceptable		
Labeling	NA	11/17/08	
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 90-495

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable pending results from other disciplines and EES

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)

Sumatriptan succinate is chemically designated as 3-[2-(dimethyl-amino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate (1:1). The empirical formula is C 14 H 21 N 3 O 2 S·C 4 H 6 O 4 , representing a molecular weight of 413.5. Sumatriptan succinate is a white to off-white powder that is readily soluble in water and in saline.

The drug product consists of a solution of the drug substance contained a in a prefilled syringe which is placed in an autoinjector.

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

Subcutaneous injection for relief of migraine headache.

C. Basis for Approvability or Not-Approval Recommendation

Approvable pending results from other disciplines and EES.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

A.Langowski/
P.Capella/
L.Longstaff/

C. CC Block

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-495 APPLICANT: Dr. Reddy's Laboratories

DRUG PRODUCT: Sumatriptan Succinate Injection 0.6 mg (base)/0.5 mL

Deficiencies:

Please be advised that your proposed Sumatriptan Autoinjector product has been evaluated for any potential concerns with respect to safety or therapeutic equivalence. We have provided the following deficiencies and recommendations:

1. Additional sample units are required to allow for full evaluation. The units do not have to contain active drug, but they should be fully functional.

2. The position of the needle after injection should be clarified and justified from the standpoint of safe handling and disposal after injection.

3. (b) (4)

4. The button on the sample unit and the actuation force data for the device suggest that the device may be difficult to fire for some individuals. Evaluation of additional samples will be helpful in this regard, but the sponsor should also provide information to support the ease of firing and operating this device in a diverse population.

5. It is known that differences in injection technique and site of injection can affect the pharmacokinetics of sumatriptan. Therefore, while the performance and specifications of the proposed device are generally similar to those of the RLD, the small differences in performance and specifications that are present (e.g. needle gauge, injection cycle time, force to displacement distance profile) have the theoretical potential to affect PK. DCR defers to DBE the decision of whether or not a BE study should be required for this product.

In addition, we have provided the following labeling deficiencies and recommendations:

6. The following additional comments pertain to the proposed patient labeling insert:

a. Wherever possible and appropriate, the proposed labeling for the generic product should mirror that for the RLD. For example, the RLD labeling instructs the user to read the leaflet several times. Unless there is justification for doing otherwise, the generic labeling should also instruct the user to read several times, and not (b) (4) as currently proposed.

b. As is done in the Imitrex labeling, the labeling for the generic should contain a section describing the parts of the injector, including figures in which relevant parts of the autoinjector device are clearly labeled.

c. The color configuration of the product needs to be clarified: the sample provided has a different color configuration than described in the proposed labeling.

d. The statement and accompanying figure stating that the device (b) (4) need to be clarified. It is difficult to understand what the sections are being referred to and how the user can ascertain that the injector is (b) (4) (b) (4)

e. The use of the safety catch mechanism needs to be clarified. It appears that the mechanism (b) (4) The sponsor needs to clarify whether or not the safety catch mechanism remains disengaged if the tip is pressed and then released without initiating an injection. If the safety lock does remain disengaged, instruction should be provided on whether or not it is safe to re-engage the safety lock, and how to do so.

f. The user should be clearly instructed not to disengage the safety feature until just before the injection is to be initiated.

g. The labeling should provide a figure and description of the viewing window with instructions on its use and on the expected appearance of the window before and after injection.

h. The sponsor should also clarify whether or not the stopper position should be inspected through the viewing window and what the appropriate position should be both before and after injection.

i. The instruction to "firmly press…against the skin" should be prefaced with "without pressing the blue button", as in the Imitrex label.

j. The instructions and the post-injection photo should describe clearly the needle position after injection and also provide information so that users can tell the difference between a spent injector unit and one that has not been injected.

k. Instruction should be provided about proper handling and disposal procedures after injection and these instructions should provide further clarification that the entire dosage delivery system is intended to be a disposable device and should be disposed of in its entirety. This clarification is necessary because this device differs significantly from the RLD device in this respect.

l. Some versions of labeling have included a directive to pull the blue cap straight off ensuring that the rubber needle shield has been removed. The sponsor should clarify whether or not this instruction is necessary and to provide justification.

m. Versions of labeling have differed with respect to when clicks will be heard upon operating the device. The sponsor should clarify at which point(s) clicks will be heard and reflect this information appropriately in labeling (e.g. (b) (4) (b) (4) upon pushing the button to initiate injection, upon completion of injection

In addition, please be advised that the review of the CMC amendments submitted in relation to the new proposed drug product manufacturing facility, Gland Pharma" is ongoing and you will be notified of any deficiencies in a separate letter.

Sincerely yours,

{See appended electronic signature page}

Glen J. Smith
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 90-495
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-647/A.Langowski/

HFD-647/P.Capella/

HFD-617/S.Eng/

TYPE OF LETTER: Not approvable

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

/s/

ANDREW J LANGOWSKI
01/06/2012

PETER CAPELLA
01/06/2012

SIMON S ENG
01/06/2012

ANDA 90-495

Sumatriptan Succinate Injection 6 mg(base)/0.5 mL

Dr. Reddy's Laboratories, Ltd

Andrew J. Langowski
OGD Chemistry Division II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 90-495

2. REVIEW #: 2

3. REVIEW DATE: Dec 1, 2009

4. REVIEWER: Andrew J. Langowski

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	4/28/09
Amendment(micro)	10/15/09
Amendment(micro)	12/2/09

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (CMC)	8/31/09

7. NAME & ADDRESS OF APPLICANT:

Name:	Dr.Reddy's Laboratories, Ltd
Address:	200 Somerset Corporate Blvd(7th fl) Bridgewater NJ 08807
Representative:	Kumara Sekar, Ph.D.
Telephone:	908-203-4937

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Sumatriptan Succinate
c) Code Name/# N/A

9. LEGAL BASIS FOR SUBMISSION: The RLD is Imitrex Injection 6 mg(base)/0.5 mL; 12mg/mL.

10. PHARMACOL. CATEGORY: Anti-hypertensive

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 6 mg(base)/0.5 mL; 12 mg/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous

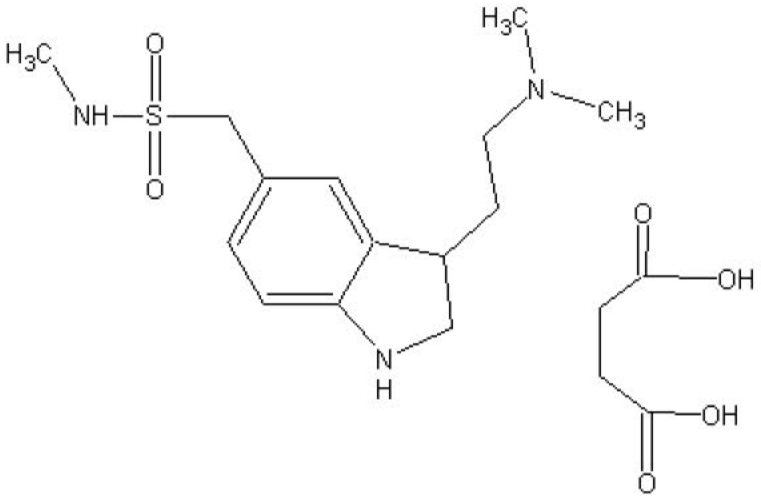
14. Rx/OTC DISPENSED: _x__Rx ___OTC

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

_____SPOTS product – Form Completed

__x___Not a SPOTS product

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



Molecular Formula: $C_{18}H_{27}N_3O_6S$

Molecular Weight: 413.40 g/mol

17. RELATED/SUPPORTING DOCUMENTS: none

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
16534	II	Dr.Reddy	Sumatriptan Succinate	1	A	Jan 2009	
(b) (4)	III	(b) (4)		4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] 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

18. STATUS:

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Pending		
Methods Validation	Deficient		
Labeling	Pending		
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 90-495

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable

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)

Sumatriptan succinate is chemically designated as 3-[2-(dimethyl-amino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate (1:1). The empirical formula is C 14 H 21 N 3 O 2 S·C 4 H 6 O 4 , representing a molecular weight of 413.5. Sumatriptan succinate is a white to off-white powder that is readily soluble in water and in saline.

The drug product consists of a solution of the drug substance contained a in a prefilled syringe which is placed in an autoinjector.

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

Subcutaneous injection for relief of migraine headache.

C. Basis for Approvability or Not-Approval Recommendation

The firm has been requested to revise the release and stability specifications, as well as, clarification of analytical method.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

A.Langowski/
G.Smith/
L.Longstaff/

C. CC Block

Following this page, 36 Pages Withheld in Full as (b)(4)

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-495 APPLICANT: Dr. Reddy's Laboratories

DRUG PRODUCT: Sumatriptan Succinate Injection 0.6 mg (base)/0.5 mL

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

1. (b) (4)

2.

(b) (4)

3.

4.

5.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 90-495
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-647/A.Langowski/

HFD-647/G.Smith/

HFD-617/L.Longstaff/

TYPE OF LETTER: NOT APPROVABLE - MINOR

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90495	ORIG-1	DR REDDYS LABORATORIES INC	SUMATRIPTAN SUCCINATE

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

/s/

ANDREW J LANGOWSKI
01/26/2010

LAURA A LONGSTAFF
01/27/2010

GLEN J SMITH
01/28/2010

Per OGD, Chemistry Review #1 was never finalized. Issues were carried over into Review #2.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-495

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090495		
Drug Product Name	Sumatriptan Succinate Injection, pre-filled syringe with auto-injector		
Strength(s)	EQ 6 mg base/0.5 mL		
Applicant Name	Dr. Reddy's Laboratories, Inc.		
Address	FTO-Unit 3, Survey No 41, Bachupally Village, Qutubullapur Mandal, Ranga Reddy District, Andhra Pradesh , 500 090, India 200 Somerset Corporate Blvd, 7th Floor, Bridgewater, NJ 08807		
Applicant's Point of Contact	Lee Banks		
Contact's Telephone Number	908-203-4951		
Contact's Fax Number	908-203-4980		
Original Submission Date(s)	April 28, 2008		
Submission Date(s) of Amendment(s) Under Review	April 13, 2009 (Resubmission) May 18, 2012 (In-vitro Testing) April 03, 2013 (BE study) Oct 24, 2013 (Study amendment)		
Reviewer	Christina Lee, Pharm.D.		
Study Number (s)	**71912**		
Study Type (s)	Fasting		
Strength (s)	1 X 6 mg		
Clinical Site	Bio-Kinetic Clinical Applications, LLC		
Clinical Site Address	1816 W. Mt. Vernon Springfield, MO 65802		
Analytical Site	(b) (4)		
Analytical Site Address			
OVERALL REVIEW RESULT	**ADEQUATE**		
WAIVER REQUEST RESULT	**NA**		
OSI REPORT RESULT	**ADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 20, 23	**FASTING**	**6 mg**	**ADEQUATE**

REVIEW OF A STUDY AMENDMENT

1 Executive Summary

This is review of a study amendment.

The firm, Dr. Reddy's Laboratories, Inc. is requesting a waiver of in vivo bioequivalence study requirements for its Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL. The reference listed drug is Imitrex® STATDOSE Injectable, EQ 6 mg base/0.5 mL, manufactured by GlaxoSmithKline. The test product is qualitatively and quantitatively the same as the reference listed drug (RLD). The test product is a pre-filled syringe assembled in an auto-injector device.

In the August 31, 2009 re-submission, the firm changed the device design from a (b) (4) (b) (4) to **a push & button** design. In addition, the firm also included in-vitro comparison studies between the test product auto injector (particularly (b) (4) Push & Button design) versus the RLD.

The Division of Bioequivalence II (DB II) has reviewed the content of the submission and denied the waiver request for *in vivo* bioequivalence study requirements for the test product, Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL. Additional in-vitro testings were required. In addition, the Agency asked the firm to conduct a single-dose two-way crossover bioequivalence study in healthy volunteers **where the subjects inject themselves using the device.**

In subsequent amendment submissions, dated May 18, 2012 and April 3, 2013, the firm responded to DB II's requests stated above. The firm's responses regarding the in-vitro testing on the device were considered adequate. However, the bioequivalence study (#71912) was considered inadequate due to: 1) inadequate LTSS data; 2) Excluding Subject Nos. 1, 8 and 34 (as outliers) from the statistical analysis of the study was not justified.

In the current amendment, dated 10/24/2013, the firm provided sufficient information regarding Subject Nos. 1, 8 and 34 who were considered as outliers and were excluded from the PK analysis. Based on the justifications provided in the current amendment, the reviewer agreed with the firm's conclusion that these three subjects (subject numbers 001, 008 and 034) were discordant outliers because of extreme response in replicate 2 (Period III and IV) when drug (Reference product) was administered at gluteal/thigh site when compared to the rest of the subjects who participated in the study and to the study outcome from replicate 1 (Period I and II, deltoid site) of the same subjects. Therefore, the firm's response is deemed adequate.

From bioequivalence point of view, the application is **adequate** with no deficiencies.

2 Table of Contents

3 Review of Amendment Submission, dated 10/24/2013

The following deficiencies were sent to the firm in the Agency letter dated Sept 04, 2013:

Bioequivalence Deficiencies:

Deficiency# 1:

The long-term storage stability (LTSS) data of 70 days@ -20°C and-70°C is insufficient. Please provide sufficient LTSS to cover the entire storage length of the BE study samples (from the time of the first blood sample drawn to the time of the last plasma sample analyzed) up to 114 days @ -20°C and -70°C.

Firm's Response:

The long-term storage stability (LTSS) data of Sumatriptan for 180 days @ -20°C and -70°C is provided in Bio analytical method validation report attached in Module 5.3.1.1.

Reviewer's Comments: The firm submitted amendment for bioanalytical method validation report (No. 42-1314), completed on 09/19/2013. Sumatriptan stability in K2EDTA human plasma was demonstrated for 180 days of long-term storage at -20°C and -70°C.

Table 17 **Long-Term Storage Stability of Sumatriptan in K_2EDTA Human Plasma at -20°C**

Concentration (ng/mL)	Day 0[a]	Day 180[b]
0.600		(b) (4)
n	6	5
Mean	0.614	0.649
S.D.	0.0184	0.0292
%CV	3.0	4.5
%RE	2.3	NC
%Diff[c]		5.7
Concentration (ng/mL)	Day 0[a]	Day 180[b]
180		(b) (4)
n	6	5
Mean	173	182
S.D.	2.14	1.52
%CV	1.2	0.8
%RE	-3.9	NC
%Diff[c]		5.2

NC: Not Calculated
[a] Day 0: Run ID 2
[b] Day 180: Run ID 7
[c] %Diff ((Mean of Day 180 - Mean of Day 0) / Mean of Day 0) x 100

Table 18 **Long-Term Storage Stability of Sumatriptan in K_2EDTA Human Plasma at -70°C**

Concentration (ng/mL)	Day 0[a]	Day 180[b]
0.600		(b) (4)
n	6	5
Mean	0.614	0.630
S.D.	0.0184	0.00635
%CV	3.0	1.0
%RE	2.3	NC
%Diff[c]		2.6
Concentration (ng/mL)	Day 0[a]	Day 180[b]
180		(b) (4)
n	6	5
Mean	173	182
S.D.	2.14	1.48
%CV	1.2	0.8
%RE	-3.9	NC
%Diff[c]		5.2

NC: Not Calculated
[a] Day 0: Run ID 2
[b] Day 180: Run ID 7
[c] %Diff: ((Mean of Day 180 - Mean of Day 0) / Mean of Day 0) x 100

Therefore, the firm's response regarding LTSS is acceptable.

Deficiency# 2:

The Fasting BE study is incomplete with the following reasons:

1. *Subject Nos. 1, 8 and 34 revealed no clinical abnormalities. Excluding these subjects from the statistical analysis of the study is not justified. After including all subjects in the study, the confidence intervals for AUCt, AUCi and Cmax do not fall within the acceptable 80-125% range. Therefore, the study is unacceptable.*

2. *The DB II does not accept results of statistical outlier tests to justify dropping subjects from a BE study. To re-evaluate the pharmacokinetic performance of subject Nos. 1, 8 and 34, you may re- dose these three subjects along with several other subjects (control group) chosen at random from the same study. Additionally, the study procedures and study drug lot numbers should be identical to Study# 71912 (original study). Alternatively, you may conduct a new fasting bioequivalence study.*

Firm's Response:

Dr. Reddy's respectfully requests the agency to reconsider the below information while making a determination on the adequacy of the available information to demonstrate bioequivalence of the test product with the reference product. A summary of data available data and previous communication with agency is provided below:

The agency indicated in the Bio-equivalence deficiency letter dated Jan 25, 2012 that "the known differences in injection technique and site of injection can affect the pharmacokinetics of sumatriptan. The small differences in performance and specifications that are present (e.g. needle gauge, injection cycle time, force to displacement distance profile) have the theoretical potential to affect PK. Therefore, the DB II recommended that you conduct a single-dose two-way crossover fasting bioequivalence study in healthy volunteers where the subjects inject themselves using the device".

In support of the above Agency's expectation, Dr. Reddy's had conducted a series of experimentation to demonstrate the equivalency of the Dr. Reddy's product against the RLD product for its performance. The data is available in Dr. Reddy's response dated May 18, 2012.

In addition, a fasting bioequivalence study in normal, healthy, adult human subjects was also conducted. The study was conducted as a replicated crossover design with subjects who were randomized into two treatment sequences A B A B and B A B A, where A=Test and B=Reference in two groups (Group 1: Subject numbers: 1 - 27, Group 2: Subject numbers: 28 - 48). For period I & II, drug administration site was deltoid and for period III & IV site was gluteal.

Since the site*treatment interaction term was not statistically significant ($p>0.05$), both the treatments (Test and Reference products) were expected to behave same at two different drug administration sites. Also, the variability due to subject*treatment interaction term was too low i.e., there was no confounding between subject and treatment.

Review of study subjects 1, 8 and 34 showed aberrant Pharmacokinetic responses in period IV only when reference product (using REFERENCE device) was administered.

Table 1. List of the Test/Reference values and ratios for PK parameters AUC_{last}, AUC_{inf} and C_{max} for subjects 1, 8 and 34 when injected at two sites

Test/Reference Ratio (%)						
Subject Number	Site: Deltoid			Site: Gluteal		
	AUC_{last} (hr*ng/ml)	AUC_{inf} (hr*ng/ml)	C_{max} (ng/ml)	AUC_{last} (hr*ng/ml)	AUC_{inf} (hr*ng/ml)	C_{max} (ng/ml)
1	102.557	101.876	106.035	33944.315	Not estimable	10543.612
8	105.659	105.555	103.746	402400.000	26913.938	57928.986
34	120.829	121.156	86.772	137297.143	64046.358	20491.981

Test Values)						
Subject Number	Site: Deltoid			Site: Gluteal		
	AUC_{last} (hr*ng/ml)	AUC_{inf} (hr*ng/ml)	C_{max} (ng/ml)	AUC_{last} (hr*ng/ml)	AUC_{inf} (hr*ng/ml)	C_{max} (ng/ml)
1	112.3	114.3	99.9	116.4	118.6	61.9
8	109.3	110.36	73	102.2	103.2	91.9
34	103.4	104.3	106.8	96.11	96.7	86.9

Reference Values)						
Subject Number	Site: Deltoid			Site: Gluteal		
	AUC_{last} (hr*ng/ml)	AUC_{inf} (hr*ng/ml)	C_{max} (ng/ml)	AUC_{last} (hr*ng/ml)	AUC_{inf} (hr*ng/ml)	C_{max} (ng/ml)
1	109.5	112.2	94.2	0.343	.	0.587
8	103.4	104.2	70.4	0.030	0.452	0.276
34	85.6	86.1	123.1	0.070	0.151	0.424

Justifications:

1. There was no abnormality in the observed data for both test and reference product (including subjects 1, 8 and 34) when administered in Deltoid region thus ruling out the concern expressed by the agency on the possibility of the small differences in performance and specifications that are present (e.g. needle gauge, injection cycle time, force to displacement distance profile) impacting the PK.

2. The reference product (using REFRENCE device) showed abnormal data in subjects 1, 8 and 34 when injected at gluteal site. However, the observed data for the subjects 1, 8 and 34 when injected with test product at gluteal region was in line with the observed data for the remaining subjects for gluteal injections. The subjects 1, 8 and 34 showed normal pharmacokinetic response with the reference product also when the product was administered in deltoid region.

3. The possibility of any aberrant behavior due to subject behavior or subject physiological system, clinical anomaly nor an analytical error is ruled out based on further investigation on observed data thus indicating that the unusual Pharmacokinetic response of these subjects for reference product (using REFERENCE device) could be attributed to RLD product failure.

4. The re-test character of the study design in multiple periods, rules out any effect on pharmacokinetic parameters due to the site of injection since the observed data at Gluteal site with test product did not show any abnormal value in comparison with the data observed for the remaining subjects in the study. The statistical data shown in 40 subjects (excluding subject numbers: 1, 8 and 34) indicates slightly lower response in gluteal site when compared to deltoid site, which is in-line with innovator's label information[1].

[1] www.accessdata fCla.gov/drugsatfda docs/labcI/20 12/020080s039s040s041 s0451b1.pdf

5. It is also observed that the reference product variability was significantly decreased (Cmax: 9 fold, AUC_{last}: 45 fold, AUC_{inf}: 23 fold) after excluding outliers (subject numbers 1, 8 and 34) for statistical analysis.

6. The observed data indicates that except for these three subjects (subject numbers 1, 8 and 34) which are discordant outliers because of extreme response in replicate 2 when drug was administered at gluteal site when compared to the rest of the subjects who participated in the study, the remaining data clearly suggests that the small differences in performance and specifications that are present (e.g. needle gauge, injection cycle time, force to displacement distance profile) did not affect the PK.

7. A statistical outlier test was performed as this is a replicated crossover design and identified that three subjects are qualified as statistical outliers by using studentized residual test for three primary PK parameters C_{max}, AUC_{last} and AUC_{inf}. The 90% confidence intervals for the Ratio of geometric means for the pharmacokinetic parameters evaluated for C_{max}, AUC_{last} and AUC_{inf} were within 80.00 - 125.00%, after excluding subject number 1, 8 and 34 which is within regulatory acceptance criteria (See Table 2. Below).

Table 2. Statistical Summary of the Comparative Bioavailability Data for Unsealed Average BE studies without outliers (Excluding Subjects 1, 8 and 34)

Sumatriptan Injection (subcutaneous)Dose (6 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study No. 71912)						
Parameters	Least Squares Geometric Means				Ratio(%)	90% C.I.
	Test (T)	N	Reference (R)	N		
AUC_{last}	105.303	44	100.517	44	104.76	103.42-106.12
AUC_{inf}	108.323	44	102.458	44	105.72	103.80-107.68
C_{max}	80.568	44	77.707	44	103.68	99.62-107.90

Note: 41 subjects completed four periods (both regions) and 3 subjects completed period 1 and 2 (deltoid region). The subject numbers 1, 8 and 34 were observed outlier at period 4, these subjects were removed from period 3 and 4 (gluteal/thigh regions) from statistical analysis

8. Reference is also made to the quality amendment dated May 18, 2012 (eCTDSeq 0012) in which Dr. Reddy's informed the agency about the several Human Factors studies done during 2011 to evaluate the Usability of the test device (b) (4). Evaluation of the (b) (4) in its final presentation, including the provision of instructions for use and video I demonstration of the use of the device is resulted in 100% successful use. Reference is also made to the Human Factors Validation report (Section 12) of Device Master File (MAF) # (b) (4)

Based on the above information and the in-vitro comparative data provided in the ANDA, Dr. Reddy's believes that the exclusion of the anomalous data for subjects 1, 8 and 34 from the final study data is justified. Since the BE study was conducted to evaluate if minor differences that are present between the test device and the reference device in performance and specifications (e.g. needle gauge, injection cycle time, force to displacement distance

profile) have any impact on the PK as pointed by the OGD Clinical consult, Dr. Reddy's believes that the available data demonstrated equivalency of the test product device and the reference product device.

Reviewer's Comments:

The following information is included in here from the original ANDA review [ANDA# 090495, REV-BIOEQ-21(Primary Review), 06/10/2013, Original-1].

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Without Subject Nos. 1, 8, and 34:

Sumatriptan Injection (subcutaneous) Dose (6 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Bioequivalence Study (Study No.71912) (N=38)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	105.92178	101.10851	1.05	103.417	106.121
AUC∞ (hr *ng/ml)	108.95796	103.04407	1.06	103.821	107.693
Cmax (ng/ml)	80.826263	77.956706	1.04	99.628	107.899

With Subject Nos. 1, 8, and 34:

Sumatriptan Injection (subcutaneous) Dose (6 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Bioequivalence Study (Study No.71912) (N=41)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	105.72425	78.861463	1.34	105.700	170.038
AUC∞ (hr *ng/ml)	108.58218	84.362456	1.29	106.216	155.966
Cmax (ng/ml)	81.108275	65.027172	1.25	104.158	149.365

Supportive Data provided by the firm in the amendment submission (04/03/2013):

1. ***Concentration Data:***

TABLE A: Plasma Concentrations (ng/ml) for Formulation A (Test) Administered at gluteal/thigh Region

Subject	Period	Sequence	0.00	0.03	0.07	0.10	0.13	0.17	0.20	0.25	0.33	0.42	0.50
1	3	ABAB	BQL	1.020	13.489	26.461	51.249	53.609	57.227	57.955	61.891	58.212	55.721
8	3	ABAB	BQL	1.732	26.991	57.009	76.013	78.834	91.974	78.689	67.769	59.093	47.850
34	3	ABAB	BQL	2.713	35.109	57.990	65.719	67.653	86.886	80.356	73.951	62.433	51.781

Subject	Period	Sequence	0.75	1.00	1.50	2.00	2.50	3.00	4.00	6.00	8.00	10.00
1	3	ABAB	53.560	40.453	24.687	18.579	13.402	11.175	6.702	3.101	1.839	0.790
8	3	ABAB	38.914	32.599	20.169	14.634	10.750	8.116	5.474	2.493	1.114	0.397
34	3	ABAB	41.164	32.104	17.683	12.967	9.481	7.382	4.466	1.607	0.707	0.282

TABLE B: Plasma Concentrations (ng/ml) for Formulation B (Reference) Administered at gluteal/thigh Region

Subject	Period	Sequence	0.00	0.03	0.07	0.10	0.13	0.17	0.20	0.25	0.33	0.42	0.50
1	4	ABAB	BQL	BQL	BQL	0.524	0.516	0.520	0.480	0.466	0.350	0.297	0.242
8	4	ABAB	BQL	BQL	0.202	0.276	0.269	0.264	BQL	BQL	BQL	BQL	BQL
34	4	ABAB	BQL	BQL	0.409	0.424	0.384	0.342	0.283	0.266	BQL	BQL	BQL

Subject	Period	Sequence	0.75	1.00	1.50	2.00	2.50	3.00	4.00	6.00	8.00	10.00
1	4	ABAB	BQL	BQL	BQL	0.587	BQL	BQL	BQL	BQL	BQL	BQL
8	4	ABAB	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
34	4	ABAB	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL

2. ***Pharmacokinetic and Statistical Tables provided as supportive data including subjects 001, 008 & 034***

TABLE C: Pharmacokinetic Parameters for Formulation A (Test) Administered at gluteal/thigh Region

Subject	Period	Sequence	AUC_{last} (ng*h/ml)	AUC_{inf} (ng*h/ml)	C_{max} (ng /ml)	t_{max} (hr)	$t_{1/2}$ (hr)	k_{el} (hr^{-1})
1	3	ABAB	116.429	118.565	61.891	0.33	1.87	0.3698
8	3	ABAB	102.246	103.177	91.974	0.20	1.62	0.4267
34	3	ABAB	96.108	96.710	86.886	0.20	1.48	0.4682

TABLE D: Pharmacokinetic Parameters for Formulation B (Reference) Administered at gluteal/thigh Region

Subject	Period	Sequence	AUC_{last} (ng*h/ml)	AUC_{inf} (ng*h/ml)	C_{max} (ng /ml)	t_{max} (hr)	$t_{1/2}$ (hr)	k_{el} (hr^{-1})
1	4	ABAB	0.343	Missing	0.587	2.00	Missing	Missing
8	4	ABAB	0.030	0.452	0.276	0.10	1.11	0.6261
34	4	ABAB	0.070	0.151	0.424	0.10	0.21	3.2945

TABLE E: Within Test and Within Reference variabilities

	Within Test CV (%)	Within Reference CV (%)
Ln (AUC_{last})	5.4	213.3
Ln (AUC_{inf})	9.0	114.9
Ln (C_{max})	17.2	127.6

Based on the data provided above and the firm's justifications in the current submission, the reviewer concluded the followings:

1. This study was conducted as replicate design, with subjects who were randomized into two treatment sequences A B A B and B A B A, where A=Test and B=Reference in two groups (Group 1: Subject numbers: 1 - 27, Group 2: Subject numbers: 28 - 48). For period I & II, drug administration site was deltoid and for period III & IV site was gluteal. The characteristic of this study design is to determine the inter-subject variabilities by comparing the statistical data (Test vs. reference) of the same subject.

2. The site*treatment interaction term was not statistically significant ($p>0.05$), both the treatments (Test and Reference products) were expected to behave the same at two different drug administration sites. Also, the variability due to subject*treatment interaction term was too low, i.e., there was no confounding between subject and treatment.

3. The statistical data shown in 44 subjects (excluding subject numbers: 001, 008 and 034 data from period 3 and 4) indicates slightly lower response in gluteal/thigh site when compared to deltoid site, which is in-line with innovator's label information.

4. The reference product variability was significantly decreased (Cmax ~ 9-fold, AUClast ~ 45 fold, AUCinf ~ 23 fold) after excluding outliers data (subject numbers 001, 008 and 034 data from period 3 and 4) for statistical analysis.

Therefore, the reviewer agreed with the firm's conclusion that these three subjects (subject numbers 001, 008 and 034) were discordant outliers because of extreme response in replicate 2 (Period III and IV) when drug (Reference product) was administered at gluteal/thigh site when compared to the rest of the subjects who participated in the study and to the study outcome from replicate 1 (Period I and II, deltoid site) of the same subjects.

4 Deficiency Comments: none.

5 Recommendations

The Division of Bioequivalence II (DB II) accepts the fasting BE study (Study No. 71912) conducted by Dr. Reddy's Laboratories, Inc. on its Sumatriptan Succinate Injection, EQ 6 mg/0.5 mL (auto-injectors), comparing to the corresponding reference product, Imitrex® STATDOSE Injectable, EQ 6 mg base/0.5 mL, manufactured by GlaxoSmithKline.

6 Comments for Other OGD Disciplines

Discipline	Comment
NA	--

7 Detailed Regulatory History (If Applicable): NA

8 Consult Reviews: NA

9 Additional attachment: None.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090495

APPLICANT: Dr. Reddy's Laboratories, Inc.

DRUG PRODUCT: Sumatriptan Succinate Injection, (Auto Injector), EQ 6 mg base/0.5 mL

The Division of Bioequivalence II (DB II) has completed its review of your submission acknowledged on the cover sheet and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews 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}

Ethan M. Stier, Ph.D., R.Ph.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

10 Outcome Page

Completed Assignment for 090495 ID: 21272

Back to Main Menu

Reviewer: Lee, Christina **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Amendment

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
21272	10/24/2013	Other	Study Amendment	1	1
				Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Study Amendment Review	
Amendment review	1
Injectable/Waiver 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/

CHRISTINA H LEE
12/02/2013

MOHEB H MAKARY
12/02/2013

ETHAN M STIER
12/03/2013

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090495
Drug Product Name	Sumatriptan Succinate Injection, pre-filled syringe with auto-injector
Strength(s)	EQ 6 mg base/0.5 mL
Applicant Name	Dr. Reddy's Laboratories, Inc. FTO-Unit 3, Survey No 41, Bachupally Village, Qutubullapur Mandal, Ranga Reddy District, Andhra Pradesh , 500 090, India
Address	200 Somerset Corporate Blvd, 7th Floor, Bridgewater, NJ 08807
Applicant's Point of Contact	Lee Banks
Contact's Telephone Number	908-203-4951
Contact's Fax Number	908-203-4980
Original Submission Date(s)	April 28, 2008
Submission Date(s) of Amendment(s) Under Review	April 13, 2009 (Resubmission) May 18, 2012 (In-vitro Testing) April 03, 2013 (BE study)
Reviewer	Christina Lee, Pharm.D.

Study Number (s)	**71912**		
Study Type (s)	Fasting		
Strength (s)	1 X 6 mg		
Clinical Site	Bio-Kinetic Clinical Applications, LLC		
Clinical Site Address	1816 W. Mt. Vernon Springfield, MO 65802		
Analytical Site	(b) (4)		
Analytical Site Address			

OVERALL REVIEW RESULT	**INADEQUATE**		
WAIVER REQUEST RESULT	**NA**		
OSI REPORT RESULT	**ADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1, 20	**FASTING**	**6 mg**	**INADEQUATE**

REVIEW OF A STUDY AMENDMENT

1 Executive Summary

This is review of a study amendment.

The firm, Dr. Reddy's Laboratories, Inc. is requesting a waiver of in vivo bioequivalence study requirements for its Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL. The reference listed drug is Imitrex® STATDOSE Injectable, EQ 6 mg base/0.5 mL, manufactured by GlaxoSmithKline. The test product is qualitatively and quantitatively the same as the reference listed drug (RLD). The test product is a pre-filled syringe assembled in an auto-injector device.

In the August 31, 2009 re-submission, the firm changed the device design from a (b) (4) to **a push & button** design. In addition, the firm also included in-vitro comparison studies between the test product auto injector (particularly (b) (4), Push & Button design) versus the RLD.

The Division of Bioequivalence II (DB II) has reviewed the content of the submission and denied the waiver request for *in vivo* bioequivalence study requirements for the test product, Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL with the following recommendations:

1. The firm is requested to perform comparative in vitro testing on 1) drug volume delivered, 2) injection time, and 3) force to fire on the test bio-lot compared to the RLD lot to demonstrate comparative performance characteristics and functionality testing of the test and the reference drug products. The firm should provide individual data for the in vitro tests to demonstrate comparable performance between the test and RLD device components. The firm should submit complete electronic EXCEL spreadsheet of individual data, mean, and %CV for these data on the test product versus Imitrex® STATDOSE Injectable. In addition, the firm should provide specifications such as breakloose force and extrusion force.

2. It is known that differences in injection technique and site of injection can affect the pharmacokinetics of sumatriptan. The small differences in performance and specifications that are present (e.g. needle gauge, injection cycle time, force to displacement distance profile) have the theoretical potential to affect PK. Therefore, the DB II recommends that the firm conducts a single-dose two-way crossover bioequivalence study in healthy volunteers **where the subjects inject themselves using the device.**

3. Considering the warning – among others - on RLD, "the fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of cardiac artery disease (CAD), and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug", consequently, the DB II recommends adequate safety monitoring be in place during the BE study. The firm may submit a protocol for the BE study to the DB II.

On May 18, 2012, the firm responded to DB II's requests stated above. The firm's responses were considered unsatisfactory. The following deficiency comments were provided to the firm in deficiency letter dated June 20, 2012:

1. The firm is requested to explain the apparent differences in the test outcomes with respect to the actuation force between the original data and the data in the current amendment submission for the test product that is nearly 46% differences (18.52 N in the current submission vs. 26.98 N in the original submission). Yet, the data for the RLD remain unchanged.

2. As pointed out in the OGD DCR clinical consult, other differences in the test product (e.g. needle gauge, injection cycle time, force to displacement distance profile) in performance and specifications that are present have the potential to affect PK. The DB II does not agree that the information submitted by the firm supports bioequivalence of its test product, Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL, pre-filled syringe with auto-injector, to the RLD, Imitrex® STATDOSE Injectable, EQ 6 mg base/0.5 mL, manufactured by GlaxoSmithKline. Therefore, the DB II recommends that the firm conducts a single-dose, two-way crossover, bioequivalence study in healthy volunteers **where the subjects inject themselves** both the test and reference products using the respective device.

3. As mentioned in the deficiency letter issued on January 25, 2012, considering the warning – among others - on RLD, "the fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of cardiac artery disease (CAD), and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug", the DB II recommends adequate safety monitoring be in place during the BE study. The firm may submit a protocol for the BE study to the DB II.

On April 03, 2013, the firm submitted an amendment in response to the Agency's deficiency comments stated above. In this amendment, the firm responded to the Agency's deficiency comments 1 and 3 adequately. As requested by DB II, the firm also conducted a randomized, two-treatment, two-sequence, four-period, replicate, single dose, crossover, bioequivalence study comparing its test product, Sumatriptan Injection, 6-mg (Dr. Reddy's Laboratories Limited, India) to IMITREX® Injection, 6-mg (GlaxoSmithKline) in normal, healthy, adult human subjects where the subjects inject themselves both the test and reference products using the respective device. The drug administration site in period 1 and 2 was the Deltoid region and in period 3 and 4 was the Gluteal/Thigh region. The BE study was considered **inadequate** due to the following deficiencies identified:

The pre-study method validation is inadequate with the following deficiency:

1. The long-term storage stability (LTSS) data of 70 days @ -20ºC and -70 ºC is insufficient. The firm is requested to provide sufficient LTSS to cover the entire storage length of the BE study samples (from the time of the first blood sample drawn to the time of the last plasma sample analyzed) up to 114 days @ -20ºC and -70 ºC.

The Fasting BE study is incomplete with the following reasons:

2. Subject Nos. 1, 8 and 34 revealed no clinical abnormalities. Excluding these subjects from the statistical analysis of the study is not justified. After including all subjects in the study, the confidence intervals for AUCt, AUC∞ and Cmax do not fall within the acceptable 80-125% range. Therefore, the study is unacceptable.

3. The DB II does not accept results of statistical outlier tests to justify dropping subjects from a BE study. To re-evaluate the pharmacokinetic performance of subject Nos. 1, 8 and 34, the firm may re-dose these three subjects along with several other subjects (control group) chosen at random from the same study. Additionally, the study procedures and study drug lot numbers should be identical to Study # 71912 (original study). Alternatively, the firm may conduct a new fasting bioequivalence study.

   The study results are presented in the following tables:

Without Subject Nos. 1, 8, and 34:

Sumatriptan Injection (subcutaneous) Dose (6 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Bioequivalence Study (Study No.71912) (N=38)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	105.92178	101.10851	1.05	103.417	106.121
AUC∞ (hr *ng/ml)	108.95796	103.04407	1.06	103.821	107.693
Cmax (ng/ml)	80.826263	77.956706	1.04	99.628	107.899

With Subject Nos. 1, 8, and 34:

Sumatriptan Injection (subcutaneous) Dose (6 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Bioequivalence Study (Study No.71912) (N=41)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	105.72425	78.861463	1.34	105.700	170.038
AUC∞ (hr *ng/ml)	108.58218	84.362456	1.29	106.216	155.966
Cmax (ng/ml)	81.108275	65.027172	1.25	104.158	149.365

OSI information:

OSI Inspection History: A Routine inspection of the Clinical site, QPS Bio-Kinetic Clinical Applications (1816 W. Mount Vernon, Springfield, MO, 65802, USA) was requested for NDA 022113 on 7/12/2011 and was completed on 11/23/2011 with an outcome of NAI.

OSI Inspection History: A Routine inspection of the Analytical site, (b) (4) (b) (4) was requested for NDA 202123 on 2/11/2011 and was completed on (b) (4) with an outcome of NAI.

Overall, the application is **inadequate**.

2 Table of Contents

3 Submission Summary

3.1 Drug Product Information

Test Product	Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL (Auto Injector)
Reference Product	Imitrex® STATDOSE Injectable, EQ 6 mg base/0.5 mL*
RLD Manufacturer	**GlaxoSmithKline**
NDA No.	**20-080**
RLD Approval Date	**Statdose: December 23, 1996**
Indication	For 1) the acute treatment of migraine attacks with or without aura and 2) the acute treatment of cluster headache episodes.

Note: Each Imitrex® (sumatriptan succinate) Injection Statdose System® 6 mg, contains 2 prefilled single-dose syringe cartridges, 1 Imitrex Statdose Pen, 1 carrying case, and a patient information leaflet with instructions for use.

- Imitrex STATDOSE EQ 4 mg base/0.5 mL (EQ 8mg base/mL) is also listed in the Orange Book as an RLD, approved on Feb 1, 2006.

3.2 PK/PD Information

Bioavailability	The bioavailability of sumatriptan via subcutaneous site injection was 97% ± 16% of that obtained following intravenous injection
Food Effect	Not indicated in the drug label
Tmax	12 minutes (range: 5 to 20 minutes) after a single 6-mg subcutaneous manual injection into the deltoid area
Metabolism	Not indicated in the drug label
Excretion	22% ± 4% was excreted in the urine as unchanged sumatriptan and 38% ± 7% as the indole acetic acid metabolite.
Half-life	115 ± 19 minutes
Relevant OGD or DB History (for details see Section 3.10, Additional Attachments)	1. Currently, there is no ANDA that is approved using the auto injection device. 2. A memo in the RLD approval letter dated December 2, 1991 states that the pharmacokinetics of sumatriptan in the elderly, and in patients with migraine were similar to that in normal healthy volunteers. The clearance and Cmax of Sumatriptan were similar between Black and Caucasian normal volunteers. Therefore, the DB II recommends the BE study can be performed in normal healthy individuals that inject themselves using the device. 3. Since the drug product has a device component (auto-injector), in addition to the formulation comparison, the DB II asks for suitable in-vitro tests to document comparative performance characteristics of the devices used in the test and reference drug products. Based on the reviews (for Epinephrine Auto Injection System) of controlled correspondences (CC 99-114, 02-297, AND 03-133), FDA's consolidated response to 2 Citizen Petitions (FDA 2007 P-0128 and 2009-P-0040), and ANDAs (b) (4) and 78-579, the DBE recommends the following *in vitro* comparative performance tests for the test and reference products:

	a) volume of solution injected and residual content of the auto-injector b) exposed needle length and needle gauge c) depth of penetration d) dose delivery time, e) force required to discharge the actuator and force of injection f) needle integrity post injection to include testing through different clothing materials of varying thickness and different angles of incidence. 4. The sponsor should devise suitable in vitro tests to document these parameters for single and multiple devices compared to the RLD. 5. On 10/27/2011, at the request of OGD DC II to the OGD Clinical Group to evaluate any potential concerns with respect to safety or therapeutic equivalence related to this drug product (Please see Section 6 for additional information on the consult).
Drug Specific Issues (if any)	The Imitrex label contains the following **bolded** precaution: 1. Patients who are advised to self-administer IMITREX Injection in medically unsupervised situations should receive instruction on the proper use of the product from the physician or other suitably qualified health care professional prior to doing so for the first time. 2. Sumatriptan label has the following contraindications: IMITREX Injection should not be given intravenously because of its potential to cause coronary vasospasm. IMITREX Injection should not be given to patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes. In addition, patients with other significant underlying cardiovascular diseases should not receive IMITREX Injection. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks. Peripheral vascular disease includes, but is not limited to, ischemic bowel disease (see WARNINGS: Other Vasospasm-Related Events and WARNINGS: Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events). Because IMITREX Injection may increase blood pressure, it should not be given to patients with uncontrolled hypertension. IMITREX Injection and any ergotamine-containing or ergot-type medication (like dihydroergotamine or methysergide) should not be used within 24 hours of each other, nor should IMITREX Injection and another 5-HT1 agonist. IMITREX Injection should not be administered to patients with hemiplegic or basilar migraine. IMITREX Injection is contraindicated in patients with hypersensitivity to sumatriptan or any of its components. IMITREX Injection is contraindicated in patients with severe hepatic

	impairment. 3. In addition to the above contraindications, the RLD label has the following warnings among others: Drug-Associated Cardiac Events and Fatalities Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of IMITREX Injection or IMITREX® (sumatriptan succinate) Tablets. Considering the extent of use of sumatriptan in patients with migraine, the incidence of these events is extremely low. The fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of CAD, and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug. In many cases, however, where there has been known underlying CAD, the relationship is uncertain

Note: Cmax after 6 mg of sumatriptan varied somewhat depending on site of injection and injection technique:

1) manual subcutaneous injection into the deltoid: 74 ± 15 ng/ml
2) manual subcutaneous injection into the thigh: 61 ± 15 ng/ml
3) auto-injector injection into the thigh: 52 ± 15 ng/ml

3.3 Review of Amendment Submission, dated 04/03/2013

The following deficiencies were sent to the firm in the deficiency letter dated June 20, 2012:

Deficiency# 1:

Please explain the apparent differences in the test outcomes with respect to the actuation force between the original data (submitted on August 31, 2009) and the data in the current amendment submission for the test product that is nearly 46% (18.52 N in the current submission vs. 26.98 N in the original submission). Yet, the data for the RLD remain unchanged.

Firm's Response:

We acknowledge the agency's comment. Based on the Human factor study outcome, the actuation force of the test device was reduced with a minor modification to the device. The differences in the values of actuation force from the original submission are attributed to the above modification. Information on the modification of the device was updated in the device master file by the device master file holder in April 2012. The data of the RLD remained unchanged as the same RLD data from the original submission has been used.

Reviewer's Comments: The firm's response is acceptable.

Deficiency# 2:

As pointed out in the OGD DCR clinical consult, other differences in the test product (e.g. needle gauge, injection cycle time, force to displacement distance profile) in performance and specifications that are present have the theoretical potential to affect PK. The DB II does not agree that the information you submitted supports bioequivalence of your test product, Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL, pre-filled syringe with auto-injector, to the RLD, Imitrex® STATDOSE Injectable, EQ 6 mg bas/ 0.5 mL, manufactured by GlaxoSmithKline. Consequently, the DB II recommends that you conduct a single-dose, two way crossover, bioequivalence study in healthy volunteers where the subjects inject themselves both the test and reference products using the respective device.

Firm's Response:

As recommended by the Agency, Dr. Reddy's Laboratories Limited has conducted an open label, balanced, randomized, two-treatment, two sequence, four-period, replicate, single dose, crossover, bioequivalence study in healthy volunteers .

Reviewer's Comments: The BE study is deemed inadequate due to deficiencies identified. Please see Appendix (Section 4.1 of this review) for complete review information on this BE study.

Deficiency# 3:

As mentioned in the deficiency letter issued on January 25, 2012, considering the warning - among others - on RLD, "the fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of cardiac artery disease (CAD), and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug", the DB II recommends adequate safety monitoring be in place during the BE study. You may submit a protocol for the BE study to the DB II.

Firm's Response:

As recommended by the Agency, adequate safety monitoring was done during the execution of the BE study. The bioequivalence study report is provided in Module 5.

Reviewer's Comments: The reviewer considers the safety monitoring during the BE study is adequate. Therefore, the firm's response to this deficiency comments is acceptable.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	No	--
Waiver requests	No	--
BCS Waivers	No	--
Amendment	Yes	1

3.5 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Validation of a Method for the Determination of Sumatriptan in Human Plasma by LC-MS/MS
Study Number	(b) (4) 42-1220
Analyte Name	Sumatriptan
Internal Standard (IS)	(b) (4)
Analytical Method Type	LC-MS/MS
Extraction Method	Solid-support liquid-liquid
Sample Volume	100 µL
QC Concentrations	0.2, 0.6, 10, and 90 ng/mL
Standard Curve Concentrations	0.2, 0.4, 2, 4, 20, 40, 85, and 100 ng/mL
Lower Limit Of Quantitation	0.2 ng/mL
Upper Limit Of Quantitation	100 ng/mL
Average Recovery of Drug (%)	74.2
Average Recovery of Internal Standard (%)	(b) (4)[a]
LLOQ QC Intraday Precision Range (%CV)	3.3 to 5.9
LLOQ QC Intraday Accuracy Range (%RE)	-9.5 to -3.5
Analytical QC Intraday Precision Range (%CV)	1.2 to 10.0
Analytical QC Intraday Accuracy Range (%RE)	-12.6 to -5.5
LLOQ QC Interday Precision (%CV)	4.8
LLOQ QC Interday Accuracy (%RE)	-6.5
Analytical QC Interday Precision Range (%CV)	1.6 to 6.0
QC Interday Accuracy Range (%RE)	-9.8 to -6.0
Stock Solution Stability in Methanol	7 Hours at Room Temperature 77 Days at -20°C
Working Solution Stability in Methanol: Water at 50:50 (v:v)	7 Hours at Room Temperature 76 Days at 4°C
Processed Sample Stability	199 Hours at 4°C
Benchtop Stability in Plasma	22 Hours at Room Temperature
Freeze/Thaw Stability in Plasma	5 Cycles at -20°C and -70°C
Benchtop Stability in Whole Blood	2 Hours at Room Temperature and 4°C
Long-term Storage Stability in Plasma	70 Days at -20°C and -70°C
Dilution Integrity	200 ng/mL diluted 10-fold
Selectivity	≤ 20.0% LLOQ for analyte; ≤ 5.0% for IS

[a] (b) (4)

Comments on the Pre-Study Method Validation:

1. The long-term storage stability (LTSS) data is insufficient. The firm is requested to provide sufficient LTSS to cover the entire storage length of the BE study samples (from the time of the first blood sample drawn to the time of the last plasma sample analyzed) up to 114 days @ -20ºC and -70 ºC.

2. The firm used K2 EDTA as anticoagulant in the pre-study validation and within study bioanalytical analysis as well as study samples.

The pre-study method validation is **inadequate**.

3.6 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies
Deltoid region

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD) (Deltoid region)						Study Report Location
					Cmax (ng/mL)	Tmax (hr)	AUClast (h•ng/mL)	AUCinf (h•ng/mL)	T½ (hr)	Kel (hr-1)	
71912	An Open Label, Balanced, Randomized, Two-Treatment, Two-Sequence, Four-Period, Replicate, Single Dose, Crossover, Bioequivalence Study of Sumatriptan Injection, 6-mg (Dr. Reddy's Laboratories Limited, India) Compared to IMITREX® Injection, 6-mg (GlaxoSmithKline) in Normal, Healthy, Adult Human Subjects	Randomized single-dose crossover	***Test product (T):*** Sumatriptan ***Dose:*** 6-mg ***Dosage Form:*** Injection ***Route:*** subcutaneous ***Product ID:*** lot number VA201	48 44* completing (25M/19F) Healthy subjects Age mean: 25.1 (18-37)	90.590 ± 20.188 (22.285)	0.17 (0.10-0.42)	106.351±15.889 (14.940)	108.135 ± 16.125 (14.912)	1.85 ± 0.27 (14.66)	0.3823 ± 0.0504 (13.1774)	This information has been extracted from the Final Integrated Clinical and Statistical Report (Pages 115-116 of 245 and 119-120 of 245)
			Reference product (R): IMITREX® ***Dose:*** 6-mg ***Dosage Form:*** Injection ***Route:*** subcutaneous ***Product ID:*** lot number C572044		87.447 ± 18.604 (21.274)	0.17 (0.07-0.42)	100.831 ± 13.630 (13.518)	102.572 ± 13.975 (13.624)	1.87 ± 0.33 (17.55)	0.3797 ± 0.0577 (15.1905)	

*The total number of subjects enrolled in the study was 48; however, only 44 subjects who completed at least one crossover during Replicate 1 (Deltoid Region).

Gluteal/Thigh region

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD) (Gluteal/Thigh region)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{last} (h•ng/mL)	AUC_{inf} (h•ng/mL)	$T_{½}$ (hr)	K_{el} (hr^{-1})	
71912	An Open Label, Balanced, Randomized, Two-Treatment, Two-Sequence, Four-Period, Replicate, Single Dose, Crossover, Bioequivalence Study of Sumatriptan Injection, 6-mg (Dr. Reddy's Laboratories Limited, India) Compared to IMITREX® Injection, 6-mg (GlaxoSmithKline) in Normal, Healthy, Adult Human Subjects	Randomized single-dose crossover	***Test product (T):*** Sumatriptan ***Dose:*** 6-mg ***Dosage Form:*** Injection ***Route:*** subcutaneous ***Product ID:*** lot number VA201	48 38* completing (21M/17F) Healthy subjects Age mean: 25.4 (18-37)	75.942 ± 16.131 (21.242)	0.20 (0.07-0.50)	108.337±14.247 (13.151)	113.660 ± 21.969 (19.328)	1.89 ± 0.39 (20.45)	0.3797 ± 0.0644 (16.9590)	This information has been extracted from the Final Integrated Clinical and Statistical Report (Pages 117-118 of 245 and 121-122 of 245)
			Reference product (R): IMITREX® ***Dose:*** 6-mg ***Dosage Form:*** Injection ***Route:*** subcutaneous ***Product ID:*** lot number C572044		72.847 ± 16.057 (22.042)	0.20 (0.10-0.50)	104.228 ± 16.168 (15.512)	106.255 ± 16.439 (15.471)	1.92 ± 0.44 (22.72)	0.3742 ± 0.0590 (15.7591)	

* 41 subjects completed Gluteal/Thigh region. Since the subject numbers 1, 8 and 34 were outliers in period 4, these subjects' data were removed from period 3 and 4 (Gluteal/Thigh region).

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Without Subject Nos. 1, 8, and 34:

Sumatriptan Injection (subcutaneous) Dose (6 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Bioequivalence Study (Study No.71912) (N=38)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	105.92178	101.10851	1.05	103.417	106.121
AUC∞ (hr *ng/ml)	108.95796	103.04407	1.06	103.821	107.693
Cmax (ng/ml)	80.826263	77.956706	1.04	99.628	107.899

With Subject Nos. 1, 8, and 34:

Sumatriptan Injection (subcutaneous) Dose (6 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Bioequivalence Study (Study No.71912) (N=41)					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	105.72425	78.861463	1.34	105.700	170.038
AUC∞ (hr *ng/ml)	108.58218	84.362456	1.29	106.216	155.966
Cmax (ng/ml)	81.108275	65.027172	1.25	104.158	149.365

Table 3. Reanalysis of Study Samples

Study No. 71912								
Reason Why Assay Was Repeated	**Number of Samples Reanalyzed: 101**				**Number of Recalculated Values Used After Reanalysis: 30**			
	Actual Number		**% of Total Assays**		**Actual Number**		**% of Total Assays**	
	Test (T)	**Reference (R)**	**T[a]**	**R[b]**	**T**	**R**	**T[a]**	**R[b]**
IS Response Low	1	0	0.028	0.000	1	0	0.028	0.000
AQL (Above Quantifiable Limit)	5	4	0.140	0.112	5	4	0.140	0.112
Investigation Based on ISR (Pre-Dilution Evaluation)	42	42	1.180	1.180	6	7	0.169	0.197
Analytical Anomaly	1	0	0.028	0.000	1	0	0.028	0.000
Bad Injection	0	1	0.000	0.028	0	1	0.000	0.028
BQL with Dilution	0	5	0.000	0.140	0	5	0.000	0.140
Total[c]	49	52	1.376	1.460	13	17	0.365	0.477

[a] % T = Number of Tests reassayed / total number of samples (3559) x 100
[b] % R = Number of References reassayed / total number of samples (3559) x 100
[c] Calculation is based on the sum of the preceding rows in the corresponding column

Total samples analyzed: 3559

Analytical Anomaly

In Run 10, Subject 023, Treatment A, Period 3, 1.5 hour resulted in a concentration that was BQL. However, the sample before (Subject 023, Treatment A, Period 3, 1 hour) and the sample after (Subject 023, Treatment A, Period 3, 2 hour) demonstrated measurable concentrations that were greater than three times the LLOQ. There was no traceable experimental error and the sample was verified. The sample was reanalyzed in duplicate and (b) (4) SOP BA-003 was followed. The reassayed values matched and are consistent with the ISR data.

Did use of recalculated plasma concentration data change study outcome? No. No PK repeats.

Comments from the Reviewer: There were no pharmacokinetic repeats. Reanalysis of samples was performed according to the SOPs.

3.7 Formulation

Location in appendix	See Section 4.2, page 41 of this review
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	**Yes**
If not acceptable, why?	N/A

3.8 In Vitro Dissolution: NA

3.9 Waiver Request(s)

Strengths for which waivers are requested	N/A
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	**N/A**
If not then why?	N/A

3.10 Deficiency Comments

The pre-study method validation is inadequate with the following deficiency:

1. The long-term storage stability (LTSS) data of 70 days @ -20ºC and -70ºC is insufficient. The firm is requested to provide sufficient LTSS to cover the entire storage length of the BE study samples (from the time of the first blood sample drawn to the time of the last plasma sample analyzed) up to 114 days @ -20ºC and -70 ºC.

The Fasting BE study is incomplete with the following reasons:

2. Subject Nos. 1, 8 and 34 revealed no clinical abnormalities. Excluding these subjects from the statistical analysis of the study is not justified. After including all subjects in the study, the confidence intervals for AUCt, AUC∞ and Cmax do not fall within the acceptable 80-125% range. Therefore, the study is unacceptable.

3. The DB II does not accept results of statistical outlier tests to justify dropping subjects from a BE study. To re-evaluate the pharmacokinetic performance of subject Nos. 1, 8 and 34, the firm may re-dose these three subjects along with several other subjects (control group) chosen at random from the same study. Additionally, the study procedures and study drug lot numbers should be identical to Study # 71912 (original study). Alternatively, the firm may conduct a new fasting bioequivalence study.

3.11 Recommendations

The Division of Bioequivalence II (DB II) finds the fasting BE study (Study No. 71912) conducted by Dr. Reddy's Laboratories, Inc. on its Sumatriptan Succinate Injection, EQ 6 mg/0.5 mL (auto-injectors), comparing to the corresponding reference product, Imitrex® STATDOSE Injectable, EQ 6 mg base/0.5 mL, manufactured by GlaxoSmithKline inadequate due to deficiencies stated above.

3.12 Comments for Other OGD Disciplines

Discipline	Comment
NA	--

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 4 Study Information

Study Number	71912	
Study Title	An Open Label, Balanced, Randomized, Two-Treatment, Two-Sequence, Four-Period, Replicate, Single Dose, Crossover, Bioequivalence Study of Sumatriptan Injection, 6-mg (Dr. Reddy's Laboratories Limited, India) Compared to IMITREX® Injection, 6-mg (GlaxoSmithKline) in Normal, Healthy, Adult Human Subjects	
Clinical Site (Name & Address)	Bio-Kinetic Clinical Applications, LLC 1816 W. Mt. Vernon Springfield, MO 65802	
Principal Investigator	Thomas Legg, D.O	
Dosing Dates	Period1*	2012-11-10 (001-027), 2012-11-17 (028-48)
	Period2	2012-11-17 (001-027), 2012-11-24 (028-48)
	Period3	2012-11-24 (001-027), 2012-12-02 (028-48)
	Period4	2012-12-02 (001-027), 2012-12-09 (028-48)
Analytical Site (Name & Address)	(b) (4)	
Analysis Dates	2012-12-04** to 2013-03-05	
Analytical Director	(b) (6) M.S. (b) (4), (b) (6)	
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	114 Days (-20°C and -70°C)	
Long-Term Storage Stability Coverage	Analyte: Sumatriptan (70 days @ -20ºC and -70 ºC)	

*The drug administration sites in period 1 and 2 were the Deltoid region and in period 3 and 4 were the Gluteal/Thigh region.
**The summary table reported the analytical date as 12/09/2012; however, the study report stated that the starting date for bioanalytical analysis was 12/04/2012.

Table 5. Product information

Product	Test Product	Reference Product
Treatment ID	T	R
Product Name	Sumatriptan Succinate Injection in pre-filled syringes 6 mg (base)/ 0.5 mL	IMITREX® 6 mg/ 0.5 mL Injection (subcutaneous)
Manufacturer	Dr. Reddy's Laboratories Limited, India	GlaxoSmithKline Research Triangle Park, NC 27709
Batch/Lot No.	VA201	C572044
Manufacture Date	09/2012	N/A
Expiration Date	N/A	02/2014
Strength	6 mg/ 0.5 mL	6 mg/ 0.5 mL
Dosage Form	Injection	Injection
Bio-Batch Size	(b) (4)	N/A
Production Batch Size	N/A	N/A
Potency (Assay)	101.1%	96.2%
Content Uniformity (mean, %CV)	N/A	N/A
Dose Administered	6-mg	6-mg
Route of Administration	Subcutaneous	Subcutaneous

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Subjects enrolled: 48 Subjects completed all periods: 43 Subjects completed at least one crossover: 44
No. of Sequences	2
No. of Periods	4
No. of Treatments	2
No. of Groups	2*
Washout Period	7 days
Randomization Scheme	ABAB: 1, 3, 5, 8, 9, 12, 13, 15, 18, 19, 21, 23, 25, 27, 30, 31, 34, 36, 38, 39, 42, 44, 45, 47 BABA: 2, 4, 6, 7, 10, 11, 14, 16, 17, 20, 22, 24, 26, 28, 29, 32, 33, 35, 37, 40, 41, 43, 46, 48
Blood Sampling Times	At pre-dose (0.00) and 0.033, 0.067, 0.1, 0.133, 0.167, 0.2, 0.25, 0.333, 0.417, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 10 hours after dosing in each period. (Total of 21 sampling points)
Blood Volume Collected/Sample	4 mL in K2 EDTA as anticoagulant

Blood Sample Processing/Storage	The samples were centrifuged at 4°C for 10 minutes at 3000 rpms for 10 minutes. All pharmacokinetic plasma samples were divided in 2 equal aliquots and placed in two screw cap tubes. Time from collection to centrifuge was within 60 minutes. Plasma samples were placed in a storage freezer at -20±12°C within 120 minutes of the blood collection. Samples were placed in a -20±12°C freezer until they were shipped to the bioanalytical laboratory.
IRB Approval	Yes. 11/02/2012
Informed Consent	Yes. 11/02/2012
Length of Fasting	Overnight of at least 10 hr before serving of test meal and 4.00 hours after dosing in each period. No food was allowed for at least 4.0 hours post-dose. In each period standard meals were served to all the subjects at about 4.0 and 9.0 hours post dose with the exception of period 4, in which no dinner was served
Length of Confinement	Subjects were admitted to the study unit prior to the beginning of the fasting period in the evening prior to study drug administration and remained in the unit until the 10 hour blood sample (Day 1) has been collected.
Safety Monitoring	Vital signs (blood pressure, pulse and oral temperature) were measured at Screening, within 2 hours of pre-dose (0 hour), at 1, 2 and 6 hours after each study drug administration (within + 40 minutes of scheduled time), at each check-out and with End of Study/Early termination procedures.

* **Group assignment:** Subjects were randomly assigned to each treatment group, as per the randomization schedule. Based on the data submitted, the study subjects were divided into two groups:
Group 1: Subject Nos. 1-27
Group 2: Subject Nos. 28-48

Comments on Study Design:

Subjects withdrew: 05 (Subject Nos. 004, 005, 015, 032 and 035)

The randomization schedule was provided to the Investigator. Each subject was randomized into one of 2 treatment sequences. Each sequence had 24 subjects.

In each period, after an overnight fast of at least 10 hours, each subject was administered 6-mg of Test Drug or RLD using an Auto-injector Pen or the IMITREX STATdose Pen®, subcutaneously. In Periods 1 and 2, the injection was given in the deltoid region. In Periods 3 and 4, the injection was given in the gluteal/thigh region as per the randomization schedule in prone or sitting position.

Treatments Administered

The subjects were trained on self-administration of Investigational Product using an Auto Injector at gluteal/thigh region of Lower limbs or deltoid region of Arm by the Investigator or designee.

The study design is acceptable.

4.1.1.2 Clinical Results

Table 7. Demographics Profile of Subjects Completing the Bioequivalence Study

Deltoid Region

Study No.71912 (Deltoid Region)			
		Treatment Groups	
		Dr. Reddy's Laboratories Limited, India's Sumatriptan Injection 6 mg (subcutaneous) N =44	GlaxoSmithKline's IMITREX® Injection 6 mg (subcutaneous) N =44
Age (years)	Mean ± SD	25.1 ± 5.7	25.1 ± 5.7
	Range	18 - 37	18 - 37
Age Groups	< 18	0	0
	18 – 40	44 (100 %)	44 (100 %)
	40 – 64	0	0
Sex	Male	25 (56.8 %)	25 (56.8 %)
	Female	19 (43.2 %)	19 (43.2 %)
Race	White or Caucasian	39 (88.6 %)	39 (88.6 %)
	Black or African American	3 (6.8 %)	3 (6.8 %)
	American Indian or Alaska Native	2 (4.5 %)	2 (4.5 %)
BMI	Mean ± SD	24.2±3.0	24.2±3.0
	Range	19.0-29.9	19.0-29.9
Other Factors			

Gluteal/Thigh Region

Study No.71912 (Gluteal/Thigh Region)			
		Treatment Groups	
		Dr. Reddy's Laboratories Limited, India's Sumatriptan Injection 6 mg (subcutaneous) N =38	GlaxoSmithKline's IMITREX® Injection 6 mg (subcutaneous) N =38
Age (years)	Mean ± SD	25.4 ± 5.8	25.4 ± 5.8
	Range	18 - 37	18 - 37
Age Groups	< 18	0	0
	18 – 40	38 (100 %)	38 (100 %)
	40 – 64	0	0
Sex	Male	21 (55.3 %)	21 (55.3 %)
	Female	17 (44.7 %)	17 (44.7 %)
Race	White or	34 (89.5 %)	34 (89.5 %)

	Caucasian		
	Black or African American	2 (5.3 %)	2 (5.3 %)
	American Indian or Alaska Native	2 (5.3 %)	2 (5.3 %)
BMI	Mean ± SD	24.0±2.9	24.0±2.9
	Range	19.0-29.4	19.0-29.4
Other Factors			

Table 8. Dropout Information, Bioequivalence Study

Subject No.	Reason	Period	Replaced?
004	withdrew consent after period 1	1	No
005	withdrew consent after period 2	2	No
015	was lost to follow-up after period 1	1	No
032	withdrew consent after period 2	2	No
035	withdrawn from study as he failed urine drug screen at period 3 check-in	3	No

Disposition of Subjects:

As per the protocol, a total of **48 subjects** were enrolled in to the study and all 48 subjects were dosed in Period I. A total of **46** subjects were dosed in period II. A total of **43** subjects were dosed in study Period III (Subject Numbers 005 and 032, withdrew consent and Subject Number 035, failed in urine drug screen at period 3 check-in). **All 43 subjects completed the clinical phase of the study.** The samples of subject No. 014 (Period III) and 039 (Period II) were not analyzed as they could not administer a large portion of the drug due to leakage –possibly due to faulty injector. These two subjects were dropped out of the analysis. Therefore, 41 subjects were analyzed in Period III and IV.

- Subject Nos. 005 and 032 who withdrew consent and Subject Number 035 who was withdrawn as he failed urine drug screen at period 3 check-in are considered for pharmacokinetic and statistical analysis (for period 1 & 2) as they have completed at least one crossover sequence in the study.

- Subject Nos. 004 and 015 were withdrawn from the study as they could not complete one crossover sequence, as these subjects completed only period 1 of the study treatments.

Table 9. Study Adverse Events, Bioequivalence Study

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study Study No.71912	
	Dr. Reddy's Laboratories Limited, India's Sumatriptan Injection 6 mg (subcutaneous) N=48	GlaxoSmithKline's IMITREX® Injection 6 mg (subcutaneous) N=48
Ear and labyrinth disorders		
Ear discomfort	1 (1.11%)	0%
Eye disorders		
Eye irritation	1 (1.11%)	1 (1.11%)
Hypoaesthesia eye	0%	1 (1.11%)
Photophobia	0%	1 (1.11%)
Gastrointestinal disorders		
Dyspepsia	1 (1.11%)	1 (1.11%)
Nausea	5 (5.56%)	5 (5.56%)
Vomiting	1 (1.11%)	3 (3.33%)
General disorders and administration site conditions		
Chest discomfort	2 (2.22%)	2 (2.22%)
Feeling hot	5 (5.56%)	5 (5.56%)
Influenza like illness	0%	1 (1.11%)
Injection site pain	2 (2.22%)	1 (1.11%)
Injection site paraesthesia	0%	1 (1.11%)
Pain	1 (1.11%)	0%
Sensation of foreign body	0%	1 (1.11%)
Injury, poisoning and procedural complications		
Arthropod bite	1 (1.11%)	0%
Laceration	0%	1 (1.11%)
Musculoskeletal and connective tissue disorders		
Back pain	1 (1.11%)	0%
Muscle tightness	1 (1.11%)	1 (1.11%)
Musculoskeletal pain	1 (1.11%)	0%
Musculoskeletal stiffness	2 (2.22%)	1 (1.11%)
Neck pain	1 (1.11%)	0%
Pain in extremity	1 (1.11%)	0%
Nervous system disorders		
Burning sensation	4 (4.44%)	8 (8.89%)
Dizziness	1 (1.11%)	2 (2.22%)
Dysgeusia	1 (1.11%)	2 (2.22%)
Headache	13 (14.44%)	16 (17.78%)
Hypoaesthesia	1 (1.11%)	0%

Body System / Adverse Event	Reported Incidence by Treatment Groups Fasted Bioequivalence Study Study No.71912	
	Dr. Reddy's Laboratories Limited, India's Sumatriptan Injection 6 mg (subcutaneous) N=48	GlaxoSmithKline's IMITREX® Injection 6 mg (subcutaneous) N=48
Paraesthesia	4 (4.44%)	4 (4.44%)
Somnolence	1 (1.11%)	0%
Renal and urinary disorder		
Urethral syndrome	1 (1.11%)	0%
Respiratory, thoracic and mediastinal disorders		
Epistaxis	2 (2.22%)	0%
Throat tightness	3 (3.33%)	1 (1.11%)
Skin and subcutaneous tissue disorders		
Erythema	0%	1 (1.11%)
Hyperhidrosis	2 (2.22%)	0%
Papule	1 (1.11%)	0%
Pruritus	1 (1.11%)	0%
Rash	1 (1.11%)	2 (2.22%)
Skin burning sensation	1 (1.11%)	1 (1.11%)
Vascular disorders		
Flushing	1 (1.11%)	1 (1.11%)

Table 10. Protocol Deviations, Bioequivalence Study

Study No.71912		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Missing samples	001 (25 Min)	010 (10 Min)
	010 (20 Min)	010 (25 Min)
	010 (30 Min)	026 (12 Min)
	014 (10 Min)	044 (6 Min)
	046 (10 Min)	046 (10 Min)
	048 (12 Min)	---
Blood draw deviations	001 (20 Min)	001 (20 Min)
	002 (20 Min)	010 (6 Min)
	002 (25 Min)	010 (10 Min)
	003 (25 Min)	010 (1.00 Hr)
	007 (8 Min)	010 (3.00 Hr)
	007 (10 Min)	010 (4.00 Hr)
	007 (12 Min)	010 (4 Min)
	009 (12 Min)	010 (30 Min)
	010 (15 Min)	012 (6 Min)
	010 (25 Min)	012 (8 Min)

Study No.71912		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
	010 (12 Min)	012 (10 Min)
	012 (15 Min)	012 (25 Min)
	012 (30 Min)	013 (4 Min)
	013 (10 Min)	013 (6 Min)
	013 (30 Min)	013 (8 Min)
	014 (6 Min)	013 (10 Min)
	016 (8.00 Hr)	014 (15 Min)
	018 (8 Min)	014 (4 Min)
	020 (10 Min)	014 (10 Min)
	020 (20 Min)	018 (6 Min)
	021 (15 Min)	018 (20 Min)
	021 (15 Min)	018 (30 Min)
	022 (6 Min)	018 (8 Min)
	022 (25 Min)	018 (12 Min)
	023 (10 Min)	020 (15 Min)
	023 (15 Min)	021 (10 Min)
	025 (8 Min)	022 (8 Min)
	027 (15 Min)	022 (10 Min)
	027 (25 Min)	022 (12 Min)
	027 (12 Min)	022 (15 Min)
	027 (20 Min)	022 (20 Min)
	036 (20 Min)	022 (25 Min)
	040 (10 Min)	024 (8 Min)
	044 (4 Min)	025 (20 Min)
	044 (25 Min)	026 (2 Min)
Blood draw deviations	044 (30 Min)	026 (12 Min)
	044 (15 Min)	027 (15 Min)
	045 (10 Min)	030 (6 Min)
	046 (25 Min)	044 (12 Min)
	047 (15 Min)	045 (15 Min)
	047 (1.50 Hr)	046 (10 Min)
	047 (2 Min)	046 (45 Min)
	047 (8 Min)	046 (12 Min)
	---	047 (8 Min)
	---	047 (20 Min)
Subject number 006 dosed late due to defective device in period 1.		
For subject number 014, a large portion of the drug did not administer due to leakage as needle was pulled away in period 3.		
For subject number 015, 12-Lead ECG, Chemistry, Hematology, Urinalysis, Vital signs were not done at EOS, as subject didn't return for end of study procedures.		
Subject number 018 released the button shortly after dosing and then pressed it once again in period 4.		
For subject number 032, 12-Lead ECG (20 Minutes Postdose), 12-Lead ECG (3 Hours Postdose) Check-out Vital Signs (10 Hours Postdose), Dose and Randomization, Meals (Day 1 Dinner), Meals (Day 1 Lunch), PK Blood Sampling, Urine Drug Screen, Vital Signs (1 Hour Postdose), Vital Signs (2 Hours		

Study No.71912		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Postdose), Vital Signs (6 Hours Postdose), Vital Signs (Within 2 Hours of Predose) were not done as he withdrew consent in period 3.		
For subject number 035, 12-Lead ECG (20 Minutes Postdose), 12-Lead ECG (3 Hours Postdose) Check-out Vital Signs (10 Hours Postdose), Dose and Randomization, Meals (Day 1 Dinner), Meals (Day 1 Lunch), PK Blood Sampling, Vital Signs (1 Hour Postdose), Vital Signs (2 Hours Postdose), Vital Signs (6 Hours Postdose), Vital Signs (Within 2 Hours of Predose) were not done as he was early exit due to a positive UDS and tested positive for Cannabinoids in Urine Drug Screen in period 3.		
For subject number 039, a large portion of the drug did not administer due to leakage. Possibly faulty injector in period 2.		
For subject number 042 predose vitals were not re-assessed at the new 2 hour predose time, as the subject was moved from group 3 to group 4 due to delay in receipt of check-in labs for confirmation of eligibility in period 1.		
For subject number 043, the predose vitals were not re-assessed at the new 2 hour predose time in period 1.		
For subject number 044, the predose vitals were not re-assessed at the new 2 hour predose time in period 1.		
For subject number 045, the predose vitals were not re-assessed at the new 2 hour predose time in period 1.		
For subject number 046, the predose vitals were not re-assessed at the new 2 hour predose time in period 1.		
For subject number 047, the predose vitals were not re-assessed at the new 2 hour predose time in period 1.		
Subject number 048 confirmed pre-dose sample was drawn 1 minute early.		

Comments on Dropouts/Adverse Events/Protocol Deviations:

- A total of 164 adverse events were reported by 35 subjects. The Principal Investigator deemed all of the adverse events to have a reasonably possible relationship to the study drug. These adverse events resolved without sequelae.

- The following subjects experienced emesis during the course of the clinical study:

Subj No.	Study Drug (Treatment A/Treatment B)	Time of Dosing	Onset		Resolved	
			Date	Time	Date	Time
43	Treatment B	10:31	2012-12-02	18:15	2012-12-02	23:00
46	Treatment B	10:34	2012-11-17	11:20	2012-11-17	11:22
48	Treatment B	08:13	2012-11-17	09:19	2012-11-17	10:00
48	Treatment A	08:13	2012-11-24	10:03	2012-11-24	10:03

The median Tmax for Sumatriptan 6 mg Injection is 0.18 hour (2x of median Tmax = 0.36 hours). Therefore, Subject Nos. 43, 46 and 48 vomiting episodes were not within 2 x of median Tmax. Based on the FDA BA/BE Guidance, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations", Subject Nos. 43, 46 and 48 should be included from the study analysis.

- Protocol deviations were related to sampling times. Time deviations that were equal to or greater than 2 minutes were adjusted to reflect actual sampling times. Adverse events and protocol deviations did not compromise the integrity of the study outcome.

4.1.1.3 Bioanalytical Results

Table 11. Assay Validation – Within the Bioequivalence Study

71912 Sumatriptan								
Parameter	**Standard Curve Samples**							
Nominal Concentration (ng/mL)	0.200	0.400	2.000	4.000	20.000	40.000	85.000	100.000
Concentration (ng/mL)	0.201	0.394	2.023	4.014	20.111	39.427	86.472	98.470
Inter day Precision (%CV)	5.5	5.1	3.7	3.1	3.2	2.7	3.1	3.4
Inter day Accuracy (%Actual)	100.5	98.5	101.2	100.4	100.6	98.6	101.7	98.5
Linearity	0.9909 – 0.9996							
Linearity Range (ng/mL)	0.200 – 100.000							
Sensitivity/LOQ (ng/mL)	0.200							
71912 Sumatriptan								
Parameter	**Quality Control Samples**							
Nominal Concentration (ng/mL)	0.600	10.000	90.000					
Concentration (ng/mL)	0.600	9.994	86.917					
Inter day Precision (%CV)	13.7	4.0	4.7					
Inter day Accuracy (%Actual)	100.0	99.9	96.6					

Comments on Study Assay Validation: Acceptable.

Any interfering peaks in chromatograms?	No.
Were 20% of chromatograms included?	Yes.
Were chromatograms serially or randomly selected?	Serially. Subj Nos. 1-13

Comments on Chromatograms: Acceptable.

Table 12. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
BA-003-14	01 Nov 2011	Bioanalytical Sample Reanalysis
LP-032-03	01 Dec 2010	Incurred Sample Reproducibility

Table 13. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes.
Did recalculation of PK parameters change the study outcome?	No. No PK repeats
Does the reviewer agree with the outcome of the repeat assays?	Yes.
If no, reason for disagreement	NA

In this study, 238 samples (6.69% of 3559 samples) were chosen to be extracted and injected for incurred sample reproducibility as per SOP titled "Incurred Samples Reproducibility" No. LP-032, dated 11/30/2010. The acceptance criteria were met as 98.7% were reproducible (At least 67% of the ISRA samples should be within ~20% of the mean of original and repeat values) for Sumatriptan Injection. Therefore, the incurred sample repeats are acceptable.

INV-13-008: An incurred sample reproducibility (ISR) test was performed in Run 25 to validate the pre-dilution scheme used in the study. Of the 162 ISR samples chosen from 15 different runs, 157 of the samples were within 20% of the original reported concentrations; however, five samples whose original concentrations were AQL but diluted the first time had concentrations that were >50% from the original concentrations. All five samples that failed were from Run 3, Subject 008, Treatment A, Period 3. A trend was observed in which the sample concentrations resulting from Subject 008, Treatment A, Period 3 may not have been accurate due to the failed ISR samples. This may have resulted from an aliquotting error.

Of the 162 samples selected to assess the pre-dilution evaluation, 96.9% met the acceptance criteria for sumatriptan. As per (b) (4) SOP LP-032, the pre-dilution evaluation (ISR) is acceptable since greater than two-thirds of the samples evaluated met pre-specified acceptance criteria.

Summary/Conclusions, Study Assays: Acceptable.

4.1.1.4 Pharmacokinetic Results

Table 14. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table and Figure 1

Bioequivalence Study, Study No.71912									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
Replicate 1 (Deltoid Region) (N=44)									
AUC0-t (hr *ng/ml)	104.11	15.11	73.13	143.40	103.18	14.83	77.97	139.23	1.01
AUC∞ (hr *ng/ml)	105.52	15.20	73.81	146.23	104.43	14.89	78.64	140.94	1.01
Cmax (ng/ml)	90.28	20.03	54.66	124.47	86.39	25.94	45.85	157.03	1.04
Tmax* (hr)	0.18	38.58	0.10	0.42	0.20	48.49	0.10	0.50	0.89
Kel (hr^{-1})	0.49	16.99	0.33	0.61	0.51	19.20	0.33	0.77	0.97
T1/2 (hr)	1.45	18.94	1.13	2.07	1.41	19.87	0.90	2.13	1.03
Replicate 2 (Gluteal/Thigh Region) (N=38) Without outliners									
AUC0-t (hr *ng/ml)	102.37	11.17	84.98	123.70	102.80	14.35	81.74	130.12	1.00
AUC∞ (hr *ng/ml)	108.46	23.55	87.23	203.42	104.36	14.01	85.18	132.26	1.04
Cmax (ng/ml)	78.01	24.07	56.40	111.09	76.51	29.04	43.07	123.06	1.02
Tmax* (hr)	0.18	30.63	0.07	0.25	0.19	56.65	0.10	0.50	0.95
Kel (hr^{-1})	0.48	22.06	0.22	0.69	0.48	18.12	0.33	0.64	1.01
T1/2 (hr)	1.53	30.66	1.01	3.20	1.50	18.34	1.08	2.10	1.02
Replicate 2 (Gluteal/Thigh Region) (N=41) With outliers									
AUC0-t (hr *ng/ml)	108.04	12.90	84.98	143.40	96.61	32.65	0.03	139.23	1.12

AUC∞ (hr *ng/ml)	113.17	20.42	88.45	203.42	98.14	32.45	0.14	140.74	1.15
Cmax (ng/ml)	76.26	20.94	43.07	111.43	67.55	36.35	0.28	114.43	1.13
Tmax* (hr)	0.22	41.96	0.07	0.50	0.25	89.60	0.10	1.50	0.88
Kel (hr^{-1})	0.44	17.28	0.22	0.55	0.55	84.84	0.11	2.78	0.81
T1/2 (hr)	1.61	21.95	1.26	3.20	1.60	52.91	0.25	6.40	1.01

* Tmax values are presented as median, range

Table 15. Geometric Means and 90% Confidence Intervals - Firm Calculated

Sumatriptan Injection (subcutaneous) Dose (6 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Bioequivalence Study (Study No.71912)						
Parameters	Least Squares Geometric Means				Ratio (%)	90% C.I.
	Test (T)	N	Reference (R)	N		
AUC_{last}	105.303	44*	100.517	44	104.76	103.42-106.12
AUC_{inf}	108.323	44	102.458	44	105.72	103.80-107.68
C_{max}	80.568	44	77.707	44	103.68	99.62-107.90

*Note: 41 subjects completed four periods (both regions) and 3 subjects completed period 1 and 2 (deltoid region). The subject numbers 1, 8 and 34 were observed outlier at period 4, the firm removed these subjects from period 3 and 4 (gluteal/thigh regions) from statistical analysis.

Table 16. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Without Subject Nos. 1, 8, and 34:

Sumatriptan Injection (subcutaneous) Dose (6 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Bioequivalence Study (Study No.71912) (N=38)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	105.92178	101.10851	1.05	103.417	106.121
AUC∞ (hr *ng/ml)	108.95796	103.04407	1.06	103.821	107.693
Cmax (ng/ml)	80.826263	77.956706	1.04	99.628	107.899

With Subject Nos. 1, 8, and 34:

Sumatriptan Injection (subcutaneous) Dose (6 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Bioequivalence Study (Study No.71912) (N=41)					
Parameter (units)	Test	Reference	Ratio	90% C.I.	
AUC0-t (hr *ng/ml)	105.72425	78.861463	1.34	105.700	170.038
AUC∞ (hr *ng/ml)	108.58218	84.362456	1.29	106.216	155.966
Cmax (ng/ml)	81.108275	65.027172	1.25	104.158	149.365

Table 17. Additional Study Information, Study No. 71912

Root mean square error, AUC0-t	0.0496	
Root mean square error, AUC∞	0.0710	
Root mean square error, Cmax	0.1540	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	38	38
Do you agree or disagree with firm's decision?	No (See Comments below)	No
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	1*
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

*At Period II, subjects #15 (Reference) demonstrated pre-dose concentration of 0.546 ng/mL. The Cmax is 88.993 ng/mL for this subject. Therefore, the measurable drug concentration at 0 hour is <5% of the respective C_{max} at given period. Therefore, the subjects' data were included in all pharmacokinetic measurements and calculations without any adjustments.

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
TEST	38	0.97	0.60	0.99
REFERENCE	38	0.98	0.89	0.99

Comments on Pharmacokinetic and Statistical Analysis:

- Subjects were recruited in two groups. However, the study was conducted at the same center, and the subject population was homogenous. Based on the following Division of Bioequivalence practice policy, ALL of the following criteria are met. Therefore, it is not necessary to include Group-by-Treatment in the statistical model:

    - the clinical study takes place at one site;
    - all study subjects have been recruited from the same enrollment pool;
    - all of the subjects have similar demographics;
    - all enrolled subjects are randomly assigned to treatment groups at study outset.

    After dropping the group-by-treatment interaction term from the model, the results of the SAS analysis and 90% confidence intervals (C.I.) are within the DB's acceptable range of 80-125%.

As the study was conducted in two groups and the study drug administered in two regions (sites) for Sumatriptan, Dr. Reddy's also provided statistical analysis of variance on the ln-transformed data AUC_{last}, AUC_{inf} and C_{max}. The data were analyzed with a model included sequence, treatment, period, group, treatment*group and treatment*site as factors and the results are mentioned below.

Effect	Pr>F		
	Ln(Cmax)	Ln(AUC0-t)	Ln(AUC∞)
Trt*Site	0.8840	0.4783	0.6699
Trt*Group	0.6151	0.9220	0.3015

Based on the results, it was observed that there is no significant effect for Treatment*site and Treatment*group. Hence the ANOVA was estimated at alpha 0.05 on the log-transformed data for C_{max}, AUC_{last}, and AUC_{inf}. The ANOVA model included sequence, treatment, period, and Group as fixed effects and subject (sequence) as random effect. The significance of the sequence effect at alpha 0.10 was calculated using the subject nested within the sequence as the error term.

- Upon reviewing of the individual pharmacokinetic profile of the study subjects, Subject Nos. 001, 008 and 034 demonstrated plasma concentrations for non-pre-dose time points as BQL for most of the sampling points for reference products while same product when administered previously in other route in period 2 had a normal pharmacokinetic response for subject Nos. 001, 008 and 34.

Dr. Reddy's provided the following justifications for excluding outlier Subject Nos. 1, 8, and 34:

Justification for excluding subjects 001, 008 and 034 (from Period 3 and Period 4) from Bioequivalence conclusion: (page 84)

The study was conducted as a replicated crossover design with subjects who were randomized into two treatment sequences ABAB and BABA, where A=Test and B=Reference in two groups (Group 1: Subject numbers: 1 – 27, Group 2: Subject numbers: 28 – 48). For period 1 & 2, drug administration site was deltoid region and for period 3 & 4 drug administration site was gluteal/thigh region.

Upon the review of the Individual pharmacokinetic profile of the study subjects, for the subject's numbers 001, 008 and 034 has aberrant pharmacokinetic response observed in period 4 when reference product was administered, while same product when administered previously in other route in period 2 had a normal pharmacokinetic response.

Concentration Tables Provided as supportive Data (Data for subjects 001, 008 & 034 at gluteal/thigh Region)

TABLE A: Plasma Concentrations (ng/ml) for Formulation A (Test) Administered at gluteal/thigh Region

Subject	Period	Sequence	0.00	0.03	0.07	0.10	0.13	0.17	0.20	0.25	0.33	0.42	0.50
1	3	ABAB	BQL	1.020	13.489	26.461	51.249	53.609	57.227	57.955	61.891	58.212	55.721
8	3	ABAB	BQL	1.732	26.991	57.009	76.013	78.834	91.974	78.689	67.769	59.093	47.850
34	3	ABAB	BQL	2.713	35.109	57.990	65.719	67.653	86.886	80.356	73.951	62.433	51.781

TABLE B (Contd…): Plasma Concentrations (ng/ml) for Formulation A (Test) Administered at gluteal/thigh Region

Subject	Period	Sequence	0.75	1.00	1.50	2.00	2.50	3.00	4.00	6.00	8.00	10.00
1	3	ABAB	53.560	40.453	24.687	18.579	13.402	11.175	6.702	3.101	1.839	0.790
8	3	ABAB	38.914	32.599	20.169	14.634	10.750	8.116	5.474	2.493	1.114	0.397
34	3	ABAB	41.164	32.104	17.683	12.967	9.481	7.382	4.466	1.607	0.707	0.282

TABLE C: Plasma Concentrations (ng/ml) for Formulation B (Reference) Administered at gluteal/thigh Region

Subject	Period	Sequence	0.00	0.03	0.07	0.10	0.13	0.17	0.20	0.25	0.33	0.42	0.50
1	4	ABAB	BQL	BQL	BQL	0.524	0.516	0.520	0.480	0.466	0.350	0.297	0.242
8	4	ABAB	BQL	BQL	0.202	0.276	0.269	0.264	BQL	BQL	BQL	BQL	BQL
34	4	ABAB	BQL	BQL	0.409	0.424	0.384	0.342	0.283	0.266	BQL	BQL	BQL

TABLE D(Contd…): Plasma Concentrations (ng/ml) for Formulation B (Reference) Administered at gluteal/thigh Region

Subject	Period	Sequence	0.75	1.00	1.50	2.00	2.50	3.00	4.00	6.00	8.00	10.00
1	4	ABAB	BQL	BQL	BQL	0.587	BQL	BQL	BQL	BQL	BQL	BQL
8	4	ABAB	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
34	4	ABAB	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL

Pharmacokinetic and Statistical Tables provided as supportive data including subjects 001, 008 & 034

TABLE E: Pharmacokinetic Parameters for Formulation A (Test) Administered at gluteal/thigh Region

Subject	Period	Sequence	AUC_{last} (ng*h/ml)	AUC_{inf} (ng*h/ml)	C_{max} (ng /ml)	t_{max} (hr)	$t_{1/2}$ (hr)	k_{el} (hr^{-1})
1	3	ABAB	116.429	118.565	61.891	0.33	1.87	0.3698
8	3	ABAB	102.246	103.177	91.974	0.20	1.62	0.4267
34	3	ABAB	96.108	96.710	86.886	0.20	1.48	0.4682

TABLE F: Pharmacokinetic Parameters for Formulation B (Reference) Administered at gluteal/thigh Region

Subject	Period	Sequence	AUC_{last} (ng*h/ml)	AUC_{inf} (ng*h/ml)	C_{max} (ng /ml)	t_{max} (hr)	$t_{1/2}$ (hr)	k_{el} (hr^{-1})
1	4	ABAB	0.343	Missing	0.587	2.00	Missing	Missing
8	4	ABAB	0.030	0.452	0.276	0.10	1.11	0.6261
34	4	ABAB	0.070	0.151	0.424	0.10	0.21	3.2945

TABLE G: With in Test and Within Reference variabilities

	Within Test CV (%)	Within Reference CV (%)
Ln (AUC_{last})	5.4	213.3
Ln (AUC_{inf})	9.0	114.9
Ln (C_{max})	17.2	127.6

TABLE H: Confidence Intervals and Final Variance Parameters for Ratio

	90% Confidence Intervals		Ratio (%)	Power (%)
	Lower (%)	Upper (%)		
Ln (AUC_{last})	105.76	169.69	133.97	46.3
Ln (AUC_{inf})	103.09	144.10	121.89	70.9
Ln (C_{max})	104.18	149.36	124.74	65.4

Dr. Reddy's conducted a Studentized residual test to confirm the outliers and Subject Numbers 001, 008 and 034 were identified as statistical outliers for three primary PK parameters C_{max}, AUC_{last} and AUC_{inf} for gluteal/thigh and hence these subjects were excluded from statistical analysis for Gluteal/ Thigh region (Period 3 and Period 4), however the results including these three outlier subjects have been provided as supportive data in Tables A thru H above.

The Test/Reference ratios for PK parameters AUC_{last}, AUC_{inf} and C_{max} for these three subjects when injected at two sites are as follows:

***Test/Reference Ratio** (%)*

Subject Number	*Site: Deltoid*			*Site: gluteal/thigh*		
	AUC_{last}	AUC_{inf}	C_{max}	AUC_{last}	AUC_{inf}	C_{max}
001	*102.557*	*101.876*	*106 035*	*33944.315*	*Not estimable*	*10543.612*
008	*105.739*	*105.864*	*103.746*	*340820.000*	*22826.770*	*33323.913*
034	*120.829*	*121.156*	*86.772*	*137297.143*	*64046.358*	*20491.981*

These three subjects (subject numbers 001, 008 and 034) were considered as discordant outliers because of extreme response in replicate 2 when drug was administered at gluteal/thigh site when compared to the rest of the subjects who participated in the study.

This study was conducted as replicate design, and it is evident that subject behavior was normal and subject physiological system might not be the contributor to this aberrant behavior. However, drug administration site was different in period 4 (gluteal/thigh region) compared to period 2 (deltoid region). The statistical data shown in 44 subjects (excluding subject numbers: 001, 008 and 034 data from period 3 and 4) indicates slightly lower response in gluteal/thigh site when compared to deltoid site, which is in-line with innovator's label information. The pharmacokinetic response in gluteal/thigh site which was observed for subject numbers 01, 08 and 34 for reference product data in period 4 was much lower than reported in the literature.

*Since the site*treatment interaction term was not statistically significant (p>0.05), both the treatments (Test and Reference products) were expected to behave the same at two different drug administration sites. Also, the variability due to subject*treatment interaction term was too low, i.e., there was no confounding between subject and treatment.*

The reference product variability was also significantly decreased (C_{max} ~ 9-fold, AUC_{last} ~ 45 fold, AUC_{inf} ~ 23 fold) after excluding outliers data (subject numbers 001, 008 and 034 data from period 3 and 4) for statistical analysis.

A thorough investigation was carried out by the principal investigator and bioanalytical investigator. The IP were administered to these subjects in presence of dosing supervisor and all the dosing compliance was checked, moreover the analytical batch was repeated due to low internal standard response but the trend observed anomaly was the same for the reanalyzed batch as that of the original run, where no concentrations were observed for most of the samples in period 4.

Reviewer's comments on Outliers subjects:

- Subject Nos. 1, 8 and 34 revealed no clinical abnormalities. Excluding these subjects from the statistical analysis of the study is not justified. After including all subjects in the study, the confidence intervals for AUCt, AUC∞ and Cmax do not fall within the acceptable 80-125% range. Therefore, the study is unacceptable.

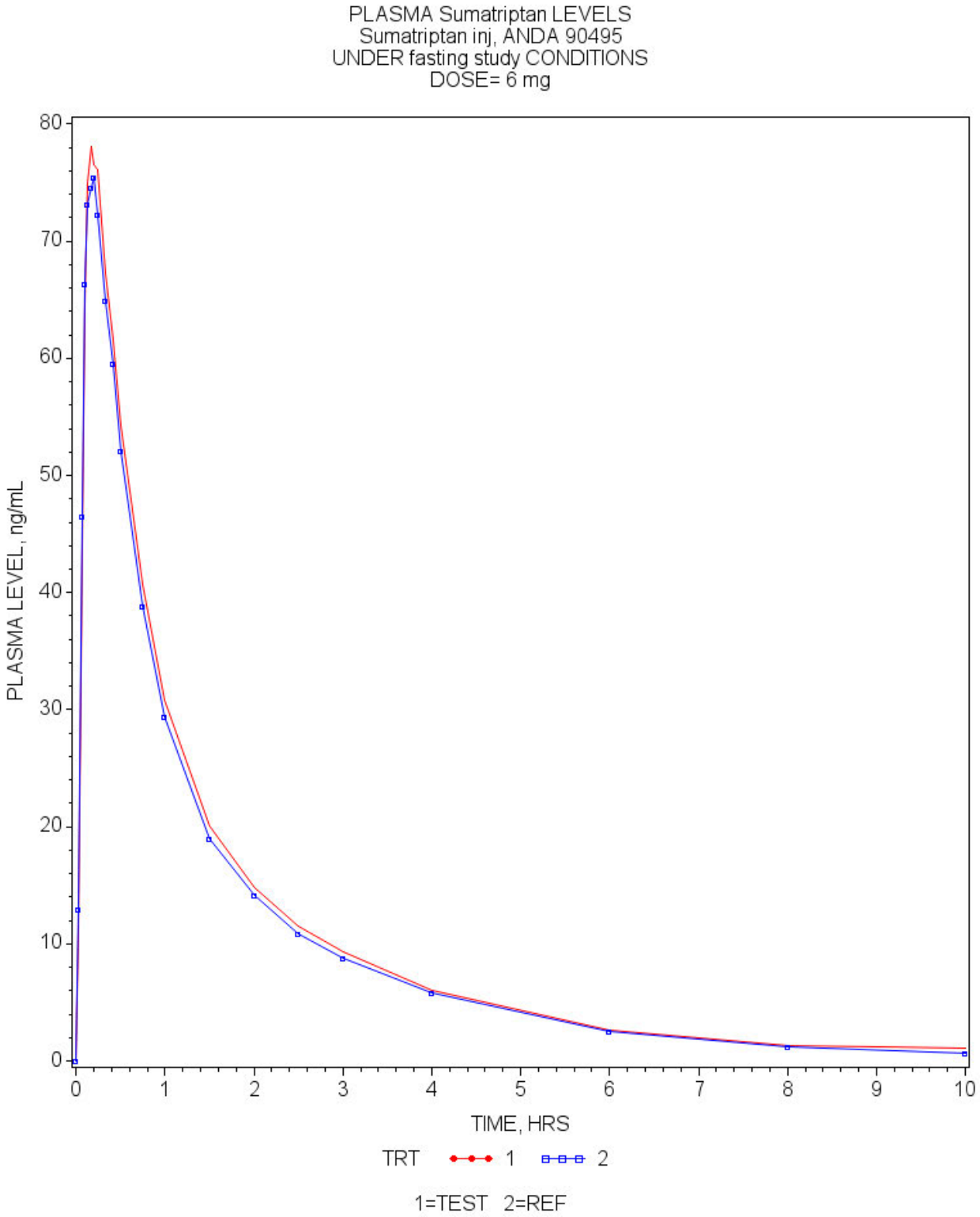
- The DB II does not accept results of statistical outlier tests to justify dropping subjects from a BE study. To re-evaluate the pharmacokinetic performance of subject Nos. 1, 8 and 34, the firm may re-dose these three subjects along with several other subjects (control group) chosen at random from the same study. Additionally, the study procedures and study drug lot numbers should be identical to Study # 71912 (original study). Alternatively, the firm may conduct a new fasting bioequivalence study.

Summary and Conclusions, Single-Dose Bioequivalence Study: The *in vivo* bioequivalence study is inadequate.

Table 18. Mean Plasma Concentrations, Single-Dose Bioequivalence Study

Sumatriptan					
Time (hr)	Test (n=38)		Reference (n=38)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.01	905.54	0.00
0.03	10.98	95.56	12.91	109.57	0.85
0.07	44.01	49.51	46.50	51.51	0.95
0.10	64.55	35.98	66.33	34.23	0.97
0.13	74.85	29.48	73.12	28.00	1.02
0.17	78.02	26.97	74.61	26.08	1.05
0.20	76.52	23.76	75.44	24.01	1.01
0.25	76.12	21.92	72.23	20.52	1.05
0.33	67.27	19.57	64.94	19.36	1.04
0.42	61.67	17.17	59.49	19.18	1.04
0.50	54.27	17.25	52.14	17.38	1.04
0.75	40.69	18.67	38.84	19.07	1.05
1.00	30.78	17.95	29.38	19.19	1.05
1.50	20.11	17.19	19.01	18.78	1.06
2.00	14.84	16.88	14.11	18.73	1.05
2.50	11.52	18.24	10.85	19.59	1.06
3.00	9.31	18.24	8.79	20.29	1.06
4.00	5.99	27.35	5.78	23.99	1.04
6.00	2.64	31.22	2.52	34.19	1.05
8.00	1.37	47.28	1.26	41.55	1.09
10.00	1.12	263.18	0.64	50.79	1.75

Figure 1. Mean Plasma-time Concentration plot, Single-Dose Bioequivalence Study



4.2 Formulation Data: [Please see original ANDA review: DARRTS: REV-BIOEQ-01(General Review), dated 01/11/2012]:

Ingredient	Amount (mg) / mL	Amount (%) / mL
Sumatriptan Succinate	(b) (4)*	(b) (4)
Sodium Chloride USP	7.0	0.7
Water for Injection USP	Quantity sufficient to 1.0 mL	Quantity sufficient

* (b) (4) mg/ mL of Sumatriptan Succinate is equivalent to 12.0 mg/ mL of Sumatriptan base

4.3 Dissolution Data: NA

4.4 Detailed Regulatory History (If Applicable): NA

4.5 Consult Reviews: NA

4.6 SAS Output

4.6.1 Fasting Study Data

90495 fasting study CONCENTRATION DATASET

(b) (4)

Following this page, 43 Pages Withheld in Full as (b)(4)

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 090495

APPLICANT: Dr. Reddy's Laboratories, Inc.

DRUG PRODUCT: Sumatriptan Succinate Injection, (Auto Injector), EQ 6 mg base/0.5 mL

The Division of Bioequivalence II (DB II) has completed its review of your submission acknowledged on the cover sheet and the following deficiencies have been identified:

The pre-study method validation is inadequate with the following deficiency:

1. The long-term storage stability (LTSS) data of 70 days @ -20°C and -70 °C is insufficient. Please provide sufficient LTSS to cover the entire storage length of the BE study samples (from the time of the first blood sample drawn to the time of the last plasma sample analyzed) up to 114 days @ -20°C and -70 °C.

The Fasting BE study is incomplete with the following reasons:

2. Subject Nos. 1, 8 and 34 revealed no clinical abnormalities. Excluding these subjects from the statistical analysis of the study is not justified. After including all subjects in the study, the confidence intervals for AUCt, AUCi and Cmax do not fall within the acceptable 80-125% range. Therefore, the study is unacceptable.

3. The DB II does not accept results of statistical outlier tests to justify dropping subjects from a BE study. To re-evaluate the pharmacokinetic performance of subject Nos. 1, 8 and 34, you may re-dose these three subjects along with several other subjects (control group) chosen at random from the same study. Additionally, the study procedures and study drug lot numbers should be identical to Study # 71912 (original study). Alternatively, you may conduct a new fasting bioequivalence study.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D., R.Ph.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

4.8 Outcome Page

Completed Assignment for 090495 ID: 19820

Back to Main Menu

Reviewer: Lee, Christina **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Amendment

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
19820	4/03/2013	Other	Study Amendment	1	1
				Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Study Amendment Review	
Amendment review	1
Injectable/Waiver 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/

CHRISTINA H LEE
05/20/2013

MOHEB H MAKARY
05/20/2013

ETHAN M STIER
06/10/2013

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090495
Drug Product Name	Sumatriptan Succinate Injection, pre-filled syringe with auto-injector
Strength(s)	EQ 6 mg base/0.5 mL
Applicant Name	Dr. Reddy's Laboratories, Inc. Bachupally, Hyderabad - 500 090, India Factory Address: Bachupally, Hyderabad 500 090, India
Address	200 Somerset Corporate Blvd, 7th Floor, Bridgewater, NJ 08807
Applicant's Point of Contact	Kimberly Ernst
Contact's Telephone Number	908-203-4937
Contact's Fax Number	908-203-4980
Original Submission Date(s)	April 28, 2008
Submission Date(s) of Amendment(s) Under Review	April 13, 2009 May 18, 2012
Reviewer	Christina Lee, Pharm.D.
OVERALL REVIEW RESULT	**INADEQUATE**
WAIVER REQUEST RESULT	**INADEQUATE**

REVIEW OF A STUDY AMENDMENT

1 EXECUTIVE SUMMARY

This is review of a study amendment.

The firm, Dr. Reddy's Laboratories, Inc. is requesting a waiver of in vivo bioequivalence study requirements for its Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL. The reference listed drug is Imitrex® STATDOSE Injectable, EQ 6 mg base/0.5 mL, manufactured by GlaxoSmithKline. The test product is qualitatively and quantitatively the same as the reference listed drug (RLD). The test product is a pre-filled syringe assembled in an auto-injector device.

In the August 31, 2009 re-submission, the firm changed the device design from a [(b) (4)] to **a push & button** design. In addition, the firm also included in-vitro comparison studies between the test product auto injector (particularly [(b) (4)], Push & Button design) versus the RLD.

The Division of Bioequivalence II (DB II) has reviewed the content of the submission and denied the waiver request for *in vivo* bioequivalence study requirements for the test product, Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL with the following recommendations:

1. The firm is requested to perform comparative in vitro testing on 1) drug volume delivered, 2) injection time, and 3) force to fire on the test bio-lot compared to the RLD

lot to demonstrate comparative performance characteristics and functionality testing of the test and the reference drug products. The firm should provide individual data for the in vitro tests to demonstrate comparable performance between the test and RLD device components. The firm should submit complete electronic EXCEL spreadsheet of individual data, mean, and %CV for these data on the test product versus Imitrex® STATDOSE Injectable. In addition, the firm should provide specifications such as breakloose force and extrusion force.

2. It is known that differences in injection technique and site of injection can affect the pharmacokinetics of sumatriptan. The small differences in performance and specifications that are present (e.g. needle gauge, injection cycle time, force to displacement distance profile) have the theoretical potential to affect PK. Therefore, the DB II recommends that the firm conducts a single-dose two-way crossover fasting bioequivalence study in healthy volunteers **where the subjects inject themselves using the device.**

3. Considering the warning – among others - on RLD, "the fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of cardiac artery disease (CAD), and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug", consequently, the DB II recommends adequate safety monitoring be in place during the BE study. The firm may submit a protocol for the BE study to the DB II.

On May 18, 2012, the firm responded to DB II's requests stated above. The firm's responses are considered unsatisfactory. The following deficiencies comments will be provided to the firm:

1. The firm is requested to explain the apparent differences in the test outcomes with respect to the actuation force between the original data and the data in the current amendment submission for the test product that is nearly 46% differences (18.52 N in the current submission vs. 26.98 N in the original submission). Yet, the data for the RLD remain unchanged.

2. As pointed out in the OGD DCR clinical consult, other differences in the test product (e.g. needle gauge, injection cycle time, force to displacement distance profile) in performance and specifications that are present have the potential to affect PK. The DB II does not agree that the information submitted by the firm supports bioequivalence of its test product, Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL, pre-filled syringe with auto-injector, to the RLD, Imitrex® STATDOSE Injectable, EQ 6 mg base/0.5 mL, manufactured by GlaxoSmithKline. Therefore, the DB II recommends that the firm conducts a single-dose, two-way crossover, fasting bioequivalence study in healthy volunteers **where the subjects inject themselves** both the test and reference products using the respective device.

3. As mentioned in the deficiency letter issued on January 25, 2012, considering the warning – among others - on RLD, "the fact that sumatriptan can cause coronary

vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of cardiac artery disease (CAD), and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug", the DB II recommends adequate safety monitoring be in place during the BE study. The firm may submit a protocol for the BE study to the DB II.

Overall, the application is **inadequate**.

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3 FIRM'S SUMISSION AND REVIEW'S COMMENTS

The following deficiencies were sent to the firm in the deficiency letter dated January 25, 2012:

Deficiency# 1:

Please perform comparative in vitro testing on 1) *drug volume delivered*, 2) *injection time, and* 3) *force to fire on the test bio-lot compared to the RLD lot to demonstrate comparative performance characteristics and functionality testing of the test and the reference drug products. Please include the following information in your submission:* 1) *individual data for the in vitro tests to demonstrate comparable performance between the test and RLD device components;* 2) *complete electronic EXCEL spreadsheet of individual data, mean, and %CV for these data on the test product versus Imitrex® STATDOSE Injectable. Finally, please provide specifications such as breakloose force and extrusion force.*

Firm's Response:

The excel spreadsheet with results of in-vitro test for drug volume delivered, injection time and force to fire (individual data, mean, and %CV) for bio batch lot and reference listed drug lot used in bioequivalence study has been provided (See detailed information in Section 7 Additional Attachment):

For the test device, larger number of samples was originally tested. For comparative purpose, the first consecutive readings of the test sample that corresponded with the RLD sample size are considered in the above table.

Reviewer's Comments:

The firm submitted the following in-vitro data:

Table 1. (b) (4) —Test product:

	Injection Time (s)	Actuation Force (N)	Delivery Volume (ml)	Retraction Depth (mm)	Protrusion Length (mm)
	(b) (4)				
Min	(b) (4)				
Max					
Mean	1.38	19.82	0.537	7.64	5.917
SD	0.13	1.33	0.006	0.24	0.097
%CV	9.62%	6.72%	1.15%	3.10%	1.64%
Mean + 3SD	1.78	23.81	0.556	8.35	6.208
Mean + 4SD	1.91	25.15	0.562	8.59	6.305
Median	1.36	19.82	0.538	7.64	5.927
n	381	382	381	382	61

Table 2. [redacted] (Statdose)—Reference product:

	Cap Removal Force (N)	Injection Time (s)	Actuation Force (N)	Delivery Volume (ml)	Protrusion Length (mm)
Min	[redacted]				
Max					
Mean	21.7	1.21	14.83	0.499	6.240
SD	7.0	0.16	2.87	0.028	0.377
%CV	32.36%	13.33%	19.31%	5.62%	6.04%
Mean + 3SD	42.8	1.70	23.43	0.583	7.369
Mean + 4SD	49.8	1.86	26.29	0.612	7.746
Median	19.8	1.215	14.46	0.499	6.36
n	22	31	50	30	31

Table 3. Summary Table of Comparison Between Test and RLD:

	Volume Delivered (ml)			Injection Time (s)			Actuation Force (N)		
[redacted] Spec.	[redacted]								
	[redacted]		STATdose	[redacted]		STATdose	[redacted]		STATdose
No of samples (n)	**381**	**30**	**30**	**431**	**31**	**31**	**382**	**50**	**50**
Min	[redacted]								
Max									
Mean	0.537	0.536	0.499	1.38	1.41	1.21	19.82	18.52	14.83
SD	0.006	0.007	0.028	0.13	0.19	0.16	1.33	1.47	2.87
%CV	1.15%	1.34%	5.62%	9.32%	13.64%	13.33%	6.72%	7.95%	19.31%
Mean + 3SD	0.556	0.558	0.583	1.76	1.99	1.70	23.81	22.94	23.43
Mean - 3SD	0.52	0.51	0.42	0.99	0.83	0.73	15.83	14.10	6.24
Median	0.538	0.537	0.499	1.36	1.33	1.22	19.82	18.66	14.46

It is note that the information provided in the above table is different comparing to the data submitted in the original submission with respect to Volume Delivered, Injection Time, and Actuation Force (Tables below were submitted on 08/31/2009):

Table 2: Dose Delivery Volume

	Specification	[redacted] Results (ml)	STATdose Results (ml)
Min	[redacted]		
Max			
Mean	N/A	0.526	0.499
Median	N/A	0.526	0.501
Standard Deviation	N/A	0.014	0.028

Table 3: Injection Cycle Time

	Specification	(b) (4) Results (sec)	STATdose Results (sec)
Min		[redacted]	
Max			
Mean	N/A	1.42	1.21
Median	N/A	1.40	1.20
Standard Deviation	N/A	0.19	0.16

Table 4: Actuation Force

	(b) (4) Results All Conditions(N)	STATdose Results (N)
Min		[redacted]
Max		
Mean	26.98	14.83
Median	26.42	14.59
Standard Deviation	2.19	2.87

It's noted that the differences of the actuation force between the original data and the data in the current amendment submission for the test product is nearly 46% (18.52 N in the current submission vs. 26.98 N in the original submission). Yet, the data for the RLD remain unchanged. Therefore, the firm will be asked to explain the apparent differences in the test outcome for its test product.

With regards to the current test data, the firm's data for the actuation force is 20% more than that of the reference device (18.52 N vs. 14.83 N). As stated in the OGD Chemistry Review [DARRTS: ANDA 90495, REV-QUALITY-03(General Review), dated 01/06/2012], the firm was requested to provide information to support the ease of firing and operating this device in a diverse population.

As pointed out in the OGD DCR clinical consult, other differences in the test product (e.g. needle gauge, injection cycle time, force to displacement distance profile) in performance and specifications that are present have the potential to affect PK. The DB II does not agree that the information submitted by the firm supports bioequivalence of its test product, Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL, pre-filled syringe with auto-injector, to the RLD, Imitrex® STATDOSE Injectable, EQ 6 mg base/0.5 mL, manufactured by GlaxoSmithKline. Therefore, the firm's request for bio-waiver pursuant to 21 CFR § 320.22(b)(1) is denied. Consequently, the DB II recommends that the firm conducts a single-dose, two-way crossover, fasting bioequivalence study in healthy volunteers **where the subjects inject themselves** both the test and reference products using the respective device.

Deficiency# 2:

It is known that differences in injection technique and site of injection can affect the pharmacokinetics of sumatriptan. The small differences in performance and specifications that are present (e.g. needle gauge, injection cycle time, force to displacement distance profile) have the theoretical potential to affect PK. Therefore, the DB II recommends that you conduct a single-dose two-way crossover fasting bioequivalence study in healthy volunteers where the subjects inject themselves using the device.

Firm's Response:

A comparative in-vitro data of the test device and the reference listed drug device (Statdose) for the following parameters is given below:

1. Injection cycle time
2. Dose delivery volume
3. Needle protrusion depth
4. Button/Actuation Force

Data demonstrated that the results are comparable to that of STATdose devices.

We would also like to confirm that there are no differences in injection technique and site of injection for the test and the reference products. Though the initial steps for assembly and steps post administration of the RLD differs from the test, the actual steps in the injection that are critical for the dose delivery are similar:

- Place the front (blue end) containing the syringe against the injection site. (The injection sites are same for the RLD and test)
- Do not touch the blue button. Press so that the grey barrel slides down.
- Push the blue button (click will be heard which will mean the injection cycle has begun).
- Wait 5 seconds (a second click will indicate that the drug has been fully delivered and the needle has been safely retracted).
- Remove the device from the injection site.

We also would like to bring to the agency's notice the following information in support of the bio-waiver for Sumatriptan Succinate Injection:

1) Both the test and reference products are parenteral solutions and their in-vivo performance is expected to be similar on account of their solution nature and qualitative (Ql) and quantitative (Q2) similarity.
2) The product is intended to be administered through subcutaneous route. The bioavailability of Sumatriptan Succinate through subcutaneous route is almost complete (97%) when compared with intravenous Sumatriptan succinate[1].
3) The site of administration (deltoid muscle vs thigh) has no impact on the bioavailability (extent of absorption) of Sumatriptan succinate.

[1] IMITREX® (Sumatriptan Succinate) Injection-Label: http://www.accessdata.fda.gov/drugsatfda docs/label/2010/020080s038Ib1.pdf

4) The method of administration (manual vs. STATdose) has no impact on the bioavailability of Sumatriptan Succinate. This is based on the fact that the drug administered through auto injector and through manual method was found to be bioequivalent. As mentioned in the prescribing information leaflet, the Tmax or amount absorbed was not significantly altered by either the site or technique of injection.
5) The absolute dose linearity across two reference listed strengths viz 8 mg/mL and 12 mg/mL exists and these two strengths are bioequivalent upon dose normalization[2].

Based on the above comparable in-vitro data of test and the reference listed drug (Imitrex STATdose) and the above mentioned facts, we request the agency for bio-waiver for Sumatriptan Succinate Injection.

Reviewer's Comments: Please reference Reviewer's Comment for Deficiency# 1. The firm's response to this request is not acceptable.

Deficiency# 3:

Considering the warning - among others - on RLD, "the fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of cardiac artery disease (CAD), and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug", the DB II recommends adequate safety monitoring be in place during the BE study. You may submit a protocol for the BE study to the DB II.

Firm's Response:

As explained in the response of point #2, we request the agency for bio-waiver for the test product.

Reviewer's Comments: Please reference Reviewer's Comments for Deficiency#1. The firm's response to this request is not acceptable.

[2] Study No.: SUM102146, GSK: http://www.google.co.in/uri?sa=t&rct=j&q=statdose%20to%20imitrex%20bioequivalence&source=web&cd=7&ved=OCEYQFjAG&ur1=http%3A%2F%2Fdownload.gskclinicalstudyregister.com%2Ffiles%2F3222.pdf&ei=RttdT4bkJILPrQfur5T Cw&usg=AFQjCNGETrSYjSWRRikAWpiACjmU9kHOiw

4 Deficiency Comments

1. The firm is requested to explain the apparent differences in the test outcomes with respect to the actuation force between the original data and the data in the current amendment submission for the test product that is nearly 46% (18.52 (N) in the current submission vs. 26.98 (N) in the original submission). Yet, the data for the RLD remain unchanged.

2. As pointed out in the OGD DCR clinical consult, other differences in the test product (e.g. needle gauge, injection cycle time, force to displacement distance profile) in performance and specifications that are present have the potential to affect PK. The DB II does not agree that the information submitted by the firm supports bioequivalence of its test product, Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL, pre-filled syringe with auto-injector, to the RLD, Imitrex® STATDOSE Injectable, EQ 6 mg base/0.5 mL, manufactured by GlaxoSmithKline. Consequently, the DB II recommends that the firm conducts a single-dose, two-way crossover, fasting bioequivalence study in healthy volunteers **where the subjects inject themselves** both the test and reference products using the respective device.

3. As mentioned in the deficiency letter issued on January 25, 2012, considering the warning – among others - on RLD, "the fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of cardiac artery disease (CAD), and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug", the DB II recommends adequate safety monitoring be in place during the BE study. The firm may submit a protocol for the BE study to the DB II.

5 Recommendations

The Division of Bioequivalence II (DB II) does not agree that the information submitted by Dr. Reddy's Laboratories, Inc. qualifies Sumatriptan Succinate Injection, EQ 6 mg/0.5 mL (auto-injectors), for a waiver of bioequivalence study requirements under 21 CFR § 320.22 (b) (1). The waiver of *in vivo* bioequivalence study requirements for Sumatriptan Succinate Injection, EQ 6 mg/0.5 mL (auto-injectors) cannot be granted at this time due to deficiency comments above.

6 Comments for Other OGD Disciplines

Discipline	Comment
NA	

7 ADDITIONAL ATTACHMENT:

[redacted] (Statdose)

	Cap Removal Force (N)	Injection Time (s)	Actuation Force (N)	Delivery Volume (ml)	Protrusion Length (mm)
Min	[redacted]				
Max					
Mean	21.7	1.21	14.83	0.499	6.240
SD	7.0	0.16	2.87	0.028	0.377
%CV	32.36%	13.33%	19.31%	5.62%	6.04%
Mean + 3SD	42.8	1.70	23.43	0.583	7.369
Mean + 4SD	49.8	1.86	26.29	0.612	7.746
Median	19.8	1.215	14.46	0.499	6.36
n	22	31	50	30	31

[redacted] (Statdose)

Cap Removal Force (N)	Injection Time (s)	Actuation Force (N)	Delivery Volume (ml)	Protrusion Length (mm)
[redacted]				

Following this page, 12 Pages Withheld in Full as (b)(4)

Attribute Comparison:

	Cap Removal Force (N)		Injection Time (s)		Actuation Force (N)		Delivery Volume (ml)		Protrusion Length (mm)		Retraction Depth (mm)	
	(b) (4)	STATdose	(b) (4)	STATdose	(b) (4)	STATdose	(b) (4)	STATdose	(b) (4)	STATdose	(b) (4)	STATdose
(b) (4) Spec.	(b) (4)											
Min	(b) (4)											
Max												
Mean	13.05	21.70	1.38	1.21	19.82	14.83	0.537	0.499	5.92	6.240	7.64	
SD	3.16	7.02	0.13	0.16	1.33	2.87	0.006	0.028	0.10	0.377	0.24	
%CV	24.18%	32.36%	9.32%	13.33%	6.72%	19.31%	1.15%	5.62%	1.64%	6.04%	3.10%	n/a
Mean + 3SD	22.52	42.78	1.76	1.70	23.81	23.43	0.556	0.583	6.21	7.369	8.35	
Mean - 3SD	3.59	0.63	0.99	0.73	15.83	6.24	0.52	0.42	5.63	5.11	6.93	
Median	12.50	19.80	1.36	1.215	19.82	14.46	0.538	0.499	5.93	6.36	7.64	
n	50	22	431	31	382	50	381	30	61	31	382	

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 090495

APPLICANT: Dr. Reddy's Laboratories, Inc.

DRUG PRODUCT: Sumatriptan Succinate Injection, (Auto Injector), EQ 6 mg base/0.5 mL

The Division of Bioequivalence II (DB II) has completed its review of your submission acknowledged on the cover sheet and the following deficiencies have been identified:

1. Please explain the apparent differences in the test outcomes with respect to the actuation force between the original data (submitted on August 31, 2009) and the data in the current amendment submission for the test product that is nearly 46% (18.52 N in the current submission vs. 26.98 N in the original submission). Yet, the data for the RLD remain unchanged.

2. As pointed out in the OGD DCR clinical consult, other differences in the test product (e.g. needle gauge, injection cycle time, force to displacement distance profile) in performance and specifications that are present have the theoretical potential to affect PK. The DB II does not agree that the information you submitted supports bioequivalence of your test product, Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL, pre-filled syringe with auto-injector, to the RLD, Imitrex® STATDOSE Injectable, EQ 6 mg base/0.5 mL, manufactured by GlaxoSmithKline. Consequently, the DB II recommends that you conduct a single-dose, two-way crossover, fasting bioequivalence study in healthy volunteers **where the subjects inject themselves** both the test and reference products using the respective device.

3. As mentioned in the deficiency letter issued on January 25, 2012, considering the warning – among others - on RLD, "the fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of cardiac artery disease (CAD), and the close proximity of the events to sumatriptan use support the conclusion that some of

these cases were caused by the drug", the DB II recommends adequate safety monitoring be in place during the BE study. You may submit a protocol for the BE study to the DB II.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

8 OUTCOME PAGE

COMPLETED ASSIGNMENT FOR 090495 ID: 16973

Back to Main Menu

Reviewer: Lee, Christina **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Amendment

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
16973	5/18/2012	Other	Study Amendment	1	1
				Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Study Amendment Review	
Amendment review	1
Injectable/Waiver 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/

CHRISTINA H LEE
06/06/2012

MOHEB H MAKARY
06/06/2012

ETHAN M STIER on behalf of BARBARA M DAVIT
06/18/2012

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090495
Drug Product Name	Sumatriptan Succinate Injection, pre-filled syringe with auto-injector
Strength(s)	EQ 6 mg base/0.5 mL
Applicant Name	Dr. Reddy's Laboratories Ltd.
Address	3600 Arco Corporate Dr, Suite 310 Charlotte, NC 28270-7104
Applicant's Point of Contact	Kumara Sekar, Ph.D.
Contact's Telephone Number	704-496-6065
Contact's Fax Number	704-496-6082
Original Submission Date(s)	April 28, 2008
Submission Date(s) of Amendment(s) Under Review	April 13, 2009
Reviewer	Christina Lee, Pharm.D.
OVERALL REVIEW RESULT	**INADEQUATE**
WAIVER REQUEST RESULT	**INADEQUATE**

REVIEW OF A WAIVER REQUEST AND A CLINICAL CONSULT

1 EXECUTIVE SUMMARY

The firm, Dr. Reddy's Laboratories, Inc. is requesting a waiver of in vivo bioequivalence study requirements for its Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL. The reference listed drug is Imitrex® STATDOSE Injectable, EQ 6 mg base/0.5 mL manufactured by GlaxoSmithKline. The test product is qualitatively and quantitatively the same as the reference listed drug (RLD). The test product is a pre-filled syringe assembled in an auto-injector device.

The firm originally submitted its request on April 30, 2008. Due to a significant difference in triggering mechanism for the test product auto-injector device comparing to the RLD, the Agency issued a Fatal Flaw Letter on 03/20/2009 [DARRTS: COR-ANDAACTION-11(Complete Response- Fatal Flaw), dated 3/20/2009]. The Agency suggested the firm either to amend or withdraw the application. Alternately, the current drug/device combination may be submitted to the Office of New Drugs, Division of Neuropharmcology Drug Product under 505(b)(2).

On August 31, 2009, the firm submitted a subsequent amendment changing the device design from a (b) (4) to **a push & button** design. In this submission, the firm also included in-vitro comparison studies between the test product auto injector (particularly (b) (4), Push & Button design) versus the RLD.

The Division of Chemistry II (DCII) has reviewed the auto-injector device used by the test product and how the device compares with that used by the RLD

(http://darrts.fda.gov:9602/darrts/viewCommunication.do?fromPage=appHistoryDirect&communicationId=2735414&fromHistoryPage=true&appPk=137316).

DCII also sent a request to the OGD Clinical Division to evaluate this proposed sumatriptan auto-injector product for any potential concerns with respect to safety or therapeutic equivalence. The OGD Clinical Division provided the following recommendation with regards to bioequivalence among others (http://darrts.fda.gov:9602/darrts/viewCommunication.do?fromPage=appHistoryDirect&communicationId=3058355&fromHistoryPage=true&appPk=137316).

It is known that differences in injection technique and site of injection can affect the pharmacokinetics of sumatriptan. Therefore, while the performance and specifications of the proposed device are generally similar to those of the RLD, the small differences in performance and specifications that are present (e.g. needle gauge, injection cycle time, force to displacement distance profile) have the theoretical potential to affect PK.

The Division of Bioequivalence II (DB II) is in agreement with the above recommendation by the Clinical Division, and denied the waiver request for *in vivo* bioequivalence study requirements for the test product, Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL. In addition, the DB II also recommends the following:

1. The firm is requested to perform comparative in vitro testing on 1) drug volume delivered, 2) injection time, and 3) force to fire on the test bio-lot compared to the RLD lot to demonstrate comparative performance characteristics and functionality testing of the test and the reference drug products. The firm should provide individual data for the in vitro tests to demonstrate comparable performance between the test and RLD device components. The firm should submit complete electronic EXCEL spreadsheet of individual data, mean, and %CV for these data on the test product versus Imitrex® STATDOSE Injectable. In addition, the firm should provide specifications such as breakloose force and extrusion force.

2. It is known that differences in injection technique and site of injection can affect the pharmacokinetics of sumatriptan. The small differences in performance and specifications that are present (e.g. needle gauge, injection cycle time, force to displacement distance profile) have the theoretical potential to affect PK. Therefore, the DB II recommends that the firm conducts a single-dose two-way crossover fasting bioequivalence study in healthy volunteers **where the subjects inject themselves using the device.**

3. Considering the warning – among others - on RLD, “the fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of cardiac artery disease (CAD), and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug”, consequently, the DB II recommends adequate safety monitoring be in place during the BE study. The firm may submit a protocol for the BE study to the DB II.

The formulation for the test product is qualitatively (Q1) and quantitatively (Q2) the same as the respective RLD product. The final acceptability of the overage of the active ingredient in the test products is deferred to the Division of Chemistry.

The application is **incomplete**. The bio-waiver request for the test product is denied.

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3 SUBMISSION SUMMARY

3.1 Drug Product Information[1]

Test Product	Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL (Auto Injector)
Reference Product	Imitrex® STATDOSE Injectable, EQ 6 mg base/0.5 mL*
RLD Manufacturer	**GlaxoSmithKline**
NDA No.	**20-080**
RLD Approval Date	**Statdose: December 23, 1996**
Indication	For 1) the acute treatment of migraine attacks with or without aura and 2) the acute treatment of cluster headache episodes.*

Note: Each Imitrex® (sumatriptan succinate) Injection Statdose System® 6 mg, contains 2 prefilled single-dose syringe cartridges, 1 Imitrex Statdose Pen, 1 carrying case, and a patient information leaflet with instructions for use.

- Imitrex STATDOSE EQ 4 mg base/0.5 mL (EQ 8mg base/mL) is also listed in the Orange Book as an RLD, approved on Feb 1, 2006.

3.2 PK/PD Information[2]

Bioavailability	The bioavailability of sumatriptan via subcutaneous site injection was 97% ± 16% of that obtained following intravenous injection
Food Effect	Not indicated in the drug label
Tmax	12 minutes (range: 5 to 20 minutes) after a single 6-mg subcutaneous manual injection into the deltoid area
Metabolism	Not indicated in the drug label
Excretion	22% ± 4% was excreted in the urine as unchanged sumatriptan and 38% ± 7% as the indole acetic acid metabolite.
Half-life	115 ± 19 minutes
Relevant OGD or DB History (for details see Section 3.10, Additional Attachments)	1. Currently, there is no ANDA that is approved using the auto injection device. 2. A memo in the RLD approval letter dated December 2, 1991 states that the pharmacokinetics of sumatriptan in the elderly, and in patients with migraine were similar to that in normal healthy volunteers. The clearance and Cmax of Sumatriptan were similar between Black and Caucasian normal volunteers. Therefore, the DB II recommends the BE study can be performed in normal healthy individuals that inject themselves using the device[3]. 3. Since the drug product has a device component (auto-injector), in addition to the formulation comparison, the DB II asks for suitable in-vitro tests to document comparative performance characteristics of the devices used in the test and reference drug products.

[1] Online Orange Book. Search word: Sumatriptan. Last accessed: 1/10/11.

[2] External Database: DailyMed Current Medication Information. Search: Sumatriptan Succinate (http://dailymed nlm nih.gov/dailymed/drugInfo.cfm?id=8551#nlm34067-9). Last accessed: 1/10/11.

[3] Enterprise Search, NDA 20080, CLINICAL Pharm\Biopharm Legacy Files. Last accessed 1/10/11.

	Based on the reviews (for Epinephrine Auto Injection System) of controlled correspondences (CC 99-114, 02-297, AND 03-133), FDA's consolidated response to 2 Citizen Petitions (FDA 2007 P-0128 and 2009-P-0040), and ANDAs (b) (4) and 78-579, the DBE recommends the following *in vitro* comparative performance tests for the test and reference products: a) volume of solution injected and residual content of the auto-injector b) exposed needle length and needle gauge c) depth of penetration d) dose delivery time, e) force required to discharge the actuator and force of injection f) needle integrity post injection to include testing through different clothing materials of varying thickness and different angles of incidence. 4. The sponsor should devise suitable in vitro tests to document these parameters for single and multiple devices compared to the RLD. 5. On 10/27/2011, at the request of OGD DC II to the OGD Clinical Group to evaluate any potential concerns with respect to safety or therapeutic equivalence related to this drug product (Please see Section 6 for additional information on the consult).
Drug Specific Issues (if any)	The Imitrex label contains the following **bolded** precaution: 1. Patients who are advised to self-administer IMITREX Injection in medically unsupervised situations should receive instruction on the proper use of the product from the physician or other suitably qualified health care professional prior to doing so for the first time. 2. Sumatriptan label has the following contraindications: IMITREX Injection should not be given intravenously because of its potential to cause coronary vasospasm. IMITREX Injection should not be given to patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes. In addition, patients with other significant underlying cardiovascular diseases should not receive IMITREX Injection. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks. Peripheral vascular disease includes, but is not limited to, ischemic bowel disease (see WARNINGS: Other Vasospasm-Related Events and WARNINGS: Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events). Because IMITREX Injection may increase blood pressure, it should not be given to patients with uncontrolled hypertension. IMITREX Injection and any ergotamine-containing or ergot-type medication (like dihydroergotamine or methysergide) should not be used within 24 hours of each other, nor should IMITREX Injection and another 5-HT1 agonist. IMITREX Injection should not be administered to patients with hemiplegic or

	basilar migraine. IMITREX Injection is contraindicated in patients with hypersensitivity to sumatriptan or any of its components. IMITREX Injection is contraindicated in patients with severe hepatic impairment. 3. In addition to the above contraindications, the RLD label has the following warnings among others: Drug-Associated Cardiac Events and Fatalities Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of IMITREX Injection or IMITREX® (sumatriptan succinate) Tablets. Considering the extent of use of sumatriptan in patients with migraine, the incidence of these events is extremely low. The fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of CAD, and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug. In many cases, however, where there has been known underlying CAD, the relationship is uncertain

Note: Cmax after 6 mg of sumatriptan varied somewhat depending on site of injection and injection technique:
1) manual subcutaneous injection into the deltoid: 74 ± 15 ng/ml
2) manual subcutaneous injection into the thigh: 61 ± 15 ng/ml
3) auto-injector injection into the thigh: 52 ± 15 ng/ml

3.3 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	--
Amendment	Yes	1
OGD Clinical Consult	Yes	1

3.4 Formulation

Location in appendix	Section 4.1, page 10
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	**Yes**
If not acceptable, why?	N/A

3.5 Waiver Request(s)

Strengths for which waivers are requested	EQ 6 mg base/0.5 mL
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	**No**
If not then why?	DB II requests 1) a fasting BE study in healthy subjects, and 2) comparative in vitro testing on a) drug volume delivered, b) injection time, and c) force to fire on the test **bio-lot compared to the RLD lot.**

3.6 Deficiency Comments

1. The firm is requested to perform comparative in vitro testing on 1) drug volume delivered, 2) injection time, and 3) force to fire on the test bio-lot compared to the RLD lot to demonstrate comparative performance characteristics and functionality testing of the test and the reference drug products. The firm should provide individual data for the in vitro tests to demonstrate comparable performance between the test and RLD device components. The firm should submit complete electronic EXCEL spreadsheet of individual data, mean, and %CV for these data on the test product versus Imitrex® STATDOSE Injectable. In addition, the firm should provide specifications such as breakloose force and extrusion force.

2. It is known that differences in injection technique and site of injection can affect the pharmacokinetics of sumatriptan. The small differences in performance and specifications that are present (e.g. needle gauge, injection cycle time, force to displacement distance profile) have the theoretical potential to affect PK. Therefore, the DB II recommends that the firm conducts a single-dose two-way crossover fasting bioequivalence study in healthy volunteers **where the subjects inject themselves using the device.**

3. Considering the warning – among others - on RLD, "the fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of cardiac artery disease (CAD), and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug", the DB II recommends adequate safety

monitoring be in place during the BE study. The firm may submit a protocol for the BE study to the DB II.

3.7 Recommendations

The Division of Bioequivalence II (DB II) does not agree that the information submitted by Dr. Reddy's Laboratories, Inc. qualifies Sumatriptan Succinate Injection, EQ 6 mg/0.5 mL (auto-injectors), for a waiver of bioequivalence study requirements under 21 CFR § 320.22 (b) (1). The waiver of *in vivo* bioequivalence study requirements for Sumatriptan Succinate Injection, EQ 6 mg/0.5 mL (auto-injectors) cannot be granted at this time due to deficiency comments above.

The firm should be informed of the above deficiency comments and recommendations.

3.9 Comments for Other OGD Disciplines

Discipline	Comment
NA	

4 APPENDIX

4.1 Formulation

Component	Test Product	Reference Products[4]
Sumatriptan	(b) (4) mg/mL*	EQ 6 mg base/0.5 mL
Sodium Chloride	7.0 mg/mL	3.5 mg/0.5 mL
Water for Injection	q.s. to 1.0 mL	QS
Total Volume	0.5 mL	

* (b) (4) mg/mL of sumatriptan succinate is equivalent to 12.0 mg/mL sumatriptan base

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?	No
Comments on the drug product formulation:	Formulation is acceptable

Comments Related to Formulation:

Qualitatively (Q_1) the test product, Sumatriptan Succinate Injection, 6 mg/0.5 mL contains the same inactive ingredients as the approved RLD. Quantitatively (Q2) the inactive ingredients in the test product are present in the same amounts as compared with the respective RLD product strength.

4.2 In Vitro Performance Comparison of Test and the RLD Devices

1. The firm received a Fatal Flaw Letter from the Agency on 03/20/2009 [DARRTS: COR-ANDAACTION-11(Complete Response- Fatal Flaw), dated 3/20/2009] due to a significant difference in triggering mechanism for the test product auto-injector device comparing to the RLD. The Agency suggested the firm either to amend or withdraw the application. Alternately, the current drug/device combination may be submitted to the Office of New Drugs, Division of Neuropharmcology Drug Product under 505(b)(2).

2. Subsequently, the firm resubmitted its application on 8/31/2009 by changing from a (b) (4) design to a push & button design. The firm conducted a study between the test product auto injector (particularly (b) (4), Push & Button design) versus the RLD. The study concluded that the (b) (4) device demonstrated equivalence in performance against the STAT dose for the following parameters:

[4] LXMain, Search NDA 20080, Imitrex. Last Accessed 1/10/11.

Parameter	Method of Testing
Cap / Needle Shield Removal Force	Tensometer, set in tensile mode
Dose Delivery Volume	Gravimetric weight of volume dispensed, in accordance with EP and USP Extractable Volume tests
RNS Removal	See "Visual Inspection"
Injection Cycle Time	Calibrated stop watch
Button Force/Actuation Force	Tensometer, set in compression mode
Needle Protrusion	Calibrated depth gauge
Spring Rate	Tensometer, set in compression mode

The applicant conducted a second study that compared the operating parameters and functionality of the (b) (4) (Push & Button) device with Imitrex® STATdose. The study compared the (b) (4) device against the STAT dose for the following parameters:

DEVICE FUNCTIONALITY SPECIFICATIONS

TEST	SPECIFICATION
Cap Removal	(b) (4)
Device Activation Force	
Dose Confirmation	
Dose Visible Confirmation	
Needle Retraction	
Injection Depth	
Injection Time	
Injection Volume	
Safety Mechanism	

Cap / Needle Shield Removal Force

The needle shield of the (b) (4) device is removed when removing the device Cap. The needle shield in the STAT dose device is removed when the assembled device is removed from the cartridge pack.

Table 1: Cap/Needle Shield Removal Force

	[redacted] Results (N)	STATdose Results (N)
Min	[redacted]	
Max		
Mean	20 (19.53)	22 (21.70)
Median	19 (19.00)	20 (19.80)
Standard Deviation	7 (7.09)	7 (7.02)

The only differences between the tests were the methods by which each type of device was secured within the tensometer. The table above compared the testing results of the two devices. The mean results between the [redacted] device and the STAT dose device, were within 2N.

Dose Delivery Volume

The dose delivery volume tested by gravimetrically weighing the liquid dispensed after actuating the devices.

Table 2: Dose Delivery Volume

	Specification	[redacted] Results (ml)	STATdose Results (ml)
Min	[redacted]		
Max			
Mean	N/A	0.526	0.499
Median	N/A	0.526	0.501
Standard Deviation	N/A	0.014	0.028

All results from the [redacted] were within the same range as the STAT dose devices tested, with the [redacted] device displaying less variability in dose, compared with the STAT dose.

Injection Cycle Time

The Injection Cycle Time is defined as the total time taken for the needle to be inserted to its predetermined depth, the drug to be delivered to the injection site and, in the case of the [redacted] the needle to be retracted.

Table 3: Injection Cycle Time

	Specification	[redacted] Results (sec)	STATdose Results (sec)
Min	[redacted]		
Max			
Mean	N/A	1.42	1.21
Median	N/A	1.40	1.20
Standard Deviation	N/A	0.19	0.16

All devices tested for Injection Cycle Time were within the specification of completing the injection cycle [redacted], as determined by the RLD labeling.

Button /Actuation Force

The Button/Actuation Force is defined as the force required to begin the injection cycle, by measuring the force to deactivate the safety interlock by pushing against the injection site and the force to depress the button to initiate the cycle.

Table 4: Actuation Force

	(b) (4) Results All Conditions(N)	STATdose Results (N)
Min		(b) (4)
Max		
Mean	26.98	14.83
Median	26.42	14.59
Standard Deviation	2.19	2.87

Needle Protrusion

The Needle Protrusion Depth is defined as the distance the needle tip protrudes beyond the front face of the device during the injection cycle as measured by a depth gauge.

Table 5: Needle Protrusion Depth

	(b) (4) Result (mm)	STATdose Result (mm)
Min		(b) (4)
Max		
Mean	6.24	6.24
Median	6.23	6.34

Spring Rate

The delivery spring from the (b) (4) and of the STATdose was tested on a tensometer to assess the forces exerted by the springs during their use within the respective devices. The spring rate is the average force over the displacement.

Needle Gauge

The proposed device has a (b) (4) gauge needle. Based on information submitted to ANDA 78319 in 2007, the Imitrex device has a 26 gauge needle[5].

Reviewer's Comments:

1. The firm is requested to perform comparative in vitro testing on 1) drug volume delivered, 2) injection time, and 3) force to fire on the test bio-lot compared to the RLD lot to demonstrate comparative performance characteristics and functionality testing of the test and the reference drug products. The firm should provide

[5] DARRTS: ANDA 090495. Clinical Consult. By Dr. Nancy Chang. Dated 12/14/2011. http://darrts fda.gov:9602/darrts/viewCommunication.do?fromPage=appHistoryDirect&communicationId=3058355&fromHistoryPage=true&appPk=137316

individual data for the in vitro tests to demonstrate comparable performance between the test and RLD device components. The firm should submit complete electronic EXCEL spreadsheet of individual data, mean, and %CV for these data on the test product versus Imitrex® STATDOSE Injectable. In addition, the firm should provide specifications such as breakloose force and extrusion force.

2. It is known that differences in injection technique and site of injection can affect the pharmacokinetics of sumatriptan. The small differences in performance and specifications that are present (e.g. needle gauge, injection cycle time, force to displacement distance profile) have the theoretical potential to affect PK. Therefore, the DB II recommends that the firm conducts a single-dose two-way crossover fasting bioequivalence study in healthy volunteers **where the subjects inject themselves using the device.**

3. Considering the warning – among others - on RLD, “the fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of cardiac artery disease (CAD), and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug”, the DB II recommends adequate safety monitoring be in place during the BE study. The firm may submit a protocol for the BE study to the DB II.

5 ANDA HISTORY

ANDAs: 79-123 (Bedford Labs)
78-067 (Sandoz)
77-907 (Teva)
78-318 (Teva)
78-593 (Wockhardt)
(b) (4)
90-495 (Dr. Reddy's)
90-641 (Sagent Strides)
(b) (4)
79-240 (Abraxis)
78-319 (Teva)
(b) (4)
77-332 (Par)
90-314 (Sagent Strides)
77-871 (Parkedale)
79-242 (Abraxis)
90-385 (Sun)
(b) (4)

Protocols: None

Controls: None

6 CONSULT REVIEWS

Division of Chemistry II review

http://darrts.fda.gov:9602/darrts/viewCommunication.do?fromPage=appHistoryDirect&communicationId=2735414&fromHistoryPage=true&appPk=137316

Division of Clinical Pharmacology review

http://darrts.fda.gov:9602/darrts/viewCommunication.do?fromPage=appHistoryDirect&communicationId=3058355&fromHistoryPage=true&appPk=137316

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 090495

APPLICANT: Dr. Reddy's Laboratories, Inc.

DRUG PRODUCT: Sumatriptan Succinate Injection, (Auto Injector), EQ 6 mg base/0.5 mL

The Division of Bioequivalence II (DB II) has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please perform comparative in vitro testing on 1) drug volume delivered, 2) injection time, and 3) force to fire on the test bio-lot compared to the RLD lot to demonstrate comparative performance characteristics and functionality testing of the test and the reference drug products. Please include the following information in your submission: 1) individual data for the in vitro tests to demonstrate comparable performance between the test and RLD device components; 2) complete electronic EXCEL spreadsheet of individual data, mean, and %CV for these data on the test product versus Imitrex® STATDOSE Injectable. Finally, please provide specifications such as breakloose force and extrusion force.

2. It is known that differences in injection technique and site of injection can affect the pharmacokinetics of sumatriptan. The small differences in performance and specifications that are present (e.g. needle gauge, injection cycle time, force to displacement distance profile) have the theoretical potential to affect PK. Therefore, the DB II recommends that you conduct a single-dose two-way crossover fasting bioequivalence study in healthy volunteers **where the subjects inject themselves using the device.**

3. Considering the warning – among others - on RLD, "the fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of cardiac artery disease (CAD), and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug", the DB II recommends

adequate safety monitoring be in place during the BE study. You may submit a protocol for the BE study to the DB II.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

7 OUTCOME PAGE

COMPLETED ASSIGNMENT FOR 090495 ID: 15762

Back to Main Menu

Reviewer: Lee, Christina **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Review

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
15762	4/28/2008	Other	Waiver Injectable	1	1
15762	12/14/2011	Other	Clinical Consult review	1	1
				Bean Total:	2

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Injectable Waiver(s)	
Strength 1 (DIW)	1
Clinical consult review	1
Injectable/Waiver Total	*2*

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/s/

CHRISTINA H LEE
01/06/2012

MOHEB H MAKARY
01/06/2012

BARBARA M DAVIT
01/11/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-495

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review

June 15, 2011

ANDA: 090495

Drug Product Name
Proprietary: N/A
Non-proprietary: Sumatriptan Succinate Injection
Drug Product Classification: N/A
Review Number: #3

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
May 26, 2011	May 26, 2011	N/A	May 31, 2011

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
April 28, 2008	1	Jan 30, 2009
Oct 5, 2009	2	Jan 12, 2010
Dec 2, 2009	2	Jan 12, 2010
Dec 21, 2009	2	Jan 12, 2010

Applicant/Sponsor
Name: Dr. Reddy's Laboratories, Inc.
Address: 3600 Arco Corporate Drive, Suite 310, Charlotte, NC, 28273-7104
Representative: Kumara Sekar, Ph.D., Sr. Director, Global Regulatory Affairs
Telephone: 908-203-4937

Name of Reviewer: John Arigo, Ph.D.

Conclusion: The submission **is recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Gratuitous Amendment

2. SUBMISSION PROVIDES FOR: Proposing a new manufacturing facility

3. MANUFACTURING SITE (new):
Gland Pharma Limited
Survey No.: 143 – 148, 150 & 151
Near Gandimaisamma Cross Roads
D.P. Pally, Quthubullapur Mandal
Ranga Reddy District
Hyderabad – 500 043

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Pre-filled 1 ml syringes, 6 mg (base)/0.5 ml. Subcutaneously administered. Single Dose.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: for the acute treatment of migraine and headache episodes.

B. SUPPORTING/RELATED DOCUMENTS:

91-316a1.doc, dated May 22, 2009 and 91-316.doc, dated Aug 21, 2009 by J. Arigo for (b) (4) (b) (4)

(b) (4) a1.doc by H. Ngai, dated 1/21/2011 for more recent (b) (4) validation data for the (b) (4).

C. REMARKS: electronic CTD. This ANDA was micro recommended in the 1/12/2010 review named 090495a1.doc.

filename: 090495a2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –

(b) (4)

(b) (4)

B. Brief Description of Microbiology Deficiencies – None identified

C. Assessment of Risk Due to Microbiology Deficiencies –

No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

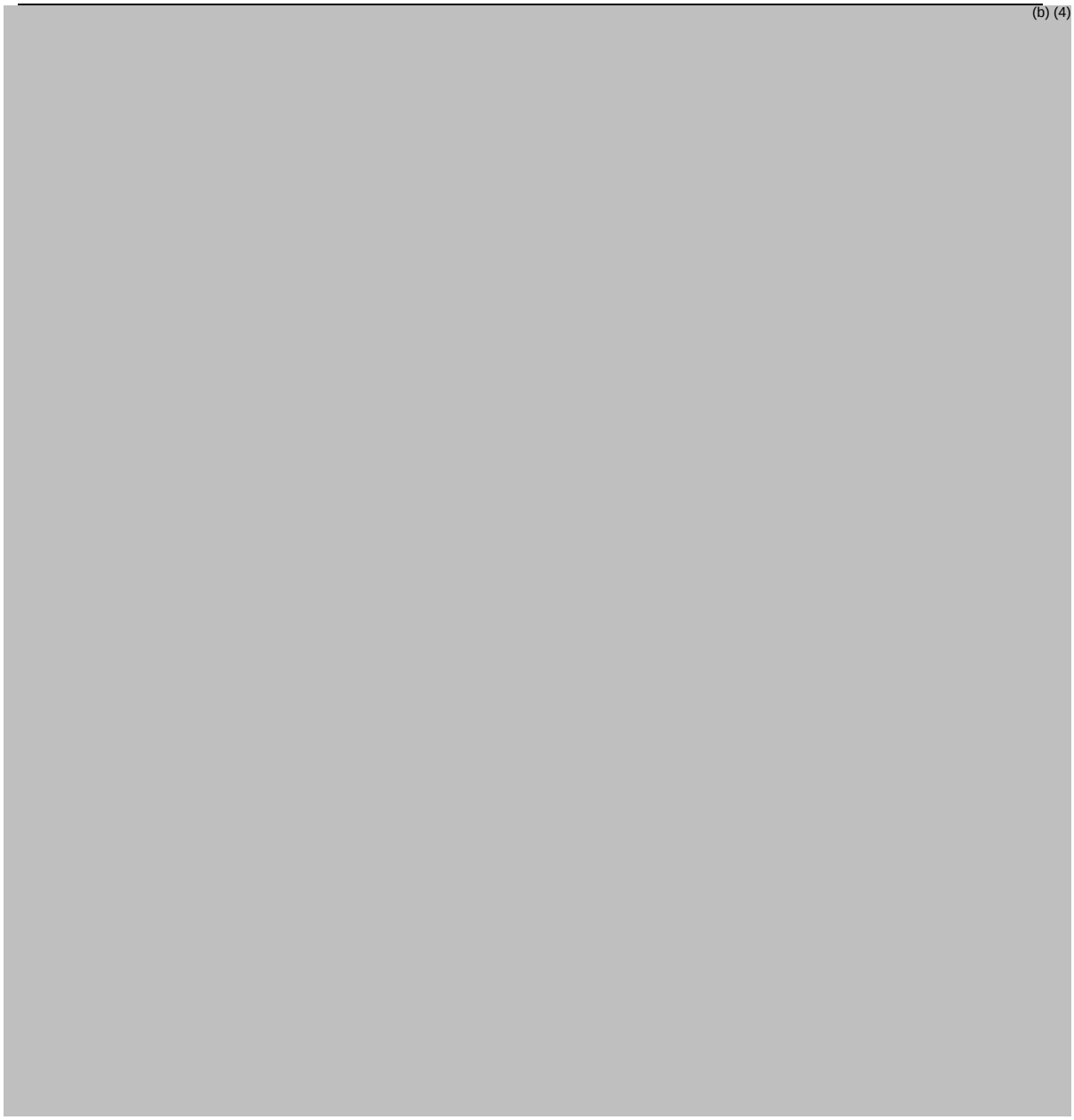
Microbiologist / John Arigo, Ph.D.
Microbiology Team Leader/ CDR Paul Dexter, M.S.

C. CC Block

cc: Field Copy

Following this page, 7 Pages Withheld in Full as (b)(4)

(b) (4)



Acceptable

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

No change in the labeling.

Acceptable

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

/s/

JOHN T ARIGO
06/29/2011

KUN SHEN
07/01/2011

PAUL L DEXTER
07/13/2011

Product Quality Microbiology Review

Jan 12, 2010

ANDA: 090495

Drug Product Name
Proprietary: N/A
Non-proprietary: Sumatriptan Succinate Injection
Drug Product Classification: N/A
Review Number: #2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
October 5, 2009	October 5, 2009	n/a	October 5, 2009
Dec 2, 2009	Dec 2, 2009	n/a	Dec 2, 2009
Dec 21, 2009	Dec 21, 2009	n/a	Dec 29, 2009

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
April 28, 2008	1	January 30, 2009

Applicant/Sponsor
Name: Dr. Reddy's Laboratories, Inc.
Address: 3600 Arco Corporate Drive, Suite 310, Charlotte, NC, 28273-7104
Representative: Kumara Sekar, Ph.D., Sr. Director, Global Regulatory Affairs
Telephone: 908-203-4937

Name of Reviewer: John Arigo, Ph.D.

Conclusion: The submission **is recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. **1.** **TYPE OF SUBMISSION:** ANDA amendment and telephone amendment.

2. **SUBMISSION PROVIDES FOR:** Response to Agency's deficiency letter

3. **MANUFACTURING SITE:**

(b) (4)

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Pre-filled 1 ml syringes, 6 mg (base)/0.5 ml. Subcutaneously administered. Single Dose.

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** for the acute treatment of migraine and headache episodes.

B. **SUPPORTING/RELATED DOCUMENTS:**

090495MicroTcon12-08-09.doc

C. **REMARKS:** e-CTD. A telephone conference was held on 12/08/09 with Jaya Ayyagari regarding the (b) (4) data.

This review was originally turned in for secondary review on October 27, 2009. The date was changed to January 12, 2010 since an amendment was filed after the first secondary review.

filename: 090495a1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable –

N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –

The drug product is (b) (4) (b) (4). The product is filled into 1ml syringes.

B. Brief Description of Microbiology Deficiencies –

none identified.

C. Assessment of Risk Due to Microbiology Deficiencies –

No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist / John Arigo, Ph.D.
Microbiology Team Leader/ CDR Paul Dexter, M.S.

C. CC Block

cc: Field Copy

Following this page, 10 Pages Withheld in Full as (b)(4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90495	ORIG-1	DR REDDYS LABORATORIES INC	SUMATRIPTAN SUCCINATE

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/s/

JOHN T ARIGO
01/20/2010

KUN SHEN
01/25/2010

NEAL J SWEENEY
05/04/2010

PAUL L DEXTER
05/05/2010

Product Quality Microbiology Review

January 30, 2009

ANDA: 90-495

Drug Product Name
Proprietary: N/A
Non-proprietary: Sumatriptan Succinate Injection
Drug Product Classification: N/A
Review Number: #1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
April 28, 2008	April 30, 2008	n/a	January 22, 2009

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
n/a		

Applicant/Sponsor
Name: Dr. Reddy's Laboratories, Inc.
Address: 3600 Arco Corporate Drive, Suite 310, Charlotte, NC, 28273-7104
Representative: Kumara Sekar, Ph.D., Sr. Director, Global Regulatory Affairs
Telephone: 704-496-6065

Name of Reviewer: John Arigo, Ph.D.

Conclusion: The submission **is not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original ANDA

2. SUBMISSION PROVIDES FOR: Initial marketing of sterile drug product

3. MANUFACTURING SITE:

(b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Pre-filled 1 ml syringes, 6 mg (base)/0.5 ml. Subcutaneously administered. Single Dose.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: for the acute treatment of migraine and headache episodes.

B. SUPPORTING/RELATED DOCUMENTS:

DMF review by Marla Stevens-Riley ((b) (4) mic3a2.doc, dated January 18, 2008) (b) (4) .doc, dated May 29, 2008, by Theodore Garnett.

C. REMARKS: e-CTD

filename: 90-495.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –

The drug product is (b) (4) (b) (4). The product is filled into 1ml syringes.

B. Brief Description of Microbiology Deficiencies –

(b) (4)

C. Assessment of Risk Due to Microbiology Deficiencies –

The safety risk associated with the microbiology deficiencies is considered low.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist / John Arigo, Ph.D.
Microbiology Team Leader/ LCDR Paul Dexter, M.S.

C. CC Block

cc: Field Copy

Following this page, 15 Pages Withheld in Full as (b)(4)

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 90-495 APPLICANT: Dr. Reddy's Laboratories

DRUG PRODUCT: Sumatriptan Succinate Injection

A. Microbiology Deficiencies:

1. (b) (4)

2.

3.

4. (b) (4)

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

1. (b) (4)

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

LCDR Paul Dexter, M.S.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

John T Arigo
2/23/2009 07:57:30 AM
MICROBIOLOGIST

Kun Shen
2/23/2009 01:21:06 PM
MICROBIOLOGIST

checked for correct file and linking

Neal Sweeney
2/25/2009 03:29:07 PM
MICROBIOLOGIST

Paul Dexter
2/26/2009 08:07:40 AM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-495

OTHER REVIEWS

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: April 6, 2012

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID

THROUGH: Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID

CC: Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID

TO: Andrew Langowski,CMC Reviewer, CDER/OGD/Division of Chemistry II

SUBJECT: **ANDA 90495**
Applicant: Dr. Reddy's Laboratories, Ltd
Device Constituent: (b) (4) autoinjector
Drug Constituent: Sumatriptan Succinate Injection
Intended Treatment: Migraine

QuynhNhu Nguyen, Combination Products Human Factors Specialist — 4/9/2012 Date

Ron Kaye, Human Factors and Device Use-Safety Team Leader — 4/9/2012 Date

Review Memo – Table of Content

CDRH Human Factors Review

Overview and Summary

The Center for Drugs Evaluation and Research (CDER), Office of Pharmaceutical Science, Division of Chemistry has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding ANDA 90495. The device constituent of this combination product references the (b) (4) autoinjector. This review provides CDRH's review and recommendations on the Human Factors related information contained in the ANDA.

The Applicant has iteratively modified the design of the device and its instructions for use as a result of prior HF testing, and conducted a re-validation study. The reviewer finds that the results of the revalidation study acceptable, and has no further questions.

Review Materials

MAF # (b) (4)

Section 5 – Executive Summary
Section 12 – Human Factors Study

CDRH Human Factors Review

Combination Product Device Information

Submission Number: ANDA 90495
Applicant: Dr. Reddy's Labs, Inc
Drug Constituent: Sumatriptan succinate, subcutaneous injection
Device Constituent: (b) (4) autoinjector
Intended treatment: migraine

CDRH Human Factors Involvement History

- 7-FEB-2012: CDRH HF was consulted to provide a review on the MAF # (b) (4) for Human Factors testing report

Review of Human Factors Related Information

Device Description

The (b) (4) autoinjector is a single use, automatic , disposable, and hidden-needle autoinjector. It is indicated for providing self-administered subcutaneous injection of fixed doses of FDA approved drug products with aqueous liquid formulations, which are presented in standard 1ml long glass (b) (4) pre-filled syringe (PFS) with staked needles.

The autoinjector contains the following sub-systems:

(b) (4)

(b) (4)

The autoinjector is intended for home use by patients and may be used by Healthcare Professionals (HCP) or caregivers.

Human Factors Testing Information

(b) (4)

As a result, (b) (4) reported that they made modifications to the device such that it now requires less actuation force, and to the written instructional materials. Additionally, video instructions and demonstrations were developed. Consequently, a re-validation study was conducted, and the test report was dated 10-Aug-2011.

This re-validation study utilized the same test protocol, (b) (4) with 48 participants (16 self-injectors, 16 home caregivers, and 16 Healthcare professionals (HCP)). The participants were asked to complete four test trials:

- Trial 1: participants were provided with a copy of the instructions and a dummy device. Participants were requested to read the IFU and perform an injector.
- Trial 2/3: Participants were provided a copy of the IFU and either a video or a demonstration by the study facilitator. Trial 2 and 3 were counterbalanced between participants with 50% receiving the video in Trial 2, followed by a demonstration in Trial 3 and 50% receiving a demonstration in Trial 2, followed by a video in Trial 3.

The results showed that 8 of the 48 participants failed to complete an injection on their first Trial:

- 3 participants (2 self-injectors and 1 HCP) completed all tasks but did not apply sufficient force when pushing the device against the injection site to release the safety mechanism and the allow the device to actuate.
- 3 participants (1 self-injector and 1 HCP and 1 caregiver) failed to press the blue button believing the device would actuate by pushing the injection site alone.
- 2 participants (2 HCP or Licensed Vocational Nurses) completed all tasks but released the pressure they were applying to the injection site when they pressed the button. They failed complete task 4 and 5 concurrently.

There were no safety concerns. However, these failures resulted in incomplete injections. Subsequent trials, Trial 2 and 3, showed improvement in the performance results. Of the 48 participants, 48 participants were able to complete all task successfully in Trial 3.

CDRH HF Review Recommendations

The Applicant has iteratively modified the design of the device and its instructions for use as a result of prior HF testing, and conducted a re-validation study. The reviewer finds that the results of the revalidation study acceptable, and has no further questions.

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/s/

TRANG Q TRAN
04/10/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: February 9, 2012
From: Jacqueline Ryan, Combination Products Team Leader WO66, RM 1257
General Hospital Devices Branch, DAGID, ODE, CDRH

To: Simon Eng, Director Regulatory CDER /OPS/PGD/DLPS/RSB
Subject: CDRH Consult, ANDA 90495 Auto injector to deliver sumatriptan

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH, regarding IND 90495. The device constituent of this combination product consists of a disposable single use autoinjector with a (b) (4) 1mL long syringe with staked (b) (4) needle to deliver sumatriptan.

2. Device Description

The (b) (4) auto injector is a fixed-dose single use disposable device indicated for assisting the self-administration of subcutaneous injections of fixed doses of DA-approved drug products with non-viscous (aqueous) liquid formulations which are presented in standard 1mL long (b) (4) prefilled syringes with staked needles.
The (b) (4) device operates as follows:

The pre-filled syringe (PFS) is contained within the device with a rigid needle shield (RNS) protecting the needle. (b) (4)
The device has a cap at one end. When the cap is in place the device can not be actuated.
The user removes the cap by pulling axially. This also removes the RNS and once this has been done the device may be actuated.
The user pushes the open end of the device against the injection site. (b) (4) (b) (4)
The button on the end of the device is pushed to actuate the device. (b) (4)
When the device is actuated, (b) (4) (b) (4) the needle extends from the open end of the device and into the injection site. When the specified injection depth is reached, (b) (4) (b) (4) the drug is delivered through the needle. (b) (4)

The device is supplied to the final assembler (b) (4)

(b) (4)

Engineering drawings are included at the conclusion of this review.

3. **Documents Reviewed**

MAF (b) (4)
ISO 11608-1:2001 Pen injectors for medical use- Part 1: Pen injectors-Requirements and test methods
ISO 10993-1:2009, Biological evaluation of medical devices- part 1: Evaluation and testing within a risk management process.

4. **CDRH Review and Comments**

CDRH's Review of the device constituent for this Combination Product consisted of an assessment of Device Performance, and Biocompatibility,

Device Performance

(b) (4) completed device performance testing according to relevant sections of ISO 11608-1:2000, Pen injectors for medical use- Requirements and test methods.
A list of specific bench tests performed is as follows:

1. Cap removal force
2. Dose delivery
3. Activation force
4. Injection time
5. Needle protrusion beyond front face of device
6. Needle retraction depth into device following injection
7. Visible and audible signals of device operation
8. Removal of rigid needle shield (RNS) from drug syringe
9. Free fall followed by performance testing
10. Environmental preconditioning (including dry heat, cold and cyclical) and storage conditions followed by performance testing
11. Visual inspection
12. Safety mechanism check

Shelf Life

(b) (4)

(b) (4)

Device Packaging and Labeling

(b) (4)

Biocompatibility

(b) (4)

5. **CDRH Recommendation**

The following deficiencies should be conveyed to the master file holder:

Device Performance

(b) (4) Please provide this additional performance testing so that we may assure that the device is safe and effective for its intended users.

Device Biocompatibility

(b) (4)

(b) (4) Please explain why your approach to

biocompatibility testing is adequate and is consistent with ISO 10993-1:2009, Biological evaluation of medical devices- part 1: Evaluation and testing within a risk management process.

If you have any questions, please contact Jacqueline Ryan at 301-796-9599.

Sincerely,

Jacqueline Ryan
Combination Products Team Leader

Concurred By:

Richard Chapman
Branch Chief, DAGID/ GHDB

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/s/

SIMON S ENG
02/09/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 90-495

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ROUTING SHEET

☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP

Division: II	Team: 23	PM: Sean Belouin

Electronic ANDA: Yes ☒ No ☐

ANDA #: 090495
Firm Name: Dr Reddy's Laboratories Limited
ANDA Name: Sumatriptan Injection USP, 0.6 mg/0.5 mL (Prefill Syringe)
RLD Name: Imitrex® Injection

Electronic AP Routing Summary Located:
V:\Chemistry Division II\Team 23\Electronic AP Summary

AP/TA Letter Located:
V:\Chemistry Division II\Team 23\APPROVAL LTRS and cGMP LETTERs

Project Manager Evaluation: **Date: 1/24/14 Initials:** SJB

☐ Previously reviewed and tentatively approved --- Date N/A
☐ Previously reviewed and CGMP Complete Response issued -- Date N/A

Original Rec'd date 4/30/08	Date of Application 4/28/08	Date Acceptable for Filing 7/15/08
Patent Certification (type) P III	Date Patent/Excl. expires N/A	Citizens' Petition/Legal Case? Yes☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒ **DMF#:** _____ (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☐ No ☒ Comment: N/A Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☒ Date: N/A	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

GDUFA User Fee Obligation Status: ☒ Met ☐ Unmet**:** ☐ Facility Fee not paid, ☐ Backlog fee not paid
EER Status: ☐ Pending ☐☐ ☒ Acceptable ☐ OAI *EES Date Acceptable: 2/12/13* ☐ Warning Letter Issued; Date: N/A
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☒ Comment:
Date of Acceptable Quality (Chemistry) 1/14/14 Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 12/3/13 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 11/7/13 Attached labeling to Letter: Yes ☐ No ☒ Comment:
Date of Acceptable Sterility Assurance (Micro) 7/13/11

Methods Val. Samples Pending: Yes ☐ No ☒**;** Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☒ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☒ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: 1/24/14 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: N/A

☒ Division

☒ Bob West / Peter Rickman

☐ Kathleen Uhl

☒Filed AP Routing Summary in DARRTs	☒Notified Firm and Faxed Copy of Approval Letter	☒ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 1/27/2014**

Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD = Imitrex STATdose NDA# 20-080 Date Checked N/A 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) ☐CGMP ☐ OTHER:	
Comments:ANDA submitted on 4/30/2008, BOS=Imitrex Injection NDA 20-080, PIII to '845 exp. 2/6/2009 with ped exclusivity. ANDA ack for filing on 4/30/2008 (LO dated 7/15/2008). There are no remaining unexpired patents or exclusivities which protect the RLD. It is noted that this ANDA references the original Imitex Injection approved in 1992. It does not reference either of the Imitrex Statdose presentations that were approved in 12/1996 or 2/2006. ANDA is eligible for immediate Full Approval.	

2. ***Labeling Endorsement***

Reviewer, Adolph E. Vezza: Labeling Team Leader, Koung U. Lee:

Date 1/24/14 Date 1/27/14

REMS required? REMS acceptable?

☐Yes ☒No ☐Yes ☐No ☒n/a

Comments:

From: Lee, Koung U
Sent: Monday, January 27, 2014 1:27 PM
To: Vezza, Adolph E; Belouin, Sean
Subject: RE: Dr. Reddy's ANDA 090495 (Sumatriptan Injection USP, 0.6 mg/0.5 mL (Prefilled Syringe)) LABELING ENDORSEMENT REQUEST **FULL APPROVAL**

I concur. Thanks.

Koung

From: Vezza, Adolph E
Sent: Friday, January 24, 2014 12:16 PM
To: Belouin, Sean; Lee, Koung U
Subject: FW: Dr. Reddy's ANDA 090495 (Sumatriptan Injection USP, 0.6 mg/0.5 mL (Prefilled Syringe)) LABELING ENDORSEMENT REQUEST **FULL APPROVAL**

Labeling still current – letter good to go -- Adolph

From: Belouin, Sean
Sent: Friday, January 24, 2014 11:55 AM

To: Vezza, Adolph E; Lee, Koung U
Subject: Dr. Reddy's ANDA 090495 (Sumatriptan Injection USP, 0.6 mg/0.5 mL (Prefilled Syringe)) LABELING ENDORSEMENT REQUEST **FULL APPROVAL**

Good Morning Adolph and Koung,

Please endorse.

Thank you!

-Sean

3. ***Paragraph IV Evaluation*** **PIV's Only**

David Read **Date 1/29/14**
OGD Regulatory Counsel **Initials rlw/for**

Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments: N/A. There are no patents or exclusivity currently listed in the "Orange Book" for this drug product.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 1/28/2014**

Chemistry Div. **II (Smith)** **InitialsGJS**
Comments:CMC Acceptable.

OGD Office Management Evaluation

5. Peter Rickman **Date 1/29/14**
Director, DLPS **Initials rlw/for**

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 ☐
Date PETS checked for first generic drug _____

Comments: Bioequivalence studies (single-dose, fasting, two-way crossover design) in healthy volunteers with the subjects injecting themselves found acceptable. In addition, the formulation of the drug product is "Q&Q" to that of the RLD. Office-level bio endorsed 12/3/13.

Clinical safety issues adequately addressed - Review dated 12/23/13 by OGD Clinical Team.

Human Factors Studies found acceptable via consult to CDRH 4/10/12.

Microbiology/Sterility Assurance found acceptable for approval (Microbiology Review #3) 7/13/11.

Final-printed labeling (FPL) found acceptable for approval 11/7/13, as endorsed 1/27/14. No REMS is required.

CMC found acceptable for approval (Chemistry Review #5) 1/14/14.

6. Robert L. West **Date 1/29/14**
Deputy Director, OGD **Initials RLWest**

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 ☐
Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 2/12/13 (Verified 1/29/14). No "OAI" Alerts noted.

There are no patents or exclusivity currently listed in the "Orange Book" for this drug product.

This is not a "first-generic" ANDA approval. Sun Pharma Global's ANDA 90-358 for this drug product (Autoinjector System) was approved on 6/21/11.

This ANDA is recommended for approval.

7. ***OGD Director Evaluation***
Kathleen Uhl

Comments: RLWest for Kathleen Uhl, M.D., Acting Director, Office of Generic Drugs 1/29/14.
First Generic Approval ☐
PD or Clinical for BE ☐
Special Scientific or Reg. Issue ☐
Press Release Acceptable ☐

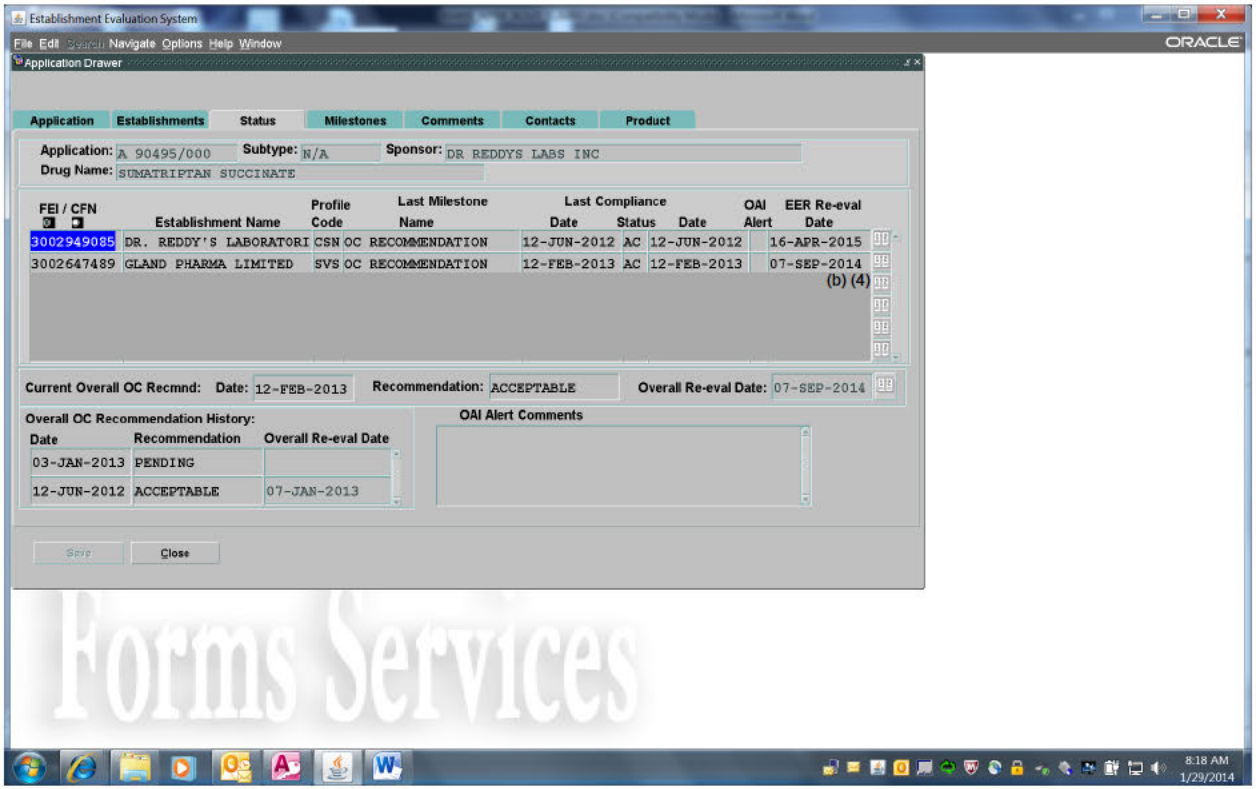
Comments:

8. Project Manager **Date 1/29/14**
Initials SJB

Comments:

Check Communication and Routing Summary into DARRTS

EES DATA:


Establishment Evaluation System
File Edit Search Navigate Options Help Window
ORACLE
Application Drawer
Application
Establishments
Status
Milestones
Comments
Contacts
Product
Application: A 90495/000
Subtype: N/A
Sponsor: DR REDDYS LABS INC
Drug Name: SUMATRIPTAN SUCCINATE
FEI / CFN
Establishment Name
Profile Code
Last Milestone Name
Last Compliance Date
Status
Date
OAI Alert
EER Re-eval Date
3002949085 DR. REDDY'S LABORATORI CSN OC RECOMMENDATION 12-JUN-2012 AC 12-JUN-2012 16-APR-2015
3002647489 GLAND PHARMA LIMITED SVS OC RECOMMENDATION 12-FEB-2013 AC 12-FEB-2013 07-SEP-2014
(b) (4)
Current Overall OC Recmnd: Date: 12-FEB-2013
Recommendation: ACCEPTABLE
Overall Re-eval Date: 07-SEP-2014
Overall OC Recommendation History:
Date
Recommendation
Overall Re-eval Date
03-JAN-2013 PENDING
12-JUN-2012 ACCEPTABLE 07-JAN-2013
OAI Alert Comments
Save
Close
Forms Services
8:18 AM
1/29/2014

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 020080 Product 003 in the OB_Rx list.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

Exclusivity Data

There is no unexpired exclusivity for this product.

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/s/

SEAN J BELOUIN
01/29/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2013-0871	
TO *(Division/Office)* Division of Clinical Review – Nitin Patel			FROM: Sukhamaya Bain	
DATE: 11/7/2013	IND NO.	ANDA NO. 090495	TYPE OF DOCUMENT Amendment – SD_23	DATE OF DOCUMENT 10/24/2013,
NAME OF DRUG Sumatriptan Injection USP		PRIORITY CONSIDERATION 15 days	CLASSIFICATION OF DRUG Anti-Migraine	DESIRED COMPLETION DATE 11/22/2013

NAME OF FIRM Dr. Reddy's Laboratories Ltd.

REASON FOR REQUEST

I. GENERAL

- Γ NEW PROTOCOL
- Γ PROGRESS REPORT
- Γ NEW CORRESPONDENCE
- Γ DRUG ADVERTISING
- Γ ADVERSE REACTION REPORT
- Γ MANUFACTURING CHANGE/ADDITION
- Γ MEETING PLANNED BY _____
- Γ PRE NDA MEETING
- Γ END OF PHASE II MEETING
- Γ RESUBMISSION
- Γ SAFETY/EFFICACY
- Γ PAPER NDA
- Γ CONTROL SUPPLEMENT
- Γ RESPONSE TO DEFICIENCY LETTER
- Γ FINAL PRINTED LABELING
- Γ LABELING REVISION
- Γ ORIGINAL NEW CORRESPONDENCE
- Γ FORMULATIVE REVIEW
- X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
Γ TYPE A OR B NDA REVIEW Γ END QF PHASE II MEETING Γ CONTROLLED STUDI ES Γ PROTOCOL REVIEW Γ OTHER	Γ CHEMISTRY Γ PHARMACOLOGY Γ BIOPHARMACEUTICS Γ OTHER

III.BIOPHARMACEUTICS

- ☐DISSOLUTION
- ☐PROTOCOL-- BIOPHARMACEUTICS
- ☐IN--VIVO WAIVER REQUEST
- ☐DEFICIENCY LETTER RESPONSE
- ☐BIOAVAILABILITY STUDIES
- ☐PHASE IV STUDIES

IV.DRUG EXPERIENCE

- ☐PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
- ☐COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐CLINICAL ☐PRECLINICAL

COMMENTS

Please see the quality amendment (SD-23) dated 24-OCT-2013, submitted in response to DCR comments dated 09-JAN-2013 (DARRTS), which were incorporated in the CR letter dated 03-SEP-2013 (DARRTS).

Please provide an electronic copy of the review to the requestor by email and cc Steven Yang, HFD-617 (Steven.Yang@FDA.HHS.gov) when it is being checked into DARRTS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* ☐MAIL ☐HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

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/s/

SUKHAMAYA BAIN
11/13/2013

STEVEN W YANG
11/13/2013

COMPLETE RESPONSE

ANDA 090495

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: Dr. Reddy's Laboratories, Inc. (U.S. Agent for: Dr. Reddy's Laboratories Limited)

TEL: 908-203-4951

FAX: 908-203-4980

ATTN: Lee Banks

FDA CONTACT PHONE: (240) 276-8566

FROM: Sean Belouin

Dear Sir:

This facsimile is in reference to your abbreviated new drug application, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

We have completed the review and have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (____ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 090495

COMPLETE RESPONSE

Dr. Reddy's Laboratories, Inc.
U.S. Agent for: Dr. Reddy's Laboratories Limited
Attention: Lee Banks
Vice President, Intellectual Property and Regulatory Affairs
200 Somerset Corporate Boulevard 7th Floor
Birdgewater, NJ 08807

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated April 28, 2008, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Sumatriptan Injection USP, 0.6 mg/0.5 mL (Prefilled Syringe).

Reference is also made to your amendments dated April 13, August 31, October 5, December 2, December 21, 2009; January 21, March 12, 2010; May 26, September 8, September 21, October 18, October 21, December 15, 2011; May 18, 2012; April 3, and April 30, 2013.

PRODUCT QUALITY

The following comments are from the OGD Division of Clinical Review:

Regarding the safety locking mechanism and instructions for using the safety mechanism:

- It is acceptable that the safety remains disengaged if the tip is pressed and then released without initiating an injection. This allows a user to change injection site if, for example, the first site does not feel to have enough fat. The device could be repositioned and the injection given.

- Since the safety remains disengaged if the device is pressed and then released without initiating an injection, the current wording, stating that the device (b) (4) (b) (4) is incorrect and potentially misleading. A user should be warned that **as long as the blue circle is visible in the medicine window, the safety catch is in the off position; the pen could fire unintentionally if the blue button is pressed by accident**.

- (b) (4)

(b) (4)

The following recommendations pertain to the instructions for use:

- Rather than running together in normal text, the warning (b) (4) and the second warning to keep out of the reach of children, should be bulleted, and/or separated, and/or bolded for clarity:
    - (b) (4)
    - Keep the Sumatriptan Succinate Auto-Injector System out of the reach of children.
- The figure in Step (b) (4) of the instructions for use attempts to demonstrate the plunger rod that can be seen through the window after injection, or in a spent device. Inspection of the viewing window prior to injection should ensure that there is clear liquid present, and also ensure that the device is not spent.
    - The "after injection" figure currently in Step (b) (4) should be moved to "before injection" Step 5 in order to show what should and what should not be visible through the window of an unspent device.
    - In both "before injection" and "after injection" figures, the important features are not clearly visible. Even with the arrow pointing to the plunger rod, it is difficult to see the plunger in the figure, as it is in the device itself. This reviewer was only able to see the plunger by holding the pen up to the light.
    - Since it is important to be certain that the liquid is clear, and that the plunger is not present, Step 5 should instruct users that if they have difficulty seeing what is in the window, they may hold the pen up to the light.
- Although needle position cannot be used to differentiate between a spent injector and one that has not been injected, you should provide information so that users can tell the difference. For example, users could be informed that if the plunger rod can be seen through the window, the device is spent and cannot be used again.
- The current instruction in Step (b) (4) does not adequately emphasize that the entire dosage delivery system is intended to be a disposable device and disposed of in its entirety. The instruction should include the word "whole" or "entire" as in, "After you have used the pen, throw away the entire pen in a special container"

- The inconsistencies between the 2 "final" versions of the IFU raise some concern as to which device this sponsor is intending to be reviewed.

    - The Sponsor should clarify whether the to-be-marketed presentation will have (b) (4)

    - The final package insert and instructions for use should be consistent, and show only images identical to the to-be-marketed device.

    - The Sponsor should clarify the color of images and text for the final labeling. The (b) (4) background of the Annotated IFU makes the text difficult to read.

- In your most recent submissions, you have not defined all abbreviations. For example, there are multiple references to the PIL but no definition for this abbreviation. This is especially important since PIL closely resembles the commonly used abbreviation PI that has been used to mean prescribing information, package insert, or patient information. The term PIL does not actually appear in your labeling, but in future communications with the Agency you should clearly define all abbreviations.

BIOEQUIVALENCE

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.

The pre-study method validation is inadequate with the following deficiency:

1. The long-term storage stability (LTSS) data of 70 days @ -20ºC and -70 ºC is insufficient. Please provide sufficient LTSS to cover the entire storage length of the BE study samples (from the time of the first blood sample drawn to the time of the last plasma sample analyzed) up to 114 days @ -20ºC and -70 ºC.

The Fasting BE study is incomplete with the following reasons:

2. Subject Nos. 1, 8 and 34 revealed no clinical abnormalities. Excluding these subjects from the statistical analysis of the study is not justified. After including all subjects in the study, the confidence intervals for AUCt, AUCi and Cmax do not fall within the acceptable 80-125% range. Therefore, the study is unacceptable.

3. The DB II does not accept results of statistical outlier tests to justify dropping subjects from a BE study. To re-evaluate the pharmacokinetic performance of subject Nos. 1, 8 and 34, you may re-dose these three subjects along with several other subjects (control

group) chosen at random from the same study. Additionally, the study procedures and study drug lot numbers should be identical to Study # 71912 (original study). Alternatively, you may conduct a new fasting bioequivalence study.

MICROBIOLOGY

The Division of Microbiology has completed its review and has no further questions at this time.

LABELING

Labeling Deficiencies determined on 8-8-13 based on your submission dated 4-30-13:

AUTOINJECTOR CARTON

1. Include a net quantity statement.

2. 2 Auto-injectors, each with a 0.5 mL prefilled syringe containing 6 mg of sumatriptan injection

INSERT

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

    a. TITLE - "SUMATRIPTAN Injection, USP"

    b. CONTRAINDICATIONS – Eighth bullet

    "Concurrent or recent …"

    c. Place a solid horizontal line at the end of this section to separate it from the "FULL PRESCRIBING INFORMATION – CONTENTS*" section.

2. FULL PRESCRIBING INFORMATION

    a. 1 INDICATIONS AND USAGE

    Limitations of Use, second bullet – Delete the second comma.

    b. 2.2 Administration Using the Autoinjector

        i. We note that the needle penetration range for the innovator has "(5 to 6 mm)" while your labeling indicates (b) (4) Please comment.

        ii. Revise the last sentence to read as follows:

"Instruct patients on the proper use of the sumatriptan autoinjector and direct them to use …"

c. 4 CONTRAINDICATIONS

Eighth bullet – "5-hydroxytryptamine1" [subscript]

d. 5.8 Increase in Blood Pressure

Revise the title of the subsection to read as shown above.

First sentence – "5-HT1" [subscript]

e. 6.1 Clinical Trials Experience - Migraine Headache

i. First paragraph, first sentence - "U.S." rather than "US"

ii. Table 1 – The data presented in the "Neurological" row is not aligned correctly.

f. 6.2 Postmarketing Experience – First paragraph, last sentence

Delete "injection".

g. 7.4 Selective Serotonin Reuptake Inhibitors/Serotonin …

Delete the second occurrence of "SNRIs".

h. 11 DESCRIPTION – Last sentence – "injection" rather than "injections"

i. 12.1 Mechanism of Action

i. First paragraph, last sentence

A. Delete "injection".

B. Place "5-" and HT1B/1D" on the same line of text.

ii. Last paragraph, last sentence

j. 14.1 Migraine – Table 3

Please note that the data has not been entered properly under the "1-Hour Data" rows. Please correct.

k. 14.2 Cluster Headache – Table 4, footnotes

Place "(n = Number of headaches treated.)" immediately under the footnote so it appears on its own line of text.

l 16 HOW SUPPLIED/STORAGE AND HANDLING

"… each with an associated single-dose prefilled syringe which contains 6 mg of sumatriptan (as the succinate salt) and 3.5 mg of sodium chloride in 0.5 mL of solution."

m. 17.8 How to Use Sumatriptan Injection

We note that the needle penetration range for the innovator has "(5 to 6 mm)" while your labeling indicates (b) (4) Please comment.

3. PATIENT INFORMATION

a. "**What should I tell** …",

i. "**Especially tell** …" - "antidepressant medicines" [delete hyphen – add "s"]

ii. "Keep a list …" – "pharmacist" [lower case "p"]

b. "How should I take …", fifth bullet – Delete the excess space between the words "be" and "given".

c. "**What are the possible** …"

i. Delete the "●" before "Symptoms of peripheral …"

ii. serotonin syndrome

A). "…using sumatriptan injection." [delete "s"]

B). "antidepressant" [delete hyphen]

iii. "Call your healthcare …", seizures – "injection" rather than "injections" [three instances]

iv. "These are not all …" - "injection" rather than "injections"

v. Bold the last two sentences ["Call your doctor … effects. You may report …"]

d. "How should I …" – Keep sumatriptan injection and …" ["injection" rather than "injections"]

e. Place trade name disclaimers at the end of this labeling piece

INFORMATION FOR THE PATIENT

See comments under INSERT – (3) PATIENT INFORMATION

INSTRUCTIONS FOR USE

1. TITLE

Reformat the title to read as shown below:

SUMATRIPTAN INJECTION
INSTRUCTIONS FOR USE OF DISPOSABLE SUMATRIPTAN AUTOINJECTOR SYSTEM

2. See further comments from Division of CLINICAL REVIEW (under **PRODUCT QUALITY** of this letter).

Revise your labeling, as instructed above, and submit electronically.

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 or your last submitted 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

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle. The resubmission to this will be considered to represent a MINOR AMENDMENT. The designation as a **RESUBMISSION/AFTER ACTION – MINOR COMPLETE RESPONSE AMENDMENT** should appear prominently in your cover letter. In addition, please designate in bold on your cover letter each review discipline (Chemistry, Labeling, Bioequivalence, Microbiology, Clinical) you are providing responses to.
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 application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

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 dose form (FDFs) or active pharmaceutical ingredient (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.

The drug product may not be legally marketed until you have been notified in writing that this application is approved. If you have any questions, call Sean Belouin, Regulatory Project Manager, at (240) 276-8566.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

KATHLEEN UHL
09/03/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO: *(Division/Office)*
Division of Clinical Review: Nancy Chang

FROM:
Andrew Langowski Consult No: 2012-0727

DATE:	IND NO.	ANDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10/23/2012		90-495	Amendment SD 17	5/18/2012

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Sumatriptan Succinate	30 days		

NAME OF FIRM Dr. Reddy's Laboratories

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE NDA MEETING
- ☐ END OF PHASE 11 MEETING
- ☐ RESUBMISSION SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☒ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(Specify Below)* _____

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER	☐ CHEMISTRY ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ PROTOCOL-- BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS

Please see the quality amendment (SD 17) dated 5/18/2012 submitted in response to our deficiency communication issued by the Agency on 12/21/2011.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

CC: ANDA

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/s/

ANDREW J LANGOWSKI
10/23/2012

PETER CAPELLA
10/24/2012

TRANG Q TRAN
10/24/2012

BIOEQUIVALENCE AMENDMENT

ANDA 090495

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Dr. Reddy's Laboratories Limited TEL: (908) 203-4937

ATTN: Kimberly Ernst FAX: (908) 203-4980

FROM: Scott Vehovic FDA CONTACT PHONE: (240) 276-8817

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on April 28, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sumatriptan Succinate Injection, Eq. 6 mg base/0.5 mL.

Reference is also made to your amendment dated April 13, 2009 and May 18, 2012.

The Division of Bioequivalence II has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **3** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request **Bioequivalence Other**

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence II, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 090495

APPLICANT: Dr. Reddy's Laboratories, Inc.

DRUG PRODUCT: Sumatriptan Succinate Injection, (Auto Injector), EQ 6 mg base/0.5 mL

The Division of Bioequivalence II (DB II) has completed its review of your submission acknowledged on the cover sheet and the following deficiencies have been identified:

1. Please explain the apparent differences in the test outcomes with respect to the actuation force between the original data (submitted on August 31, 2009) and the data in the current amendment submission for the test product that is nearly 46% (18.52 N in the current submission vs. 26.98 N in the original submission). Yet, the data for the RLD remain unchanged.

2. As pointed out in the OGD DCR clinical consult, other differences in the test product (e.g. needle gauge, injection cycle time, force to displacement distance profile) in performance and specifications that are present have the theoretical potential to affect PK. The DB II does not agree that the information you submitted supports bioequivalence of your test product, Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL, pre-filled syringe with auto-injector, to the RLD, Imitrex® STATDOSE Injectable, EQ 6 mg base/0.5 mL, manufactured by GlaxoSmithKline. Consequently, the DB II recommends that you conduct a single-dose, two-way crossover, fasting bioequivalence study in healthy volunteers **where the subjects inject themselves** both the test and reference products using the respective device.

3. As mentioned in the deficiency letter issued on January 25, 2012, considering the warning – among others - on RLD, "the fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of cardiac artery disease (CAD), and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug", the DB II recommends adequate safety monitoring be in place during the BE study. You may submit a protocol for the BE study to the DB II.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

ETHAN M STIER on behalf of BARBARA M DAVIT
06/19/2012

For Consulting Center Use Only:

Date Received: _____
Assigned to: _____
Date Assigned: _____
Assigned by: _____

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division:
Mail Code: HF
Consulting Reviewer Name: Quynh Nhu Nguyen
Building/Room #:
Phone #:
Fax #:
Email Address:
RPM/CSO Name and Mail Code:

From (Originating Center):
Center: CDER/OPS/OGD
Division: II
Mail Code: HF 630
Requesting Reviewer Name: Andrew Langowski
Building/Room #: MPN II/E-222
Phone#:
Fax #:
Email Address: Andrew.Langowski@fda hhs.gov
RPM/CSO Name and Mail Code:
Requesting Reviewer's Concurring Supervisor's Name: Peter Capella

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 02/07/2012

Requested Completion Date: 04/07/2012

Submission/Application Number: 090495
(Not Barcode Number)

Submission Type: MAF # (b) (4)
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: ☑ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination ☐ Drug-device-biologic combination ☐ Not a combination product

Submission Receipt Date: _____

Official Submission Due Date: _____

Name of Product: Sumatriptan Succinate Injection 6 mg (base) 0.5 mg

Name of Firm: Dr. Reddy's Labs, Inc.

Intended Use: To relieve a migraine attack.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

We would like CDRH to review and comment on the Sponsor's Human Factors report.

Documents to be returned to Requesting Reviewer? ☐ Yes ☑ No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: ☐ Consultative Review ☐ Collaborative Review

(940 characters max -- use additional sheet if necessary)
Please review MAF #. (b) (4), the auto injector (b) (4) for patients to self-administer Sumatriptan Succinate Injection 6 mg (base) 0.5 mg. I also have the actual autoinjector samples in my office, please call Simon at 240-276-8529 if you need them. I also combined the form with the Chemistry Review for additional info regarding the autoinjector as well as Jackie's email comment here.
"Simon, There is a revised Human Factors report in the MAF. The sponsor had previously submitted a human factors report which was reviewed (b) (4). The Human Factors team now requires a separate consult. Please send a consult to Quynh Nhu Nguyen to review the new revised report. Quynh, there is only one paper copy of the MAF which the file room [illegible] will forward it to you as soon as I am done, Thanks, Jackie"
Thank you Quynh.

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/s/

SIMON S ENG
02/07/2012

TRANG Q TRAN
02/07/2012

BIOEQUIVALENCE AMENDMENT

ANDA 090495

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Dr. Reddy's Laboratories Limited TEL: (704) 496-6065

ATTN: Kumara Sekar FAX: (704) 496-6082

FROM: Scott Vehovic FDA CONTACT PHONE: (240) 276-8817

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on April 28, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sumatriptan Succinate Injection, Eq. 6 mg base/0.5 mL.

Reference is also made to your amendment dated April 13, 2009.

The Division of Bioequivalence II has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **3** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request **Bioequivalence Other**

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence II, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 090495

APPLICANT: Dr. Reddy's Laboratories, Inc.

DRUG PRODUCT: Sumatriptan Succinate Injection, (Auto Injector), EQ 6 mg base/0.5 mL

The Division of Bioequivalence II (DB II) has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please perform comparative in vitro testing on 1) drug volume delivered, 2) injection time, and 3) force to fire on the test bio-lot compared to the RLD lot to demonstrate comparative performance characteristics and functionality testing of the test and the reference drug products. Please include the following information in your submission: 1) individual data for the in vitro tests to demonstrate comparable performance between the test and RLD device components; 2) complete electronic EXCEL spreadsheet of individual data, mean, and %CV for these data on the test product versus Imitrex® STATDOSE Injectable. Finally, please provide specifications such as breakloose force and extrusion force.

2. It is known that differences in injection technique and site of injection can affect the pharmacokinetics of sumatriptan. The small differences in performance and specifications that are present (e.g. needle gauge, injection cycle time, force to displacement distance profile) have the theoretical potential to affect PK. Therefore, the DB II recommends that you conduct a single-dose two-way crossover fasting bioequivalence study in healthy volunteers **where the subjects inject themselves using the device.**

3. Considering the warning – among others - on RLD, "the fact that sumatriptan can cause coronary vasospasm, that some of

these events have occurred in patients with no prior cardiac disease history and with documented absence of cardiac artery disease (CAD), and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug", the DB II recommends adequate safety monitoring be in place during the BE study. You may submit a protocol for the BE study to the DB II.

Sincerely yours,

{See appended electronic signature page}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

BARBARA M DAVIT
01/24/2012

QUALITY DEFICIENCY - MINOR

ANDA 090495

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: Dr. Reddy's Laboratories Limited

TEL: 908-203-4937

ATTN: Jaya Ayyagari

FAX: 908-203-4980

FROM: Sean Belouin

FDA CONTACT PHONE: (240) 276-8566

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated 4-28-2008 , submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sumatriptan Succinate Injection in Pre-filled Syringes, 6 mg(base)/0.5 ml (Autoinjector).

The Division of Chemistry and our Clinical Review team have completed its review of the submission referenced above and has identified deficiencies which are presented on the attached ____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Effective 01-Aug-2010, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

List of Deficiencies to Be Communicated to the Applicant

ANDA: 090495 APPLICANT: Dr. Reddy's Laboratories Inc.

DRUG PRODUCT: Sumatriptan Succinate Injection in Pre-filled Syringes, 6 mg(base)/0.5 ml (Autoinjector).

The deficiency presented below represents a **MINOR** deficiency.

Please be advised that your proposed Sumatriptan Autoinjector product has been evaluated for any potential concerns with respect to safety or therapeutic equivalence. We have provided the following deficiencies and recommendations:

1. Additional sample units are required to allow for full evaluation. The units do not have to contain active drug, but they should be fully functional.

2. The position of the needle after injection should be clarified and justified from the standpoint of safe handling and disposal after injection.

3. (b) (4)

4. The button on the sample unit and the actuation force data for the device suggest that the device may be difficult to fire for some individuals. Evaluation of additional samples will be helpful in this regard, but the sponsor should also provide information to support the ease of firing and operating this device in a diverse population.

5. It is known that differences in injection technique and site of injection can affect the pharmacokinetics of sumatriptan. Therefore, while the performance and specifications of the proposed device are generally similar to those of the RLD, the small differences in performance and specifications that are present (e.g. needle gauge, injection cycle time, force to displacement distance profile) have the theoretical potential to affect PK. DCR defers to DBE the decision of whether or not a BE study should be required for this product.

In addition, we have provided the following labeling deficiencies and recommendations:

6. The following additional comments pertain to the proposed patient labeling insert:

a. Wherever possible and appropriate, the proposed labeling for the generic product should mirror that for the RLD. For example, the RLD labeling instructs the user to read the leaflet several times. Unless there is justification for doing otherwise, the generic labeling should also instruct the user to read several times, and not (b) (4) as currently proposed.

b. As is done in the Imitrex labeling, the labeling for the generic should contain a section describing the parts of the injector, including figures in which relevant parts of the autoinjector device are clearly labeled.

c. The color configuration of the product needs to be clarified: the sample provided has a different color configuration than described in the proposed labeling.

d. The statement and accompanying figure stating that the device (b) (4) need to be clarified. It is difficult to understand what the sections are being referred to and how the user can ascertain that the injector (b) (4) (b) (4)

e. The use of the safety catch mechanism needs to be clarified. It appears that the mechanism (b) (4) The sponsor needs to clarify whether or not the safety catch mechanism remains disengaged if the tip is pressed and then released without initiating an injection. If the safety lock does remain disengaged, instruction should be provided on whether or not it is safe to re-engage the safety lock, and how to do so.

f. The user should be clearly instructed not to disengage the safety feature until just before the injection is to be initiated.

g. The labeling should provide a figure and description of the viewing window with instructions on its use and on the expected appearance of the window before and after injection.

h. The sponsor should also clarify whether or not the stopper position should be inspected through the viewing window and what the appropriate position should be both before and after injection.

i. The instruction to "firmly press…against the skin" should be prefaced with "without pressing the blue button", as in the Imitrex label.

j. The instructions and the post-injection photo should describe clearly the needle position after injection and also provide information so that users can tell the difference between a spent injector unit and one that has not been injected.

k. Instruction should be provided about proper handling and disposal procedures after injection and these instructions should provide further clarification that the entire dosage delivery system is intended to be a disposable device and should be disposed of in its entirety. This clarification is necessary because this device differs significantly from the RLD device in this respect.

l. Some versions of labeling have included a directive to pull the blue cap straight off ensuring that the rubber needle shield has been removed. The sponsor should clarify whether or not this instruction is necessary and to provide justification.

m. Versions of labeling have differed with respect to when clicks will be heard upon operating the device. The sponsor should clarify at which point(s) clicks will be heard and reflect this information appropriately in labeling (e.g. (b) (4) (b) (4) upon pushing the button to initiate injection, upon completion of injection

In addition, please be advised that the review of the CMC amendments submitted in relation to the new proposed drug product manufacturing facility, Gland Pharma" is ongoing and you will be notified of any deficiencies in a separate letter.

Sincerely yours,

{See appended electronic signature page}

Glen J. Smith
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

PETER CAPELLA
12/21/2011
For Glen Smith

For Consulting Center Use Only:

Date Received: _____
Assigned to: _____
Date Assigned: _____
Assigned by: _____

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division:
Mail Code: HF
Consulting Reviewer Name:
Building/Room #:
Phone #:
Fax #:
Email Address:
RPM/CSO Name and Mail Code:

From (Originating Center):
Center: CDER/OPS/OGD
Division: II
Mail Code: HF 630
Requesting Reviewer Name: Andrew Langowski
Building/Room #: MPN II/E-222
Phone#:
Fax #:
Email Address: Andrew.Langowski@fda hhs.gov
RPM/CSO Name and Mail Code: Simon Eng 617
Requesting Reviewer's Concurring Supervisor's Name: Peter Capella

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 10-25-2011

Requested Completion Date: 1-25-2012

Submission/Application Number: 090495
(Not Barcode Number)

Submission Type: MAF# (b) (4)
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: ☑ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination ☐ Drug-device-biologic combination ☐ Not a combination product

Submission Receipt Date: 4-30-2008

Official Submission Due Date: _____

Name of Product: Sumatriptan Succinate Injection 6 mg (base) 0.5 mg

Name of Firm: Dr. Reddy's Labs, Inc.

Intended Use: To relieve a migraine attack.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

LOA for Dr. Reddy's Labs, Inc. and from (b) (4)

Documents to be returned to Requesting Reviewer? ☐ Yes ☑ No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: ☐ Consultative Review ☐ Collaborative Review

(940 characters max -- use additional sheet if necessary)
We would like CDRH to review and comment on the Sponsor's LOA from (b) (4) for MAF #-(b) (4), the auto injector (b) (4) for patients to self-administer Sumatriptan Succinate Injection 6 mg (base) 0.5 mg. I also have the actual autoinjector samples in my office, please call Project Manager Simon Eng 240-276-8529 if you need them. I also combined the form with the Chemistry Review for additional info regarding the autoinjector. Thank you.

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/s/

SIMON S ENG
10/27/2011

TRANG Q TRAN
10/27/2011

QUALITY DEFICIENCY - MINOR

ANDA 90-495

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Dr. Reddy's Laboratories Limited TEL: (908) 203-4937

ATTN: Kumara Sekar FAX: (908) 203-4980

FROM: Laura Longstaff FDA CONTACT PHONE: (240) 276-8566

Dear Sir or Madam:

This facsimile is in reference to your abbreviated new drug application dated April 28, 2009, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sumatriptan Injection, 6 mg/0.5 mL (pfs).

Reference is also made to your amendment dated August 31, 2009.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-495 APPLICANT: Dr. Reddy's Laboratories

DRUG PRODUCT: Sumatriptan Succinate Injection 0.6 mg (base)/0.5 mL

The deficiencies presented below represent MINOR deficiencies.

Deficiencies:

1. (b) (4)

2.

3. (b) (4)

4.

5.

Sincerely yours,

{See appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90495	ORIG-1	DR REDDYS LABORATORIES INC	SUMATRIPTAN SUCCINATE

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/s/

GLEN J SMITH
01/28/2010

TELEPHONE MEMO

ANDA: **090495**

FIRM: Dr. Reddy's Laboratories, Inc.

TELEPHONE #: 908-203-4977

PARTICIPANTS: John Arigo and Jaya Ayyagari

DATE: 12-08-09

SUBJECT: [redacted] (b) (4)

REQUESTED BY: FDA/John Arigo

The application lacks validation information for the [redacted] (b) (4) from [redacted] (b) (4)

Ms. Ayyagari asked what type of information is required for the [redacted] (b) (4) [redacted] (b) (4)

I told Jaya that a full validation study is required. This information may come directly from [redacted] (b) (4) The applicant asked if it is possible to reference a DMF. I told her that it was. In case a DMF was not available I told her that we look for information regarding the [redacted] (b) (4) Jaya will get back to her manufacturing personnel for this information.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90495	ORIG-1	DR REDDYS LABORATORIES INC	SUMATRIPTAN SUCCINATE

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/s/

JOHN T ARIGO
12/18/2009

FAX – Microbiology Deficiencies Enclosed

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855-2773 (240-276-8408)

TO: Kumara Sekar		**FROM:** Kun Shen
Dr. Reddy's Laboratories Limited		Microbiology Project Manager
PHONE: (908) 203-4937		**PHONE:** (240) 276-8722
FAX: (908) 203-4980		**FAX:** (240) 276-8725

Total number of pages, excluding this cover sheet: 3

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

Microbiology Deficiencies:

Enclosed are the microbiology deficiencies for **ANDA 90-495, Sumatriptan Succinate Injection**. The submission reviewed was submitted on April 28, 2008. Please respond to this communication as quickly as possible. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review. The response to this communication will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT-RESPONSE TO MICROBIOLOGY DEFICIENCIES should appear prominently in your cover letter.

Should you also have other outstanding deficiencies, for review purposes, please attempt to consolidate your responses into a single submission for this application.

If you have questions, feel free to call Kun Shen, Bonnie McNeal or Mark Anderson.

LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 90-495 APPLICANT: Dr. Reddy's Laboratories

DRUG PRODUCT: Sumatriptan Succinate Injection

A. Microbiology Deficiencies:

1.

2.

3.

(b) (4)

4. [redacted] (b) (4)

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

1. [redacted] (b) (4)

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

LCDR Paul Dexter, M.S.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90495	ORIG-1	DR REDDYS LABORATORIES LTD	SUMATRIPTAN SUCCINATE

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/s/

PAUL L DEXTER
09/23/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 90-495

Dr. Reddy's Laboratories, Inc.
U.S. Agent for Dr. Reddy's Laboratories, Limited
Attention: Kumara Sekar, Ph.D.
3600 Arco Corporation Drive
Suite 310
Charlotte, NC 28273

Dear Sir:

This letter is in reference to your abbreviated new drug application dated April 30, 2008, submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act for Sumatriptan Succinate Injection, 6 mg (base)/0.5 mL (Auto Injector).

Please be advised that the triggering mechanism for your proposed autoinjector device appears to differ significantly from that currently employed by the Reference Listed Drug. This difference raises potential safety and/or effectiveness issues related to the use of your drug product. These issues have resulted in your application being considered Not Approvable by the Office of Generic Drugs unless substantial changes are made to your autoinjector device. Alternately, the current drug/device combination may be submitted to the Office of New Drugs, Division of Neuropharmacology Drug Products under 505(b)(2).

The file is now closed. It is required that an action described under 21 CFR §314.120 and 21 CFR §314.96 be taken, which will either amend or withdraw this application. If the test product is reformulated, the appropriate information regarding bioequivalence, chemistry, manufacturing, controls and labeling information should be included. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered as a MAJOR Amendment and should be so designated in your cover letter. If there is substantial disagreement with our reasons for not approving this application, a hearing request can be submitted.

If you have any questions, please contact Laura Longstaff at (240)276-8566. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Robert L. West
3/20/2009 02:11:13 PM
Deputy Director, for Gary Buehler

Telephone Fax

ANDA 90-495

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park
North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8951

TO: Dr. Reddy's Laboratories, Limited TEL: 704-496-6065

ATTN: Kumara Sekar FAX: 704-496-6082

FROM: Chan Park

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sumatriptan Succinate Injection.

Pages (including cover): 6
SPECIAL INSTRUCTIONS:

Labeling Comments:

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 90-495 Date of Submission: April 28, 2008

Applicant's Name: Dr. Reddy's Laboratories, Limited

Established Name: Sumatriptan Succinate Injection, (b) (4) 6 mg (base)/0.5 mL

Labeling Deficiencies:

1. (b) (4)

2. CONTAINER LABEL FOR AUTO-INJECTION SYSTEM

   Please explain what this proposed label is for. Will it be placed on the auto-injector containing the prefilled syringe? We believe that this label should not be on the auto-injector as it will interfere with the proper use of the auto-injector. Please comment.

3. (b) (4)

4. CARTON - 2 Auto-Injectors with Prefilled Syringe

   a. Relocate the route of administration. See comment 3(b) above.

   b. Add an asterisk (*) to read "*Each Auto-Injector with prefilled syringe…".

   c. See comment 3(f) above.

   d. Include the terms "Sterile, nonpyrogenic".

   e. Include the text (b) (4)

h. Revise to read as follows:

This carton contains:

- 2 Auto-injectors, [redacted] (b) (4)
- Instructions for use/Information for the patient
- Prescribing Information

5. INSERT

a. WARNINGS

Please include the following subsection to appear immediately after the "Other Vasospasm-Related Events" subsection.

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome may occur with triptans, including treatment with sumatriptan, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram) or SNRI (e.g., venlafaxine, duloxetine) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

b. PRECAUTIONS

i. Information for Patients

A) Please verify that your statement "With the autoinjector, the needle penetrates approximately 1/4 of an inch (5 to 6mm)." is accurate.

B) Include the following text as the new last paragraph:

Patients should be cautioned about the risk of serotonin syndrome with the use of sumatriptan or other triptans, especially during combined use with SSRIs or SNRIs.

ii. Drug Interactions - Revise this subsection to red as follows:

Drug Interactions: ***Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome:*** Cases of life-threatening serotonin syndrome have been reported during combined use of SSRIs or SNRIs and triptans (see WARNINGS).

Migraine Prophylactic Medications: There is no evidence that concomitant use of migraine prophylactic medications has any effect on the efficacy of sumatriptan. In 2 Phase III trials in the US, a retrospective analysis of 282 patients who had been using prophylactic drugs (verapamil n = 63, amitriptyline n = 57, propranolol n = 94, for 45 other drugs n = 123) were compared to those who had not used prophylaxis (N = 452). There were no differences in relief rates at 60 minutes postdose for sumatriptan injection, whether or not prophylactic medications were used.

Ergot-Containing Drugs: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and sumatriptan within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

Monoamine Oxidase-A Inhibitors: MAO-A inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure. Therefore, the use of sumatriptan in patients receiving MAO-A inhibitors is not ordinarily recommended. If the clinical situation warrants the combined use of sumatriptan and an MAOI, the dose of sumatriptan employed should be reduced (see CLINICAL PHARMACOLOGY: Drug Interactions: *Monoamine Oxidase Inhibitors* and WARNINGS: Concomitant Drug Use).

c. DOSAGE AND ADMINISTRATION

i. Penultimate paragraph:

See 5(b)(i)(A) above.

ii. Last paragraph:

(b) (4)

d. HOW SUPPLIED

i. 2nd paragraph - Revise to read:

… single-dose prefilled syringe 6 mg(base)/0.5 mL and…

ii. 3rd paragraph - Revise to read:

(b) (4)

6. INFORMATION FOR THE PATIENT

Please revise the patient information to be the same as the one posted at the DailyMeds website except the following:

Talk to your healthcare…injection (2. Important questions … injection) - Revise the 9th bullet to read as follows and include the disclaimer statements at the end of the labeling.

- Are you taking any medicine for depression or other health problems such as a monoamine oxidase inhibitor, selective serotonin reuptake inhibitor (SSRI), or serotonin norepinephrine reuptake inhibitor (SNRI)? Common SSRIs are citalopram HBr (CELEXA®), escitalopram oxalate (LEXAPRO®), paroxetine (PAXIL®), fluoxetine (PROZAC®/SARAFEM®), olanzapine/fluoxetine (SYMBYAX®), sertraline (ZOLOFT®), and fluvoxamine. Common SNRIs are duloxetine (CYMBALTA®) and venlafaxine (EFFEXOR®).

7. INSTRUCTIONS FOR USE LEAFLET

i. We note that your proposed instructions are incomplete missing the pictorial illustrations for the figures. Please complete these in your next submission.

ii. Your proposed autoinjector is under review. We will defer the comment for the instructions for the autoinjector pending the acceptance of your proposed device. We will not request the final printed labeling until all issues associated with your proposed device is resolved.

Revise the labeling as described above and submit final printed labeling electronically. Please provide the labeling in the Structured Product Labeling (SPL) as well as pdf. format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. 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

To facilitate review of your next submission please provide a side-by-side comparison of your proposed labeling with your last labeling submission with all differences annotated and explained.

If you have any questions, please call Dr. Chan Park at 240-276-8951 or send e-mail to chan.park@fda.hhs.gov

{See appended electronic signature page}

_____

William Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Lillie Golson
11/17/2008 06:50:39 PM
Lillie Golson for Wm. Peter Rickman

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 90-495 **FIRM NAME**: DR REDDY'S LABORATORIES LIMITED

PIV: NO **Electronic or Paper Submission:** ELECTRONIC (ECTD FORMAT)

RELATED APPLICATION(S): NA

First Generic Product Received? NO

Bio Assignments:		
☒ **BPH**	☐ **BCE**	☒ **Micro Review !!!Yes, MICRO Review NEEDED!!!**
☐ **BST**	☐ **BDI**	

DRUG NAME: SUMATRIPTAN SUCCINATE
DOSAGE FORM: INJECTION,
6 MG(BASE)/0.5 ML(12 MG/ML) IN PRE-FILLED SYRINGES
Random Queue: 9
Chem Team Leader: Smith, Glen J Chem PM: Laura Longstaff Labeling Reviewer: Chan Park
Bio PM: Christina Thompson

Letter Date: APRIL 28, 2008 **Received Date**: APRIL 30, 2008

Comments: EC - 1 YES **On Cards:** YES
Therapeutic Code: 2011110 MIGRAINE

Archival copy: ELECTRONIC (ECTD FORMAT) **Sections** I
Review copy: NA E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST LISA TAN **Date July 3, 2008**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: _____ **Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:

CONTACT INFO: KUMARA SEKAR, Ph.D. 704.496.6065 ksekar@drreddys.com (US AGENT: DR REDDY LABS, INC.)
****LETTER OF NON-REPUDIATION ON FILE****

REQUEST: NONE

COMMUNICATION: NONE

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: APRIL 28, 2008	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature)	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) NA or Disclosure Statement (Form FDA 3455) NA	☒
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) '845 EXP 8/6/2008 W/PED 2/06/2009 U-72 TREATMENT OF MIGRAINE 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☒ PIV ☐ (Statement of Notification) ☐ 3. Expiration of Patent(s): 2/6/2009 a. Pediatric exclusivity submitted? YES b. Expiration of Pediatric Exclusivity? YES 4. Exclusivity Statement: YES **There is no unexpired exclusivity for this product.**	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient 16534 b. Type III DMF authorization letter(s) for container closure (b) (4) 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) YES	☒

1.12.11	**Basis for Submission** NDA# : 20-080 Ref Listed Drug: IMITREX Firm: GLAXOSMITHKLINE ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use SAME 2. Active ingredients SAME 3. Inactive ingredients SAME 4. Route of administration SAME 5. Dosage Form SAME 6. Strength SAME	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): YES	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) YES **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained YES **1.14.1.3** 1 package insert (content of labeling) submitted electronically YES ***Was a proprietary name request submitted? NO (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained YES **1.14.3.3** 1 RLD label and 1 RLD container label YES	☒

MODULE 2
SUMMARIES ACCEPTABLE

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** YES **Word Processed e.g., MS Word** YES A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** YES **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** YES **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** YES **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **N/A** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** **Word Processed e.g., MS Word** **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary Table 4. Bioanalytical Method Validation Table 6. Formulation Data **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies Table 3. Statistical Summary of the Comparative BA Data **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies	☐

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) DR REDDY'S LAB LTD. 2. Function or Responsibility YES 3. Type II DMF number for API 16534 4. CFN or FEI numbers NOT PROVIDED	☒
3.2.S.3	**Characterization**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** Testing specifications and data from drug substance manufacturer(s) YES **3.2.S.4.2 Analytical Procedures** YES **3.2.S.4.3 Validation of Analytical Procedures** 1. Spectra and chromatograms for reference standards and test samples YES 2. Samples-Statement of Availability and Identification of: a. Drug Substance SUMATRIPTAN SUCCINCATE b. Same lot number(s) ADAA0167 **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) YES 2. Applicant certificate of analysis YES **3.2.S.4.5 Justification of Specification**	☒
3.2.S.5	**Reference Standards or Materials**	☒
3.2.S.6	**Container Closure Systems** Sumatriptan succinate Auto-Injector System includes 2 Auto-Injectors, each containing a single-dose 6 mg prefilled syringe and instructions for use. (b) (4)	☒
3.2.S.7	**Stability**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1 Description and Composition of the Drug Product ☒

1. Unit composition YES
2. Inactive ingredients and amounts are appropriate per IIG Q1/Q2

3.2.P.2 Pharmaceutical Development ☒

Pharmaceutical Development Report YES

3.2.P.3 Manufacture ☒

3.2.P.3.1 Manufacture(s) (Finished Dosage Manufacturer and Outside Contract Testing Laboratories)

1. Name and Full Address(es)of the Facility(ies) (b) (4)
2. CGMP Certification: YES
3. Function or Responsibility YES
4. CFN or FEI numbers NOT PROVIDED

3.2.P.3.2 Batch Formula YES

3.2.P.3.3 Description of Manufacturing Process and Process Controls

1. Description of the Manufacturing Process YES
2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified

Sumatriptan Succinate Injection	ANDA Stability Batch	Proposed Commercial Batch
Fill Volume	(b) (4)	
Container Material		
Closure Material Manufacture/ Formulation		
Syringe Size		
Batch Size (L)		
Batch Size (Syringes)		
Ingredients	**Ingredient Amount/ Batch**	**Ingredient Amount/ Batch**
Sumatriptan Succinate	(b) (4)	
Sodium Chloride, USP		
Water for Injection, USP		

(b) (4)

3. If sterile product: (b) (4) PLS SEE BELOW.
4. Reprocessing Statement YES

3.2.P.3.4 Controls of Critical Steps and Intermediates

3.2.P.3.5 Process Validation and/or Evaluation

(b) (4)

(b) (4)

3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified YES **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) YES 2. Suppliers' COA (specifications and test results) YES **3.2.P.4.2 Analytical Procedures** **3.2.P.4.3 Validation of Analytical Procedures** **3.2.P.4.4 Justification of Specifications** Applicant COA YES	☒

MODULE 3
3.2.P DRUG PRODUCT

ACCEPTABLE

<table>
<tr><td>3.2.P.5</td><td>Controls of Drug Product
3.2.P.5.1 Specification(s) YES
3.2.P.5.2 Analytical Procedures YES
3.2.P.5.3 Validation of Analytical Procedures
Samples - Statement of Availability and Identification of:
1. Finished Dosage Form INJECTION
2. Same lot numbers 226-13-001
3.2.P.5.4 Batch Analysis
Certificate of Analysis for Finished Dosage Form YES
3.2.P.5.5 Characterization of Impurities
3.2.P.5.6 Justification of Specifications</td><td>☒</td></tr>
<tr><td>3.2.P.7</td><td>Container Closure System
1. Summary of Container/Closure System (if new resin, provide data) YES
2. Components Specification and Test Data YES
3. Packaging Configuration and Sizes
<table><tr><th>Component</th><th>Supplier</th><th>Address</th></tr><tr><td></td><td></td><td>(b) (4)</td></tr></table>4. Container/Closure Testing YES
5. Source of supply and suppliers address YES</td><td>☒</td></tr>
<tr><td>3.2.P.8</td><td>3.2.P.8.1 Stability (Finished Dosage Form)
1. Stability Protocol submitted YES
2. Expiration Dating Period (b) (4) MONTH EXP
3.2.P.8.2 Post-approval Stability and Conclusion
Post Approval Stability Protocol and Commitments YES
3.2.P.8.3 Stability Data
1. 3 month accelerated stability data YES
2. Batch numbers on stability records the same as the test batch YES</td><td>☒</td></tr>
</table>

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available)** **3.2.R.2.S Comparability Protocols** **3.2.R.3.S Methods Validation Package NO** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation YES Theoretical Yield SEE BELOW Actual Yield SEE BELOW Packaged Yield SEE BELOW **3.2.R.1.P.2 Information on Components** YES **3.2.R.2.P Comparability Protocols** YES **3.2.R.3.P Methods Validation Package** NO Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS **N/A**

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☐
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☐

	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. Summary Bioequivalence tables: Table 10. Study Information Table 12. Dropout Information Table 13. Protocol Deviations **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information Table 16. Composition of Meal Used in Fed Bioequivalence Study **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples **5.3.7** **Case Report Forms and Individual Patient Listing**	☐
5.4	**Literature References**	☐
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) NA 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: NO	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

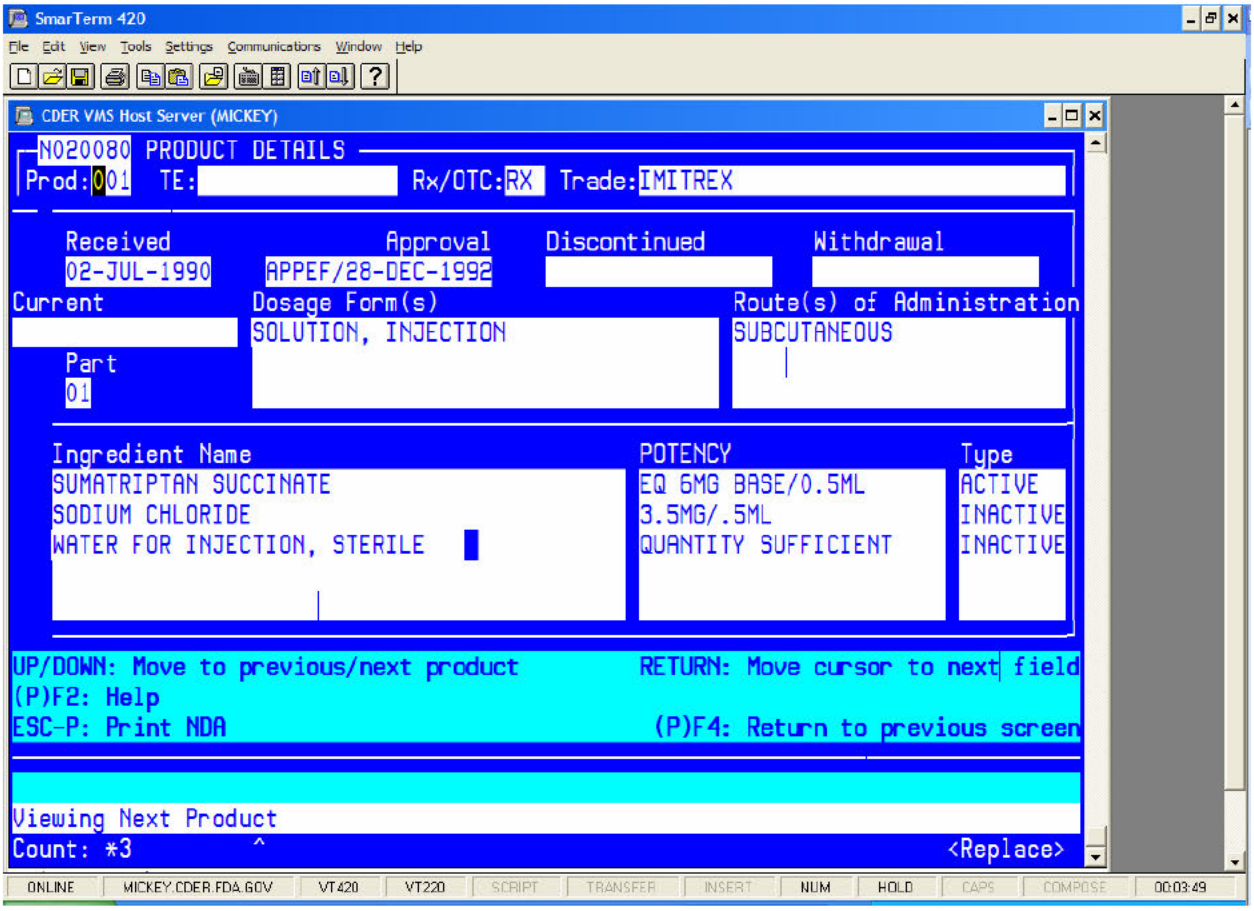
Updated 5/28/08

3.0 COMPOSITION STATEMENT

The qualitative and quantitative formulation of the drug product, stating the name, quality standard, pharmaceutical function and concentration of each ingredient, whether active or inactive, used in the manufacturing of Sumatriptan Succinate Injection are provided in the table below. This listing is inclusive of all materials used during the manufacture of the drug product whether or not they are present in the finished product

Component	Quality Standard	Function	Sumatriptan Succinate Injection
Sumatriptan Succinate[1]	In house Standard	Drug Substance	(b) (4) mg/mL[1]
Sodium Chloride	USP	(b) (4)	7.0 mg/mL
Water for Injection	USP		q.s. to 1.0 mL
Total Volume			0.5 mL

[1] (b) (4) mg/mL of sumatriptan succinate is equivalent to 12.0 mg/mL sumatriptan base



Do the differences between this formulation and the RLD present potential concerns with respect to therapeutic equivalence?

The composition of the RLD based on the package insert and Dr. Reddy's formulation are identical Therefore there are no potential concerns with respect to therapeutic equivalence.

Comparison of Dr. Reddy's and the Reference Listed Drug's (RLD's) Formulation

	Dr. Reddy's	RLD (GSK)
Ingredient	**Sumatriptan Succinate Injection**	**Imitrex® (Sumatriptan Succinate) Injection**
Active Ingredient	Sumatriptan Succinate	Sumatriptan Succinate
Active Ingredient Concentration	12 mg/ mL (equivalent base)	12 mg/ mL (equivalent base)
Label Claim	**6 mg/ 0.5 mL**	**6 mg/ 0.5 mL**
Inactive Ingredients	Sodium Chloride 7 mg/mL	Sodium Chloride 7 mg/mL
(b) (4)	Q.S. to 1.0 mL with Water for Injection, USP	Q.S. to 1.0 mL with Water for Injection, USP

(b) (4)

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/s/

Martin Shimer

7/15/2008 08:26:48 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 90-495

Dr. Reddy's Laboratories, Inc.
U.S. Agent for Dr. Reddy's Laboratories, Limited
Attention: Kumara Sekar, Ph.D.
3600 Arco Corporate Drive
Suite 310
Charlotte, NC 28273

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Sumatriptan Succinate Injection, 6 mg/0.5 mL (pfs)

DATE OF APPLICATION: April 28, 2008

DATE (RECEIVED) ACCEPTABLE FOR FILING: April 30, 2008

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Laura Longstaff
Project Manager
240-276-8566

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Martin Shimer
7/15/2008 08:26:17 AM
Signing for Wm Peter Rickman