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Approval Package for:

APPLICATION NUMBER:

ANDA 090358Orig1s000

Name: Sumatriptan Succinate Injection
6 mg / 0.5 mL

Sponsor: Sun Pharmaceutical Industries, Inc.

Approval Date: June 21, 2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 090358

Sun Pharmaceutical Industries, Inc.
U.S. Agent for: Sun Pharma Global FZE
Attention: Vincent P. Andolina
Sr. Director, Regulatory Affairs
270 Prospect Plains Rd.
Cranbury, NJ 08512

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated January 18, 2008, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Sumatriptan Succinate Injection, 6 mg (base)/0.5 mL, packaged in a Single-dose Syringe with AutoInjector.

Reference is also made to your amendments dated January 21, June 1, December 21, 2009; June 1, July 15, August 21, 2010; and April 18, 2011.

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 Succinate Injection, 6 mg (base)/0.5 mL, packaged in a Single-dose Syringe with AutoInjector to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Imitrex STATdose System, 6 mg (base)/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 505-1(i).

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
Division of Drug Marketing, Advertising, and Communications
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 Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

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/U_CM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
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

06/21/2011

Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090358Orig1s000

LABELING

47335- PJPI 0299A

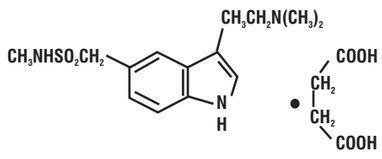
Rx only

Sumatriptan Succinate Injection

For Subcutaneous Use Only.

DESCRIPTION

Sumatriptan succinate injection is a selective 5 hydroxytryptamine, receptor subtype 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 succinate injection is a clear, colorless to pale yellow, sterile, nonpyrogenic solution for subcutaneous injection. Each 0.5 mL of sumatriptan succinate injection 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 solution is approximately 4.2 to 5.3. The osmolality of injection is 291 mOsmol.

CLINICAL PHARMACOLOGY

Mechanism of Action: Sumatriptan has been demonstrated to be a selective agonist for a vascular 5 hydroxytryptamine, receptor subtype (probably a member of the 5 HT_{1D} family) with no significant affinity (as measured using standard radioligand binding assays) or pharmacological activity at 5 HT_2, 5 HT_3 receptor subtypes or at alpha$_1$, alpha$_2$, or beta adrenergic; dopamine$_1$; dopamine$_2$; muscarinic; or benzodiazepine receptors.

The vascular 5 HT_1 receptor subtype to which sumatriptan binds selectively, and through which it presumably exerts its antimigrainous effect, has been shown to be present on cranial arteries in both dog and primate, on the human basilar artery, and in the vasculature of the isolated dura mater of humans. In these tissues, sumatriptan activates this receptor to cause vasoconstriction, an action in humans correlating with the relief of migraine and cluster headache. In the anesthetized dog, sumatriptan selectively reduces the carotid arterial blood flow with little or no effect on arterial blood pressure or total peripheral resistance. In the cat, sumatriptan selectively constricts the carotid arteriovenous anastomoses while having little effect on blood flow or resistance in cerebral or extracerebral tissues.

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.

Pharmacokinetics: Pharmacokinetic parameters following a 6 mg subcutaneous injection into the deltoid area of the arm in 9 males (mean age, 33 years; mean weight, 77 kg) were systemic clearance: 1,194 ± 149 mL/min (mean ± S.D.), distribution half life: 15 ± 2 minutes, terminal half life: 115 ± 19 minutes, and volume of distribution central compartment: 50 ± 8 liters. Of this dose, 22% ± 4% was excreted in the urine as unchanged sumatriptan and 38% ± 7% as the indole acetic acid metabolite.

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}) 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 study, 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.

The bioavailability of sumatriptan via subcutaneous site injection to 18 healthy male subjects was 97% ± 16% of that obtained following intravenous injection. 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.

Special Populations: ***Renal Impairment:*** The effect of renal impairment on the pharmacokinetics of sumatriptan has not been examined, but little clinical effect would be expected as sumatriptan is largely metabolized to an inactive substance.

Hepatic Impairment: The effect of hepatic disease on the pharmacokinetics of subcutaneously and orally administered sumatriptan has been evaluated. There were no statistically significant differences in the pharmacokinetics of subcutaneously administered sumatriptan in hepatically impaired patients compared to healthy controls. However, the liver plays an important role in the presystemic clearance of orally administered sumatriptan. Accordingly, the bioavailability of sumatriptan following oral administration may be markedly increased in patients with liver disease. In 1 small study of hepatically impaired patients (N = 8) matched for sex, age, and weight with healthy subjects, the hepatically impaired patients had an approximately 70% increase in AUC and C_{max} and a T_{max} 40 minutes earlier compared to the healthy subjects.

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

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

Drug Interactions: ***Monoamine Oxidase Inhibitors*****:** In vitro studies with human microsomes suggest that sumatriptan is metabolized by monoamine oxidase (MAO), predominantly the A isoenzyme. In a study of 14 healthy females, pretreatment with MAO A inhibitor decreased the clearance of sumatriptan. Under the conditions of this experiment, the result was a 2 fold increase in the area under the sumatriptan plasma concentration x time curve (AUC), corresponding to a 40% increase in elimination half life. No significant effect was seen with an MAO B inhibitor.

Pharmacodynamics:

Typical Physiologic Responses:

Blood Pressure: (see WARNINGS: Increase in Blood Pressure)

Peripheral (small) Arteries: In healthy volunteers (N = 18), a study 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 patients in clinical studies carried out during sumatriptan's development as a treatment for migraine were not accompanied by any clinically significant changes in heart rate.

Respiratory Rate: Experience gained during the clinical development of sumatriptan as a treatment for migraine failed to detect an effect of the drug on respiratory rate.

CLINICAL TRIALS

Migraine: In US controlled clinical trials enrolling more than 1,000 patients during migraine attacks who were experiencing moderate or severe pain and 1 or more of the symptoms enumerated in Table 2, onset of relief began as early as 10 minutes following a 6 mg sumatriptan succinate injection. Smaller doses of sumatriptan may also prove effective, although the proportion of patients obtaining adequate relief is decreased and the latency to that relief is greater.

In 1 well controlled study where placebo (n = 62) was compared to 6 different doses of sumatriptan succinate injection (n = 30 each group) in a single attack, parallel group design, the dose response relationship was found to be as shown in Table 1.

Table 1. Dose Response Relationship for Efficacy

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

* 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 US well controlled clinical trials in 1,104 migraine patients with moderate or severe migraine pain, the onset of relief was rapid (less than 10 minutes) with sumatriptan succinate injection 6 mg. Headache relief, as evidenced by a reduction in pain from severe or moderately severe to mild or no headache, was achieved in 70% of the patients within 1 hour of a single 6 mg subcutaneous dose of sumatriptan succinate injection. Headache relief was achieved in approximately 82% of patients within 2 hours, and 65% of all patients were pain free within 2 hours.

Table 2 shows the 1 and 2 hour efficacy results for sumatriptan succinate injection 6 mg.

Table 2. Efficacy Data From US Phase III Trials

	Study 1		Study 2	
1-Hour Data	Placebo (n 190)	Sumatriptan 6 mg (n 384)	Placebo (n 180)	Sumatriptan 6 mg (n 350)
Patients with pain relief (grade 0/1)	18%	70%*	26%	70%*
Patients with no pain	5%	48%*	13%	49%*
Patients without nausea	48%	73%*	50%	73%*
Patients without photophobia	23%	56%*	25%	58%*
Patients with little or no clinical disability†	34%	76%*	34%	76%*
	Study 1		Study 2	
2-Hour Data	Placebo‡	Sumatriptan 6 mg§	Placebo‡	Sumatriptan 6 mg§
Patients with pain relief (grade 0/1)	31%	81%*	39%	82%*
Patients with no pain	11%	63%*	19%	65%*
Patients without nausea	56%	82%*	63%	81%*
Patients without Photophobia	31%	72%*	35%	71%*
Patients with little or No clinical disability†	42%	85%*	49%	84%*

* $p<0.05$ versus placebo.

† A successful outcome in terms of clinical disability was defined prospectively as ability to work mildly impaired or ability to work and function normally.

‡ Includes patients that may have received an additional placebo injection 1 hour after the initial injection.

§ Includes patients that may have received an additional 6 mg of sumatriptan succinate injection 1 hour after the initial injection.

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

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

Cluster Headache: The efficacy of sumatriptan succinate injection in the acute treatment of cluster headache was demonstrated in 2 randomized, double blind, placebo controlled, 2 period crossover trials. Patients age 21 to 65 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 patients receiving 6 mg of sumatriptan succinate injection compared to those who received placebo (see Table 3). One study evaluated a 12 mg dose; there was no statistically significant difference in outcome between patients randomized to the 6 and 12 mg doses.

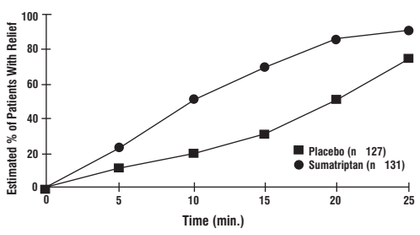
Table 3. Efficacy Data From the Pivotal Cluster Headache Studies

	Study 1		Study 2	
	Placebo (n 39)	Sumatriptan 6 mg (n 39)	Placebo (n 88)	Sumatriptan 6 mg (n 92)
Patients with pain relief (no/mild) 5 minutes postinjection	8%	21%	7%	23%*
10 minutes postinjection	10%	49%*	25%	49%*
15 minutes postinjection	26%	74%*	35%	75%*

* $p<0.05$.
(n = Number of headaches treated.)

The Kaplan Meier (product limit) Survivorship Plot (Figure 1) provides an estimate of the cumulative probability of a patient with a cluster headache obtaining relief after being treated with either sumatriptan or placebo.

Figure 1. Time to Relief From Time of Injection*



*Patients taking rescue medication were censored at 15 minutes.

The plot was constructed with data from patients 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 sumatriptan treated headaches).

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

INDICATIONS AND USAGE

Sumatriptan succinate injection is indicated for 1) the acute treatment of migraine attacks with or without aura and 2) the acute treatment of cluster headache episodes.

Sumatriptan succinate injection is not for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS).

CONTRAINDICATIONS

Sumatriptan succinate injection should not be given intravenously because of its potential to cause coronary vasospasm.

Sumatriptan succinate 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 sumatriptan succinate 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 sumatriptan succinate injection may increase blood pressure, it should not be given to patients with uncontrolled hypertension.

Sumatriptan succinate 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 sumatriptan succinate injection and another 5-HT_1 agonist.

Sumatriptan succinate injection should not be administered to patients with hemiplegic or basilar migraine.

Sumatriptan succinate injection is contraindicated in patients with hypersensitivity to sumatriptan or any of its components.

Sumatriptan succinate injection is contraindicated in patients with severe hepatic impairment.

WARNINGS

Sumatriptan succinate injection should only be used where a clear diagnosis of migraine or cluster headache has been established. The prescriber should be aware that cluster headache patients often possess one or more predictive risk factors for coronary artery disease (CAD).

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events:

Sumatriptan should not be given to patients with documented ischemic or vasospastic CAD (see CONTRAINDICATIONS). It is strongly recommended that sumatriptan not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of or consistent with coronary artery vasospasm or myocardial ischemia, sumatriptan should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of sumatriptan injection take place in the setting of a physician's office or similar medically staffed and equipped facility. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following sumatriptan succinate injection, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of sumatriptan and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use sumatriptan. In considering this recommendation for periodic cardiovascular evaluation, it is noted that patients with cluster headache are predominantly male and over 40 years of age, which are risk factors for CAD.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to sumatriptan.

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 sumatriptan succinate injection or 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.

Premarketing Experience With Sumatriptan: Among the more than 1,900 patients with migraine who participated in premarketing controlled clinical trials of subcutaneous sumatriptan, there were 8 patients who sustained clinical events during or shortly after receiving sumatriptan that may have reflected coronary artery vasospasm. Six of these 8 patients had ECG changes consistent with transient ischemia, but without accompanying clinical symptoms or signs. Of these 8 patients, 4 had either findings suggestive of CAD or risk factors predictive of CAD prior to study enrollment.

Of 6,348 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of oral sumatriptan, 2 experienced clinical adverse events shortly after receiving oral sumatriptan that may have reflected coronary vasospasm. Neither of these adverse events was associated with a serious clinical outcome.

Among approximately 4,000 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of sumatriptan nasal spray, 1 patient experienced an asymptomatic subendocardial infarction possibly subsequent to a coronary vasospastic event.

Postmarketing Experience With Sumatriptan: Serious cardiovascular events, some resulting in death, have been reported in association with the use of sumatriptan succinate injection or sumatriptan succinate tablets. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by sumatriptan or to reliably assess causation in individual cases. On clinical grounds, the longer the latency between the administration of sumatriptan succinate injection and the onset of the clinical event, the less likely the association is to be causative. Accordingly, interest has focused on events beginning within 1 hour of the administration of sumatriptan succinate injection.

Cardiac events that have been observed to have onset within 1 hour of sumatriptan administration include: coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia and ventricular fibrillation, cardiac arrest, and death.

Some of these events occurred in patients who had no findings of CAD and appear to represent consequences of coronary artery vasospasm. However, among domestic reports of serious cardiac events within 1 hour of sumatriptan administration, the majority had risk factors predictive of CAD and the presence of significant underlying CAD was established in most cases (see CONTRAINDICATIONS).

Drug-Associated Cerebrovascular Events and Fatalities: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with oral or subcutaneous sumatriptan, and some have resulted in fatalities. The relationship of sumatriptan to these events is uncertain. In a number of cases, it appears possible that the cerebrovascular events were primary, sumatriptan having been administered in the incorrect belief the symptoms experienced were a consequence of migraine when they were not.

As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. It should also be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., cerebrovascular accident, transient ischemic attack).

Other Vasospasm-Related Events: Sumatriptan may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported. Very rare reports of transient and permanent blindness and significant partial vision loss have been reported with the use of sumatriptan. Visual disorders may also be part of a migraine attack.

Serotonin Syndrome: The development of a potentially life threatening serotonin syndrome may occur with triptans, including treatment with sumatriptan succinate injection, 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).

Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients with and without a history of hypertension.

Sumatriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS). Sumatriptan should be administered with caution to patients with controlled hypertension as transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients.

Concomitant Drug Use: In patients taking MAO A inhibitors, sumatriptan plasma levels attained after treatment with recommended doses are nearly double those obtained under other conditions. Accordingly, the coadministration of sumatriptan and an MAO A inhibitor is not generally recommended. If such therapy is clinically warranted, however, suitable dose adjustment and appropriate observation of the patient is advised (see CLINICAL PHARMACOLOGY: Drug Interactions: *Monoamine Oxidase Inhibitors*).

Use in Women of Childbearing Potential: (see PRECAUTIONS: Pregnancy)

Hypersensitivity: Hypersensitivity (anaphylaxis/anaphylactoid) reactions have occurred on rare occasions in patients receiving sumatriptan. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens (see CONTRAINDICATIONS).

PRECAUTIONS

General: Chest, jaw, or neck tightness is relatively common after administration of sumatriptan succinate injection. Chest discomfort and jaw or neck tightness have been reported following use of sumatriptan succinate tablets and have also been reported infrequently following the administration of sumatriptan nasal spray. Only rarely have these symptoms been associated with ischemic ECG changes. However, because sumatriptan may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following sumatriptan should be evaluated for the presence of CAD or a predisposition to Prinzmetal variant angina before receiving additional doses of sumatriptan and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud syndrome, following sumatriptan should be evaluated for atherosclerosis or predisposition to vasospasm (see WARNINGS: Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events and WARNINGS: Other Vasospasm Related Events).

Sumatriptan should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as impaired hepatic or renal function.

There have been rare reports of seizure following administration of sumatriptan. Sumatriptan should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold.

Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine or cluster headache or who experience a headache that is atypical for them. There have been rare reports where patients received sumatriptan for severe headaches that were subsequently shown to have been secondary to an evolving neurologic lesion (see WARNINGS: Drug Associated Cerebrovascular Events and Fatalities). For a given attack, if a patient does not respond to the first dose of sumatriptan, the diagnosis of migraine or cluster headache should be reconsidered before administration of a second dose.

Binding to Melanin-Containing Tissues: Because sumatriptan binds to melanin, it could accumulate in melanin rich tissues (such as the eye) over time. This raises the possibility that sumatriptan could cause toxicity in these tissues after extended use. However, no effects on the retina related to treatment with sumatriptan were noted in any of the toxicity studies. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long term ophthalmologic effects (see CLINICAL PHARMACOLOGY: Melanin Binding).

Corneal Opacities: Sumatriptan causes corneal opacities and defects in the corneal epithelium in dogs; this raises the possibility that these changes may occur in humans. While patients were not systematically evaluated for these changes in clinical trials, and no specific recommendations for monitoring are being offered, prescribers should be aware of the possibility of these changes (see CLINICAL PHARMACOLOGY: Corneal Opacities).

Patients who are advised to self-administer sumatriptan succinate 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.

Information for Patients: With the autoinjector, the needle penetrates approximately 4 to 7 mm. Since the injection is intended to be given subcutaneously, intramuscular or intravascular delivery should be avoided. Patients should be directed to use injection sites with an adequate skin and subcutaneous thickness to accommodate the length of the needle. See PATIENT INFORMATION at the end of this labeling for the text of the separate leaflet provided for patients.

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.

Laboratory Tests: No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with sumatriptan.

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 succinate 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).

Drug/Laboratory Test Interactions: Sumatriptan is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In carcinogenicity studies, rats and mice were given sumatriptan by oral gavage (rats, 104 weeks) or drinking water (mice, 78 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.

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). In 2 cytogenetics assays (the in vitro human lymphocyte assay and the in vivo rat micronucleus assay) sumatriptan was not associated with clastogenic activity.

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.

Pregnancy: Teratogenic Effects: 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/m^2 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. Sumatriptan succinate injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In assessing this information, the following additional findings should be considered.

Embryolethality: When given intravenously to pregnant rabbits daily throughout the period of organogenesis, sumatriptan caused embryolethality at doses at or close to those producing maternal toxicity. The mechanism of the embryolethality is not known. These doses were approximately equivalent to the maximum single human dose of 6 mg on a mg/m^2 basis.

The intravenous administration of sumatriptan to pregnant rats throughout organogenesis at doses that are approximately 20 times a human dose of 6 mg on a mg/m^2 basis, did not cause embryolethality. Additionally, in a study of pregnant rats given subcutaneous sumatriptan daily prior to and throughout pregnancy, there was no evidence of increased embryo/fetal lethality.

Teratogenicity: Term fetuses from Dutch Stride rabbits treated during organogenesis with oral sumatriptan exhibited an increased incidence of cervicothoracic vascular and skeletal abnormalities. The functional significance of these abnormalities is not known. The highest no effect dose for these effects was 15 mg/kg/day, approximately 50 times the maximum single dose of 6 mg on a mg/m^2 basis.

In a study in rats dosed daily with subcutaneous sumatriptan prior to and throughout pregnancy, there was no evidence of teratogenicity.

Nursing Mothers: Sumatriptan is excreted in human breast milk following subcutaneous administration. Infant exposure to sumatriptan can be minimized by avoiding breastfeeding for 12 hours after treatment with sumatriptan succinate injection.

Pediatric Use: Safety and effectiveness of sumatriptan succinate injection in pediatric patients under 18 years of age have not been established; therefore, sumatriptan succinate injection is not recommended for use in patients under 18 years of age.

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

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

Postmarketing experience documents that serious adverse events have occurred in the pediatric population after use of subcutaneous, oral, and/or intranasal sumatriptan. These reports include events 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 events in pediatric patients who might receive injectable, oral, or intranasal sumatriptan are not presently available, the use of sumatriptan in patients aged younger than 18 years is not recommended.

Geriatric Use: The use of sumatriptan in elderly patients is not recommended because elderly patients are more likely to have decreased hepatic function, they are at higher risk for CAD, and blood pressure increases may be more pronounced in the elderly (see WARNINGS: Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events).

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following the use of sumatriptan succinate injection or tablets. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS: Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events, and PRECAUTIONS: General).

Significant hypertensive episodes, including hypertensive crises, have been reported on rare occasions in patients with or without a history of hypertension (see WARNINGS: Increase in Blood Pressure).

Among patients in clinical trials of subcutaneous sumatriptan succinate injection (N = 6,218), up to 3.5% of patients withdrew for reasons related to adverse events.

Incidence in Controlled Clinical Trials of Migraine Headache: Table 4 lists adverse events that occurred in 2 large US, Phase III, placebo controlled clinical trials in migraine patients following either a single 6 mg dose of sumatriptan succinate injection or placebo. Only events that occurred at a frequency of 2% or more in groups treated with sumatriptan succinate injection 6 mg and occurred at a frequency greater than the placebo group are included in Table 4.

Table 4. Treatment Emergent Adverse Experience Incidence in 2 Large Placebo Controlled Migraine Clinical Trials: Events Reported by at Least 2% of Patients Treated With Sumatriptan Succinate Injection 6 mg*

	Percent of Patients Reporting	
Adverse Event	Sumatriptan Succinate 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	59	24
Miscellaneous		
Jaw discomfort	2	0

Folding
350--2 --87.5 mm
430--8 zigzag--48 mm

350 mm

Size: 350x430 mm

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

*The sum of the percentages cited is greater than 100% because patients may experience more than 1 type of adverse event. Only events that occurred at a frequency of 2% or more in groups treated with sumatriptan succinate injection and occurred at a frequency greater than the placebo groups are included.

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

Incidence in Controlled Trials of Cluster Headache: In the controlled clinical trials assessing sumatriptan's efficacy as a treatment for cluster headache, no new significant adverse events associated with the use of sumatriptan were detected that had not already been identified in association with the drug's use in migraine.

Overall, the frequency of adverse events reported in the studies of cluster headache were generally lower. Exceptions include reports of paresthesia (5% sumatriptan, 0% placebo), nausea and vomiting (4% sumatriptan, 0% placebo), and bronchospasm (1% sumatriptan, 0% placebo).

Other Events Observed in Association With the Administration of Sumatriptan Succinate Injection: In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open and uncontrolled studies, the role of sumatriptan succinate injection in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided.

Event frequencies are calculated as the number of patients reporting an event divided by the total number of patients (N = 6,218) exposed to subcutaneous sumatriptan succinate injection. All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in at least 1/100 patients, infrequent adverse events are those occurring in 1/100 to 1/1,000 patients, and rare adverse events are those occurring in fewer than 1/1,000 patients.

Cardiovascular: Infrequent were hypertension, hypotension, bradycardia, tachycardia, palpitations, pulsating sensations, various transient ECG changes (nonspecific ST or T wave changes, prolongation of PR or QTc intervals, sinus arrhythmia, nonsustained ventricular premature beats, isolated junctional ectopic beats, atrial ectopic beats, delayed activation of the right ventricle), and syncope. Rare were pallor, arrhythmia, abnormal pulse, vasodilatation, and Raynaud syndrome.

Endocrine and Metabolic: Infrequent was thirst. Rare were polydipsia and dehydration.

Eye: Frequent was vision alterations. Infrequent was irritation of the eye.

Gastrointestinal: Frequent were abdominal discomfort and dysphagia. Infrequent were gastroesophageal reflux and diarrhea. Rare were peptic ulcer, retching, flatulence/eructation, and gallstones.

Musculoskeletal: Frequent were muscle cramps. Infrequent were various joint disturbances (pain, stiffness, swelling, ache). Rare were muscle stiffness, need to flex calf muscles, backache, muscle tiredness, and swelling of the extremities.

Neurological: Frequent was anxiety. Infrequent were mental confusion, euphoria, agitation, relaxation, chills, sensation of lightness, tremor, shivering, disturbances of taste, prickling sensations, paresthesia, stinging sensations, facial pain, photophobia, and lacrimation. Rare were transient hemiplegia, hysteria, globus hystericus, intoxication, depression, myoclonia, monoplegia/diplegia, sleep disturbance, difficulties in concentration, disturbances of smell, hyperesthesia, dysesthesia, simultaneous hot and cold sensations, tickling sensations, dysarthria, yawning, reduced appetite, hunger, and dystonia.

Respiratory: Infrequent was dyspnea. Rare were influenza, diseases of the lower respiratory tract, and hiccoughs.

Skin: Infrequent were erythema, pruritus, and skin rashes and eruptions. Rare was skin tenderness.

Urogenital: Rare were dysuria, frequency, dysmenorrhea, and renal calculus.

Miscellaneous: Infrequent were miscellaneous laboratory abnormalities, including minor disturbances in liver function tests, "serotonin agonist effect," and hypersensitivity to various agents. Rare was fever.

Other Events Observed in the Clinical Development 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 studies, 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.

Breasts: Breast swelling, cysts, disorder of breasts, lumps, masses of breasts, nipple discharge, primary malignant breast neoplasm, and tenderness.

Cardiovascular: Abdominal aortic aneurysm, angina, atherosclerosis, cerebral ischemia, cerebrovascular lesion, heart block, peripheral cyanosis, phlebitis, thrombosis, and transient myocardial ischemia.

Ear, Nose, and Throat: Allergic rhinitis; disorder of nasal cavity/sinuses; ear, nose, and throat hemorrhage; ear infection; external otitis; feeling of fullness in the ear(s); hearing disturbances; hearing loss; Meniere disease; nasal inflammation; otalgia; sensitivity to noise; sinusitis; tinnitus; and upper respiratory inflammation.

Endocrine and Metabolic: Elevated thyrotropin stimulating hormone (TSH) levels; endocrine cysts, lumps, and masses; fluid disturbances; galactorrhea; hyperglycemia; hypoglycemia; hypothyroidism; weight gain; and weight loss.

Eye: Accommodation disorders, blindness and low vision, conjunctivitis, disorders of sclera, external ocular muscle disorders, eye edema and swelling, eye hemorrhage, eye itching, eye pain, keratitis, mydriasis, and visual disturbances.

Gastrointestinal: Abdominal distention, colitis, constipation, dental pain, dyspeptic symptoms, feelings of gastrointestinal pressure, gastric symptoms, gastritis, gastroenteritis, gastrointestinal bleeding, gastrointestinal pain, hematemesis, hypersalivation, hyposalivation, intestinal obstruction, melena, nausea and/or vomiting, oral itching and irritation, pancreatitis, salivary gland swelling, and swallowing disorders.

Hematological Disorders: Anemia.

Mouth and Teeth: Disorder of mouth and tongue (e.g., burning of tongue, numbness of tongue, dry mouth).

Musculoskeletal: Acquired musculoskeletal deformity, arthralgia and articular rheumatitis, arthritis, intervertebral disc disorder, muscle atrophy, muscle tightness and rigidity, musculoskeletal inflammation, and tetany.

Neurological: Apathy, aggressiveness, bad/unusual taste, bradylogia, cluster headache, convulsions, depressive disorders, detachment, disturbance of emotions, drug abuse, facial paralysis, hallucinations, heat sensitivity, incoordination, increased alertness, memory disturbance, migraine, motor dysfunction, neoplasm of pituitary, neuralgia, neurotic disorders, paralysis, personality change, phobia, phonophobia, psychomotor disorders, radiculopathy, raised intracranial pressure, rigidity, stress, syncope, suicide, and twitching.

Respiratory: Asthma, breathing disorders, bronchitis, cough, and lower respiratory tract infection.

Skin: Dry/scaly skin, eczema, herpes, seborrheic dermatitis, skin nodules, tightness of skin, and wrinkling of skin.

Urogenital: Abnormal menstrual cycle, abortion, bladder inflammation, endometriosis, hematuria, increased urination, inflammation of fallopian tubes, intermenstrual bleeding, menstruation symptoms, micturition disorders, urethritis, and urinary infections.

Miscellaneous: Contusions, difficulty in walking, edema, hematoma, hypersensitivity, fever, fluid retention, lymphadenopathy, overdose, speech disturbance, swelling of extremities, swelling of face, and voice disturbances.

Pain and Other Pressure Sensations: Chest pain and/or heaviness, neck/throat/jaw pain/tightness/pressure, and pain (location specified).

Postmarketing Experience (Reports for Subcutaneous or Oral Sumatriptan): The following section enumerates potentially important adverse events that have occurred in clinical practice and that have been reported spontaneously to various surveillance systems. The events enumerated represent reports arising from both domestic and nondomestic use of oral or subcutaneous dosage forms of sumatriptan. The events enumerated include all except those already listed in the ADVERSE REACTIONS section above or those too general to be informative. Because the reports cite events reported spontaneously from worldwide postmarketing experience, frequency of events and the role of sumatriptan succinate injection in their causation cannot be reliably determined. It is assumed, however, that systemic reactions following sumatriptan use are likely to be similar regardless of route of administration.

Blood: Hemolytic anemia, pancytopenia, thrombocytopenia.

Cardiovascular: Atrial fibrillation, cardiomyopathy, colonic ischemia (see WARNINGS), Prinzmetal variant angina, pulmonary embolism, shock, thrombophlebitis.

Ear, Nose, and Throat: Deafness.

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

Gastrointestinal: Ischemic colitis with rectal bleeding (see WARNINGS), xerostomia.

Hepatic: Elevated liver function tests.

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

Non-Site Specific: Angioneurotic edema, cyanosis, death (see WARNINGS), temporal arteritis.

Psychiatry: Panic disorder.

Respiratory: Bronchospasm in patients with and without a history of asthma.

Skin: Exacerbation of sunburn, hypersensitivity reactions (allergic vasculitis, erythema, pruritus, rash, shortness of breath, urticaria; in addition, severe anaphylaxis/anaphylactoid reactions have been reported [see WARNINGS: Hypersensitivity]), photosensitivity. Following subcutaneous administration of sumatriptan, 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.

DRUG ABUSE AND DEPENDENCE

The abuse potential of sumatriptan succinate injection cannot be fully delineated in advance of extensive marketing experience. One clinical study enrolling 12 patients with a history of substance abuse failed to induce subjective behavior and/or physiologic response ordinarily associated with drugs that have an established potential for abuse.

OVERDOSAGE

Patients (N = 269) have received single injections of 8 to 12 mg without significant adverse effects. Volunteers (N = 47) have received single subcutaneous doses of up to 16 mg without serious adverse events.

No gross overdoses in clinical practice have been reported. Coronary vasospasm was observed after intravenous administration of sumatriptan succinate injection (see CONTRAINDICATIONS). 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 half life of elimination of sumatriptan is about 2 hours (see CLINICAL PHARMACOLOGY: Pharmacokinetics), and therefore monitoring of patients after overdose with sumatriptan succinate injection should continue while symptoms or signs persist, and for at least 10 hours.

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

DOSAGE AND ADMINISTRATION

The maximum single recommended adult dose of sumatriptan succinate injection is 6 mg injected subcutaneously. If side effects are dose limiting, then lower doses may be used (see Table 1).

The maximum recommended dose that may be given in 24 hours is two 6 mg injections separated by at least 1 hour. Controlled clinical trials have failed to show that clear benefit is associated with the administration of a second 6 mg dose in patients who have failed to respond to a first injection.

In patients receiving MAO inhibitors, decreased doses of sumatriptan should be considered (see WARNINGS: Concomitant Drug Use and CLINICAL PHARMACOLOGY: Drug Interactions: *Monoamine Oxidase Inhibitors*).

An autoinjector is available for use with the 6 mg prefilled syringe to facilitate self administration in patients using the 6 mg dose. With this autoinjector, the needle penetrates approximately 4 to 7 mm. Since the injection is intended to be given subcutaneously, intramuscular or intravascular delivery should be avoided. Patients should be directed to use injection sites with an adequate skin and subcutaneous thickness to accommodate the length of the needle.

In patients receiving doses other than 6 mg, only the 6 mg single dose vial dosage form should be used. Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

HOW SUPPLIED

Sumatriptan succinate injection, 6 mg/0.5 mL contains sumatriptan 6 mg (base) as the succinate salt and is supplied as a clear, colorless to pale yellow, sterile, nonpyrogenic solution as follows:

(NDC 47335 276 40) sumatriptan succinate injection autoinjector with 1 prefilled single dose syringe and instructions for use.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature].

Protect from light.

PATIENT INFORMATION

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

Information for the Patient

Sumatriptan Succinate Injection

Read this leaflet carefully before you start to take sumatriptan succinate injection. Keep the leaflet for reference because it gives you a summary of important information about sumatriptan succinate injection.

Read the leaflet that comes with each refill of your prescription because there may be new information.

This leaflet does not have all the information about sumatriptan succinate injection. Ask your healthcare provider for more information or advice.

What is sumatriptan succinate injection?

Sumatriptan succinate injection is a 5 HT, agonist. It is also called a "triptan." You should use it only if you have a prescription.

Sumatriptan succinate injection is used to relieve your migraine or cluster headache. Sumatriptan succinate injection is not used to prevent attacks or reduce the number of attacks you have. Use sumatriptan succinate injection only to treat an actual migraine or cluster headache attack.

The decision to use sumatriptan succinate injection is one that you and your healthcare provider should make together, taking into account your personal needs and health.

Talk to your healthcare provider before taking sumatriptan succinate injection

1. Risk factors for heart disease:

Tell your healthcare provider if you have risk factors for heart disease such as:

- high blood pressure,
- high cholesterol,
- obesity,
- diabetes,
- smoking,
- strong family history of heart disease,
- you are postmenopausal, or
- you are a male over 40 years of age.

If you do have risk factors for heart disease, your healthcare provider should check you for heart disease to see if sumatriptan succinate injection is right for you.

Although most of the people who have taken sumatriptan succinate injection have not had any serious side effects, some have had serious heart problems. Deaths have been reported, but these were rare considering the extensive worldwide use of sumatriptan succinate injection. Usually, serious problems happened in people with known heart diseases. It was not clear whether sumatriptan succinate injection had anything to do with these deaths.

2. Important questions to consider before taking sumatriptan succinate injection:

If the answer to any of the following questions is **YES** or if you do not know the answer, then please talk with your healthcare provider before you use sumatriptan succinate injection.

- Are you pregnant? Do you think you might be pregnant? Are you trying to become pregnant? Are you using inadequate contraception? Are you breastfeeding?
- Do you have any chest pain, heart disease, shortness of breath, or irregular heartbeats? Have you had a heart attack?
- Do you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal or a male over 40)?
- Have you had a stroke, transient ischemic attacks (TIAs), or Raynaud syndrome?
- Do you have high blood pressure?
- Have you ever had to stop taking this or any other medicine because of an allergy or other problems?
- Are you taking any other migraine medicines, including other 5 HT, agonists (triptans) or any other medicines containing ergotamine, dihydroergotamine, or methysergide?
- Are you taking any medicine for depression or other disorders such as monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), or serotonin norepinephrine reuptake inhibitors (SNRIs)? 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®*).
- Have you had, or do you have, any disease of the liver or kidney?
- Have you had, or do you have, epilepsy or seizures?
- Is this headache different from your usual migraine attacks?

Remember, if you answered **YES** to any of the above questions, then talk with your healthcare provider about it.

Important points about sumatriptan succinate injection

1. The use of sumatriptan succinate injection during pregnancy:

Do not use sumatriptan succinate injection if you are pregnant, think you might be pregnant, are trying to become pregnant, or are not using adequate contraception unless you have talked with your healthcare provider about this.

2. How to use sumatriptan succinate injection:

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 migraine start, but it may be given at any time during an attack.

You may give a second injection if your migraine symptoms come back. If your symptoms do not get better after the first injection, do not give a second injection for the same attack without first talking with your healthcare provider. Do not give more than two 6 mg doses in any 24 hour period. Allow at least 1 hour between each dose.

3. What to do if you take an overdose:

If you have taken more medicine than has been prescribed for you, contact either your healthcare provider, hospital emergency department, or nearest poison control center immediately.

4. How to store your medicine:

Keep your medicine in a safe place where children cannot reach it. It may be harmful to children.

Store your medicine away from heat and light. Keep your medicine in the packaging provided. Do not store at temperatures above 77°F (25°C).

The expiration date of your medicine is printed on both autoinjector and prefilled single dose syringe. If your medicine has expired, throw it away as instructed.

If your healthcare provider decides to stop your treatment, do not keep any leftover medicine unless your healthcare provider tells you to. Throw away your medicine as instructed.

Some possible side effects of sumatriptan succinate injection

1. Some patients feel pain or tightness in the chest or throat when using sumatriptan succinate injection. If this happens to you, then discuss it with your healthcare provider before using any more sumatriptan succinate injection. If the chest pain is severe or does not go away, call your healthcare provider right away.
2. Call your healthcare provider right away if you have sudden and/or severe abdominal pain following sumatriptan succinate injection.
3. Some people may have a reaction called serotonin syndrome when they use certain types of antidepressants, SSRIs or SNRIs, while taking sumatriptan succinate injection. Symptoms may include confusion, hallucinations, fast heartbeat, feeling faint, fever, sweating, muscle spasm, difficulty walking, and/or diarrhea. Call your doctor immediately if you have any of these symptoms after taking sumatriptan succinate injection.
4. Shortness of breath; wheeziness; heart throbbing; swelling of eyelids, face, or lips; or a skin rash, skin lumps, or hives happens rarely. If it happens to you, then tell your healthcare provider right away. Do not take any more sumatriptan succinate injection unless your healthcare provider tells you to.
5. Some people may feel tingling, heat, flushing (redness of face lasting a short time), heaviness, or pressure after using sumatriptan succinate injection. A few people may feel drowsy, dizzy, tired, or sick. If you have any of these symptoms, tell your healthcare provider at your next visit.
6. You may have pain or redness at the site of injection, but this usually lasts less than an hour.
7. If you feel unwell in any other way or have any symptoms that you do not understand, you should contact your healthcare provider right away.

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Folding
350--2 --87.5 mm
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350 mm

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Information for the Patient
Sumatriptan Succinate Injection

See the other side for "Instructions for Use" for Autoinjector.

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- you are postmenopausal, or
- you are a male over 40 years of age.

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Although most of the people who have taken sumatriptan succinate injection have not had any serious side effects, some have had serious heart problems. Deaths have been reported, but these were rare considering the extensive worldwide use of sumatriptan succinate injection. Usually, serious problems happened in people with known heart diseases. It was not clear whether sumatriptan succinate injection had anything to do with these deaths.

2. Important questions to consider before taking sumatriptan succinate injection:
If the answer to any of the following questions is **YES** or if you do not know the answer, then please talk with your healthcare provider before you use sumatriptan succinate injection.
- Are you pregnant? Do you think you might be pregnant? Are you trying to become pregnant? Are you using inadequate contraception? Are you breastfeeding?
- Do you have any chest pain, heart disease, shortness of breath, or irregular heartbeats? Have you had a heart attack?
- Do you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal or a male over 40)?
- Have you had a stroke, transient ischemic attacks (TIAs), or Raynaud syndrome?
- Do you have high blood pressure?
- Have you ever had to stop taking this or any other medicine because of an allergy or other problems?
- Are you taking any other migraine medicines, including other 5 HT$_1$ agonists (triptans) or any other medicines containing ergotamine, dihydroergotamine, or methysergide?
- Are you taking any medicine for depression or other disorders such as monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), or serotonin norepinephrine reuptake inhibitors (SNRIs)? 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®*).
- Have you had, or do you have, any disease of the liver or kidney?
- Have you had, or do you have, epilepsy or seizures?
- Is this headache different from your usual migraine attacks?

Remember, if you answered **YES** to any of the above questions, then talk with your healthcare provider about it.

Important points about sumatriptan succinate injection

1. The use of sumatriptan succinate injection during pregnancy:
Do not use sumatriptan succinate injection if you are pregnant, think you might be pregnant, are trying to become pregnant, or are not using adequate contraception unless you have talked with your healthcare provider about this.

2. How to use sumatriptan succinate injection:
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 migraine start, but it may be given at any time during an attack.
You may give a second injection if your migraine symptoms come back. If your symptoms do not get better after the first injection, do not give a second injection for the same attack without first talking with your healthcare provider. Do not give more than two 6 mg doses in any 24-hour period. Allow at least 1 hour between each dose.

3. What to do if you take an overdose:
If you have taken more medicine than has been prescribed for you, contact either your healthcare provider, hospital emergency department, or nearest poison control center immediately.

4. How to store your medicine:
Keep your medicine in a safe place where children cannot reach it. It may be harmful to children.
Store your medicine away from heat and light. Keep your medicine in the packaging provided. Do not store at temperatures above 77°F (25°C).
The expiration date of your medicine is printed on both autoinjector and prefilled single-dose syringe. If your medicine has expired, throw it away as instructed.
If your healthcare provider decides to stop your treatment, do not keep any leftover medicine unless your healthcare provider tells you to. Throw away your medicine as instructed.

Some possible side effects of sumatriptan succinate injection
1. Some patients feel pain or tightness in the chest or throat when using sumatriptan succinate injection. If this happens to you, then discuss it with your healthcare provider before using any more sumatriptan succinate injection. If the chest pain is severe or does not go away, call your healthcare provider right away.
2. Call your healthcare provider right away if you have sudden and/or severe abdominal pain following sumatriptan succinate injection.
3. Some people may have a reaction called serotonin syndrome when they use certain types of antidepressants, SSRIs or SNRIs, while taking sumatriptan succinate injection. Symptoms may include confusion, hallucinations, fast heartbeat, feeling faint, fever, sweating, muscle spasm, difficulty walking, and/or diarrhea. Call your doctor immediately if you have any of these symptoms after taking sumatriptan succinate injection.
4. Shortness of breath; wheeziness; heart throbbing; swelling of eyelids, face, or lips; or a skin rash, skin lumps, or hives happens rarely. If it happens to you, then tell your healthcare provider right away. Do not take any more sumatriptan succinate injection unless your healthcare provider tells you to.
5. Some people may feel tingling, heat, flushing (redness of face lasting a short time), heaviness, or pressure after using sumatriptan succinate injection. A few people may feel drowsy, dizzy, tired, or sick. If you have any of these symptoms, tell your healthcare provider at your next visit.
6. You may have pain or redness at the site of injection, but this usually lasts less than an hour.
7. If you feel unwell in any other way or have any symptoms that you do not understand, you should contact your healthcare provider right away.

*The following are registered trademarks of their respective manufacturers: CELEXA®/Forest Pharmaceuticals, Inc.; LEXAPRO®/Forest Pharmaceuticals, Inc.; PAXIL®/GlaxoSmithKline; PROZAC®/Eli Lilly and Company; SARAFEM®/Eli Lilly and Company & Warner Chilcott, Inc.; SYMBYAX®/Eli Lilly and Company; ZOLOFT®/Pfizer Pharmaceuticals; CYMBALTA®/Eli Lilly and Company; EFFEXOR®/Wyeth Pharmaceuticals, Inc.

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SUN PHARMACEUTICAL INDUSTRIES LTD.

Manufactured by:
Sun Pharmaceutical Ind. Ltd.
Halol-Baroda Highway,
Halol-389 350, Gujarat, India.

CARACO PHARMACEUTICAL LABORATORIES, LTD.
Distributed by:
Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Drive, Detroit, MI 48202

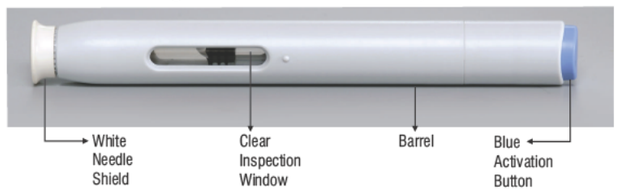
Folding
365--2 zigzag--121.66 mm
198--2 --49.5 mm

365 mm
Front Side

Size: 365x198 mm

HOW TO USE
Autoinjector for Sumatriptan Succinate Injection, 6 mg/0.5 mL

Figure 1 (frontal view of autoinjector)



This leaflet explains how to use the sumatriptan succinate autoinjector. Read it TWICE before you begin the first step. If you have any questions, ask your doctor or pharmacist. For use only patients for whom a 6 mg dose has been prescribed.

CAUTIONS:
Check the expiration date on the autoinjector label.
Keep the autoinjector in its box until you are ready to use it.
Keep the sumatriptan succinate injection autoinjector out of the reach of children.
Do not remove the white needle shield from the autoinjector until you are ready to inject.
NEVER put the white needle shield back into the autoinjector after injection.
NEVER put or press thumb, fingers, or hand over white needle cover.
Check the appearance of sumatriptan succinate injection, through the inspection window. It must be a clear, colorless to pale yellow solution. Do not inject the solution if it looks discolored or cloudy or contains lumps, flakes, or particles.

HOW TO USE THE AUTOINJECTOR
Wash your hands thoroughly.

Find a comfortable, well-lit place and put everything you need where you can reach it (autoinjector, alcohol or sterile swabs).

Identify the application area with an adequate fatty tissue layer on top part of the thigh or back of the arm. Do not inject into areas where the skin is tender, bruised, red, or hard (See Figure 2).

Wipe the injection site with alcohol or a new sterile swab and allow your skin to dry. Do not touch this area again before giving the injection.

Take out the injector from show box.

Figure 2

Pick up the autoinjector in one hand and smoothly remove the white needle shield by pulling it straight off. Do not twist it off, and do not recap the white needle shield, as either of these may damage the needle inside the autoinjector. The autoinjector has a cover that will protect you from needle sticks or loss of drug by accidental bumping or touching (See Figure 3).

Figure 3

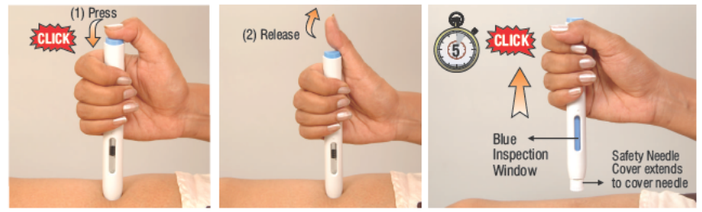
Without pressing the blue activation button, place the open end of the autoinjector on the injection site, straight up at a right angle (90°) and push the safety needle cover firmly against the skin to unlock. **Continue to hold firmly against the skin** (See Figure 4).

Figure 4

To start the injection (1) Press the Blue Button (first click will sound), (2) immediately release your thumb. This starts the injection. Do not lift the autoinjector off the skin. Wait until you hear the second 'click'. Once you hear the second click, lift the autoinjector straight up from the injection site. The injection is finished. The safety needle cover on the autoinjector will automatically extend to cover the needle. The needle will not be visible now.

If you did not remove your thumb from the blue button, the second 'click' cannot be heard. If this happens, slowly count to 5 before lifting the autoinjector from the injection site.
The inspection window will be blue, confirming the injection is complete. Verify that the inspection window is blue to ensure that the injection is complete before lifting the autoinjector (See Figure 5).

Figure 5

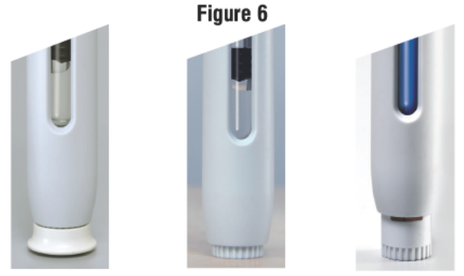


The needle safety cover will move down over the needle and lock into place. There is no need to replace the white needle shield.

If the inspection window is not blue, do not try to use the autoinjector again.
If you suspect you have not received the full dose, do not repeat the injection using a new autoinjector.

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

Figure 6



Discard sumatriptan succinate injection autoinjector after use.
NEVER ATTEMPT TO REUSE AN AUTOINJECTOR

PJPI0300A

Folding
365--2 zigzag--121.66 mm
198--2 --49.5 mm

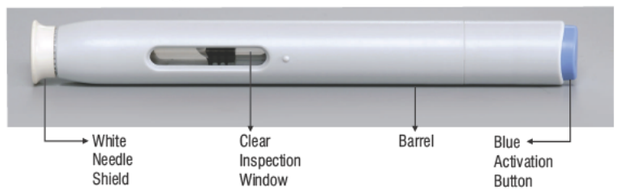
365 mm
Back Side

Size: 365x198 mm

(b) (4) color

HOW TO USE
Autoinjector for Sumatriptan Succinate Injection, 6 mg/0.5 mL

Figure 1 (frontal view of autoinjector)



This leaflet explains how to use the sumatriptan succinate autoinjector. Read it TWICE before you begin the first step. If you have any questions, ask your doctor or pharmacist. For use only patients for whom a 6 mg dose has been prescribed.

CAUTIONS:
Check the expiration date on the autoinjector label.
Keep the autoinjector in its box until you are ready to use it.
Keep the sumatriptan succinate injection autoinjector out of the reach of children.
Do not remove the white needle shield from the autoinjector until you are ready to inject.
NEVER put the white needle shield back into the autoinjector after injection.
NEVER put or press thumb, fingers, or hand over white needle cover.
Check the appearance of sumatriptan succinate injection, through the inspection window. It must be a clear, colorless to pale yellow solution. Do not inject the solution if it looks discolored or cloudy or contains lumps, flakes, or particles.

HOW TO USE THE AUTOINJECTOR
Wash your hands thoroughly.

Find a comfortable, well-lit place and put everything you need where you can reach it (autoinjector, alcohol or sterile swabs).

Identify the application area with an adequate fatty tissue layer on top part of the thigh or back of the arm. Do not inject into areas where the skin is tender, bruised, red, or hard (See Figure 2).

Wipe the injection site with alcohol or a new sterile swab and allow your skin to dry. Do not touch this area again before giving the injection.

Take out the injector from show box.

Figure 2

Pick up the autoinjector in one hand and smoothly remove the white needle shield by pulling it straight off. Do not twist it off, and do not recap the white needle shield, as either of these may damage the needle inside the autoinjector. The autoinjector has a cover that will protect you from needle sticks or loss of drug by accidental bumping or touching (See Figure 3).

Figure 3

Without pressing the blue activation button, place the open end of the autoinjector on the injection site, straight up at a right angle (90°) and push the safety needle cover firmly against the skin to unlock. **Continue to hold firmly against the skin** (See Figure 4).

Figure 4

To start the injection (1) Press the Blue Button (first click will sound), (2) immediately release your thumb. This starts the injection. Do not lift the autoinjector off the skin. Wait until you hear the second 'click'. Once you hear the second click, lift the autoinjector straight up from the injection site. The injection is finished. The safety needle cover on the autoinjector will automatically extend to cover the needle. The needle will not be visible now.

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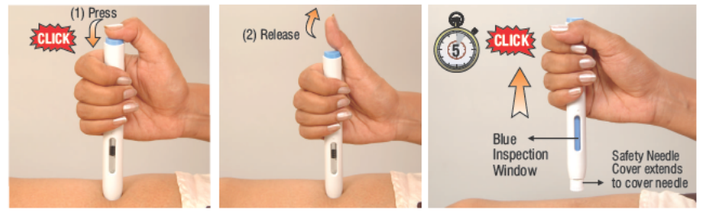
The inspection window will be blue, confirming the injection is complete. Verify that the inspection window is blue to ensure that the injection is complete before lifting the autoinjector (See Figure 5).

Figure 5

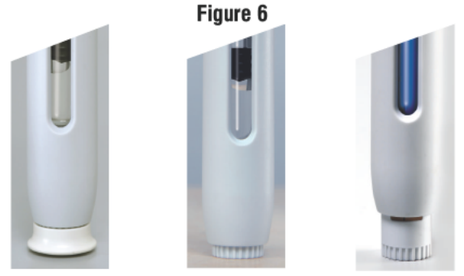


The needle safety cover will move down over the needle and lock into place. There is no need to replace the white needle shield.

If the inspection window is not blue, do not try to use the autoinjector again.
If you suspect you have not received the full dose, do not repeat the injection using a new autoinjector.

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

Figure 6



Before use (With White needle Shield) | Before use (Without White needle Shield) | After use (Needle safety cover down)

Discard sumatriptan succinate injection autoinjector after use.
NEVER ATTEMPT TO REUSE AN AUTOINJECTOR

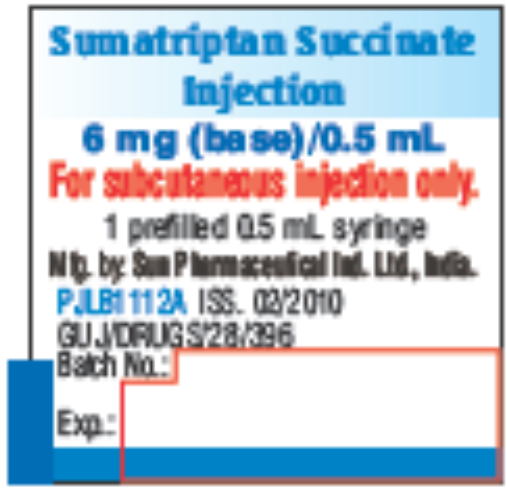
PJPI0300A

Folding
365--2 zigzag--121.66 mm
198--2 --49.5 mm

365 mm
Back Side

Size: 365x198 mm

(b) (4) color



Size: 20x20mm

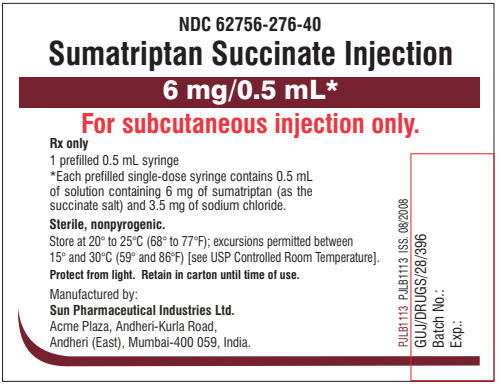
(b) (4)

Black

(b) (4)

Unvarnished area
16 x 5.5 mm

Transparent label



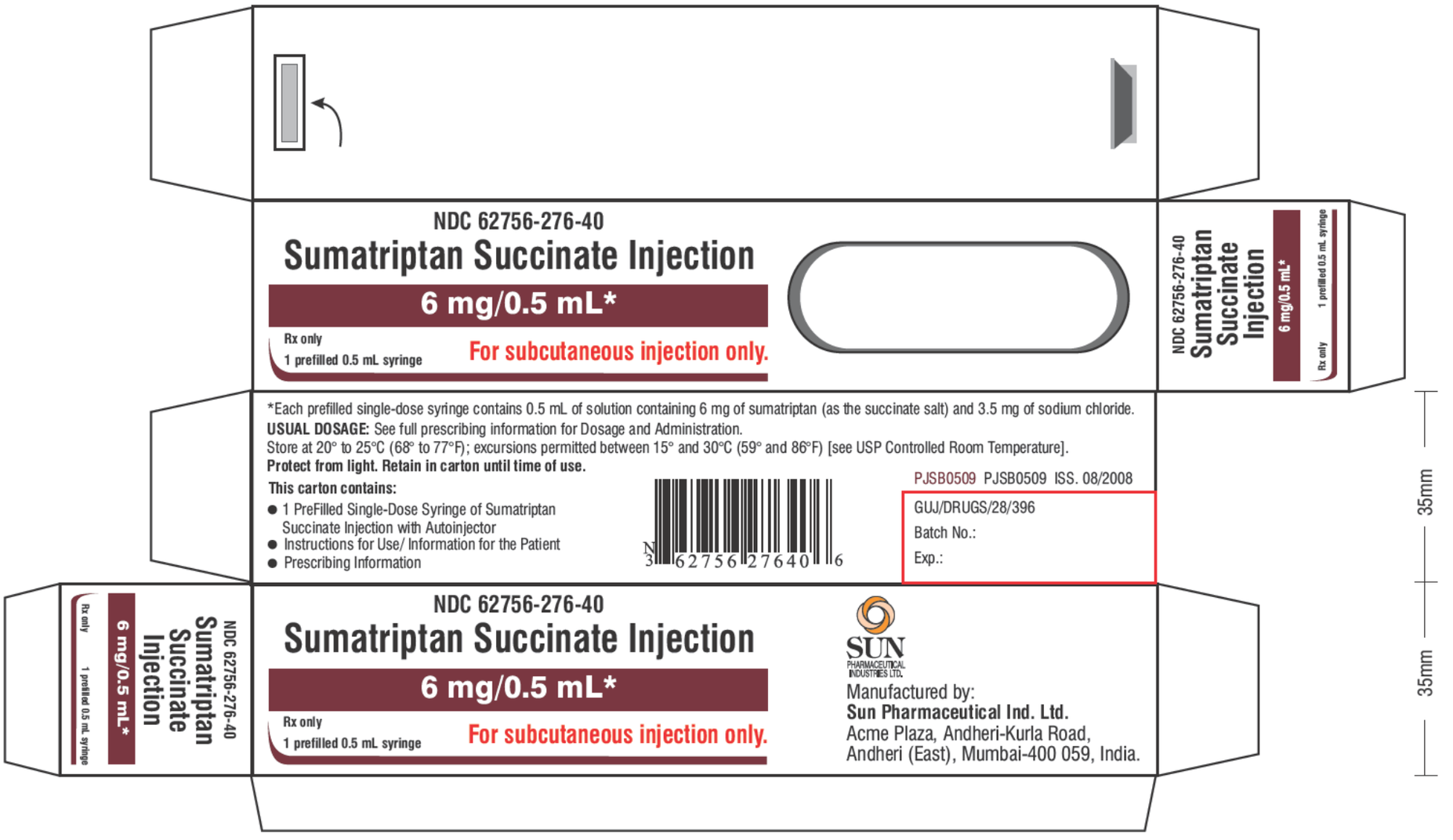
65mm

Size: 65x50mm

Unvarnish area: 11x30mm

Black

(b) (4)



Black

(b) (4)

Size: 35x35x165mm

Unvarnish area: 46x16.5mm

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090358Orig1s000

LABELING REVIEWS

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

ANDA Number: 90-358 Date of Submission: January 18, 2008

Applicant's Name: Sun Pharmaceutical Industries Ltd.

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

Labeling Deficiencies:

1. GENERAL COMMENT

   Your stability test protocol does not justify your proposed storage temperature statement. Please revise the statement on all labeling pieces to read (b) (4) (b) (4) and/or comment.

2. CONTAINER - 0.5 mL Single-dose Prefilled Syringe

   a. Revise the expression of strength to read "6 mg (base)/0.5 mL" and ensure that the strength appears sufficiently prominent.

   b. Include the route of administration.

   c. Please include the net quantity statement, if space permits.

3. BLISTER - 1 Single-dose Prefilled Syringe

   a. See GENERAL COMMENT above.

   b. Consolidate "6 mg" and "0.5 mL" and revise to read "6 mg/0.5 mL*".

   c. Revise to read "*Each prefilled…". [note the asterisk]

   d. Increase the prominence of the route of administration.

   e. Include the net quantity statement "1 prefilled 0.5 mL syringe".

   f. Your drug product appears to be light sensitive. Include the text "Retain in carton until time of use." in a prominent manner after the statement "Protect from light."

   g. Print the text "Protect from light." in bold face type to enhance the prominence.

4. CARTON

   a. See comments under blister, whichever applicable.

   b. Include the terms "USUAL DOSAGE:" to read "USUAL DOSAGE: See full…".

5. INSERT

   a. DESCRIPTION

      i. 2nd paragraph, 1st sentence:

         The molecular formula… [rather than (b) (4)]

      ii. Last paragraph, 1st sentence:

…succinate injection contains 6 mg of sumatriptan… [delete (b) (4) (b) (4)]

b. WARNINGS - Include the following subsection immediately prior to the "Increase in Blood Pressure" subsection:

Serotonin Syndrome:

The development of a potentially life-threatening serotonin syndrome may occur with triptans, including treatment with sumatriptan succinate injection, 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).

c. PRECAUTIONS

i. Information for patients

Please verify that the needle of your proposed injector penetrates approximately (b) (4) as described in your proposed labeling.

ii. Drug Interactions

A) Include the following text as the first sub-subsection:

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).

B) Include the sub-subsection headings for the first three paragraphs to read as follows:

Migraine Prophylactic Medications: There is no evidence…

Ergot-Containing Drugs: Ergot-containing drugs have…

Monoamine Oxidize-A Inhibitors: MAO-A inhibitors…

C) Delete the last paragraph (b) (4) in its entirety.

iii. Pregnancy: Pregnancy Category C

Revise this subsection heading to read "Pregnancy: Teratogenic Effects: Pregnancy Category C". We refer you to 21 CFR 201.57(f)(6).

d. DOSAGE AND ADMINISTRATION

i. Penultimate paragraph

See comment 5(c)(i) above.

ii. Last paragraph, 2nd sentence:

…6 mg single dose vial dosage form should… [add "vial"]

e. HOW SUPPLIED

i. First paragraph, 1st sentence:

Revise to read "…Injection, 6 mg/0.5 mL contains sumatriptan 6 mg (base) as the succinate salt…

ii. First paragraph, 2nd sentence:

….autoinjector with 1 pre-filled single dose… [rather than (b) (4)

iii. See GENERAL COMMENT above regarding storage statement.

6. INFORMATION FOR THE PATIENT

a. GENERAL

i. Describe your plan for supplying the patient information leaflet with your product., which will be dispensed to the patients.

ii. Upon further review, we ask that you revise the patient information leaflet to be the same as the innovator's leaflet posted on the DailyMeds website, except the ones described below.

b. 2. Important questions to consider… Injection (8th bullet) - Revise to read as follows:

- Are you taking any medicine for depression or other disorders such as monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), or serotonin norepinephrine reuptake inhibitors (SNRIs)? 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®).*

c. Storing Your Medicine

i. Revise to read "Do not store at temperature above 25°C (77°F).". We refer you to the GENERAL COMMENT above.

ii. 3rd paragraph

A) You included the statement "(the expiration date is printed (b) (4) (b) (4)". Is this an accurate statement?

B) Include the following text as the new last sentence of this paragraph:

(b) (4)

d. Include the disclaimer statements for the brand drug names.

6. INSTRUCTIONS FOR USE

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 issue associated with your proposed device is resolved.

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

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 submitted labeling with all differences annotated and explained.

FOR THE RECORD:

1. MODEL LABELING - Imitrex® Injection was last approved 2/1/06. (NDA 20-080/S-036). However, the innovator's pending labeling submitted on 4/11/07 was used as a model. Also, the comments from the review of ANDA (b) (4) was used in this review. See below for detail.

   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 5(b) 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 06,2008	U-72		
020080	001	5037845*PED	FEB 06,2009		III	None

Exclusivity Data

There is no unexpired exclusivity for this product.

U-72 TREATMENT OF MIGRAINE

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD - Store between 2° and 30°C (36° and 86°F). Protect from light.
ANDA - Store (b) (4) Protect from light
See GENERAL COMMENT above.

(b) (4)

Stability Protocol
Accelerated stability data (40°C/75 % RH, 0,1,2,& 3 months) and room temperature stability data (25°C/60 % RH, 0 & 3 months) have been provided for the drug product.

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

- Autoinjector and one 6 mg/0.5 mL Single-dose prefilled syringe, Instruction for Use

8. Manufacturer - Sun Pharmaceuticals Industries, Ltd.

9. Container/Closure system

One labeled Prefilled Syringe of Sumatriptan Succinate Injection, 6 mg/0.5 ml is assembled in auto injector device and packed in a show box along with the package insert.

Type	Description	Supplier	DMF #
Prefilled syringe	1 mL (b) (4) glass barrel with attached 27 gauge needle & ½ inch length	(b) (4)	(b) (4)
Stopper	Black (b) (4) plunger stopper		

The (b) (4) Disposable auto injector works with a preinstalled, pre-filled syringe to conveniently and safely deliver a preset dose at the press of a button.. The auto injector device includes Sumatriptan Succinate injection 6 mg/mL, 0.5 mL in a 1 mL long barrel syringe with staked on 27 gauge 1/2" needle. The auto injector devices consist of front assembly and rear assembly.

Date of Review: 5/21//08 Date of Submission: 12/31/08

Primary Reviewer: Chan Park Date:

Team Leader: Lillie Golson Date:

cc:

ANDA: 90-358
DUP/DIVISION FILE
HFD-613/CPark/LGolson (no cc)
V:\FIRMSNZ\SUN\LTRS&REV\90358NA1.LABELING.doc
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
5/30/2008 02:08:17 PM
LABELING REVIEWER

Lillie Golson
6/4/2008 10:25:39 AM
LABELING REVIEWER

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

ANDA Number: 90-358 Date of Submission: September 5, 2008 and September 1, 2009

Applicant's Name: Sun Pharmaceutical Industries Ltd.

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

Labeling Deficiencies:

1. CONTAINER - 0.5 mL Single-dose Prefilled Syringe

   a. Please ensure that all text appears sufficiently legible.

   b. Please enhance the prominence of the route of administration by increasing the font size and/or by any other means. If space is a concern, you may delete text "Accme Plaza, Andheri-Kurla Road" from the manufacturer's address to free up space. We refer you to 21 CFR 201.1(h)(6)(i) for guidance.

2. BLISTER - 1 Single-dose Prefilled Syringe

   Satisfactory in FPL as of 9/5/08 submission

3. CARTON - 1 x 1 Single-dose Prefilled Syringe

   Satisfactory in FPL as of 9/5/08 submission

4. INSERT - PRECAUTIONS, Information for Patients:

   We acknowledge that you (b) (4) the depth of penetration to "4 to 7 mm" (b) (4) (b) (4) The change in the depth of penetration may potentially affect Tmax and in turn Cmax as well. The acceptability of this change is currently being reviewed by the CMC and Bioequivalence divisions. We defer comment pending completion of review by these divisions.

5. INFORMATION FOR THE PATIENT

   We acknowledge that you will provide one PPI (with "Instructions for Use" printed on another side) for each Autoinjector with a prefilled single dose system. We recommend that you include the following statement in a prominent manner in your patient information leaflet, preferably at the beginning of the leaflet.

   See the other side for "Instructions for Use" for Autoinjector.

6. INSTRUCTIONS FOR USE

   a. The currently proposed labeling for the operation and directions for use of the proposed device are not expected to raise clinical safety concerns for this generic product. However, we may need to further review your proposed language to ensure that the patients understand the instructions and appropriately follow the directions for use.

   b. We acknowledge that you revised the injection time, which is reflected in the revised Figure. 5 and associated instruction. This revision is currently being reviewed by the Bioequivalence division. We will defer the comment for the "Instructions for Use" pending the completion of your proposed device.

   c. We will not request the final printed labeling until all issues associated with your proposed device is resolved.

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

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 pending labeling submitted on 4/11/07 was used as a model. Also, the comments from the review of ANDA (b) (4) was used in this review. See below for detail.

   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 DailyMed, except the comment 5(b) 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 DailyMed 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 DARRTS.

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

There is no unexpired patent and exclusivity for this product.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

RLD - Store between 2^{o} and 30^{o}C (36^{o} and 86^{o}F). Protect from light.

ANDA - Store at 20^{o} and 25^{o}C (68^{o} and 77^{o}F); excursions permitted to 15^{o} to 30^{o}C (59^{o} to 86^{o}F) [see USP Controlled Room Temperature]

(b) (4)

Stability Protocol
Accelerated stability data (40°C/75 % RH, 0,1,2,& 3 months) and room temperature stability data (25°C/60 % RH, 0 & 3 months) have been provided for the drug product.

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

- Autoinjector and one 6 mg/0.5 mL Single-dose prefilled syringe, Instruction for Use

8. Manufacturer - Sun Pharmaceuticals Industries, Ltd.

9. Container/Closure system

One labeled Prefilled Syringe of Sumatriptan Succinate Injection, 6 mg/0.5 ml is assembled in auto injector device and packed in a show box along with the package insert.

Type	Description	Supplier	DMF #
Prefilled syringe	1 mL (b) (4) glass barrel with attached 27 gauge needle & ½ inch length	(b) (4)	(b) (4)
Stopper	Black (b) (4) plunger stopper		

The (b) (4) Disposable auto injector works with a preinstalled, pre-filled syringe to conveniently and safely deliver a preset dose at the press of a button.. The auto injector device includes Sumatriptan Succinate injection 6 mg/mL, 0.5 mL in a 1 mL long barrel syringe with staked on 27 gauge 1/2" needle. The auto injector devices consist of front assembly and rear assembly.

10. The sponsor will provide one PPI (with Instructions for Use printed on another side) for each Autoinjector with a prefilled single dose system.

11. The comments regarding "Instructions for Use" for Autoinjector are based on the following reviews and emails:

a. The following five comments are from the clinical review of MO dated 11/18/09. The review was based on the sponsor's revised instructions for use submitted 9/1/09.

1. Because differences in injection time and other differences in device performance and design, such as the difference in needle gauge, might affect the plasma concentration profile for sumatriptan, and Cmax in particular, we recommend that human PK studies be requested to demonstrate bioequivalence.

2. In addition, the large fluctuation in injection times observed in stability testing, should be addressed. Consideration could be given to requesting BE data from products of various ages and also examining for inter-individual variation in plasma level profiles that could result from large device-to-device variations in injection times. Alternatively, consideration could be given to setting specifications that would minimize such variability.

Response: The following comment is from the Bio review performed on 12/18/09 in response to above MO's comment:

The Division of Bioequivalence (DBE) is in agreement with the above recommendations by the clinical team, and denies a waiver request for *in vivo* bioequivalence study requirements for the test Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL. The DBE requests a single-dose two-way crossover fasting bioequivalence study where the subjects inject themselves both the test and reference products using the respective device. DBE also requests that the firm performs comparative in vitro testing on 1) drug volume delivered, 2) injection time, and 3) force to fire for the test biobatch lot and stability lots with and the RLD. In addition, the DBE recommends conducting each of these in vitro tests – 1) drug volume delivered, 2) injection time, and 3) force to fire.

These comparisons should be made directly between the stability lot versus the RLD. This in vitro testing on the stability lots should address the large fluctuation in injection times observed in stability testing.

In addition, the CMC review had raised concerns about defects observed for the full assembled device during syringe integrity testing and the completeness of the stability data.

3. The currently proposed labeling for the operation and directions for use of the proposed device are not expected to raise clinical safety concerns for this generic product. However, it would be optimal to assess the ability of patients to understand and appropriately follow the directions for use.

Response: Regarding the concern addressed in this comment, we may need to consult OSE. However, it may wait until all the issues associated with Autoinjector are resolved.

From: Park, Chan H
Sent: Friday, January 15, 2010 11:36 AM
To: Hoppes, Charles V
Subject: Instructions for Use
Importance: High

Hi Charlie,

I have an application for Sumatriptan Injection, which includes Autoinjector. The MO reviewed the autoinjector and "Instruction for Use". I vaguely remember that we usually consult DMEPA for an "Instruction for Use" to see whether the language is plain enough for the lay people to understand. Is it mandated? Who is the person who is specialized in this review? Please advise. Thanks,

From: Hoppes, Charles V
Sent: Friday, January 15, 2010 11:49 AM
To: Park, Chan H
Subject: RE: Instructions for Use

Chan,

It doesn't go to DMEPA but another Division in OSE. You could put it in the CDER OSE mail box and DARRT the consult.

Jeanne Best used to review these but has moved on.

Hope that helps, Charlie.

4. It is not clear if the proposed labeling changes submitted by Sun on 9/1/09 are accompanied by any corresponding changes in the proposed device. It would seem that the injection times reported during stability testing do not support the proposed labeling; however, the clinical team will defer to CMC the determination of whether or not the specifications and actual performance parameters of the device adequately support the proposed change in labeling, and if the performance remains adequate throughout the proposed shelf life for this product.

5. The proposed labeling is not adequate for patients who require doses other than 6 mg. Whereas, Sun is proposing to market only the 6 mg single-dose autoinjector, the labeling should clearly state that this product is not appropriate for patients who require other dosing strengths

Response: See email below:

From: Park, Chan H
Sent: Friday, January 15, 2010 8:23 AM
To: Chang, Nancy
Cc: Park, Chan H
Subject: RE: 90-358 (Sumatriptan Injection)

Hi Nancy,

I was also aware of your labeling concern as you addressed in your review, so I requested the sponsor in my last review to revise the language to read "In patients receiving doses other than 6 mg, only the 6 mg single-dose **vial dosage form** should be used." from (b) (4) The sponsor revised the language (b) (4) as requested. This revised language is the same as the one appearing in the innovator's drug product for the 6 mg autoinjector. Thanks,.
Chan

From: Chang, Nancy
Sent: Friday, January 15, 2010 9:05 AM
To: Park, Chan H
Subject: RE: 90-358 (Sumatriptan Injection)

Thanks Chan!
Nancy

12. See the following question and response to/from MO:

From: Park, Chan H
Sent: Thursday, January 14, 2010 2:19 PM
To: Chang, Nancy
Cc: Park, Chan H
Subject: 90-358 (Sumatriptan Injection)

Dear Nancy,

I have the following labeling question regarding this application:

The sponsor revised the patient information section of the insert to read "With the autoinjector, the needle penetrate approximately 4 to 7 mm" from (b) (4) proposed originally. The sponsor claims that the penetration data indicating this revised value has been provided in the stability specification for function tests of drug delivery device. The RLD's autoinjector penetrates 5 to 6 mm. Is this difference acceptable in the clinical view point? Please advise. Thanks, Chan

---

From: Chang, Nancy
Sent: Thursday, January 14, 2010 3:26 PM
To: Park, Chan H
Cc: Smith, Glen J; Davit, Barbara M; Hixon, Dena R
Subject: RE: 90-358 (Sumatriptan Injection)

Hi Chan,

Yes, a difference in needle penetration does have the potential to alter the clinical effect. Because of the various differences between this product and the RLD that could potentially impact the clinical effect, DBE is going to be requesting BE studies so that the sponsor can demonstrate that their product is going to be therapeutically equivalent. However (b) (4)

(b) (4)

Barbara: do you have any thoughts on how and whether this could be appropriately tested in a BE study?

Chan, I've also attached my earlier review of this application for your reference because there had been a labeling concern about potentially confusing labeling concerning the use of doses other than 6 mg.

Thanks,
Nancy

Finalized - ANDA 90358 General...

From: Davit, Barbara M
Sent: Thursday, January 14, 2010 4:47 PM
To: Chang, Nancy; Park, Chan H
Cc: Smith, Glen J; Hixon, Dena R
Subject: RE: 90-358 (Sumatriptan Injection)

Nancy:

I think that a difference in needle penetration would be reflected in the results of the BE study. It could potentially affect Tmax, which would in turn impact Cmax.

In addition, the two DBEs are now more attentive to differences in Tmax between the test and reference products, particularly in cases such as this in which the time to peak plasma concentration (Tmax) could be clinically significant.

Therefore, I don't think that we need to add any additional study requests.

Barbara

13. See the following question and response to/from Chemist:

From: Park, Chan H
Sent: Thursday, January 14, 2010 2:32 PM
To: Pineiro-Sanchez, Mayra
Cc: Park, Chan H
Subject: 90-358

Hi Mayra,

The sponsor revised the patient information section of the insert to read "With the autoinjector, the needle penetrate approximately 4 to 7 mm" from (b) (4) proposed originally. The sponsor claims that the penetration data indicating this revised value has been provided in the stability specification for function tests of drug delivery device. Can you please confirm that the sponsor's claim is accurate? Thanks,

Chan

From: Pineiro-Sanchez, Mayra
Sent: Friday, January 15, 2010 11:07 AM
To: Park, Chan H
Subject: RE: 90-358

4 to 7 mm is specified in the stability specifications. See below for EDR location reference. I have not yet reviewed this amendment. Needle penetration is critical to drug effectiveness. Sun is still to perform BIO studies.

Thanks,
Mayra

Date of Review: 1/15/10 Date of Submission: 9/5/08 & 9/1/09

Primary Reviewer: Chan Park Date:

Team Leader: Lillie Golson Date:

cc:

ANDA: 90-358
DUP/DIVISION FILE
HFD-613/CPark/LGolson (no cc)
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Review

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90358	ORIG-1	SUN PHARMACEUTICAL INDUSTRIES LTD	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/

CHAN H PARK
01/29/2010

LILLIE D GOLSON
02/16/2010

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

ANDA Number: 090358 Date of Submission: March 1, 2010

Applicant's Name: Sun Pharmaceutical Industries Ltd.

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

Labeling Deficiencies:

1. CONTAINER - 0.5 mL Single-dose Prefilled Syringe

   Satisfactory in FPL as of the **3/1/10** submission

2. BLISTER (AUTOINJECTOR LABEL) - 1 Single-dose Prefilled Syringe

   Satisfactory in FPL as of 9/5/08 submission

3. CARTON - 1 x 1 Single-dose Prefilled Syringe

   Satisfactory in FPL as of 9/5/08 submission

4. PACKAGE INSERT LABELING

   Please be advised that an updated innovator's labeling for Imitrex® Injection was approved July 21, 2010. Please revise your labeling accordingly as follows:

   a. PRECAUTIONS

      i. Information for Patients - Include the following text as the 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. Nursing Mothers - Revise tor read as follows:

         Sumatriptan is excreted in human breast milk following subcutaneous administration. Infant exposure to sumatriptan can be minimized by avoiding breastfeeding for 12 hours after treatment with sumatriptan succinate injection.

   b. ADVERSE REACTIONS [Postmarketing Experience (Reports for Subcutaneous or Oral Sumatriptan) - Neurological:

      …dysphasia, serotonin syndrome, subarachnoid hemorrhage. [added "serotonin syndrome"]

5. INFORMATION FOR THE PATIENT

   Satisfactory in FPL as of the 3/1/10 submission

6. INSTRUCTIONS FOR USE

   a. GENERAL

      If you have any assessment data regarding the ability of patients to understand and appropriately follow the directions for use of autoinjector, please submit.

b. CAUTIONS - 5th statement:

We believe that it is preferable to include the text "after injection" to read "…into the autoinjector after injection.".

c. HOW TO USE THE AUTOINJECTOR

i. Print the title in upper case letters to enhance the prominence.

ii. Please clearly separate each instruction including a figure by allowing space between instructions. It may help the patients better understand the instructions.

iii. We ask that you include a reference to the associated figure in each instruction. Please refer to the following as an example:

Identify the application area with an adequate fatty tissue layer on… bruised, red, or hard. (See Figure 2)

iv. Middle panel, last paragraph:

It is possible that the completion of injection may not be ensured by slowly counting to 5 as the speed of counting may vary patient to patient. The inspection window of your device turns blue when the injection is completed. Taking this into consideration, we strongly recommend that you relocate the statement "The inspection window will… before lifting the autoinjector." appearing after the figure 5 to appear immediately after the last paragraph of the middle panel to read as follows. Please revise accordingly and/or comment:

If you did not remove your thumb from the blue button, the second "click" cannot be heard. If this happens, slowly count to 5 before lifting the autoinjector from the injection site. The inspection window will be blue, confirming the injection is complete. Verify that the injection window is blue to ensure that the injection is complete before lifting the autoinjector (See Figure 5)..

7. STRUCTURED PRODUCT LABELING (SPL)

We note that you did not include SPL in your submission. Please include SPL in your next submission.

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 (NDA 020080/S-038), approved 7/21/10.

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 077332.

5. PATENTS/EXCLUSIVITIES

   There is no unexpired patent and exclusivity for this product.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   RLD - Store between 2° and 30°C (36° and 86°F). Protect from light.

   ANDA - Store at 20° and 25°C (68° and 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]

   (b) (4)

   Stability Protocol
   Accelerated stability data (40°C/75 % RH, 0,1,2,& 3 months) and room temperature stability data (25°C/60 % RH, 0 & 3 months) have been provided for the drug product.

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

- Autoinjector and one 6 mg/0.5 mL Single-dose prefilled syringe, Instruction for Use

8. Manufacturer - Sun Pharmaceuticals Industries, Ltd.

9. Container/Closure system

One labeled Prefilled Syringe of Sumatriptan Succinate Injection, 6 mg/0.5 ml is assembled in auto injector device and packed in a show box along with the package insert.

Type	Description	Supplier	DMF #
Prefilled syringe	1 mL (b) (4) glass barrel with attached 27 gauge needle & ½ inch length	(b) (4)	(b) (4)
Stopper	Black (b) (4) plunger stopper		

The (b) (4) Disposable auto injector works with a preinstalled, pre-filled syringe to conveniently and safely deliver a preset dose at the press of a button.. The auto injector device includes Sumatriptan Succinate injection 6 mg/mL, 0.5 mL in a 1 mL long barrel syringe with staked on 27 gauge 1/2" needle. The auto injector devices consist of front assembly and rear assembly.

10. The sponsor will provide one PPI (with "Instructions for Use printed on the back side) for each Autoinjector with a prefilled single dose system.

11. The comments regarding "Instructions for Use" for Autoinjector are based on the following reviews and emails:

a. The following five comments are from the clinical review of MO dated 11/18/09. The review was based on the sponsor's revised instructions for use submitted 9/1/09.

1. Because differences in injection time and other differences in device performance and design, such as the difference in needle gauge, might affect the plasma concentration profile for sumatriptan, and Cmax in particular, we recommend that human PK studies be requested to demonstrate bioequivalence.

2. In addition, the large fluctuation in injection times observed in stability testing, should be addressed. Consideration could be given to requesting BE data from products of various ages and also examining for inter-individual variation in plasma level profiles that could result from large device-to-device variations in injection times. Alternatively, consideration could be given to setting

specifications that would minimize such variability.

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Response: Regarding the concern addressed in this comment, we may need to consult OSE. However, it may wait until all the issues associated with Autoinjector are resolved.

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Response: See email below:

From: Park, Chan H
Sent: Friday, January 15, 2010 8:23 AM
To: Chang, Nancy
Cc: Park, Chan H
Subject: RE: 90-358 (Sumatriptan Injection)

Hi Nancy,

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Sent: Friday, January 15, 2010 9:05 AM
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Subject: RE: 90-358 (Sumatriptan Injection)

Thanks Chan!
Nancy

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Dear Nancy,

I have the following labeling question regarding this application:

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Subject: RE: 90-358 (Sumatriptan Injection)

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Barbara: do you have any thoughts on how and whether this could be appropriately tested in a BE study?

Chan, I've also attached my earlier review of this application for your reference because there had been a labeling concern about potentially confusing labeling concerning the use of doses other than 6 mg.

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Nancy

Finalized - ANDA
90358 General...

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Nancy:

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Therefore, I don't think that we need to add any additional study requests.

Barbara

13. See the following question and response to/from Chemist:

From: Park, Chan H
Sent: Thursday, January 14, 2010 2:32 PM
To: Pineiro-Sanchez, Mayra
Cc: Park, Chan H
Subject: 90-358

Hi Mayra,

The sponsor revised the patient information section of the insert to read "With the autoinjector, the needle penetrate approximately 4 to 7 mm" from (b) (4) proposed originally. The sponsor claims that the penetration data indicating this revised value has been provided in the stability specification for function tests of drug delivery device. Can you please confirm that the sponsor's claim is accurate? Thanks,

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From: Pineiro-Sanchez, Mayra
Sent: Friday, January 15, 2010 11:07 AM
To: Park, Chan H
Subject: RE: 90-358

4 to 7 mm is specified in the stability specifications. See below for EDR location reference. I have not yet reviewed this amendment. Needle penetration is critical to drug effectiveness. Sun is still to perform BIO studies.

Thanks,
Mayra

14. The bio review signed off 6/11/20 indicates that the injection time less than 5 seconds, as indicated on the label is acceptable. The bio division has the following conclusion:

The Division of Bioequivalence deems the test product Sumatriptan Succinate Injection Pre-filled Syringe with Auto-injector, EQ 6 mg base/0.5 mL, manufactured by Sun Pharmaceuticals Industries, Ltd to be bioequivalent to the reference product Imitrex® Statdose, EQ 6 mg base/0.5 mL manufactured by GlaxoSmithKline.

Date of Review: 8/3/10 Date of Submission: 3/1/10

Primary Reviewer: Chan Park Date:

Team Leader: Lillie Golson Date:

cc:

ANDA: 90-358
DUP/DIVISION FILE
HFD-613/CPark/LGolson (no cc)
C:\Documents and Settings\parkc\MY DOCUMENTS\90358NA3.LABELING.doc

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90358	ORIG-1	SUN PHARMACEUTICAL INDUSTRIES LTD	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/

CHAN H PARK
08/17/2010

LILLIE D GOLSON
08/18/2010

(APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 090358 Date of Submission: August 21, 2010

Applicant's Name: Sun Pharmaceutical Industries Ltd.

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

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

REMS Check Boxes

REMS required?
☐ Yes ☒ No

REMS acceptable?
☐ Yes ☐ No ☒ n/a

CONTAINER - 0.5 mL Single-dose Prefilled Syringe

Satisfactory in FPL as of the **3/1/10** submission

BLISTER (AUTOINJECTOR LABEL) - 1 Single-dose Prefilled Syringe

Satisfactory in FPL as of **9/5/08** submission

CARTON - 1 x 1 Single-dose Prefilled Syringe

Satisfactory in FPL as of **9/5/08** submission

PROFESSIONAL PACKAGE INSERT LABELING

Satisfactory in FPL as of the 8/21/10 submission

INFORMATION FOR THE PATIENT

Satisfactory in FPL as of the 8/21/10 submission

INSTRUCTIONS FOR USE

Satisfactory in FPL as of the 8/21/10 submission

STRUCTURED PRODUCT LABELING

Satisfactory as of the 8/21/10 submission

REVISIONS NEEDED POST-APPROVAL:

None

FOR THE RECORD:

1. MODEL LABELING - Imitrex® Injection (NDA 020080/S-038), approved 7/21/10.

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 077332.

5. PATENTS/EXCLUSIVITIES

   There is no unexpired patent and exclusivity for this product.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   RLD - Store between 2^{o} and 30^{o}C (36^{o} and 86^{o}F). Protect from light.

   ANDA - Store at 20^{o} and 25^{o}C (68^{o} and 77^{o}F); excursions permitted to 15^{o} to 30^{o}C (59^{o} to 86^{o}F) [see USP Controlled Room Temperature]

   (b) (4)

   Stability Protocol
   Accelerated stability data (40°C/75 % RH, 0,1,2,& 3 months) and room temperature stability data (25°C/60 % RH, 0 & 3 months) have been provided for the drug product.

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

   - Autoinjector and one 6 mg/0.5 mL Single-dose prefilled syringe, Instruction for Use

8. Manufacturer - Sun Pharmaceuticals Industries, Ltd.

9. Container/Closure system

One labeled Prefilled Syringe of Sumatriptan Succinate Injection, 6 mg/0.5 ml is assembled in auto injector device and packed in a show box along with the package insert.

Type	Description	Supplier	DMF #
Prefilled syringe	1 mL (b) (4) glass barrel with attached 27 gauge needle & ½ inch length	(b) (4)	(b) (4)
Stopper	Black (b) (4) plunger stopper		

The (b) (4) Disposable auto injector works with a preinstalled, pre-filled syringe to conveniently and safely deliver a preset dose at the press of a button.. The auto injector device includes Sumatriptan Succinate injection 6 mg/mL, 0.5 mL in a 1 mL long barrel syringe with staked on 27 gauge 1/2" needle. The auto injector devices consist of front assembly and rear assembly.

10. The sponsor will provide one PPI (with "Instructions for Use printed on the back side) for each Autoinjector with a prefilled single dose system.

11. The comments regarding "Instructions for Use" for Autoinjector are based on the following reviews and emails:

a. The following five comments are from the clinical review of MO dated 11/18/09. The review was based on the sponsor's revised instructions for use submitted 9/1/09.

1. Because differences in injection time and other differences in device performance and design, such as the difference in needle gauge, might affect the plasma concentration profile for sumatriptan, and Cmax in particular, we recommend that human PK studies be requested to demonstrate bioequivalence.

2. In addition, the large fluctuation in injection times observed in stability testing, should be addressed. Consideration could be given to requesting BE data from products of various ages and also examining for inter-individual variation in plasma level profiles that could result from large device-to-device variations in injection times. Alternatively, consideration could be given to setting specifications that would minimize such variability.

Response: The following comment is from the Bio review performed on 12/18/09 in response to above MO's comment:

The Division of Bioequivalence (DBE) is in agreement with the above recommendations by the clinical team, and denies a waiver request for *in vivo* bioequivalence study requirements for the test Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL. The DBE requests a single-dose two-way crossover fasting bioequivalence study where the subjects inject themselves both the test and reference products using the respective device. DBE also requests that the firm performs comparative in vitro testing on 1) drug

volume delivered, 2) injection time, and 3) force to fire for the test biobatch lot and stability lots with and the RLD. In addition, the DBE recommends conducting each of these in vitro tests – 1) drug volume delivered, 2) injection time, and 3) force to fire. These comparisons should be made directly between the stability lot versus the RLD. This in vitro testing on the stability lots should address the large fluctuation in injection times observed in stability testing.

In addition, the CMC review had raised concerns about defects observed for the full assembled device during syringe integrity testing and the completeness of the stability data.

3. The currently proposed labeling for the operation and directions for use of the proposed device are not expected to raise clinical safety concerns for this generic product. However, it would be optimal to assess the ability of patients to understand and appropriately follow the directions for use.

Response: Regarding the concern addressed in this comment, we may need to consult OSE. However, it may wait until all the issues associated with Autoinjector are resolved.

4. It is not clear if the proposed labeling changes submitted by Sun on 9/1/09 are accompanied by any corresponding changes in the proposed device. It would seem that the injection times reported during stability testing do not support the proposed labeling; however, the clinical team will defer to CMC the determination of whether or not the specifications and actual performance parameters of the device adequately support the proposed change in labeling, and if the performance remains adequate throughout the proposed shelf life for this product.

5. The proposed labeling is not adequate for patients who require doses other than 6 mg. Whereas, Sun is proposing to market only the 6 mg single-dose autoinjector, the labeling should clearly state that this product is not appropriate for patients who require other dosing strengths

Response: See email below:

From: Park, Chan H
Sent: Friday, January 15, 2010 8:23 AM
To: Chang, Nancy
Cc: Park, Chan H
Subject: RE: 90-358 (Sumatriptan Injection)

Hi Nancy,

I was also aware of your labeling concern as you addressed in your review, so I requested the sponsor in my last review to revise the language to read "In patients receiving doses other than 6 mg, only the 6 mg single-dose **vial dosage form** should be used." from (b) (4) [redacted] The sponsor revised the language (b) (4) as requested. This revised language is the same as the one appearing in the innovator's drug product for the 6 mg autoinjector. Thanks,.
Chan

From: Chang, Nancy
Sent: Friday, January 15, 2010 9:05 AM
To: Park, Chan H
Subject: RE: 90-358 (Sumatriptan Injection)

Thanks Chan!
Nancy

12. See the following question and response to/from MO:

From: Park, Chan H
Sent: Thursday, January 14, 2010 2:19 PM
To: Chang, Nancy
Cc: Park, Chan H
Subject: 90-358 (Sumatriptan Injection)

Dear Nancy,

I have the following labeling question regarding this application:

The sponsor revised the patient information section of the insert to read "With the autoinjector, the needle penetrate approximately 4 to 7 mm" from (b) (4) proposed originally. The sponsor claims that the penetration data indicating this revised value has been provided in the stability specification for function tests of drug delivery device. The RLD's autoinjector penetrates 5 to 6 mm. Is this difference acceptable in the clinical view point? Please advise. Thanks, Chan

---

From: Chang, Nancy
Sent: Thursday, January 14, 2010 3:26 PM
To: Park, Chan H
Cc: Smith, Glen J; Davit, Barbara M; Hixon, Dena R
Subject: RE: 90-358 (Sumatriptan Injection)

Hi Chan,

Yes, a difference in needle penetration does have the potential to alter the clinical effect. Because of the various differences between this product and the RLD that could potentially impact the clinical effect, DBE is going to be requesting BE studies so that the sponsor can demonstrate that their product is going to be therapeutically equivalent. However (b) (4) .

(b) (4)

Barbara: do you have any thoughts on how and whether this could be appropriately tested in a BE study?

Chan, I've also attached my earlier review of this application for your reference because there had been a labeling concern about potentially confusing labeling concerning the use of doses other than 6 mg.

Thanks,
Nancy

Finalized - ANDA 90358 General...

From: Davit, Barbara M
Sent: Thursday, January 14, 2010 4:47 PM
To: Chang, Nancy; Park, Chan H
Cc: Smith, Glen J; Hixon, Dena R
Subject: RE: 90-358 (Sumatriptan Injection)

Nancy:

I think that a difference in needle penetration would be reflected in the results of the BE study. It could potentially affect Tmax, which would in turn impact Cmax.

In addition, the two DBEs are now more attentive to differences in Tmax between the test and reference products, particularly in cases such as this in which the time to peak plasma concentration (Tmax) could be clinically significant.

Therefore, I don't think that we need to add any additional study requests.

Barbara

13. See the following question and response to/from Chemist:

From: Park, Chan H
Sent: Thursday, January 14, 2010 2:32 PM
To: Pineiro-Sanchez, Mayra
Cc: Park, Chan H
Subject: 90-358

Hi Mayra,

The sponsor revised the patient information section of the insert to read "With the autoinjector, the needle penetrate approximately 4 to 7 mm" from (b) (4) (b) (4) proposed originally. The sponsor claims that the penetration data indicating this revised value has been provided in the stability specification for function tests of drug delivery device. Can you please confirm that the sponsor's claim is accurate? Thanks,

Chan

From: Pineiro-Sanchez, Mayra
Sent: Friday, January 15, 2010 11:07 AM
To: Park, Chan H
Subject: RE: 90-358

4 to 7 mm is specified in the stability specifications. See below for EDR location reference. I have not yet reviewed this amendment. Needle penetration is critical to drug effectiveness. Sun is still to perform BIO studies.

Thanks,
Mayra

14. The bio review signed off 6/11/20 indicates that the injection time less than 5 seconds, as indicated on the label is acceptable. The bio division has the following conclusion:

> The Division of Bioequivalence deems the test product Sumatriptan Succinate Injection Pre-filled Syringe with Auto-injector, EQ 6 mg base/0.5 mL, manufactured by Sun Pharmaceuticals Industries, Ltd to be bioequivalent to the reference product Imitrex® Statdose, EQ 6 mg base/0.5 mL manufactured by GlaxoSmithKline.

15. The sponsor submitted clinical report (8/21/10) on the ability of the patients to follow the direction for the autoinjector appropriately. This study was done in India and the instructions for use is slightly different from the one the sponsor proposed in the application for the U.S. market. See below the email to/from the M.O. in this regard:

From: Park, Chan H
Sent: Thursday, September 30, 2010 12:35 PM
To: Chang, Nancy
Cc: Park, Chan H
Subject: RE: 90358 (Sumatriptan Succinate Injection)

Hi Nancy,

Thank you so much for your detailed response. Your response gives me a sense of peace to accept the sponsor's proposed labeling for Instruction for Use. The direction contains a watch with 5 seconds on it and also ask the patients count slowly to 5 before lifting the autoinjector from the injection site.

With appreciation,
Chan

From: Chang, Nancy
Sent: Thursday, September 30, 2010 10:54 AM
To: Park, Chan H
Cc: Hixon, Dena R; Patel, Nitin K. (CDER/OGD)
Subject: RE: 90358 (Sumatriptan Succinate Injection)

Hi Chan,

Thanks for forwarding this to me and for bringing to my attention the differences in instructions for use – there is a good chance I would not have caught that otherwise. In my review of this product and its labeling, except for the wording relating to patients receiving doses other than 6 mg, I didn't have any specific concerns about the adequacy of the directions for use, and the comment about assessments of the ability of patients to understand and appropriately follow directions for use was a comment that really should be applied to all of our autoinjector products, and perhaps even to all of our drug/device products. Given that we don't have an established policy on this, however, it is probably not something we can require of all sponsors at this point unless there is a specific concern.

With that in mind, the fact that we have any data at all on usability and adequacy of instructions is actually a very good thing, even if there are some minor changes in the instructions for use. If we were very serious about using this study to assess the adequacy of the instructions for use and the usability of the device, there are a number of areas where the study was really not well designed for this purpose. That being said, the reportedly high rate of correct use and the lack of reports describing clinically concerning misuse are somewhat reassuring and would not raise any new concerns.

So while I would say that this study is clearly inadequate to demonstrate that the device is likely to be used correctly in the marketplace, it is somewhat reassuring and doesn't raise any new concerns. I don't think any further comments to the sponsor are needed at this point.

One other question I did want to clarify with you though: as you recall, there had been an initial concern because the directions called for a much longer injection time than the 5 second time in the Imitrex label. The sponsor proposed to change it to 5 seconds, consistent with Imitrex, and we were happy with that as long as CMC agreed that these new instructions were consistent with the product performance specs. I see that the use study that was submitted has a 15 second injection time in the directions. Can you confirm that the labeling up for approval is for 5 seconds?

Thanks,
Nancy

From: Park, Chan H
Sent: Wednesday, September 29, 2010 5:14 PM
To: Chang, Nancy
Cc: Park, Chan H
Subject: FW: 90358 (Sumatriptan Succinate Injection)
Importance: High

Hi Nancy,

I realized from the sponsor's cover letter that the clinical study was performed in India for the autoinjector with slightly different instruction for use. I wonder whether you still feel necessary to review the report as the instruction is not the same as the one proposed in this application for the U.S. market. Thank you for your help,

Chan

From: Park, Chan H
Sent: Wednesday, September 29, 2010 4:27 PM
To: Chang, Nancy
Cc: Park, Chan H; Golson, Lillie D
Subject: 90358 (Sumatriptan Succinate Injection)
Importance: High

Hi Nancy,

Based on your review comment (11/18/09 in the DARRTS) of the autoinjector proposed in this application, I sent the sponsor the comment to read "**If you have any assessment data regarding the ability of patients to understand and appropriately follow the directions for use of autoinjector, please submit.".**
The sponsor submitted their clinical study report on 8/21/10 in response to my comment. Attached, please find the sponsor's clinical study report. Can you possibly take a look at this? The summary/conclusion states that well over 90% of the patients followed the instructions properly without any problems. If you have any comments for the sponsor, please let me know. I believe that all other disciplines are acceptable for approval and the labeling is the only pending issue. Thanks you very much for your help,

Chan
<< File: 90358.clinical.pdf >>

Date of Review: 10/4/10 Date of Submission: 8/21/10
Primary Reviewer: Chan Park Date:

Team Leader: Lillie Golson Date:

---

cc:
ANDA: 90-358
DUP/DIVISION FILE
HFD-613/CPark/LGolson (no cc)
C:\Documents and Settings\parkc\MY DOCUMENTS\90358.AP.LABELING.doc

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

/s/

CHAN H PARK
10/04/2010

LILLIE D GOLSON
10/04/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090358Orig1s000

CHEMISTRY REVIEWS

ANDA 90-358

Sumatriptan Succinate Injection
6 mg/0.5 mL (Auto-Injector)

Sun Pharmaceutical Industries Ltd.
Mumbai, INDIA

Mayra L. Piñeiro-Sánchez, Ph.D.
Office of Generic Drugs
Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 90-358

2. REVIEW #: 1

3. REVIEW DATE: November 18, 2008

4. REVIEWER: Mayra L. Piñeiro-Sánchez, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
FDA: Acknowledgement Letter	May 2, 2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	December 31, 2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Sun Pharmaceutical Industries Ltd.
Address:	Acme Plaza, Andheri-Kurla Road Andheri (East) Mumbai-400059 India
US Agent:	Kendle International
Representative:	Mr. Anthony Celeste

Chemistry Review Data Sheet

Address: 7361 Calhoun Place
Suite 500
Rockville MD, 20855-2765

Telephone: 301-838-3120

Fax: 301-838-3182

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:
b) Non-Proprietary Name (USAN): Sumatriptan Succinate Injection, 6 mg/0/5 mL

9. LEGAL BASIS FOR SUBMISSION:
IMITREX® Injection
GlaxoSmithKline – NDA #20-865

U.S. Patent #	**Expiration Date**	**Certification**
4816470(PED)	June 28, 2007	Paragraph II
5037845(PED)	February 6, 2009	Paragraph III

There are no unexpired exclusivities.

10. PHARMACOL. CATEGORY: For acute treatment of Migraine

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 6 mg/0.5 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

Chemistry Review Data Sheet

__X__Not a SPOTS product

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

Sumatriptan Succinate

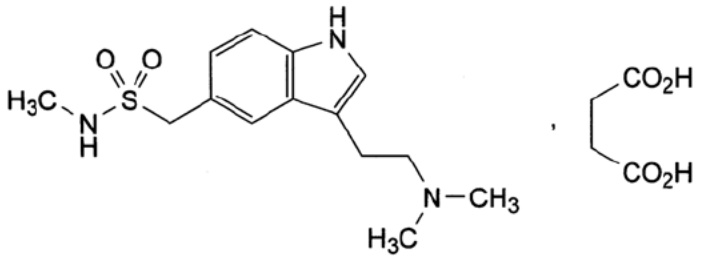
Chemical name: [3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl]-N-methylmethanesulphonamide hydrogen butanedioate.

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

M. W.: 413.5

CAS #: [103628-48-4]

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE1	STATUS2	DATE REVIEW COMPLETED	COMMENTS
19372	II	Sun	API	3	Adequate	1/31/07	S. Bain
[redacted] (b) (4)				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	Deficient	11/17/08	H. Ngai
EES	Acceptable	7/24/08	
Methods Validation	Acceptable	11/18/08	Per Chemistry review
Labeling	Deficient	6/3/08	C. Park
Bioequivalence	Pending		Bio Waiver included within ANDA (1.12.15)
EA	Categorical Exclusion		
Radiopharmaceutical	N/A		
Sample Request	Auto-Injector Device	11/18/08	Per Chemistry review

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 90-358

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is not recommended for 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)

The Drug Substance is compendial. The drug product does not have a USP monograph. Sun Pharmaceutical is both the API and drug product manufacturer.

Sumatriptan Succinate is a white to almost white powder. It is freely soluble in water, sparingly soluble in methanol, and practically insoluble in methylene chloride. The controls for the drug substance established in the DMF and ANDA are identical. (b) (4) impurities are identified. Controls established are in accordance to USP, DMF, and office requirements.

The drug substance is formulated into Sumatriptan Succinate Injection 0.6 mg/mL (auto injector). The drug product is Q1/Q2 with the RLD. The Container/Closure consists of a prefilled syringe inside an auto-injector. The auto-injector differs from that marketed by the RLD.

Storage of the product at controlled room temperature is recommended. An expiration dating of (b) (4) months is requested based on three months stability data provided.

B. Basis for Approvability or Not-Approval Recommendation

Deficiencies identified should be addressed before the application may be approved.

Following this page, 22 pages withheld in full (b)(4)

R3 Methods Validation Package
See section P.5.3 above.

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

A. Labeling & Package Insert *Unsatisfactory*

Deficient per C. Park (4/30/08).
The DESCRIPTION and HOW SUPPLIED sections of the labeling have been found deficient per Labeling review (C. Park). The applicant is requested to change the DESCRIPTION to specify " 6 mg" instead of "(b) (4)". Other changes requested are minor in nature.

B. Environmental Assessment or Claim of Categorical Exclusion *Satisfactory*

The firm claims a categorical exclusion from the need for an environmental assessment, as provided for under 21 CFR Part 25.31(a), for an ANDA for which the drug product will not increase the use of the active moiety (1.12).

III. List of Deficiencies to Be Communicated to the Applicant

ANDA: 90-358 APPLICANT: Sun Pharmaceuticals, India

.

DRUG PRODUCT: Sumatriptan Succinate Injection 6 mg/0.5 mL (Auto-Injector)

A. Deficiencies

The deficiencies presented below represent MINOR deficiencies.

1. Regarding the Sumatriptan Succinate API:
   a. Since the drug substance is the subject of a USP monograph, please provide justifications based on USP in addition to Ph. Eur.
   b. The chemical name for all impurities should be specified in the list of specifications.
2. Please establish a time from the start of manufacture to packaging in the proposed market container. If applicable, proposed hold time periods should be supported be adequate data.
3. Regarding the controls for release of the finished drug product:
   a. Effective July 1, 2008, all Abbreviated New Drug Applications must demonstrate that the subject drug product is in compliance with USP Residual Solvents <467> prior to receiving Approval or Tentative Approval. Please refer to the information posted on the Office of Generic Drugs website for guidance on the required documentation.
   b. Chemical names for impurities should be specified in the list of specifications.
4. [redacted] (b) (4) Please provide pertinent revised documentation modified accordingly.
5. Regarding data provided for the glass barrel:
   a. We acknowledge the test procedures, specification and data for the glass barrel. We note that the test procedures do not correspond to the specifications and CoA. Please submit revised documentation showing agreement.
   b. [redacted] (b) (4)
   c. A CoA from the syringe manufacturer should be included. Please submit.
   d. The "Conformity Certificate" provided on page 95 of section 3.2.P.7 is not readable. Please submit a readable copy.

6. Regarding data provided for the plunger stopper:
   a. [redacted] (b) (4)
   b.
   c.
   d.
7. Regarding the information provided for the auto-injector:
   a. A statement is included indicating that the device quality failures observed during the qualification of assembly process, are to be corrected and re-validation performed prior to regular production (p. 269). No additional studies are included within the ANDA. Please submit.
   b. Please indicate if the manufacturing package for the proposed auto-injector has been previously submitted to CDRH for review. Pertinent documentation should be submitted if applicable.
8. Please submit updated stability data.

B. In addition to the deficiencies noted above, please note and acknowledge the following comments in your response

   Samples of the auto-injector should be provided. Please submit samples of your autoinjector (placebo filled) product along with samples of the RLD directly to:

   Office of Generic Drugs
   Attention: Mayra Pineiro-Sanchez/Glen Smith
   HFD-640
   Division of Chemistry II
   7500 Standish Place
   Rockville, MD 20855

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

cc: ANDA 90-358
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/MPiñeiro-Sánchez/

HFD-647/GJSmith/

HFD-617/LLongstaff/

F/T by

V:\FIRMSNZ\TEVA\LTRS&REV\90358cr01.NA.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

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

/s/

Mayra Pineiro-Sanchez
12/31/2008 01:53:12 PM
CHEMIST

Glen Smith
1/5/2009 07:24:45 AM
CHEMIST

Laura Longstaff
1/12/2009 12:04:47 PM
CSO

ANDA 90-358

Sumatriptan Succinate Injection
6 mg/0.5 mL (Auto-Injector)

Sun Pharmaceutical Industries Ltd.
Mumbai, INDIA

Mayra L. Piñeiro-Sánchez, Ph.D.
Office of Generic Drugs
Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 90-358

2. REVIEW #: 2d

3. REVIEW DATE: May 12, 2010
   October 6, 2010 – Include amendment to [redacted] (b) (4) the expiry period to 18 months.

4. REVIEWER: Mayra L. Piñeiro-Sánchez, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
FDA: Acknowledgement Letter	May 2, 2008
Original submission	December 31, 2007
Minor Amendment – 1st	January 21, 2009
E-mail communication (see attachment)	September 9, 2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Telephone amendment	December 21, 2009
Amendment	July 15, 2010

7. NAME & ADDRESS OF APPLICANT:

Name: Sun Pharmaceutical Industries Ltd.

Chemistry Review Data Sheet

Address:	Acme Plaza, Andheri-Kurla Road Andheri (East) Mumbai-400059 India
US Agent:	Kendle International
Representative:	Mr. Anthony Celeste
Address:	7361 Calhoun Place Suite 500 Rockville MD, 20855-2765
Telephone:	301-838-3120
Fax:	301-838-3182

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:
b) Non-Proprietary Name (USAN): Sumatriptan Succinate Injection, 6 mg/0/5 mL

9. LEGAL BASIS FOR SUBMISSION:
IMITREX® Injection
GlaxoSmithKline – NDA #20-865

U.S. Patent #	**Expiration Date**	**Certification**
4816470(PED)	June 28, 2007	Paragraph II
5037845(PED)	February 6, 2009	Paragraph III

There are no unexpired exclusivities.

10. PHARMACOL. CATEGORY: For acute treatment of Migraine

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 6 mg/0.5 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:

Sumatriptan Succinate

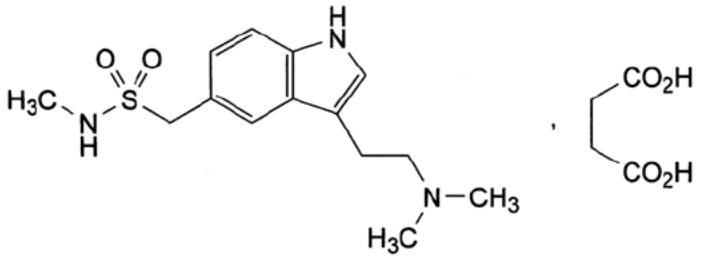
Chemical name: [3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-yl]-N-methylmethanesulphonamide hydrogen butanedioate.

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

M. W.: 413.5

CAS #: [103628-48-4]

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE1	STATUS2	DATE REVIEW COMPLETED	COMMENTS

Chemistry Review Data Sheet

19372	II	Sun	API	3	Adequate	1/9/09	S. Bain
[redacted] (b) (4)				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	Acceptable	1/13/09	H. Ngai
EES	Acceptable	7/24/08	
Methods Validation	Acceptable	11/18/08	Per Chemistry review
Labeling	Acceptable	10/4/10	C. Park
Bioequivalence	Acceptable	6/11/10	L. Williamson Bio Waiver included within ANDA (1.12.15)
EA	Categorical Exclusion		
Radiopharmaceutical	N/A		
Sample Request	Auto-Injector Device	11/18/08	Per Chemistry review

19. ORDER OF REVIEW

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

The Chemistry Review for ANDA 90-358

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is recommended for 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)

The Drug Substance is compendial. The drug product does not have a USP monograph. Sun Pharmaceutical is both the API and drug product manufacturer.

Sumatriptan Succinate is a white to almost white powder. It is freely soluble in water, sparingly soluble in methanol, and practically insoluble in methylene chloride. The controls for the drug substance established in the DMF and ANDA are identical. (b) (4) impurities are identified. Controls established are in accordance to USP, DMF, and office requirements.

The drug substance is formulated into Sumatriptan Succinate Injection 0.6 mg/mL (auto injector). The drug product is Q1/Q2 with the RLD. The Container/Closure consists of a prefilled syringe inside an auto-injector. The auto-injector differs from that marketed by the RLD.

Storage of the product at controlled room temperature is recommended. An expiration dating of (b) (4) months is requested based on three months stability data provided.

B. Basis for Approvability or Not-Approval Recommendation

All CMC issues have been addressed satisfactorily. Labeling and BIO are acceptable.

Following this page, 28 pages withheld in full (b)(4)

P.8.1 ***Stability Summary and Conclusion***
P.8.2 ***Postapproval Stability Protocol and Stability Commitment***
P.8.3 ***Stability Data***

A APPENDICES
N/A
A.1 Facilities and Equipment (biotech only)
A.2 Adventitious Agents Safety Evaluation
A.3 Novel Excipients

R REGIONAL INFORMATION
R1 Executed Batch Records
Executed batch records are provided for Lots #JK70920. Refer to section P.3.3.

R2 Comparability Protocols
N/A

R3 Methods Validation Package
See section P.5.3 above.

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

A. Labeling & Package Insert *Satisfactory*

Acceptable per C. Park (10/4/10).

B. Environmental Assessment or Claim of Categorical Exclusion *Satisfactory*

The firm claims a categorical exclusion from the need for an environmental assessment, as provided for under 21 CFR Part 25.31(a), for an ANDA for which the drug product will not increase the use of the active moiety (1.12).

III. List of Deficiencies to Be Communicated to the Applicant

ANDA: 90-358 APPLICANT: Sun Pharmaceuticals, India

.

DRUG PRODUCT: Sumatriptan Succinate Injection 6 mg/0.5 mL (Auto-Injector)

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

cc: ANDA 90-358
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/MPiñeiro-Sánchez/

HFD-647/PCapella/

HFD-617/LLongstaff/

F/T by

90358cr02d_AP.doc

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/

MAYRA L PINEIRO SANCHEZ
10/13/2010

PETER CAPELLA
10/13/2010

LAURA A LONGSTAFF
10/13/2010

ANDA 90-358

Sumatriptan Succinate Injection
6 mg/0.5 mL (Auto-Injector)

Sun Pharmaceutical Industries Ltd.
Mumbai, INDIA

Mayra L. Piñeiro-Sánchez, Ph.D.
Office of Generic Drugs
Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 90-358

2. REVIEW #: 2d

3. REVIEW DATE: May 12, 2010
   October 6, 2010 – Include amendment to [redacted] (b) (4) the expiry period to 18 months.

4. REVIEWER: Mayra L. Piñeiro-Sánchez, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
FDA: Acknowledgement Letter	May 2, 2008
Original submission	December 31, 2007
Minor Amendment – 1st	January 21, 2009
E-mail communication (see attachment)	September 9, 2009

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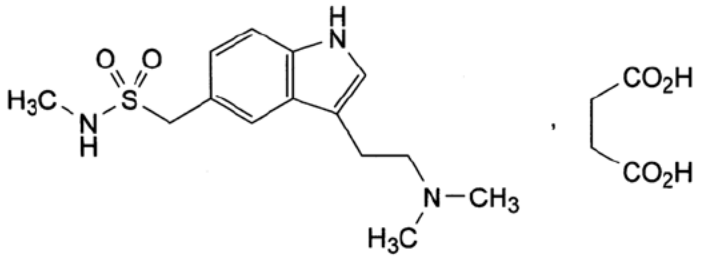

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Sample Request	Auto-Injector Device	11/18/08	Per Chemistry review

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The Chemistry Review for ANDA 90-358

The Executive Summary

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A. Recommendation and Conclusion on Approvability

The ANDA is recommended for approval.

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Storage of the product at controlled room temperature is recommended. An expiration dating of (b) (4) months is requested based on three months stability data provided.

B. Basis for Approvability or Not-Approval Recommendation

All CMC issues have been addressed satisfactorily. Labeling and BIO are acceptable.

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P.8.1 ***Stability Summary and Conclusion***
P.8.2 ***Postapproval Stability Protocol and Stability Commitment***
P.8.3 ***Stability Data***

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A.3 Novel Excipients

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Executed batch records are provided for Lots #JK70920. Refer to section P.3.3.

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N/A

R3 Methods Validation Package
See section P.5.3 above.

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

A. Labeling & Package Insert *Satisfactory*

Acceptable per C. Park (10/4/10).

B. Environmental Assessment or Claim of Categorical Exclusion *Satisfactory*

The firm claims a categorical exclusion from the need for an environmental assessment, as provided for under 21 CFR Part 25.31(a), for an ANDA for which the drug product will not increase the use of the active moiety (1.12).

III. List of Deficiencies to Be Communicated to the Applicant

ANDA: 90-358 APPLICANT: Sun Pharmaceuticals, India

.

DRUG PRODUCT: Sumatriptan Succinate Injection 6 mg/0.5 mL (Auto-Injector)

None

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

cc: ANDA 90-358
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-640/MPiñeiro-Sánchez/

HFD-647/PCapella/

HFD-617/LLongstaff/

F/T by

90358cr02d_AP~1_Corrected.doc

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/

MAYRA L PINEIRO SANCHEZ
11/02/2010

PETER CAPELLA
11/02/2010

LAURA A LONGSTAFF
11/03/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090358Orig1s000

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090358
Drug Product Name	Sumatriptan Succinate Injection, pre-filled syringe with auto-injector
Strength(s)	EQ 6 mg base/0.5 mL
Applicant Name	Sun Pharmaceutical Industries Ltd.
Address	Acme Plaza, Andheri-Kurla Road Andheri (East), Mumbai-400059, India
Applicant's Point of Contact	Mr. Anthony Celeste
Contact's Telephone Number	(301) 838-3120
Contact's Fax Number	
Original Submission Date(s)	January, 18, 2008
Submission Date(s) of Amendment(s) Under Review	
Reviewer	Leah N. Williamson, Ph.D.
OVERALL REVIEW RESULT	**INADEQUATE**
WAIVER REQUEST RESULT	**INADEQUATE**

1 EXECUTIVE SUMMARY

The firm requests 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 auto-injector device. . 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:7777/darrts/ViewDocument?documentId=090140af801ae294). DCII consulted the OGD clinical group because of an apparent difference in injection times between the proposed test and RLD autoinjector devices for sumatriptan. Specifically, the proposed device instructed users to hold in place until a second "click" or for a count of (b) (4) The RLD device instructs users to hold in place for "at least 5 seconds". The clinical group was asked to advise on the whether this difference would be consistent with therapeutic equivalence from a clinical standpoint. Since that time, OGD has received a submission from the firm (9/1/09) revising the proposed labeling to reflect a 5 second injection time.

In addition, the CMC review had raised concerns about defects observed for the full assembled device during syringe integrity testing and the completeness of the stability data.

The OGD clinical group provided the following recommendation among others (http://darrts.fda.gov:7778/darrts/ViewDocument?documentId=090140af801ae294).

1. Because differences in injection time and other differences in device performance and design, such as the difference in needle gauge, might affect the plasma concentration profile for sumatriptan, and Cmax in particular, we recommend that human PK studies be requested to demonstrate bioequivalence.

2. In addition, the large fluctuation in injection times observed in stability testing should be addressed. Consideration could be given to requesting BE data from products of various ages and also examining for inter-individual variation in plasma level profiles that could result from large device-to-device variations in injection times. Alternatively, consideration could be given to setting specifications that would minimize such variability.

3. The currently proposed labeling for the operation and directions for use of the proposed device are not expected to raise clinical safety concerns for this generic product. However, it would be optimal to assess the ability of patients to understand and appropriately follow the directions for use.

The Division of Bioequivalence (DBE) is in agreement with the above recommendations by the clinical team, and denies a waiver request for *in vivo* bioequivalence study requirements for the test Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL. The DBE requests a single-dose two-way crossover fasting bioequivalence study where the subjects inject themselves both the test and reference products using the respective device. DBE also requests that the firm performs comparative in vitro testing on 1) drug volume delivered, 2) injection time, and 3) force to fire for the test biobatch lot and stability lots with and the RLD. In addition, the DBE recommends conducting each of these in vitro tests – 1) drug volume delivered, 2) injection time, and 3) force to fire. These comparisons should be made directly between the stability lot versus the RLD. This in vitro testing on the stability lots should address the large fluctuation in injection times observed in stability testing.

The application is incomplete.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL
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.*

***Drug Specific Issues:**

1. The Imitrex label contains the following bolded precaution:
   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

3.2 Contents of Submission

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

3.3 Formulation

Location in appendix	Section 3.8, Page 8
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

3.4 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?	DBE requests a fasting BE study in patients.

3.5 Deficiency Comments

1. As recommended by the OGD clinical group, "*Because differences in injection time and other differences in device performance and design, such as the difference in needle gauge, might affect the plasma concentration profile for sumatriptan, and Cmax in particular, we recommend that human PK studies be requested to demonstrate bioequivalence*", the DBE 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.

2. The firm should perform comparative in vitro testing on 1) drug volume delivered, 2) injection time, and 3) force to fire for the biobatch lot and the RLD. The firm should submit an EXCEL spreadsheet of individual data, mean, and %CV for these data on the test product versus Imitrex® STATDOSE Injectable

3. To address the large fluctuation in injection times observed in stability testing, the DBE recommends that the firm conducts additional in vitro testing on 1) drug volume delivered, 2) injection time, and 3) force to fire for the biobatch lot and the stability lots. The firm should submit an EXCEL spreadsheet of individual data, mean, and %CV for these data on the test producs bio- and stability lots.

4. 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 CAD (cardiac artery disease), and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug", the DBE recommends adequate safety monitoring be in place during the BE study. The firm may also submit a protocol for the BE study to DBE.

3.6 Recommendations

The Division of Bioequivalence (DBE) does not agree that the information submitted Sun Pharmaceutical Industries, Limited demonstrates that Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL, pre-filled syringe with auto-injector meets the requirements of Section 21 CFR § 320.22(b)(1). The DBE denies the waiver of in vivo bioequivalence testing be granted due to the deficiencies above.

3.7 Comments for Other OGD Disciplines

Discipline	Comment
	None

3.8 Formulation Data

Test Product

Component	mg/mL
Sumatriptan Succinate, Ph. Eur.	(b) (4)
Sodium Chloride, USP	7.00
Water for Injection, USP	q.s. to 1 ml
(b) (4)	**

* (b) (4)

**

Comparative Formulation

	Test Product (Sumatriptan Succinate Injection)	RLD (Imitrex® Injection)*
Ingredient	**Quantity per 0.5 mL**	**Quantity per 0.5 mL**
Sumatriptan Succinate	(b) (4)	
Sodium Chloride, USP	3.50	3.50
Water for Injection, USP	q.s. to 0.5 ml	q.s. to 0.5 ml
(b) (4)	--	--

(b) (4)

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

3.9 Detailed Regulatory History (If Applicable)

ANDAs: 79-123 (Bedford Labs)
78-067 (Sandoz)
77-907 (Teva)
78-318 (Teva)
78-593 (Wockhardt)
(b) (4)
90-641 (Sagent Strides)
(b) (4)
79-240 (Abraxis)
(b) (4)
77-332 (Par)
90-314 (Sagent Strides)
77-871 (Parkedale)
79-242 (Abraxis)

Protocols: None

Controls: None

3.10 Consult Reviews

Division of Chemistry II review

http://darrts.fda.gov:7777/darrts/ViewDocument?documentId=090140af801ae294

Justification of performing study in healthy subjects

A memo in the RLD approval letter dated December 2, 1991 (http://fdaesearch.fda.gov:81/SecureES/loadNativeDocument.do?theId=17279729&theLib=darrts_lib#xml=http://fdaesearch.fda.gov:81/SecureES/loadPdfDocument.do?theId=17279729&theLib=darrts_lib) 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 DBE recommends the BE study can be performed in normal healthy individuals that inject themselves using the device.

3.11 Additional Attachments

E-mail correspondence from clinical team

Chandra:

Thanks for the quick response. I agree with both of your proposals, let's finish up this review.

Barbara

From: Chaurasia, Chandra S
Sent: Wednesday, December 09, 2009 4:03 PM
To: Davit, Barbara M
Cc: Dhariwal, Kuldeep R; Williamson, Leah
Subject: FW: Finalized - ANDA 90358 General Review (REV-CLINICAL-03)

Barbara:

Forwarding Dena's response. Recommendation #2 is quite clear now, I would think we may go with in vitro comparisons for the injection time and volume (main concerns of the Clinical Team) for the stability batch(es) vs. biolot batch.

With respect to dose-administration - patient-administered or by the nurse -, in my opinion the subject-self-administered is a right way to do as it is reflective of the 'real-use' situation. The Sponsor should have procedures designed to educate the enrolled-subjects on how to use the medication - either through a dummy trial and/or a video movie or any other way they can come up with.

Having said this, we will, of course, go by your suggestions and inputs.

Thanks,
Chandra

From: Chang, Nancy
Sent: Wednesday, December 09, 2009 1:53 PM
To: Chaurasia, Chandra S
Cc: Hixon, Dena R
Subject: RE: Finalized - ANDA 90358 General Review (REV-CLINICAL-03)

Hi Chandra,

I certainly think it is a good idea to make sure that patients are able to use the product appropriately, and that is the basis for recommendation #3. However, in my mind, it really doesn't matter whether that is done as a separate study or as part of a PK study. Any time that subjects do administer to themselves during a PK study, whether or not there is going to be a separate real-use study, it would certainly be best if the PK study would include procedures to collect information about correct use and about the subjects' understanding of the directions.

Re your second bullet, yes I agree, recommendation #2 could certainly be addressed with in vitro testing and specs.

Nancy

From: Chaurasia, Chandra S
Sent: Wednesday, December 09, 2009 1:24 PM
To: Hixon, Dena R; Chang, Nancy
Cc: Davit, Barbara M; Dhariwal, Kuldeep R; Smith, Glen J; Williamson, Leah; Catterson, Debra M
Subject: RE: Finalized - ANDA 90358 General Review (REV-CLINICAL-03)

Good afternoon Dena and Nancy,

We are currently preparing BE recommendations for Sun's ANDA on this drug product, and would like to have your inputs on the followings:

- With respect to the BE recommendations # 1 and 2., should the subjects administer the drug themselves - as one would do in the real situation considering the product is auto injector and self-administered - or, should the drug be administered by qualified health care professional (nurses) as this will minimize the individual errors and variations associated with each subject.
- With respect to recommendation #2, it seems you are recommending to conduct additional BE study on the aged batch due to fluctuations in injection time in stability testing. Alternatively, could this variation issue be addressed by comparing the in vitro testing, e.g., the injection time and volume delivered between the fresh and stored batches - with an statistical criterion associated with these parameters (injection time and volume delivered) comparison. As such, we are going to include these in vitro tastings with the bio batch in our recommendation to the firm.

As I understand, Sun wants to have a meeting with the Agency on its ANDA as soon as possible, and we would like to provide our recommendations soon. With this in mind, we are requesting your response at the earliest convenient time.

Thanks,
Chandra

BIOEQUIVALENCE DEFICIENCIES

ANDA: 090358

APPLICANT: Sun Pharmaceutical Industries Ltd.

DRUG PRODUCT: Sumatriptan Succinate Injection
EQ 6 mg base/0.5 mL (pre-filled syringe with auto-injector)

The Division of Bioequivalence (DBE) has completed its review of your submission and the following deficiencies have been identified:

1. The DBE does not agree that the information submitted by you demonstrates that Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL, pre-filled syringe with auto-injector meets the requirements of Section 21 CFR § 320.22(b)(1).

2. Because differences in injection time and other differences in device performance and design, such as the difference in needle gauge, might affect the plasma concentration profile for sumatriptan, and Cmax in particular, we recommend that an in vivo study with pharmacokinetic (PK) endpoints be conducted to demonstrate bioequivalence. Therefore, the DBE recommends that you conduct a single-dose two-way crossover fasting bioequivalence study in healthy subjects. The study subjects should inject themselves both the test and reference products using the respective auto-device.

3. Please also conduct comparative in vitro testings on 1) drug volume delivered, 2) injection time, and 3) force to fire. These in vitro tests should be conducted on the biobatch lot and the reference listed drug (RLD). Please submit an EXCEL spreadsheet of individual data, mean, and %CV for these data on the test product versus Imitrex® STATDOSE Injectable

4. In addition to the in vitro testing above, to address the large fluctuation in injection times observed in stability testing, the DBE recommends that you conduct

additional in vitro testing on 1) drug volume delivered, 2) injection time, and 3) force to fire stability lots. These data should be compared to data from the RLD. Please submit an EXCEL spreadsheet of individual data, mean, and %CV for these data on the test products bio- and stability lots.

5. Considering the warning – among others - on the reference listed drug, "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 (cardiac artery disease), and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug", the DBE recommends adequate safety monitoring be in place during the bioequivalence study. You may also submit a protocol for the BE study.

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

3.12 Outcome Page

ANDA: 90-358
Completed Assignment for 90358 ID: 7500

Reviewer: Williamson, Leah **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: Sumatriptan Succinate injection

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
7500	1/18/2008	Other	Waiver Injectable	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Injectable Waiver(s)	
Strength 1 (DIW)	1
Injectable/Waiver Total	*1*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90358	ORIG-1	SUN PHARMACEUTICAL INDUSTRIES LTD	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/

LEAH N WILLIAMSON
12/18/2009

CHANDRA S CHAURASIA
12/18/2009

BARBARA M DAVIT
12/18/2009

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090358
Drug Product Name	Sumatriptan Succinate Injection, pre-filled syringe with auto-injector
Strength(s)	EQ 6 mg base/0.5 mL
Applicant Name	Sun Pharmaceutical Industries Ltd.
Address	Acme Plaza, Andheri-Kurla Road Andheri (East), Mumbai-400059, India
Applicant's Point of Contact	Anne Toland
Contact's Telephone Number	609-495-2823
Contact's Fax Number	609-495-2711
Original Submission Date(s)	January, 18, 2008
Submission Date(s) of Amendment(s) Under Review	February 22, 2010 and March 12, 2010
Reviewer	Leah N. Williamson, Ph.D.

Study Number (s)	PKD/07/068	PKD/10/033	PKD/10/048
Study Type (s)	Subcutaneous Injection (Dose administration by In-house physician)	Subcutaneous Injection (Self administered dose by subjects, Thigh Region)	Subcutaneous Injection (Self administered dose by subjects Deltoid Region)
Strength (s)	6 mg	6 mg	6 mg
Clinical Site	Sun Pharmaceutical Industries Ltd.		
Clinical Site Address	Tandalja, Vadodara – 390 020. (INDIA)		
Analytical Site	Sun Pharmaceutical Industries Ltd.		
Analytical Site Address	Tandalja, Vadodara -390020, India		

OVERALL REVIEW RESULT	**INADEQUATE**		
DSI REPORT STATUS	**INADEQUATE**		
BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
10	**FASTING STUDY**	**6 mg**	**ADEQUATE**
12	**FASTING STUDY**	**6 mg**	**INADEQUATE**
12	**FASTING STUDY**	**6 mg**	**INADEQUATE**
10	**IN VITRO STUDY**	**6 mg**	**ADEQUATE**

REVIEW OF AN AMENDMENT

1. EXECUTIVE SUMMARY

On January 18, 2008 Sun Pharmaceutical Industries requested 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 auto-injector device. 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:7777/darrts/ViewDocument?documentId=090140af801ae294).
DCII consulted the OGD clinical group because of an apparent difference in injection times between the proposed test and RLD autoinjector devices for sumatriptan. Specifically, the proposed device instructed users to hold in place until a second "click" or for a count of (b) (4) The RLD device instructs users to hold in place for "at least 5 seconds". The clinical group w asked to advise on the whether this difference would be consistent with therapeutic equivalence from a clinical standpoint. Since that time, OGD has received a submission from the firm (9/1/09) revising the proposed labeling to reflect a 5 second injection time.

In addition, the CMC review had raised concerns about defects observed for the full assembled device during syringe integrity testing and the completeness of the stability data.

The OGD clinical group provided the following recommendation among others (http://darrts.fda.gov:7778/darrts/ViewDocument?documentId=090140af801ae294).

1. Because differences in injection time and other differences in device performance and design, such as the difference in needle gauge, might affect the plasma concentration profile for sumatriptan, and Cmax in particular, we recommend that human PK studies be requested to demonstrate bioequivalence.

2. In addition, the large fluctuation in injection times observed in stability testing should be addressed. Consideration could be given to requesting BE data from products of various ages and also examining for inter-individual variation in plasma level profiles that could result from large device-to-device variations in injection times. Alternatively, consideration could be given to setting specifications that would minimize such variability.

3. The currently proposed labeling for the operation and directions for use of the proposed device are not expected to raise clinical safety concerns for this generic product. However, it would be optimal to assess the ability of patients to understand and appropriately follow the directions for use.

The Division of Bioequivalence (DBE) was in agreement with the above recommendations by the clinical team, and denied a waiver request for *in vivo* bioequivalence study requirements for the test Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL. The DBE requested a single-dose two-way crossover fasting bioequivalence study where the subjects inject themselves both the test and reference products using the respective device. DBE also requested that the firm perform comparative in vitro testing on 1) drug volume delivered, 2) injection time, and 3) force to fire for the test biobatch lot and stability lots with and the RLD. In addition, the DBE recommended conducting each of these in vitro tests – 1) drug volume delivered, 2) injection time, and 3) force to fire. These comparisons should be made directly between the stability lot versus the RLD. This in vitro testing on the stability lots should address the large fluctuation in injection times observed in stability testing.

In the February 22, 2010 amendment, the firm submitted the results of a fasting bioequivalence study (study # PKD/07/068) on its Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL comparing with the reference listed drug IMITREX® (Sumatriptan Succinate) Injection, EQ 6 mg base/0.5 mL. The BE study was designed as a single-dose, two-way crossover study in healthy males. An in-house physician administered the injection to the subjects. The firm states that the study # PKD/07/068 was already completed before receiving the deficiency letter from DBE. Since the DBE recommends self-administration of the drug for the BE evaluation of sumatriptan succinate injection, pre-filled syringe with auto-injector, the results of the study using physician-administered dose (Study # PKD/07/068) will be used for informational purposes only. Thus, only an abbreviated review of this study is done by the reviewer. The fasting BE study PKD/07/068 meets the 90% confidence interval criteria for the PK measures summarized in the table below:

Sumatriptan 1 × 6 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. PKD/07/068, N=27					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	125.59	121.85	1.03	99.70	106.56
AUC∞ (hr *ng/ml)	131.57	127.41	1.03	100.05	106.57
Cmax (ng/ml)	107.44	102.96	1.04	97.52	111.67

As stated above the DBE recommends self-administration of the drug for the BE evaluation of sumatriptan succinate injection, pre-filled syringe with auto-injector, therefore, the firm submitted another amendment dated March 12, 2010 consisting of two BE studies (PKD/10/033 and PKD/10/048). Each of these two studies used self-administration by the study subjects – Study #PKD/10/033 using the self-administration in the thigh region, and Study #PKD/10/048 in the deltoid region.

Each BE study was designed as a single-dose, two-way crossover study in healthy males. The fasting BE studies are incomplete pending firm's explanation on drug administration as to why the auto-injector should be held for 15 seconds while the injection time is 5 seconds. The results of the fasting BE studies are summarized below:

Sumatriptan 1 × 6 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. PKD/10/033, N=23					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	132.42	137.45	0.96	92.43	100.42
AUC∞ (hr *ng/ml)	137.87	144.43	0.95	91.87	99.19
Cmax (ng/ml)	109.11	120.27	0.91	84.71	97.15

Sumatriptan 1 × 6 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. PKD/10/048, N=24					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	125.09	131.15	0.95	91.12	99.84
AUC∞ (hr *ng/ml)	130.78	136.41	0.96	91.76	100.16
Cmax (ng/ml)	116.02	118.66	0.98	90.39	105.76

A Division of Scientific Investigations (DSI) inspection is pending for the analytical and clinical site for a related ANDA (for cause).

The application is inadequate pending explanation of dose administration.

2. RESPONSE TO DEFICIENCIES

Supporting Document 10

1. The DBE does not agree that the information submitted by you demonstrates that Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL, pre-filled syringe with auto-injector meets the requirement of Section 21 CFR § 320.22(b)(1).

Firm's Response:
We hereby acknowledge agency's comment for Sun's request for biowaiver pursuant to 21 CFR § 320.22(b)(1). Please note that fasting bioequivalence study in healthy subjects has been conducted for Sun's proposed product and Reference listed drug IMITREX® (Sumatriptan Succinate) Injection. Complete report of this bioequivalence study has been provided.

Reviewer's Comment:
The results of the BE study are found in the appendix. The fasting BE study is adequate.

2. Because differences in injection time and other differences in device performance and design, such as the difference in needle gauge, might affect the plasma concentration profile for sumatriptan, and Cmax in particular, we recommend that an in vivo study with pharmacokinetic (PK) endpoints be conducted to demonstrate bioequivalence. Therefore, the DBE recommends that you conduct a single-dose two-way crossover fasting bioequivalence study in healthy subjects. The study subjects should inject themselves both the test and reference products using the respective auto-device.

Firm's Response:
Please note that we have conducted single-dose two-way crossover fasting bioequivalence study in healthy subjects. Complete report for this study has been provided.

Please also note that bioequivalence study for Sumatriptan Succinate injection 6 mg base/0.5 mL prefilled syringe with auto injector was already completed before receiving this recommendation. In this study drug administration was done by in-house physician instead of study subjects injecting themselves. Injection by physician was selected considering following aspects:

- To have specificity for both period as it is site specific injection as site is pre marked before dosing.
- Self administration is 1st time for volunteer. To avoid loss of subjects due to improper dosing/incomplete dosing.
- Both the devices (of test and reference product) have similar final delivery steps which are 'Press against the site of delivery', and 'press the actuator button'. Whether the volunteers administer study medication to themselves or the study physicians administer study medication to volunteers, it will not make a difference

with respect to the depth of needle penetration, duration of the injection and volume delivered which could be the parameters affecting BE.

We therefore request for acceptance of method of dosing used for the existing bioequivalence study, as study drug administration (pressing of actuator button), done by study physician shall not have any impact on BE conclusion.

Reviewer's Comment:
As noted above, in the most current amendment dated March 12, 2010 the firm has provided results of two BE studies PKD/10/033 and PKD/10/048. These studies have been reviewed in full in this document. In addition, an abbreviated review of the BE study PKD/07/068 wherein the drug administration was done by in-house physician was done. Each of these studies does meet the 90% confidence interval for each of the three PK parameters. Please see the recommendation and Appendix section for more details.

3. Please also conduct comparative in vitro testings on 1) drug volume delivered, 2) injection time, and 3) force to fire. These in vitro tests should be conducted on the biobatch lot and the reference listed drug (RLD). Please submit an EXCEL spreadsheet of individual data, mean, and %CV for these data on the test product versus Imitrex® STATDOSE Injectable.

Firm's Response:
Please note that 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. Please note that reference listed drug used in bio study has expired, hence testing and data has been provided for this expired RLD sample (batch #C298885; Expiry: April 2009) and on one additional batch of RLD (batch #C401623, Expiry: January 2011).

Reviewer's Comment:
The firm submitted the following in-vitro data:

Biostudy lot vs. Expired RLD lot

Test product: Sumatriptan Succinate Injection, 6mg/ 0.5ml PFS (US) B.No.JK70920 Date of Analysis: 29-Aug-2007			
Sr. No.	Activation force(kg)	Injection time (sec)	Deliverable volume (ml)
1	[redacted] (b) (4)		
2			
3			
4			
5			
6			
7			
8			
9			
10			
Max.			
Min.			
Mean	0.97	1.88	0.5107
Std. dev.	0.05	0.05	0.0031
%CV	5.15	2.80	0.60

Reference product: IMITREX US Innovator (Sumatriptan Succinate Injection, 6mg/ 0.5ml PFS) Additional Innovator lot data (Lot No.: C29885, Exp Dt.: Apr 2009) Date of Analysis: 08-Feb-2010			
Sr. No.	Activation force(kg)	Injection time (sec)	Deliverable volume (ml)
1	[redacted] (b) (4)		
2			
3			
4			
Max.			
Min.			
Mean	1.69	1.37	0.5006
Std. dev.	0.19	0.05	0.0043
%CV	10.99	4.01	0.8572

	Activation force	Injection time	Deliverable volume
Percent Difference	-74.33	26.88	1.98

Expired RLD lot vs. Fresh RLD lot

Reference product: IMITREX US Innovator (Sumatriptan Succinate Injection, 6mg/ 0.5ml PFS) Additional Innovator lot data (Lot No.: C29885, Exp Dt.: Apr 2009) Date of Analysis: 08-Feb-2010			
Sr. No.	Activation force(kg)	Injection time (sec)	Deliverable volume (ml)
1	(b) (4)		
2			
3			
4			
Max.			
Min.			
Mean	1.69	1.37	0.5006
Std. dev.	0.19	0.05	0.0043
%CV	10.99	4.01	0.8572

Reference product: IMITREX US Innovator (Sumatriptan Succinate Injection, 6mg/ 0.5ml PFS) (Lot.No.C401623 , Exp-Jan 2011) Date of Analysis: 08-Feb-2010			
Sr. No.	Activation force(kg)	Injection time (sec)	Deliverable volume (ml)
1	(b) (4)		
2			
3			
4			
5			
6			
Max.			
Min.			
Mean	1.29	1.30	0.5054
Std. dev.	0.22	0.11	0.0027
%CV	17.15	8.27	0.5430

	Activation force	Injection time	Deliverable volume
Percent Difference	23.56	5.04	-0.95

The data meet the firm's acceptance criteria (Supporting Document #9, Attachment 2)

08	Function test of Drug delivery device :		
	Test	Method	Specification
8.1	Description	(b) (4)	
8.2	Shield remover Removal force		
	Neddle cover pre-injection force		
8.3	Actuator button safety force		
8.4	Activation force		
	Injection time		
	Deliverable volume		
	Injection depth		
8.5	Needle cover override force		
	Separation force		

The %CV's for the test product are all less than 6%. The difference in injection time between the test and reference devices is (b) (4) seconds. The label states that the patient should slowly count to 5 before lifting the auto-injector from the injection site. The injection time data for the firm's device is therefore adequate. The %CV for the injection volume is less than 1% for both the test and reference products. The firm's data for the activation force is 77% less than that of the reference device. The firm's device is therefore easier to inject than the reference device. The firm's data is adequate.

4. In addition to the in vitro testing above, to address the large fluctuation in injection times observed in stability testing, the DBE recommends that you conduct additional in vitro testing on 1) drug volume delivered, 2) injection time, and 3) force to fire stability lots. These data should be compared to data from the RLD. Please submit an EXCEL spreadsheet of individual data, mean, and %CV for these data on the test products bio- and stability lots.

Firm's Response:
Please note that Sun's batch #JK70920A used for bioequivalence study is also stability lot. Fluctuation in injection time has been observed at 3 month and 9 months station. Following explanation for the observed values has been provided in response to telephone amendment for chemistry section (submitted on 22 December 09).

Please also note that in long term storage stability studies, results for injection time at 3 month station (b) (4) and 9 month (b) (4) are found to be (b) (4) and (b) (4) the (b) (4) specification of (b) (4) seconds. Subsequently 12, 18 and 24 months stability studies data for injection time are well within the specification.

Additionally excel spreadsheet with results of drug volume delivered, injection time and force to fire, from recent batch #JK91196A has been provided. In this data injection time of units tested are consistent and well within the proposed specification. Data for test and RLD lots used in bioequivalence study has been provided.

Reviewer's Comment:
The firm provided the following data on the biostudy lot:

Test product: Sumatriptan Succinate Injection, 6mg/ 0.5ml PFS (US) B.No.JK91196A Date of Analysis: 02-Sep-2009 to 11-Sep-2009			
Sr. No.	Activation force(kg)	Injection time (sec)	Deliverable volume (ml)
1	(b) (4)		
2			
3			
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10			
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38	(b) (4)
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79	
80	
81	
82	
83	

84	(b) (4)		
85			
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92			
93			
94			
95			
96			
97			
98			
Max			
Min			
Mean	0.90	1.73	0.4973
Std. dev.	0.04	0.19	0.0046
%CV	4.84	11.26	0.9170

The %CV for the injection time is high at 11%; however, the average injection time meets the firm's specification of (b) (4) seconds. The average injection time of the test product is 1.73 seconds while the average for the RLD is 1.37 seconds. The activation force of the test product is (b) (4) (b) (4) than the RLD (b) (4), however; it is within the acceptance criteria (0.5-1.6 kg). The injection volume for the test product is (b) (4) than the RLD (b) (4) (b) (4), and is within the acceptance criteria (0.44-0.53). The RLD labeling states that the injection volume is 0.5 mL. The %CVs were low for the test product's injection force and injection volume (4.84% and 0.917%. The firm's data is adequate.

5. Considering the warning – among others - on the reference listed drug, "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 (cardiac artery disease), and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug", the DBE recommends adequate safety monitoring be in place during the bioequivalence study. You may also submit a protocol for the BE study.

Firm's Response:
Please note that bioequivalence study for Sumatriptan Succinate injection 6 mg base/0.5 mL pre-filled syringe with auto injector has already been completed prior to receiving this communication.

During this study, following safety precautions were taken:

- ECG was measured at 1 hour plus or minus 30 minutes post dose and as when recommended by study physician. All subjects ECG were found normal without any abnormalities except subject 17 (sinus bradycardia-period II-reference product) and subject 19 (sinus bradycardia-period II-test product). However, there is no cardiac ischemia in any of the ECGs.

- There were no extra ECGs taken based on any clinical findings during study.

- Vital signs (blood pressure and pulse rate) were measured at various time points like pre-dose and at 1, 2, 4 hrs post-dose and at check out after drug administration. All vitals were reported normal.

During pre-study screening procedure before enrollment, subject's cardiac history were asked in details as well as examined for the same. All subjects enrolled in the study were not having history or any evidence of cardiovascular disorder.

All above safety precautions and assessment are considered to be sufficient to assess subject's safety during the study, based on warning mentioned on reference listed drug package insert.

Reviewer's Comment:
The firm's response is adequate.

Supporting Document 12 submitted in the most recent amendment dated March 12, 2010

Firm's Comments:
Please find enclosed the following bioequivalence study reports:

1. Study PDK/10/033: Bioequivalence of Sumatriptan Succinate 6 mg/0.5 mL subcutaneous injection of Sun Pharmaceutical Industries, Ltd India and Imitrex® 6 mg/0.5 mL (Sumatriptan Succinate) subcutaneous injection of GlaxoSmithKline, Research Triangle Park, NC 27709- **self administration by subjects themselves at the top part of thigh region.**

2. Study PDK/10/048: Bioequivalence of Sumatriptan Succinate 6 mg/0.5 mL subcutaneous injection of Sun Pharmaceutical Industries, Ltd India and Imitrex® 6 mg/0.5 mL (Sumatriptan Succinate) subcutaneous injection of GlaxoSmithKline, Research Triangle Park, NC 27709- **self administration by subjects themselves at deltoid region on left side.**

Reviewer's Comment:
The results of the BE studies are found in the Appendix. Both fasting BE studies are acceptable.

3. APPENDIX

3.1 Pre-Study Bioanalytical Method Validation

Information Requested	Sumatriptan
Bioanalytical method validation report location	**5-3-1-4 (Section 16-6); Page – 1 - 63**
Study Report Number	**Report No.: MV/STP/108**
Analyte	Sumatriptan
Internal standard (IS)	(b) (4)
Method description	LC-MS/MS
Limit of quantitation	2.00 ng/ml
% recovery (and %CV) at each concentration tested	QC Low : 84.6 %, QC Med A: 78.1 %, QC Med B: 77.3%, QC High : 81.9%
Average recovery of IS (%)	92.5%
Standard curve concentrations (ng/mL)	2.00, 4.00, 10.00, 30.01, 90.03, 165.06, 220.08, 275.10
QC concentrations (ng/mL)	Low QC : 5.00 Medium QC A : 55.02 Medium QC B : 110.04 High QC : 200.08
QC Intraday precision range (%)	2.1 % to 4.7 %
QC Intraday accuracy range (%)	85.3 % to 100.7 %
QC Interday precision range (%)	0.8% to 4.7%
QC Interday accuracy range (%)	97.4% to 111.3%
Bench-top stability (hrs)	Approx. 7 hours at room temperature in Human EDTA K_3 Plasma Approx. 7 hours at room temperature in Human CPDA Plasma
Stock stability (days)	21 days @ 2-8°C

Processed stability (hrs)	Approx. 48 hours @ 8°C ± 2°C
Freeze-thaw stability (cycles)	03 cycles
Long-term storage stability (days)	169 days @ -20° ± 5°C
Dilution integrity	3 times of CS8 concentration (825.31 ng/ml) diluted 5 folds.
Selectivity	No interference observed in blank plasma samples.

SOPs submitted	ATP/01/STP "Determination of Sumatriptan in human plasma using liquid chromatography method with tandem mass spectrometry-thermo discovery max"
Bioanalytical method is acceptable	Yes

Comments on the Pre-Study Method Validation:

K_3ETDA and Citrate Phosphate Dextrose Anticoagulant (CPDA) were used as the anticoagulants in the method validation. An anticoagulant effect study was performed and found acceptable. Subject samples were collected in vacutainers containing K_3EDTA.

The same method validation was used for all three studies.

Method validation is acceptable.

3.2 In Vivo Studies

Table 1. Summary of all in vivo Bioequivalence Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage, Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: Mean (Range)	Mean Pharmacokinetic Parameters[1] (+/- SD) (N = 27)						
					Cmax (ng/mL)	Tmax (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{0-inf} (ng*hr/mL)	T1/2 (hr)	Kel (1/hr)	Study Report Location
PKD/07/068	To monitor the safety of the subjects participating in the study and to assess the bioequivalence of Sumatriptan Succinate 6 mg/0.5 ml subcutaneous injection of Sun Pharmaceutical Industries Ltd, India and Imitrex® 6 mg/0.5 ml (Sumatriptan Succinate) subcutaneous injection of GlaxoSmithKline, Research Triangle Park, NC 27709, in 28 healthy human adult subjects, under fasting conditions.	A Randomized, open label, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study with washout period of 5 days between each drug administration under fasting conditions.	**Test:** Sumatriptan Succinate 6 mg/0.5 ml /Injection /Subcutaneous Batch No: JK70920A	27 healthy male subjects (27/0) Mean age (Range) : 27.9 (19-39)	108.032 +/- 19.3976 (18.0)	0.200 (0.050 - 0.350)	126.1600 +/- 20.43794 (16.2)	132.5034 +/- 21.06438 (15.9)	1.5440 +/- 0.31460 (20.4)	0.46598 +/- 0.089010 (19.1)	Section 5.3.1.2 (2.Synopsis)
			Reference: Imitrex® (Sumatriptan Succinate) 6 mg/0.5 ml /Injection /Subcutaneous Lot No.: C298885		104.273 +/- 24.7192 (23.7)	0.200 (0.050 - 0.416)	121.4858 +/- 18.68289 (15.4)	126.9790 +/- 18.94348 (14.9)	1.5005 +/- 0.32572 (21.7)	0.48262 +/- 0.103070 (21.4)	

[1] **Arithmetic mean ± standard deviations (% CV) except for Tmax (Range) for which the median are reported.**

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage, Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: Mean (Range)	Mean Pharmacokinetic Parameters[1] (+/- SD) (Sumatriptan) (N=23)						
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{0-inf} (ng*hr/mL)	$T_{1/2}$ (hr)	K_{el} (1/hr)	Study Report Location
PKD_10_033	To monitor the safety of the subjects participating in the study and to assess the bioequivalence of Sumatriptan Succinate 6 mg/0.5 ml subcutaneous injection of Sun Pharmaceutical Industries Ltd, India and Imitrex® 6 mg/0.5 ml (Sumatriptan Succinate) subcutaneous injection of GlaxoSmithKline, Research Triangle Park, NC 27709 administered at top part of thigh region, in 24 healthy human adult subjects under fasting conditions.	A Randomized, open label, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study with 6 days washout period between each drug administration under fasting conditions.	**Test:** Sumatriptan Succinate 6 mg/ 0.5ml/ Injection / Subcutaneous Batch No: JK91196	23 healthy male subjects (23/0) Mean age (Range) : 29.7 (19 - 42)	113.185 +/- 30.7104 (27.1)	0.250 (0.100 – 0.417)	134.2000 +/- 20.88707 (15.6)	139.6450 +/- 21.22135 (15.2)	1.5541 +/- 0.42770 (27.5)	0.47439 +/- 0.114088 (24.0)	Section 5.3.1.2 (Section 2 Synopsis)
			Reference: Imitrex® (Sumatriptan Succinate) 6 mg/ 0.5ml/Injection/ Subcutaneous Lot No: C401623		124.523 +/- 32.1278 (25.8)	0.167 (0.100 – 0.333)	139.8072 +/- 25.04180 (17.9)	146.9253 +/- 26.12685 (17.8)	1.7832 +/- 1.00597 (56.4)	0.44045 +/- 0.110289 (25.0)	

[1]**Arithmetic mean ± standard deviations (% CV) except for T_{max} (Range) for which the median are reported.**

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: Mean (Range)	Mean Pharmacokinetic Parameters[1] (+/- SD) (Sumatriptan) (N=24)						
					C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-t} (ng*hr/mL)	AUC_{0-inf} (ng*hr/mL)	$T_{1/2}$ (hr)	K_{el} (1/hr)	Study Report Location
PKD_10_048	To monitor the safety of the subjects participating in the study and to assess the bioequivalence of Sumatriptan Succinate 6 mg/0.5 ml subcutaneous injection of Sun Pharmaceutical Industries Ltd, India and Imitrex® 6 mg/0.5 ml (Sumatriptan Succinate) subcutaneous injection of GlaxoSmithKline, Research Triangle Park, NC 27709 administered at the deltoid region on left side, in 24 healthy human adult subjects under fasting conditions.	A Randomized, open label, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study with 6 days washout period between each drug administration under fasting conditions.	**Test:** Sumatriptan Succinate 6 mg/ 0.5ml/ Injection / Subcutaneous Batch No: JK91196	24 healthy male subjects (24/0) Mean age (Range) : 32.2 (21 - 50)	118.349 +/- 24.6554 (20.8)	0.200 (1.000 – 0.417)	126.5826 +/- 20.11950 (15.9)	132.2650 +/- 20.52316 (15.5)	1.4593 +/- 0.52480 (36.0)	0.51267 +/- 0.116320 (22.7)	Section 5.3.1.2 (Section 2 Synopsis)
			Reference: Reference: Imitrex® (Sumatriptan Succinate) 6 mg/ 0.5ml/Injection/ Subcutaneous Lot No: C401623		121.174 +/- 25.6621 (21.2)	0.200 (1.000 – 0.333)	133.0598 +/- 23.56056 (17.7)	138.2737 +/- 23.64149 (17.1)	1.4350 +/- 0.34404 (24.0)	0.50497 +/- 0.099077 (19.6)	

[1]Arithmetic mean ± standard deviations (% CV) except for T_{max} (Range) for which the median are reported.

Table 2. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Sumatriptan 1 × 6 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study No. PKD/07/068, N=27					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng hr/mL)	124.36	120.04	1.04	100.97	106.29
AUC∞ (ng hr/mL)	130.68	125.56	1.04	101.34	106.91
Cmax (ng/mL)	106.27	101.68	1.05	98.08	111.36

Sumatriptan 1 × 6 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study No. PKD/10/033, N=23					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng hr/mL)	132.42	137.45	0.96	92.43	100.42
AUC∞ (ng hr/mL)	137.87	144.43	0.95	91.87	99.19
Cmax (ng/mL)	109.11	120.27	0.91	84.71	97.15

Sumatriptan 1 × 6 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study No. PKD/10/048, N=24					
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (ng hr/mL)	125.09	131.15	0.95	91.12	99.84
AUC∞ (ng hr/mL)	130.78	136.41	0.96	91.76	100.16
Cmax (ng/mL)	116.02	118.66	0.98	90.39	105.76

Table 3. Reanalysis of Study Samples

Study No. PKD_07_068 Sumatriptan Succinate 6 mg/ 0.5 ml S.C. injection (Fasting) Location in final report: 5-3-1-4 (Section 16-5); Page 23								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual Number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Unacceptable internal standard response	22	12	2.14	1.17	22	12	2.14	1.17
Incomplete Analysis	1	0	0.10	0.00	1	0	0.10	0.00
Sample repeated to obtain confirming value	4	0	0.39	0.00	3	0	0.29	0.00
Inconsistent Profile	0	1	0.00	0.10	0	1	0.00	0.10
Rejected analytical run	101	95	9.84	9.26	86	93	8.38	9.06
Total	**128**	**108**	**12.48**	**10.53**	**112**	**106**	**10.92**	**10.33**

Note: Total 1026 samples were analyzed.

Study No. PKD_10_033 Sumatriptan Succinate 6mg/0.5ml Subcutaneous Injection (Fasting) Location in final report: 5-3-1-4 (Section 16-5); Page 21								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual Number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Unacceptable internal standard response	1	1	0.11	0.11	1	1	0.11	0.11
Inconsistent Profile	1	0	0.11	0.00	1	0	0.11	0.00
Rejected analytical run	38	38	4.35	4.35	37	38	4.24	4.35
Total	**40**	**39**	**4.58**	**4.47**	**39**	**39**	**4.47**	**4.47**

Note: Total 873 samples were analyzed.

Study No. PKD_10_048 Sumatriptan Succinate 6mg/0.5ml Subcutaneous Injection (Fasting) Location in final report: 5-3-1-4 (Section 16-5); Page 23								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual Number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Unacceptable internal standard response	16	25	1.78	2.78	16	25	1.78	2.78
Incomplete analysis	1	2	0.11	0.22	1	2	0.11	0.22
Sample reanalyzed to obtain confirming value	1	1	0.11	0.11	1	1	0.11	0.11
Rejected analytical run	38	37	4.22	4.11	38	35	4.22	3.89
Total	**56**	**65**	**6.22**	**7.22**	**56**	**63**	**6.22**	**7.00**

Note: Total 900 samples were analyzed.

Did use of recalculated plasma concentration data change study outcome?

No

Comments from the Reviewer:

The reviewer repeated the statistical analysis using the original values for the four samples that were repeated due to 1) Sample repeated to obtain confirming value and 2) Inconsistent profile. The repeat statistical analysis was acceptable.

3.3 Formulation

Components	mg/ml
Sumatriptan Succinate, Ph. Eur.	(b) (4) 1
Sodium Chloride, USP	7.00
Water for Injection, USP	q.s. to 1 ml
(b) (4)	*2

*1 (b) (4)

*2

Formulation was previously found acceptable in the first BE review, and was Q1/Q2 the same with respect to the reference listed drug Imitrex Injection (6 mg/mL) (http://darrts.fda.gov:7778/darrts/ViewDocument?documentId=090140af801b5223).

3.4 In Vitro Dissolution

Location of DBE Dissolution Review	N/A
Source of Method (USP, FDA or Firm)	
Medium	
Volume (mL)	
USP Apparatus type	
Rotation (rpm)	
DBE-recommended specifications	
If a modified-release tablet, was testing done on ½ tablets?	
F2 metric calculated?	
If no, reason why F2 not calculated	
Is method acceptable?	
If not then why?	

3.5 Waiver Request(s)

Strengths for which waivers are requested	N/A
Proportional to strength tested in vivo?	
Is dissolution acceptable?	
Waivers granted?	
If not then why?	

3.6 Deficiency Comments

1. The clinical reports for studies PKD_10_033 and PKD_10_048 state that the injection was continued to hold firmly against the skin up to second click sound/approximately 15 seconds. The firm should explain why the auto-injector should be held for 15 seconds while the injection time is ≤ 5 seconds in the firm's BE study design, and the firm's proposed label states "*To start the injection (1) Press the Blue Button(first click will sound), (2)immediately release your thumb. …Once you hear the second click, lift the autoinjector straight up from the injection site… The injection is finished…If you did not remove your thumb from the blue button, the second 'click' cannot be heard. If this happens, slowly count to 5 before lifting the autoinjector from the injection site*."

3.7 Recommendations

1. The Division of Bioequivalence finds the fasting BE study PKD_10_033 conducted by Sun Pharmaceuticals Industries, Ltd on its Sumatriptan Succinate Injection with autoinjector device, 6 mg/0.5 mL, Lot # JK91196 comparing it to GlaxoSmithKline's Imitrex® Statdose, 6 mg/0.5 mL, Lot # C401623 incomplete due to deficiency above.

2. The Division of Bioequivalence finds the fasting BE study PKD_10_048 conducted by Sun Pharmaceuticals Industries, Ltd on its Sumatriptan Succinate Injection with autoinjector device, 6 mg/0.5 mL, Lot # JK91196 comparing it to GlaxoSmithKline's Imitrex® Statdose, 6 mg/0.5 mL, Lot # C401623 incomplete due to deficiency above.

3.8 Individual Study Reviews

3.8.1 Single-dose Fasting Bioequivalence Study

3.8.1.1 Study Design

Table 4 Study Information

Study Number	**PKD/07/068**
Study Title	A randomized, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Sumatriptan Succinate 6 mg/0.5 ml subcutaneous injection of Sun Pharmaceutical Industries Ltd, India and Imitrex® 6 mg/0.5 ml (Sumatriptan Succinate) subcutaneous injection of GlaxoSmithKline, Research Triangle Park, NC 27709, in 28 healthy human adult subjects.
Clinical Site (Name & Address)	Sun Pharmaceutical Industries Ltd. Tandalja, Vadodara – 390 020. (INDIA) Phone: 91-265-2350789, 91-265-6615500
Principal Investigator	Dr. Aman Khanna
Dosing Dates	Period I: 1st November 2007; Period II: 6th November 2007
Analytical Site (Name & Address)	Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara -390020, India Tel: 91-265-2350789, 91-265-6615500
Analysis Dates	From 5th December 2007 to 15th December 2007
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	From 1st November 2007 to 15th December 2007 (45 days)

Table 5. Product information

Product	**Test**	**Reference**
Treatment ID	A	B
Product Name	Sumatriptan Succinate Injection, 6 mg/0.5 mL	IMITREX® (sumatriptan succinate) Injection
Manufacturer	Sun Pharmaceutical Industries Ltd., India	GlaxoSmithKline Research Triangle Park, NC 27709
Batch/Lot No.	JK70920A	C298885
Manufacture Date	06/2007	
Expiration Date		04/2009
Strength	6 mg (base)/0.5 mL	6 mg (base)/0.5 mL

Dosage Form	Injection	Injection
Bio-Batch Size	(b) (4)	
Production Batch Size		
Potency (Assay)	99.8 %	100.4 %
Content Uniformity (mean, %CV)	N/A	
Dose Administered*	1 × 6.0 mg	1 × 6.0 mg
Route of Administration	Subcutaneous	Subcutaneous

* One injection of Sumatriptan Succinate 6 mg/0.5 mL by subcutaneous route in deltoid region on left side at the pre-fixed site.

For test product: The prefilled injection system was dosed by the physician. The lid was taken off. The injection was pressed firmly against the pre decided area and the blue button was pressed to give a click sound. After pressing, release slowly over 10 seconds.

For Reference Product: Administration of Imitrex® injection was done by the physician as per illustration given along with product leaflet.

Table 6. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	29 enrolled (includes 1 standby), 27 completed and included in statistical analysis.
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	5 days
Randomization Scheme	AB: 1, 2, 5, 7, 11, 12, 15, 16, 17, 18, 22, 24, 25, and 27. BA: 3, 4, 6, 8, 9, 10, 13, 14, 19, 20, 21, 23, 26, and 28.
Blood Sampling Times	Prior to dosing (0), 3, 6, 9, 12, 15, 20, 25, 30, 35, 45 minutes, 1, 2, 3, 4, 5, 6, 7, and 8 hours post-dose.
Blood Volume Collected/Sample	5 mL/sample in vacutainers containing K_3EDTA.
Blood Sample Processing/Storage	Samples were centrifuged at 3000 rpm at 4°C for 10 minutes. Plasma was stored at -20°C pending analysis.
IRB Approval	Approved October 13, 2007
Informed Consent	Yes
Length of Fasting	10 hours
Length of Confinement	From 12 hours prior to drug administration until after the 8-hour post-dose blood draw.
Safety Monitoring	Adverse events were monitored throughout the study.

Comments on Study Design:

The drug was administered by the physician. The DBE recommends the dose to be self-administered by the subject. The study design is not acceptable.

Table 7. Geometric Means and 90% Confidence Intervals - Firm Calculated

Sumatriptan 1 × 6 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study, Study No. PKD/07/068, N=27				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	124.36	120.04	1.04	100.97 to 106.29
AUC∞ (hr *ng/ml)	130.68	125.56	1.04	101.34 to 106.91
Cmax (ng/ml)	106.27	101.68	1.05	98.08 to 111.36

Table 8. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Sumatriptan 1 × 6 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study, Study No. PKD/07/068, N=27					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	124.36	120.04	1.04	100.97	106.29
AUC∞ (hr *ng/ml)	130.68	125.56	1.04	101.34	106.91
Cmax (ng/ml)	106.27	101.68	1.05	98.08	111.36

Comments on Pharmacokinetic and Statistical Analysis:

1. Four subjects had first measurable drug concentration as Cmax, however, the sampling times were adequate with the first time being 3 minutes.

2. The 90% confidence intervals for $\ln AUC_{0\text{-}t}$, $\ln AUC_{\infty}$ and $\ln C_{max}$ reported by the firm agree well with reviewer's calculations.

3. The 90% confidence intervals for $\ln AUC_{0\text{-}t}$, $\ln AUC_{\infty}$ and $\ln C_{max}$ are within the acceptable limits of 80-125%.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The drug was administered by the physician. The DBE recommends the dose to be self-administered by the subject. The fasting *in vivo* bioequivalence study is not acceptable.

3.8.2 Single-dose Fasting Bioequivalence Study

3.8.2.1 Study Design

Table 9 Study Information

Study Number	**PKD_10_033**
Study Title	A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Sumatriptan Succinate 6 mg/0.5 ml subcutaneous injection of Sun Pharmaceutical Industries Ltd, India and Imitrex® 6 mg/0.5 ml (Sumatriptan Succinate) subcutaneous injection of GlaxoSmithKline, Research Triangle Park, NC 27709, in 24 healthy human adult subjects, under fasting conditions.
Clinical Site (Name & Address)	Sun Pharmaceutical Industries Ltd. Tandalja, Vadodara – 390 020 (India) Phone No.: 91-265-2350789, 91-265-6615500
Principal Investigator	Dr. Aman Khanna
Dosing Dates	Period I: 3rd February 2010; Period II: 9th February 2010
Analytical Site (Name & Address)	Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara -390020, Gujarat, India. Tel: 91-265-2350789, 91-265-6615500
Analysis Dates	From 21st February, 2010 to 27th February, 2010
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	From 3rd January 2010 to 27th February, 2010 (25 days)

Table 10. Product information

Product	**Test**	**Reference**
Treatment ID	A	B
Product Name	Sumatriptan Succinate Injection, 6 mg/0.5 mL	IMITREX® (sumatriptan succinate) Injection
Manufacturer	Sun Pharmaceutical Industries Ltd., India	GlaxoSmithKline Research Triangle Park, NC 27709
Batch/Lot No.	JK91196	C401623
Manufacture Date	05/2009	
Expiration Date		01/2011
Strength	6 mg (base)/0.5 mL	6 mg (base)/0.5 mL
Dosage Form	Injection	Injection
Bio-Batch Size	(b) (4)	

Production Batch Size	(b) (4)	
Potency (Assay)	97.1 %	100.7 %
Content Uniformity (mean, %CV)	N/A	
Dose Administered*	1 × 6.0 mg	1 × 6.0 mg
Route of Administration	Subcutaneous	Subcutaneous

* One injection of Sumatriptan Succinate 6 mg/0.5 mL by subcutaneous route in top part of thigh region. The dosing activity was carried out by subject himself.

For test product: The auto injector system was used for dosing. White needle shield was removed smoothly by pulling it strait off. Open end of the auto injector was placed straight up at right angle (90°) on the pre identified injection site, without pressing the blue activation button. Safety needle cover was pushed firmly against the skin to unlock. Injection was continued to hold firmly against the skin. Injection was started by pressing the blue button to give a first click sound. Thumb was released immediately after first click sound. Injection was continued to hold firmly against the skin up to second click sound /approximately 15 seconds. Auto injector was lifted straight up form the injection site, after verification of inspection window as blue.

For Reference Product: Without pushing the blue button, loaded pen was pressed firmly against pre identified injection site so that the gray barrel slides down toward the blue section that holds the syringe cartridge. Blue button was pushed and pen was held at least for 5 seconds to complete the injection.

Table 11. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	24 enrolled, 23 completed and included in statistical analysis
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	6 days
Randomization Scheme	AB: 2, 3, 5, 6, 10, 11, 13, 15, 17, 18, 23, and 24. BA: 1, 4, 7, 8, 9, 12, 14, 16, 19, 20, 21, and 22.
Blood Sampling Times	Prior to dosing (0), 3, 6, 9, 12, 15, 20, 25, 30, 35, 45 minutes, 1, 2, 3, 4, 5, 6, 7, and 8 hours post-dose.
Blood Volume Collected/Sample	5 mL/sample in vacutainers containing K_2EDTA.
Blood Sample Processing/Storage	Samples were centrifuged at 3000 rpm at 4°C for 10 minutes. Plasma was stored at or below -20°C pending analysis.
IRB Approval	Approved January 30, 2010
Informed Consent	Yes
Length of Fasting	10 hours
Length of Confinement	From 12 hours prior to dosing until after the 8-hour post-dose blood draw.
Safety Monitoring	Adverse events were monitored throughout the study.

Comments on Study Design:

The clinical report states that the injection was continued to hold firmly against the skin up to second click sound /approximately 15 seconds. The firm should explain why the injector should be held for 15 seconds while the injection time is 5 seconds. The study design is incomplete (please see the Biomanagement Meeting Minutes in Additional Attachments Section 7).

3.8.2.2 Clinical Results

Table 12. Demographics Profile of Subjects Completing the Bioequivalence Study

		Study No. PKD_10_033 (Fasting)	
		Treatment Groups	
		Test Product N= 23	Reference Product N=23
Age (Years)	Mean ± SD	29.7+/- 7.04	29.7+/- 7.04
	Range	19 - 42	19 - 42
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18-40	22 (95.65%)	22 (95.65%)
	41-64	1 (4.35%)	1 (4.35%)
	65-75	0 (0.00%)	0 (0.00%)
	>75	0 (0.00%)	0 (0.00%)
Sex	Female	0 (0.00%)	0 (0.00%)
	Male	23 (100%)	23 (100%)
Race	Asian	23 (100%)	23 (100%)
	Black	0 (0.00%)	0 (0.00%)
	Caucasian	0 (0.00%)	0 (0.00%)
	Hispanic	0 (0.00%)	0 (0.00%)
	Other	0 (0.00%)	0 (0.00%)
BMI	Mean ± SD	20.80+/- 1.710	20.80+/- 1.710
	Range	18.7– 24.7	18.7– 24.7
Other factors		-	-

Subject no. 1 (BA) was dropped due to voluntarily withdrawn after dosing in period I.

Table 13. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
1	Withdrew himself without any reason, voluntarily from the study after dosing in period I	I	NO

Table 14. Study Adverse Events, Fasting Bioequivalence Study

	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study No.: PKD_10_033	
Med DRA System Organ Class Preferred Terms	Adverse Events	
	Test n (%)	Reference n (%)
Adverse event considered for both formulation*		
Investigations		
Haemoglobin decreased	1 (50.0)	
Neutrophil count decreased	1 (50.0)	
Total	**2 (100.0)**	

*Since no hematology and biochemistry assessment was done after period I, the adverse events are considered for both the formulation.

Table 15. Protocol Deviations, Fasting Bioequivalence Study

None

Comments on Dropouts/Adverse Events/Protocol Deviations:

One subject withdrew voluntarily after period I dosing. Adverse events were mild to moderate. There were no protocol deviations. There was no impact on the outcome of the study.

3.8.2.3 Bioanalytical Results

Table 16. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. PKD 10 033 Analyte Name : Sumatriptan								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	2.00	4.00	10.01	30.04	90.11	165.20	220.27	272.83
Inter Day Precision (% C.V.)	2.5	5.3	5.3	4.9	3.7	3.6	5.7	5.2
Inter Day Accuracy (% Actual)	0.2	-1.8	2.5	3.4	1.3	1.2	-4.0	-2.4
Linearity	0.9956 to 0.9999 (r Value)							
Linearity range (ng/mL)	2.00 to 272.83							
Limit Of Quantitation (ng/mL)	2.00							

Parameter	**Quality Control Samples**				
Concentration (ng/mL)	5.50	16.50	55.99	112.48	222.45
Inter Day Precision (% C.V.)	8.1	7.5	6.6	7.6	8.2
Inter Day Accuracy (% Actual)	-1.6	0.2	0.3	-1.1	-6.3

Comments on Study Assay Validation:

Assay validation is acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes (Subjects #2-6)
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Chromatograms are acceptable.

Table 17. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
PKD/S/019	10/08/2009	Sample reanalysis and Reporting of Final concentrations.

		(Revision No.: 03)

Table 18. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

One sample was reassayed for inconsistent profile. The reviewer repeated the statistical analysis using the original concentration value. There was no impact on the outcome of the study.

3.8.2.4 Pharmacokinetic Results

Table 19. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table **Error! Reference source not found.**30 and Figure **Error! Reference source not found.**1.

Fasting Bioequivalence Study, Study No. PKD/10/033									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *ng/ml)	134.200	15.56	95.31	173.56	139.807	17.91	104.19	199.71	0.96
AUC∞ (hr *ng/ml)	139.645	15.20	100.17	178.73	146.925	17.78	109.36	204.63	0.95
Cmax (ng/ml)	113.185	27.13	60.79	163.65	124.523	25.80	67.89	183.55	0.91
Tmax* (hr)	0.250	.	0.10	0.42	0.167	.	0.10	0.33	1.50
Kel (hr^{-1})	0.474	24.05	0.27	0.76	0.440	25.04	0.11	0.57	1.08
T1/2 (hr)	1.554	27.52	0.91	2.59	1.783	56.42	1.22	6.10	0.87

* Tmax values are presented as median, range

Table 20. Geometric Means and 90% Confidence Intervals - Firm Calculated

Sumatriptan 1 × 6 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. PKD/10/033, N=23				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	132.42	137.45	96.34	92.43 to 100.42
AUC∞ (hr *ng/ml)	137.87	144.43	95.46	91.87 to 99.19
Cmax (ng/ml)	109.11	120.27	90.72	84.71 to 97.15

Table 21. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Sumatriptan 1 × 6 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. PKD/10/033, N=23					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	132.42	137.45	0.96	92.43	100.42
AUC∞ (hr *ng/ml)	137.87	144.43	0.95	91.87	99.19
Cmax (ng/ml)	109.11	120.27	0.91	84.71	97.15

Table 22. Additional Study Information, Fasting Study No. PKD/10/033

Root mean square error, AUC0-t	0.0816	
Root mean square error, AUC∞	0.0755	
Root mean square error, Cmax	0.1350	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	23	23
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	23	0.96	0.92	0.98
Reference	23	0.95	0.80	0.98

Comments on Pharmacokinetic and Statistical Analysis:

1. The 90% confidence intervals for $\ln AUC_{0\text{-}t}$, $\ln AUC_{\infty}$ and $\ln C_{max}$ reported by the firm agree well with reviewer's calculations.

2. The 90% confidence intervals for $\ln AUC_{0\text{-}t}$, $\ln AUC_{\infty}$ and $\ln C_{max}$ are within the acceptable limits of 80-125%.

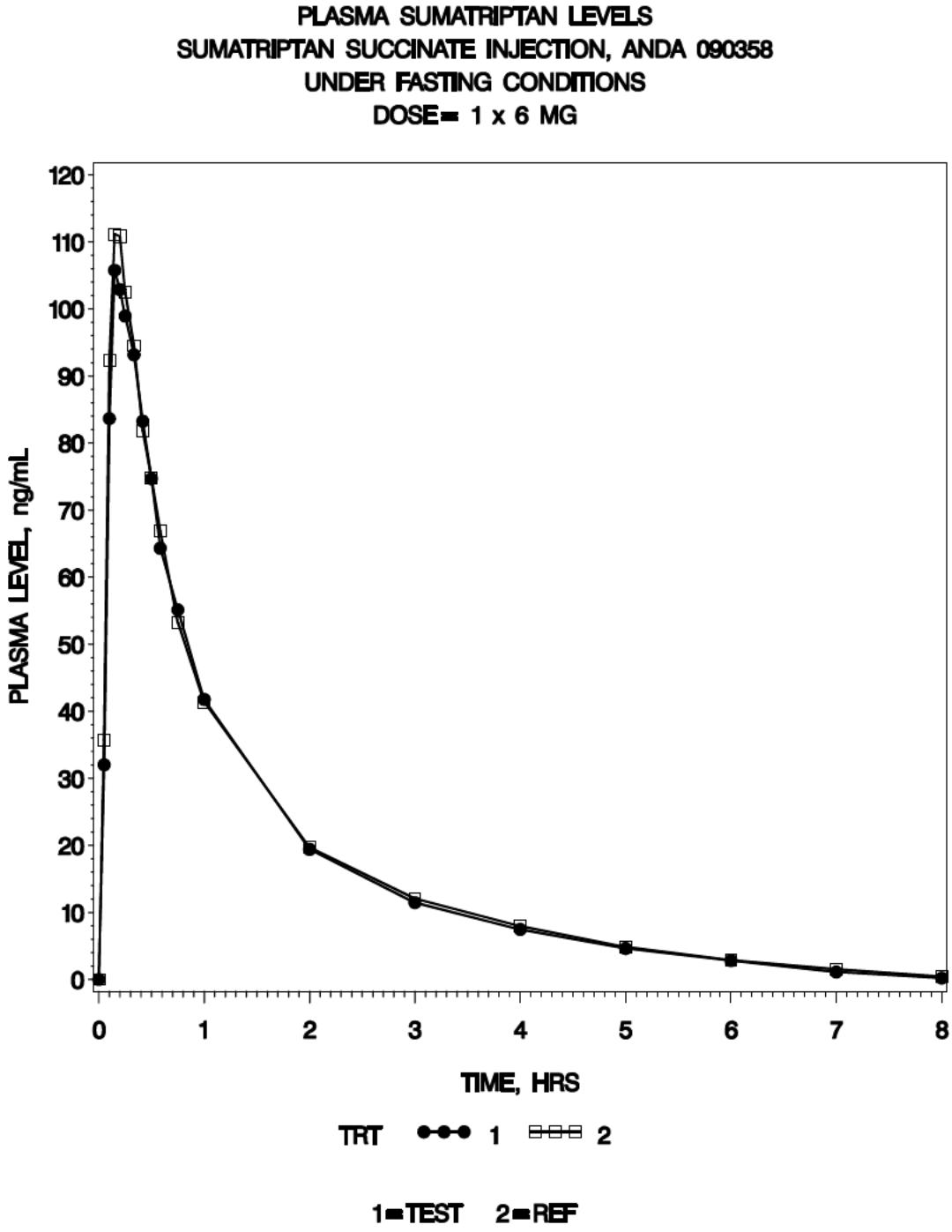
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The fasting *in vivo* bioequivalence study is incomplete due to the deficiency mentioned in the deficiency section above.

Table 23. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Sumatriptan					
Time (hr)	Test (n=23)		Reference (n=23)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.05	21.82	125.31	45.97	72.19	0.47
0.10	76.55	44.83	100.24	34.34	0.76
0.15	97.98	33.86	118.97	29.64	0.82
0.20	102.75	27.35	110.96	23.96	0.93
0.25	100.04	26.80	101.39	23.33	0.99
0.33	94.65	22.50	93.05	21.71	1.02
0.42	83.11	18.19	82.00	26.60	1.01
0.50	75.04	18.87	74.47	25.25	1.01
0.58	66.28	17.93	64.94	23.62	1.02
0.75	55.63	37.17	52.72	25.59	1.06
1.00	42.73	22.79	40.38	23.98	1.06
2.00	19.04	18.27	20.06	17.80	0.95
3.00	11.39	15.61	12.13	22.75	0.94
4.00	7.25	21.08	8.18	24.90	0.89
5.00	4.47	19.68	5.02	27.81	0.89
6.00	2.73	30.32	3.00	42.96	0.91
7.00	1.16	108.61	1.49	103.79	0.78
8.00	0.09	479.58	0.59	204.64	0.16

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



3.8.3 Single-dose Fasting Bioequivalence Study

3.8.3.1 Study Design

Table 24 Study Information

Study Number	**PKD_10_048**
Study Title	A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Sumatriptan Succinate 6 mg/0.5 ml subcutaneous injection of Sun Pharmaceutical Industries Ltd, India and Imitrex® 6 mg/0.5 ml (Sumatriptan Succinate) subcutaneous injection of GlaxoSmithKline, Research Triangle Park, NC 27709, in 24 healthy human adult subjects, under fasting conditions.
Clinical Site (Name & Address)	Sun Pharmaceutical Industries Ltd. Tandalja, Vadodara – 390 020 (India) Phone No.: 91-265-2350789, 91-265-6615500
Principal Investigator	Dr. Aman Khanna.
Dosing Dates	Period I: 5th February 2010; Period II: 11th February 2010
Analytical Site (Name & Address)	Sun Pharmaceutical Industries Ltd., Tandalja, Vadodara -390020 Gujarat, India. Tel: 91-265-2350789, 91-265-6615500
Analysis Dates	From 28th February, 2010 to 8th March, 2010
Analytical Director	(b) (6)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	From 5th February, 2010 to 8th March, 2010 (32 days)

Table 25. Product information

Product	**Test**	**Reference**
Treatment ID	A	B
Product Name	Sumatriptan Succinate Injection, 6 mg/0.5 mL	IMITREX® (sumatriptan succinate) Injection
Manufacturer	Sun Pharmaceutical Industries Ltd., India	GlaxoSmithKline Research Triangle Park, NC 27709
Batch/Lot No.	JK91196	C401623
Manufacture Date	05/2009	
Expiration Date		01/2011
Strength	6 mg (base)/0.5 mL	6 mg (base)/0.5 mL
Dosage Form	Injection	Injection
Bio-Batch Size	(b) (4)	

Production Batch Size	(b) (4)	
Potency (Assay)	97.1 %	100.7 %
Content Uniformity (mean, %CV)	N/A	
Dose Administered*	1 × 6.0 mg	1 × 6.0 mg
Route of Administration	Subcutaneous	Subcutaneous

* Subjects administered a single dose of the study medication by subcutaneous route at the deltoid region of the left side. The dosing was carried out by the subject himself.

For Test Product
The auto injector system was used for dosing. White needle shield was removed smoothly by pulling it strait off. Open end of the auto injector was placed straight up at right angle (90°) on the pre identified injection site, without pressing the blue activation button. Safety needle cover was pushed firmly against the skin to unlock. Injection was continued to hold firmly against the skin. Injection was started by pressing the blue button to give a first click sound. Thumb was released immediately after first click sound. Injection was continued to hold firmly against the skin up to second click sound /approximately 15 seconds. Auto injector was lifted straight up form the injection site, after verification of inspection window as blue.

For Reference Product
Without pushing the blue button, loaded pen was pressed firmly against pre identified injection site so that the gray barrel slides down toward the blue section that holds the syringe cartridge. Blue button was pushed and pen was hold at least for 5 seconds to complete the injection.

Table 26. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	24 enrolled, completed, and included in statistical analysis.
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	6 days
Randomization Scheme	AB: 2, 3, 5, 6, 10, 11, 13, 15, 17, 18, 23, and 24. BA: 1, 4, 7, 8, 9, 12, 14, 16, 19, 20, 21, and 22.
Blood Sampling Times	Prior to dosing (0), 3, 6, 9, 12, 15, 20, 25, 30, 35, 45 minutes, 1, 2, 3, 4, 5, 6, 7, and 8 hours post-dose.
Blood Volume Collected/Sample	5 mL/sample in vacutainers containing K_2EDTA.
Blood Sample Processing/Storage	Blood samples were centrifuged at 300 rpm at 4°C for 10 minutes. Plasma was stored at or below -20°C pending analysis.
IRB Approval	Approved January 30, 2010
Informed Consent	Yes
Length of Fasting	10 hours
Length of Confinement	12 hours prior to dosing until after the 8-hour post-dose blood draw.
Safety Monitoring	Adverse events were monitored throughout the study.

Comments on Study Design:

The clinical report states that the injection was continued to hold firmly against the skin up to second click sound /approximately 15 seconds. The firm should explain why the injector should be held for 15 seconds while the injection time is 5 seconds. The study design is incomplete.

3.8.3.2 Clinical Results

Table 27. Demographics Profile of Subjects Completing the Bioequivalence Study

		Study No. PKD_10_048 (Fasting)	
		Treatment Groups	
		Test Product N= 24	Reference Product N=24
Age (Years)	Mean ± SD	32.2 +/- 8.26	32.2 +/- 8.26
	Range	21 – 50	21 – 50
Age Groups	< 18	0 (0.00%)	0 (0.00%)
	18-40	18 (75.00%)	18 (75.00%)
	41-64	6 (25.00%)	6 (25.00%)
	65-75	0 (0.00%)	0 (0.00%)
	>75	0 (0.00%)	0 (0.00%)
Sex	Female	0 (0.00%)	0 (0.00%)
	Male	24 (100%)	24 (100%)
Race	Asian	24 (100%)	24 (100%)
	Black	0 (0.00%)	0 (0.00%)
	Caucasian	0 (0.00%)	0 (0.00%)
	Hispanic	0 (0.00%)	0 (0.00%)
	Other	0 (0.00%)	0 (0.00%)
BMI	Mean ± SD	21.80 +/- 1.986	21.80 +/- 1.986
	Range	18.7 - 24.9	18.7 - 24.9
Other factors		-	-

Table 28. Dropout Information, Fasting Bioequivalence Study

N/A

Table 29. Study Adverse Events, Fasting Bioequivalence Study

	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study No.: PKD_10_048	
Med DRA System Organ Class Preferred Terms	Adverse Events	
	Test n (%)	Reference n (%)
Gastrointestinal disorders		
Nausea	1 (33.3)	0 (0.0)
Dyspepsia	1 (33.3)	0 (0.0)
Nervous system disorders		
Dizziness	1 (33.3)	0 (0.0)
Total	**3 (100.0)**	**0 (0.0)**
Adverse event considered for both formulation*		
Investigations		
White blood cell count increased	1 (100.0)	
Total	**1 (100.0)**	

*Since no hematology assessment was done after period I until checkout of period II, these adverse events are considered for both the formulation.

Table 30. Protocol Deviations, Fasting Bioequivalence Study

Type	Subject #s (Test)	Subject #s (Ref.)
For subject no. 18 to 24, there is deviation in measuring 1.0 h post dose ECG. The maximum deviation is of 12 minutes in period I.	Subject No. 18, 20, 22 and 24 (4 Subjects)	Subject No.19, 21 and 23 (3 Subjects)
To treat the adverse event, subject no. 16 was given one glass of water at 9:02 am to swallow the tablet during the water restriction period of 1 hour post dose in period II.	Subject No. 16 (1 subject)	NA
Subject 16 remained in supine position from 9:35 am to 10:15 am, i.e. for 40 minutes, during posture restriction of 2 hours post dose in period II. The dosing time of subject was 8:30 am.	Subject No. 16 (1 subject)	NA

Comments on Dropouts/Adverse Events/Protocol Deviations:

There were no dropouts during the study. All adverse events were mild. There was no impact on the outcome of the study.

3.8.3.3 Bioanalytical Results

Table 31. Assay Validation – Within the Fasting Bioequivalence Study

Bioequivalence Study No. PKD_10_048 Analyte Name : Sumatriptan								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	2.02	4.03	9.83	29.50	88.51	162.28	216.37	268.00
Inter Day Precision (% C.V.)	3.2	6.0	4.9	3.4	4.1	3.9	4.9	4.5
Inter Day Accuracy (% Actual)	-0.2	0.3	-0.9	3.0	0.5	1.0	-1.9	-1.8
Linearity	0.9949 to 0.9996 (r Value)							
Linearity range (ng/mL)	2.02 to 268.00							
Limit Of Quantitation (ng/mL)	2.02							

Parameter	**Quality Control Samples**				
Concentration (ng/mL)	5.57	16.72	56.74	113.98	225.43
Inter Day Precision (% C.V.)	6.7	13.9	9.3	9.1	10.8
Inter Day Accuracy (% Actual)	-3.6	-4.8	-2.1	-5.5	-6.9

Comments on Study Assay Validation:

Assay validation is acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes (Subjects #1-5)
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms:

Chromatograms are acceptable.

Table 32. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
PKD/S/019	10/08/2009	Sample reanalysis and Reporting of Final concentrations. (Revision No.: 03)

Table 33. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	

Summary/Conclusions, Study Assays:

Two samples were reassayed to obtain confirming value. The reviewer repeated the statistical analysis using the original concentration values. There was no impact on the outcome of the study.

3.8.3.4 Pharmacokinetic Results

Table 34. Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in **Error! Reference source not found.**Table 45 and Figure 2.

Fasting Bioequivalence Study, Study No. PKD/10/048									
Parameter (units)	**Test**				**Reference**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC0-t (hr *ng/ml)	126.583	15.89	90.87	170.47	133.060	17.71	97.80	188.81	0.95
AUC∞ (hr *ng/ml)	132.265	15.52	97.46	175.03	138.274	17.10	102.79	193.20	0.96
Cmax (ng/ml)	118.349	20.83	87.75	169.23	121.174	21.18	79.41	175.41	0.98
Tmax* (hr)	0.200	.	0.10	0.42	0.200	.	0.10	0.33	1.00
Kel (hr^{-1})	0.513	22.69	0.21	0.69	0.505	19.62	0.30	0.73	1.02
T1/2 (hr)	1.459	35.97	1.00	3.26	1.435	23.97	0.95	2.30	1.02

* Tmax values are presented as median, range

Table 35. Geometric Means and 90% Confidence Intervals - Firm Calculated

Sumatriptan 1 × 6 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study, Study No. PKD/10/048, N=24				
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (hr *ng/ml)	125.09	131.15	95.38	91.12 to 99.84
AUC∞ (hr *ng/ml)	130.78	136.41	95.87	91.76 to 100.16
Cmax (ng/ml)	116.02	118.66	97.77	90.39 to 105.76

Table 36. Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Sumatriptan 1 × 6 mg Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study, Study No. PKD/10/048, N=24					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr *ng/ml)	125.09	131.15	0.95	91.12	99.84
AUC∞ (hr *ng/ml)	130.78	136.41	0.96	91.76	100.16
Cmax (ng/ml)	116.02	118.66	0.98	90.39	105.76

Table 37. Additional Study Information, Fasting Study No. PKD/10/048

Root mean square error, AUC0-t	0.0922	
Root mean square error, AUC∞	0.0883	
Root mean square error, Cmax	0.1585	
	Test	Reference
Kel and AUC∞ determined for how many subjects?	24	24
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	24	0.96	0.92	0.97
Reference	24	0.96	0.95	0.98

Comments on Pharmacokinetic and Statistical Analysis:

1. The 90% confidence intervals for $\ln AUC_{0\text{-}t}$, $\ln AUC_{\infty}$ and $\ln C_{max}$ reported by the firm agree well with reviewer's calculations.

2. The 90% confidence intervals for $\ln AUC_{0\text{-}t}$, $\ln AUC_{\infty}$ and $\ln C_{max}$ are within the acceptable limits of 80-125%.

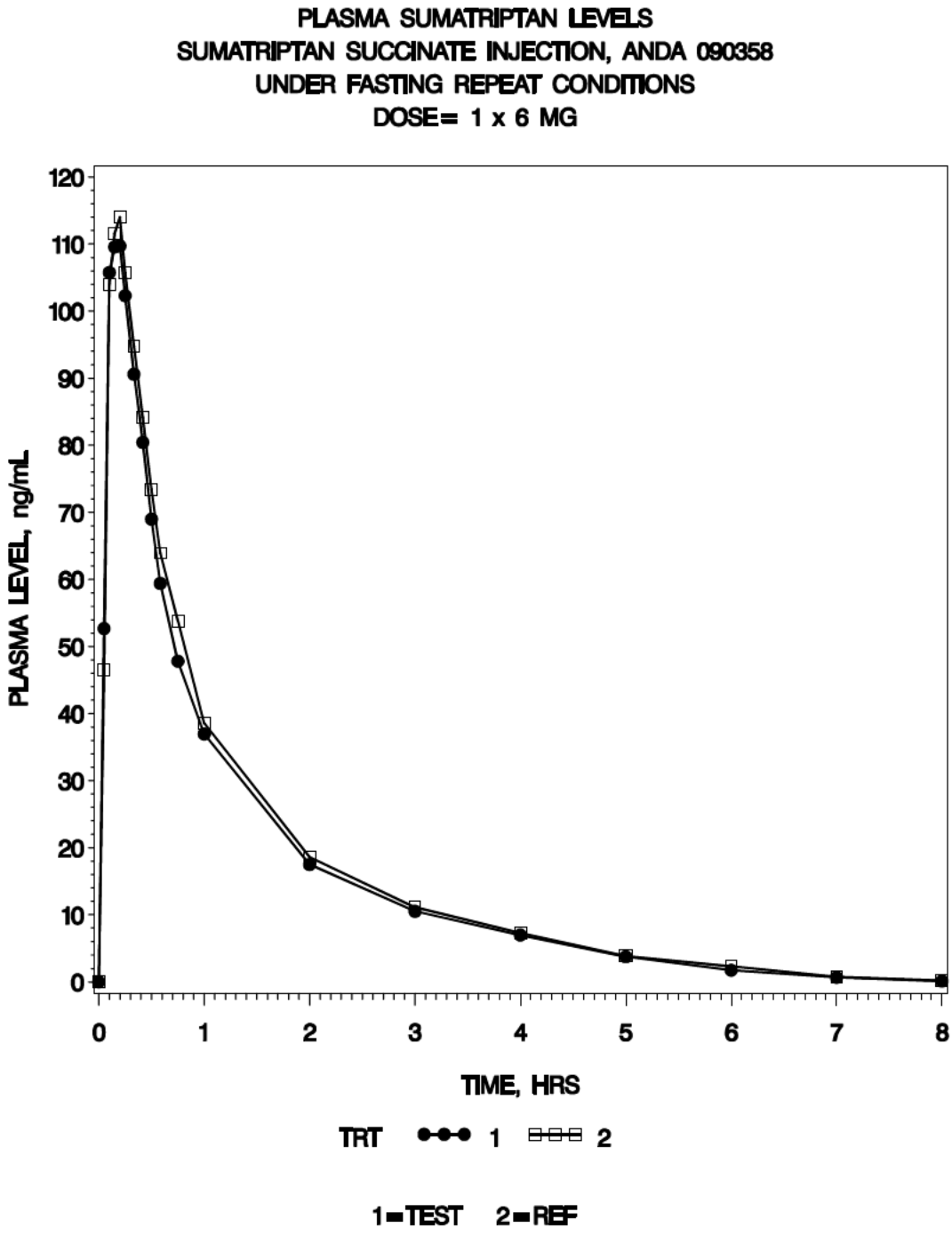
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The fasting *in vivo* bioequivalence study is incomplete due to the deficiency mentioned in the deficiency section above.

Table 38. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Sumatriptan					
Time (hr)	Test (n=24)		Reference (n=24)		T/R Ratio
	Mean (ng/mL)	% CV	Mean (ng/mL)	% CV	
0.00	0.00	.	0.00	.	.
0.05	52.68	44.68	46.54	60.84	1.13
0.10	105.77	24.51	103.94	22.92	1.02
0.15	109.58	21.05	111.58	25.87	0.98
0.20	109.72	16.88	113.99	19.56	0.96
0.25	102.30	13.90	105.69	17.05	0.97
0.33	90.58	13.67	94.72	16.74	0.96
0.42	80.43	16.02	84.13	24.32	0.96
0.50	68.98	15.71	73.40	17.43	0.94
0.58	59.41	14.29	63.94	21.32	0.93
0.75	47.81	14.30	53.85	20.51	0.89
1.00	36.96	20.22	38.57	22.64	0.96
2.00	17.50	19.38	18.61	17.79	0.94
3.00	10.53	20.91	11.13	24.11	0.95
4.00	6.99	23.35	7.31	25.49	0.96
5.00	3.76	25.35	3.86	26.90	0.97
6.00	1.74	91.62	2.32	59.80	0.75
7.00	0.67	181.20	0.73	162.59	0.91
8.00	0.12	489.90	0.20	340.27	0.60

Figure 2. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



3.9 SAS Output

Study # PKD_10_033

3.9.1 Fasting Study Data

FASTING CONCENTRATION DATASET

(b) (4)

[redacted]

Following this page, 60 pages withheld in full (b)(4) SAS output

4. COMMENTS FOR OTHER OGD DISCIPLINES

Discipline	Comment
All	DSI inspection pending for clinical and analytical site for ANDA [redacted] (b) (4) (for cause). Requested 1/4/2010.

5. ADDITIONAL ATTACHMENTS

Bio Management Meeting Minutes (4/6/2010)

Discussion Topic #2: ANDA 090358 Sumatriptan Succinate Injection (Sun)

The test product is a pre-filled syringe assembled in an auto-injector device. The Division of Chemistry II (DCII) has reviewed the auto-injector device used for the test product and compared it with the RLD. DCII contacted the OGD clinical group because of an apparent difference in injection times (the test product instructs users to hold in place until a second "click" or for a count of (b) (4) the RLD instructs users to hold in place for "at least 5 seconds"). The firm was asked to revise the instructions to "hold in place for 5 seconds." It was noted by the reviewer that the firm's protocol for the biostudy states that the test device should be held in place for 15 seconds, which does not match the instructions for either the test or reference products. How should we proceed?

Management Discussion:

Please ask the firm to explain why they instructed subjects to hold the injector in place for 15 seconds, while the labeling states different instructions for use.

BIOEQUIVALENCE DEFICIENCIES

ANDA:	090358
APPLICANT:	Sun Pharmaceutical Industries, Ltd.
DRUG PRODUCT:	Sumatriptan Succinate Pre-filled Syringe with Auto-injector, EQ 6 mg base/0.5 mL

The Division of Bioequivalence (DBE) has completed its review and the following deficiency has been identified:

The clinical reports for bioequivalence studies PKD_10_033 and PKD_10_048 state that the injection was to be held firmly against the skin up to second click sound/approximately 15 seconds. Please explain why the auto-injector should be held for 15 seconds while the injection time is ≤ 5 seconds in your BE study design, and your proposed label states *"To start the injection (1) Press the Blue Button(first click will sound), (2)immediately release your thumb. …Once you hear the second click, lift the autoinjector straight up from the injection site… The injection is finished…If you did not remove your thumb from the blue button, the second 'click' cannot be heard. If this happens, slowly count to 5 before lifting the autoinjector from the injection site."*

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

6. OUTCOME PAGE

ANDA: 090358

Completed Assignment for 90358 ID: 10727

Reviewer: Williamson, Leah **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: Sumatriptan Device

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
10727	2/22/2010	Bioequivalence Study	Fasting Study	1	1
10727	2/22/2010	Bioequivalence Study	In-Vitro Study (Nasal, Binding)	1	1
10727	3/12/2010	Bioequivalence Study	Fasting Study	1	1
10727	3/12/2010	Bioequivalence Study	Fasting Study	1	1
				Bean Total:	4

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Typical BE Study Applications

BE Study Fasting	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Fasting Study Total	*3*
BE Study Fasting	
Clinical (Common to all APIs)	1
Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Fasting Study Total	*3*
BE Study Fasting	
Clinical (Common to all APIs)	1

Bioanalytical (API 1)	1
Statistical Analysis (API 1)	1
Fasting Study Total	*3*

In Vitro Study Review

Analysis of In Vitro Study Data	1
In Vitro Study Review Total	*1*
Grand Total	**10**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90358	ORIG-1	SUN PHARMACEUTICAL INDUSTRIES LTD	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/

LEAH N WILLIAMSON
05/17/2010

CHANDRA S CHAURASIA
05/17/2010

ETHAN M STIER on behalf of BARBARA M DAVIT
05/18/2010

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090358		
Drug Product Name	Sumatriptan Succinate Injection, pre-filled syringe with auto-injector		
Strength(s)	EQ 6 mg base/0.5 mL		
Applicant Name	Sun Pharmaceutical Industries Ltd.		
Address	Acme Plaza, Andheri-Kurla Road Andheri (East), Mumbai-400059, India		
Applicant's Point of Contact	Anne Toland		
Contact's Telephone Number	609-495-2823		
Contact's Fax Number	609-495-2711		
Original Submission Date(s)	January, 18, 2008		
Submission Date(s) of Amendment(s) Under Review	June 1, 2010		
Reviewer	Leah N. Williamson, Ph.D.		
Study Number (s)	PKD/07/068	PKD/10/033	PKD/10/048
Study Type (s)	Subcutaneous Injection (Dose administration by In-house physician)	Subcutaneous Injection (Self administered dose by subjects, Thigh Region)	Subcutaneous Injection (Self administered dose by subjects Deltoid Region)
Strength (s)	6 mg	6 mg	6 mg
Clinical Site	Sun Pharmaceutical Industries Ltd.		
Clinical Site Address	Tandalja, Vadodara – 390 020. (INDIA)		
Analytical Site	Sun Pharmaceutical Industries Ltd.		
Analytical Site Address	Tandalja, Vadodara -390020, India		
OVERALL REVIEW RESULT	**ADEQUATE**		
DSI REPORT STATUS	**ADEQUATE**		

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
10	**FASTING STUDY**	**6 mg**	**ADEQUATE**
12	**FASTING STUDY**	**6 mg**	**ADEQUATE**
12	**FASTING STUDY**	**6 mg**	**ADEQUATE**
10	**IN VITRO STUDY**	**6 mg**	**ADEQUATE**

REVIEW OF AN AMENDMENT

1 EXECUTIVE SUMMARY

On January 18, 2008, Sun Pharmaceutical Industries requested 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 auto-injector device.

The Division of Bioequivalence (DBE) was in agreement with the recommendations by the clinical team (http://darrts.fda.gov:7778/darrts/ViewDocument?documentId=090140af801ae294), and denied a waiver request for *in vivo* bioequivalence study requirements for the test Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL. The DBE requested a single-dose two-way crossover fasting bioequivalence study where the subjects inject themselves both the test and reference products using the respective device. DBE also requested that the firm perform comparative in vitro testing on 1) drug volume delivered, 2) injection time, and 3) force to fire for the test biobatch lot and stability lots with and the RLD. In addition, the DBE recommended conducting each of these in vitro tests – 1) drug volume delivered, 2) injection time, and 3) force to fire. These comparisons should be made directly between the stability lot versus the RLD. This in vitro testing on the stability lots should address the large fluctuation in injection times observed in stability testing.

In the February 22, 2010 amendment, the firm submitted the results of a fasting bioequivalence study (study # PKD/07/068) on its Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL comparing with the reference listed drug IMITREX® (Sumatriptan Succinate) Injection, EQ 6 mg base/0.5 mL. The BE study was designed as a single-dose, two-way crossover study in healthy males. An in-house physician administered the injection to the subjects. The firm stated that the study # PKD/07/068 was already completed before receiving the deficiency letter from DBE. Since the DBE recommends self-administration of the drug for the BE evaluation of sumatriptan succinate injection, pre-filled syringe with auto-injector, the results of the study using physician-administered dose (Study # PKD/07/068) was used for informational purposes only.

The firm submitted another amendment dated March 12, 2010 consisting of two BE studies (PKD/10/033 and PKD/10/048). Each of these two studies used self-administration by the study subjects – Study #PKD/10/033 using the self-administration in the thigh region, and Study #PKD/10/048 in the deltoid region. Each BE study was designed as a single-dose, two-way crossover study in healthy males. The fasting BE studies were incomplete pending firm's explanation on drug administration as to why the auto-injector should be held for 15 seconds while the injection time is 5 seconds (http://darrts.fda.gov:7777/darrts/ViewDocument?documentId=090140af801d70da).

In this amendment, the firm has provided an explanation on the discrepancy of drug administration time. The firm's response is acceptable.

No Division of Scientific Investigations (DSI) inspection is pending or necessary.

The application is adequate.

2 RESPONSE TO DEFICIENCIES

1. The clinical reports for bioequivalence studies PKD_10_033 and PKD_10_048 state that the injection was to be held firmly against the skin up to second click sound/approximately 15 seconds. Please explain why the auto-injector should be held for 15 seconds while the injection time is ≤ 5 seconds in your BE study design, and your proposed label states "To start the injection (1) Press the Blue Button(first click will sound), (2)immediately release your thumb. ...Once you hear the second click, lift the autoinjector straight up from the injection site... The injection is finished...If you did not remove your thumb from the blue button, the second 'click' cannot be heard. If this happens, slowly count to 5 before lifting the autoinjector from the injection site."

Firm's Response
Please note that in bioequivalence studies instruction stating to hold injection for 15 seconds was based on Sun's labeling which was originally submitted in the ANDA. Subsequently a labeling amendment was submitted on September 1, 2009, to revise injection time to 5 seconds. This revision was done to match injection time as per RLD, data generated on Sun's device also indicated that injection time was below 5 seconds hence on its basis injection time was revised from 15 seconds to 5 seconds.

Injection time is governed by functioning of auto-injector and design to complete injection within 5 seconds. In-vitro data demonstrating injection time of not more than 5 seconds was included in Telephone amendment to CMC section submitted 22 December 09, same data is reproduced below for your ready reference.

Batch #	Batch Size	Sample Size	Mean Injection Time (s)	Std. Dev.	Max. (s)	Min. (s)
JK92832	(b) (4)		1.66	0.09		(b) (4)
JK92774			1.63	0.10		
JK92831			1.61	0.11		

An auto-injector starts with pressing of blue button with help of thumb and completion of injection is indicated by second click, in case if thumb is not removed from blue button, second click indicating completion of injection cannot be heard and hence to ensure that injection is complete counting up to 5 seconds is recommended.

Since injection is always completed within 5 seconds, auto-injector held at injection site up to 15 seconds in bioequivalence studies shall not have any impact, i.e., irrespective of

time interval suggested for lifting of auto-injector from injection site, injection is always completed within 5 seconds.

Additionally, we have also conducted in-vitro study on 50 auto-injectors. Data indicating time required for injection, click interval (time interval between first and second click) and injection volume obtained in this study has been provided, which demonstrates that labeled volume is delivered in less than 5 seconds (as indicated by injection time and click interval). Example screen shot of instrument used for in-vitro measurement is also provided.

Reviewer's Comments

The firm has provided the following in-vitro data:

Product Name : Sumatriptan succinate for Injection 6mg/0.5 ml
Batch no. : JKJ0770

Pull no.	Injection time *	Click interval *	Inj_Extend *	Injection volume * (b) (4)
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				
29				
30				

Pull no.	Injection time *	Click interval *	Inj_Extend *	Injection volume *
31	(b) (4)			
32				
33				
34				
35				
36				
37				
38				
39				
40				
41				
42				
43				
44				
45				
46				
47				
48				
49				
50				

* Note: Testing parameter as

- Injection time : The time between Start and End.
- Click interval : The time from the Button is pressed to the retraction is detected.
- Inj. Extend : The time between the button retraction and the Injection end.
- Inj. Volume : Total volume delivered.

The injection times are less than 5 seconds which is indicated on the label. The firm's response is acceptable.

3 DEFICIENCY COMMENTS

None

4 RECOMMENDATIONS

1. The Division of Bioequivalence accepts the fasting BE study PKD_10_033 conducted by Sun Pharmaceuticals Industries, Ltd on its Sumatriptan Succinate Injection Pre-filled Syringe with Auto-injector, EQ 6 mg base/0.5 mL, Lot # JK91196 comparing it to GlaxoSmithKline's Imitrex® Statdose, EQ 6 mg base/0.5 mL, Lot # C401623.

2. The Division of Bioequivalence accepts the fasting BE study PKD_10_048 conducted by Sun Pharmaceuticals Industries, Ltd on its Sumatriptan Succinate Injection Pre-

filled Syringe with Auto-injector, EQ 6 mg base/0.5 mL, Lot # JK91196 comparing it to GlaxoSmithKline's Imitrex® Statdose, EQ6 mg mg/0.5 mL, Lot # C401623.

3. The Division of Bioequivalence deems the test product Sumatriptan Succinate Injection Pre-filled Syringe with Auto-injector, EQ 6 mg base/0.5 mL, manufactured by Sun Pharmaceuticals Industries, Ltd to be bioequivalent to the reference product Imitrex® Statdose, EQ 6 mg base/0.5 mL manufactured by GlaxoSmithKline.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	090358
APPLICANT:	Sun Pharmaceutical Industries, Ltd.
DRUG PRODUCT:	Sumatriptan Succinate Pre-filled Syringe with Auto-injector, EQ 6 mg base/0.5 mL

The Division of Bioequivalence (DBE) has completed its review 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}

Barbara M. Davit, Ph.D., J.D.
Acting Director
Division of Bioequivalence II
Office of Generic Drugs
Center for Drug Evaluation and Research

5 OUTCOME PAGE

ANDA: 090358

Completed Assignment for 90358 ID: 11367

Reviewer: Williamson, Leah **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: Sumatriptan Device

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
11367	6/1/2010	Other	Study Amendment	1	1
				Bean Total:	1

DIVISION OF BIOEQUIVALENCE 2 REVIEW COMPLEXITY SUMMARY

Study Amendment (s)	
Study Amendment Dissolution data resubmitted	1
Study Amendment Total	*1*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90358	ORIG-1	SUN PHARMACEUTICAL INDUSTRIES LTD	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/

LEAH N WILLIAMSON
06/11/2010

CHANDRA S CHAURASIA
06/11/2010

BARBARA M DAVIT
06/11/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090358Orig1s000

MEDICAL REVIEW

MEDICAL CONSULTATION

To:	**Glen Smith** **Lead Chemist, DCII, OGD**
Re:	**ANDA 090358 Sumatriptan Succinate Injection 6 mg /0.5 mL Autoinjector**
Sponsor:	**Sun Pharmaceutical Industries Ltd.**
RLD:	**NDA 020080 Imitrex®, GlaxoSmithKline, approved 12/28/92**
Date of Review:	**November 5, 2009**
Consultant:	**Nancy Chang, M.D.** **Medical Officer, Office of Generic Drugs**
Through:	**Dena Hixon, M.D.** **Associate Director for Medical Affairs, OGD**

Background

DCII originally consulted the OGD clinical group because of an apparent difference in injection times between the proposed and RLD and ANDA 090358 autoinjector devices for sumatriptan. Specifically, the proposed device instructed users to hold in place until a second "click" or for a count of (b) (4) The RLD device instructs users to hold in place for "at least 5 seconds". The clinical group was asked to advise on the whether this difference would be consistent with therapeutic equivalence from a clinical standpoint. Since that time, OGD has received a submission from the firm (9/1/09) revising the proposed labeling to reflect a 5 second injection time.

In addition, the CMC review had raised concerns about defects observed for the full-assembled device during syringe integrity testing and the completeness of the stability data.

Imitrex Drug Information

Indications, Use and Pharmacology

Sumatriptan is a selective 5-HT1 receptor agonist and is thought to relieve migraine and cluster headache through its vasoconstrictive activity. Imitrex is indicated for 1) the acute treatment of migraine attacks with or without aura and 2) the acute treatment of cluster headache episodes.

The maximum recommended single adult dose is 6 mg SQ. If side effects are dose limiting then lower doses may be used. In clinical trials, it was found that smaller doses of sumatriptan may also prove effective, although the proportion of patients obtaining

adequate relief is decreased and the latency to that relief is greater. The maximum recommended total dose that may be given in 24 hours is two 6-mg injections separated by at least 1 hour.

Imitrex Injection is not recommended for use in patients under 18 years of age, although off label use in pediatrics has been documented.

After a 6-mg SQ injection, bioavailability was 97%, distribution and terminal half-lives were 15 and 115 minutes, respectively, and Tmax was 12 minutes. Onset of headache relief begins as early as 10 minutes following injection. The same dose injected SQ into the thigh gave a Cmax of 61 +/- 15 ng/mL by manual injection versus 52+/- 15 ng/mL by autoinjector techniques. Neither the Tmax nor the amount absorbed was significantly altered by either the site or technique of injection.

Contraindications and Precautions

Contraindications to Imitrex include:

a. intravenous administration because of its potential to cause coronary vasospasm
b. patients with a history, symptoms or signs of ischemic cardiac, cerebrovascular or peripheral vascular syndromes.
c. patients with significant underlying cardiovascular diseases
d. patients with uncontrolled hypertension
e. use within 24 hours of using any ergotamine-containing or ergot-type medication
f. patients with severe hepatic impairment

Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm and death have been reported within a few hours of injection. Other vasospastic reactions, including peripheral vascular ischemia and colonic ischemia have been reported. Significant elevation in blood pressure, including hypertensive crisis have been reported even in patients without a history of hypertension.

The Imitrex label contains the following bolded precaution:

> **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.**

Additional precautions:

Information for Patients: With the autoinjector, the needle penetrates approximately 1/4 of an inch (5 to 6 mm). Since the injection is intended to be given subcutaneously, intramuscular or intravascular delivery should be avoided. Patients should be directed to use injection sites with an adequate skin and subcutaneous thickness to accommodate the

length of the needle. See PATIENT INFORMATION at the end of this labeling for the text of the separate leaflet provided for patients.

Adverse Events

Serious cardiac events, including some that have been fatal, have occurred following the use of IMITREX Injection or Tablets. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation.

Significant hypertensive episodes, including hypertensive crises, have been reported on rare occasions in patients with or without a history of hypertension.

In clinical trials, 10.8% of patients who received Imitrex 6 mg SQ reported injection site reactions, compared to 6.5% of patients who received placebo. Local reactions including redness, pain, stinging, induration, swelling, contusion, subcutaneous bleeding, and on rare occasions, lipoatrophy or lipohypertrophy have been reported.

Patients (N=269) have received single injections of 8-12 mg without significant adverse effects, and volunteers (N=47) have received single subcutaneous doses of up to 16 mg without serious adverse events. However, coronary vasospasm was observed after intravenous administration of Imitrex Injection.

The labeling does not comment on the dose-relatedness of adverse events associated with Imitrex.

Imitrex STATdose System

A patient leaflet (separate from the prescribing information) is dispensed in the carton containing the Imitrex autoinjector product, and this describes the use of the system. One side of the leaflet contains general drug information for the patient, including the following instructions for use:

> ***How to Use IMITREX Injection*** **(from patient information leaflet)**
> Before injecting IMITREX, check with your doctor on acceptable injection sites and see the instructions inside the carton on discarding empty syringes and reloading an autoinjector device.
> **Never reuse a syringe.**
> For adults, the usual dose is a single injection given just below the skin. It should be given as soon as the symptoms of your migraine appear, but it may be given at any time during an attack.

The other side of the leaflet contains a detailed description of the system with directions for use:

10000000022892

How To Use The IMITREX STATdose System®

IMITREX® (SUMATRIPTAN SUCCINATE)

This leaflet explains how to use the IMITREX STATdose System.

Read it TWICE before you begin the first step. If you have any questions, ask your doctor or pharmacist.

For use only by patients for whom a 4- or 6-mg dose has been prescribed.

Do not load the IMITREX STATdose Pen® until you are ready to give an injection.
Keep the IMITREX STATdose System out of the reach of children.

THE SYSTEM PARTS

The 4-mg yellow cartridge pack and the 6-mg blue cartridge pack each contain 2 syringe cartridges. (**Note:** The 6-mg blue cartridge pack is shown in the following instructions, but these instructions also apply to the 4-mg yellow cartridge pack.)

A cartridge pack and grey IMITREX STATdose Pen come already loaded into the grey carrying case for your convenience.

The IMITREX STATdose Pen is used to automatically inject the medicine from a syringe cartridge. Do not touch the blue button on the IMITREX STATdose Pen until you are ready to give a dose.

Extra cartridge packs are available separately.

Figure 1

HOW TO LOAD THE IMITREX STATdose PEN

Do not load the IMITREX STATdose Pen until you are ready to give an injection.

Open the lid of the carrying case. The IMITREX STATdose Pen is already in its place (see Figure 2).

Note: Do not use a syringe cartridge if the tamper-evident seal is broken or missing.

Remove the tamper-evident seal from one container of the cartridge pack. The containers have been labeled "A" and "B" to help you keep track of your doses; always use the container marked "A" before the container marked "B".

Discard the seal and open the cartridge lid (see Figure 2).


Figure 2

CAUTION: DO NOT TOUCH THE BLUE BUTTON ON TOP OF THE IMITREX STATdose PEN UNTIL READY TO INJECT.

Grasp the IMITREX STATdose Pen by the ridges at the top (see Figure 3). Take it out of the carrying case.

Note: The spring mechanism in the IMITREX STATdose Pen is primed and ready for use when you take the IMITREX STATdose Pen out of the carrying case. If the white plunger rod is sticking out from the lower end of the IMITREX STATdose Pen, put the IMITREX STATdose Pen back into the carrying case and press down firmly until you feel it click. Remove from carrying case.

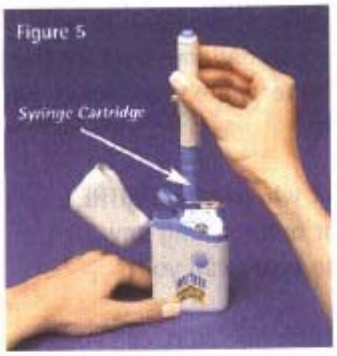

Figure 3


Figure 4

To load the syringe cartridge, insert the IMITREX STATdose Pen into the cartridge pack and turn clockwise until it will no longer turn (about half a turn) (see Figure 4).

Grasping the ridges, pull the loaded IMITREX STATdose Pen **straight out**. You may feel some resistance; again be careful not to press the blue button (see Figure 5).

The IMITREX STATdose Pen is now loaded and ready for use.

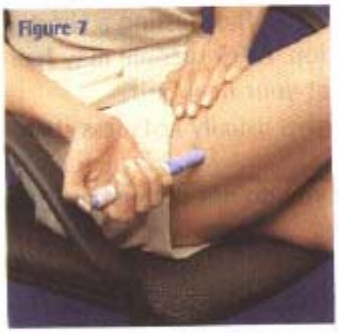


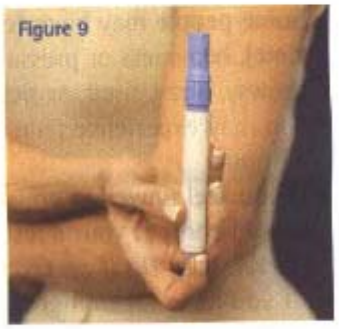
Do not try to put the loaded IMITREX STATdose Pen back into the carrying case as this will damage the needle.

Note: A safety feature is provided that prevents accidental firing until you are ready. The device will only work when pressed against the skin and the grey section slides down to the blue section (see Figure 6).

HOW TO USE THE IMITREX STATdose PEN

Before injecting, identify an area with an adequate fatty tissue layer. Clean the skin area to be injected. To inject, press the loaded IMITREX STATdose Pen against the skin so that the grey section slides down to the blue section (see Figures 7 and 8).





This releases the safety catch. While holding the IMITREX STATdose Pen against the skin, firmly push the blue button. Then hold the IMITREX STATdose Pen still for **at least 5 seconds**. If the IMITREX STATdose Pen is removed from the skin too soon, not all of the medicine will be released.

After 5 seconds, carefully remove the IMITREX STATdose Pen (see Figure 9). The needle will be showing. DO NOT TOUCH THE NEEDLE.

Immediately return the used syringe cartridge into the cartridge pack by pushing the IMITREX STATdose Pen down into the empty side of the cartridge pack as far as it will go (see Figure 10).

Then turn the IMITREX STATdose Pen counterclockwise about half a turn until the pen is released from the syringe cartridge (see Figure 11).

Pull the empty IMITREX STATdose Pen out of the cartridge pack and close the lid over the used syringe cartridge.

Note: Because the device has now been used, the white plunger rod will stick out from the lower end of the IMITREX STATdose Pen (see Figure 12).

Put the IMITREX STATdose Pen back into the carrying case and press down firmly until you feel it click. Close the carrying case lid. If the lid will not close, you have not primed the device for the next use. Push the pen down until you feel it click, and then close the lid.

Note: This action primes the spring mechanism in the IMITREX STATdose Pen for the next use.

After both syringe cartridges have been used, remove the cartridge pack and discard.

NEVER ATTEMPT TO REUSE A SYRINGE CARTRIDGE.

Figure 12

HOW TO REMOVE THE USED CARTRIDGE PACK

Figure 13

Figure 14

When both doses have been used, the cartridge pack should be removed from the carrying case.

- Open the carrying case lid.
- Hold the carrying case with one hand and press the 2 blue buttons located on either side of the carrying case (see Figure 13).
- Gently pull out the cartridge pack with the other hand (see Figure 14). When the used syringe cartridges are properly inserted (see Figure 11), the cartridge pack is a disposable, protective case intended to avoid possible needle sticks or misuse of syringes.

HOW TO INSERT A NEW CARTRIDGE PACK

Remove the new cartridge pack from its package (see Figure 15). DO NOT REMOVE THE TAMPER-EVIDENT SEALS. Push the cartridge pack and smoothly slide the cartridge pack into the carrying case, clicking it down into place (see Figure 16).

The cartridge pack is in the right position when the blue buttons show through the holes in the carrying case (see Figure 17). Close the lid.

Figure 15

Figure 16

Figure 17

Sun Sumatriptan Succinate Injection Prefilled Syringe with Autoinjector

The following table comparing Sun's autoinjector device with the RLD is taken from the original ANDA submission and edited for clarification:

Sun's Proposed Auto injector Device	Reference listed Drug Auto injector device
Pre filled syringe assembled in Autoinjector in final pack	Pre filled syringes (Cartridge system) and autoinjector are separately available in final pack
Disposable autoinjector device	Reusable autoinjector device
White needle shield present, it must be removed before injection	Needle shield is not present
Click sound for indication on starting & completion of injection	No click sound
Safety needle cover present, which covers the needle after injection	Safety needle cover not present, the needle is exposed after injection
No need to replace the white needle shield after injection. Dispose of the autoinjector after use.	Place the used cartridge (PFS) in cartridge box. Autoinjector pen is kept separately for further reuse.

The following tables, also taken from the ANDA, provide some additional comparisons of the Imitrex and the proposed Sun devices.

7. Product characteristics

Item #	Description	Imitrex GSK device	(b) (4) Sun Pharma device
1	Use	Reusable	Single-use, disposable
2	Syringe	1ml Short 26G 1/2" stacked on needle	1ml Long 27G 1/2" stacked on needle
3	Drug	6 mg/0.5 ml treat for Sumatriptan	6 mg/0.5 ml treat for Sumatriptan
4	Configuration	Two-piece, with syringe user assembly	One-piece, integrated syringe no assembly
5	Device profile dimension	D 17~mm x L ~148.90 mm	D (b) (4) mm x L (b) (4) mm
6	Number of component (not including syringe)	(b) (4)	

8.1 Break-loose and extrusion force

Test item	Imitrex GSK device (kg)			[redacted] Sun Pharma device (kg)		
	Mean value	Max. value	Min. value	Mean value	Max. value	Min. value
Break-loose force	0.08	[redacted]		0.31	[redacted]	
Extrusion force	0.83			0.27		
Instron cross head speed	Break-loose force [redacted] Extrusion force =					

A "Final function test" submitted with the ANDA reported mean, max and min injection times of 1.2, [redacted] seconds, respectively for 10 Imitrex devices. The corresponding Sun device times were 2.01, [redacted] respectively.

Of greater concern, stability data showed a large fluctuation in injection times for the Sun device, with values ranging from [redacted] seconds at 0 months to [redacted] seconds at 3 months, with intermediate values observed at 6, 9, and 12 months (limit $\leq$ 10 sec). There was no clear temporal trend in injection time values over the stability testing period.

The following is excerpted from the "How to Use" section of the proposed product labeling. Note that this includes the revised wording from Sun's 9/1/09 submission:

[redacted]

Following this page, 2 pages withheld in full (b)(4) Draft labeling

Summary/Discussion

From an operational standpoint, the proposed autoinjector is fairly similar to the RLD, with the following notable exceptions:

- The RLD requires loading of the prefilled syringes into a reusable autoinjector device, whereas the proposed device is a pre-loaded non-reusable autoinjector.
- Sun's proposed autoinjector comes with a needle shield that must be removed before injection.
- The needle of the RLD device remains exposed after injection, whereas the Sun device has a safety needle cover that automatically covers the needle after injection.
- The Sun device has click indicators signaling the start and end of injection.
- In the original ANDA submission, it appeared that the users would need to hold the device during injection for (b) (4) seconds ((b) (4) as for the RLD device). The revised instructions for the Sun device effectively eliminate this operational difference.

Sumatriptan is a non-emergency use product with significant toxicities. As such, compared to an autoinjector for emergency use, it can be reasonably expected that users are likely to read the directions for use, and minor delays in administration of an injection related to differences in design and learning a new device would not be an overriding safety concern. On the other hand, design differences that could cause accidental injections and misfires by users who are accustomed to the RLD device could represent a significant safety concern, as intravascular injections and injections into end-circulations (e.g. fingers) could be potentially catastrophic.

The operational differences between the Sun and RLD devices would not be expected to cause more accidental injections and misfires in users switching between the two devices because the basic operational sequence and design is essentially the same for these devices, with the same required 2-step activation sequence, which is intended to prevent accidental misfires. While the need to remove the safety shield prior to injection may result in a delay of successful operation of the device if a user does not read instructions, this would not be expected to cause a higher misfire rate than the RLD or to cause misfires in users experienced with the RLD device.

A (b) (4) injection time could cause a higher rate of incomplete injections in users accustomed to the RLD device; however, this is only likely to occur in users who do not follow the instructions for use, and the consequence of an incomplete injection would be reduced efficacy. Incomplete injections would not be expected to compromise safety if users follow the labeling instructions, which clearly indicate that injections should not be repeated even if it is suspected that a full dose was not administered. The extent to which users can be relied upon to follow the labeled directions for use for such a generic device is unknown.

On the other hand, a (b) (4) injection time, and a large variance in injection times, could contribute to differences in the plasma concentration profiles, both between RLD and Sun

devices, and also from one Sun device to another, thereby potentially affecting the safety and therapeutic effect profile for this drug.

An additional concern was noted in a side-by-side review of product labeling. Because this ANDA is only intended for a 6 mg pre-filled device, labeling references to the 4 mg dose and the 6 mg single-dose vial (which are available for Imitrex) have been omitted. Thus, the following wording is proposed for the Sun product:

> An autoinjector is available for use with the 6 mg prefilled syringe to facilitate self-administration in patients using the 6 mg dose....
> In patients receiving doses other than 6 mg, only the 6 mg single-dose dosage form should be used....

The comparable wording from the RLD is as follows:

> An autoinjection device is available for use with the 4- and 6- mg prefilled syringe cartridges to facilitate self-administration in patients using the 4- or 6- mg dose....
> In patients receiving doses other than 4 or 6 mg, only the 6-mg single-dose vial dosage form should be used....

The proposed wording by Sun is potentially confusing and might lead to the interpretation that the 6 mg autoinjector should be used for all doses. It does not clearly explain that the 6-mg single-dose dosage form described is a vial available only from another manufacturer, and that 4-mg dosage forms are also available from another manufacturer.

Recommendations

1. Because differences in injection time and other differences in device performance and design, such as the difference in needle gauge, might affect the plasma concentration profile for sumatriptan, and Cmax in particular, we recommend that human PK studies be requested to demonstrate bioequivalence.

2. In addition, the large fluctuation in injection times observed in stability testing, should be addressed. Consideration could be given to requesting BE data from products of various ages and also examining for inter-individual variation in plasma level profiles that could result from large device-to-device variations in injection times. Alternatively, consideration could be given to setting specifications that would minimize such variability.

3. The currently proposed labeling for the operation and directions for use of the proposed device are not expected to raise clinical safety concerns for this generic product. However, it would be optimal to assess the ability of patients to understand and appropriately follow the directions for use.

4. It is not clear if the proposed labeling changes submitted by Sun on 9/1/09 are accompanied by any corresponding changes in the proposed device. It would seem that the injection times reported during stability testing do not support the proposed labeling; however, the clinical team will defer to CMC the determination of whether or not the specifications and actual performance parameters of the device adequately support the proposed change in labeling, and if the performance remains adequate throughout the proposed shelf life for this product.

5. The proposed labeling is not adequate for patients who require doses other than 6 mg. Whereas, Sun is proposing to market only the 6 mg single-dose autoinjector, the labeling should clearly state that this product is not appropriate for patients who require other dosing strengths.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90358	ORIG-1	SUN PHARMACEUTICAL INDUSTRIES LTD	SUMATRIPTAN SUCCINATE

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/s/

NANCY S CHANG
11/17/2009

DENA R HIXON
11/18/2009
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090358Orig1s000

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review

October 15, 2008

ANDA: 90-358

Drug Product Name
Proprietary: N/A
Non-proprietary: Sumatriptan Succinate Injection
Drug Product Priority Classification: N/A

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
1/18/2008	1/18/2008	N/A	9/18/2008

Applicant/Sponsor
Name: Sun Pharmaceutical Industries, Ltd
Address: Acme Plaza, Andheri Kurla Road, Andheri(E), Mumbai-400 059, India
US Agent: Kendle International, 7361, Calhoun Place, Suite 500, Rockville, MD 20855-2765
Representative: Anthony Celeste
Telephone: (301) 838-3120

Name of Reviewer: Helen Ngai, 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: Halol-Broda Highway, Halol-389 350, Gujarat, India

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: sterile solution, subcutaneous injection, 6 mg of sumatriptan/0.5 mL. Maximum recommended dose is two 6-mg injections separated by 1 hour over 24 hours, for a total of 12 mg (over 24 hours).

5. METHOD(S) OF STERILIZATION: (b) (4) (b) (4)

6. PHARMACOLOGICAL CATEGORY: Sumatriptan is a selective agonist for a vascular 5-hydroxytryptamine$_1$ [5-HT$_1$] receptor subtype. It is intended to relieve migraine or cluster headaches (anti-migraine).

B. SUPPORTING/RELATED DOCUMENTS:

- ANDA 78-737 and micro review 78-737a1 (9/6/08 by J. Wells): validation study information for (b) (4)

C. REMARKS: None.

filename: 90-358.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 can be found in the "Product Quality Microbiology Review" 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 - (b) (4)

B. Brief Description of Microbiology Deficiencies – Incomplete reference to DMF (b) (4) (b) (4) Incomplete (b) (4) (b) (4) and validation information. Incomplete endotoxin testing dilution used during production.

C. Assessment of Risk Due to Microbiology Deficiencies - The safety risk due to microbiology deficiencies is considered moderate.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist /Helen Ngai, Ph.D.
Microbiology Team Leader/LCDR Paul Dexter, M.S.

C. CC Block
cc: Field Copy

Following this page, 9 pages withheld in full (b)(4)

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 90-358 APPLICANT: Sun Pharmaceutical Industries

DRUG PRODUCT: Sumatriptan Succinate Injection

Microbiology Deficiencies:

1. Please describe (b) (4) .

2. Please indicate how (b) (4) .

3. In regard to validation of (b) (4) :

a) (b) (4)

b)

4. Please provide an updated Letter of Authorization from DMF (b) (4) [redacted]

5. Please provide the dilution of the drug product that will be used to test for endotoxins during routine production.

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/

Helen Ngai
11/25/2008 01:25:21 PM
MICROBIOLOGIST

Mark Anderson
11/25/2008 02:05:19 PM
MICROBIOLOGIST

checked for correct linking

Neal Sweeney
12/4/2008 02:56:52 PM
MICROBIOLOGIST

Paul Dexter
12/5/2008 07:37:30 AM
MICROBIOLOGIST

Product Quality Microbiology Review

January 9, 2009

ANDA: 90-358

Drug Product Name
Proprietary: N/A
Non-proprietary: Sumatriptan Succinate Injection
Drug Product Priority Classification: N/A

Review Number: 2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
12/29/2008	12/29/2008	N/A	01/06/2009

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Review Date(s)
1/18/2008	1	10/15/2008

Applicant/Sponsor
Name: Sun Pharmaceutical Industries, Ltd
Address: Acme Plaza, Andheri Kurla Road, Andheri(E), Mumbai-400 059, India
US Agent: Kendle International, 7361, Calhoun Place, Suite 500, Rockville, MD 20855-2765
Representative: Anthony Celeste
Telephone: (301) 838-3120

Name of Reviewer: Helen Ngai, 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: Original ANDA

2. SUBMISSION PROVIDES FOR: Initial marketing of sterile drug product

3. MANUFACTURING SITE: Halol-Broda Highway, Halol-389 350, Gujarat, India

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: sterile solution, subcutaneous injection, 6 mg of sumatriptan/0.5 mL. Maximum recommended dose is two 6-mg injections separated by 1 hour over 24 hours, for a total of 12 mg (over 24 hours).

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Sumatriptan is a selective agonist for a vascular 5-hydroxytryptamine$_1$ [5-HT$_1$] receptor subtype. It is intended to relieve migraine or cluster headaches (anti-migraine).

B. SUPPORTING/RELATED DOCUMENTS:

- ANDA 78-737 and micro review 78-737a1 (9/6/08 by J. Wells): validation study information for (b) (4)

C. REMARKS: None.

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - (b) (4)

B. Brief Description of Microbiology Deficiencies - None identified

C. Assessment of Risk Due to Microbiology Deficiencies - None; sufficient sterility assurance information is provided.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist /Helen Ngai, Ph.D.
Microbiology Team Leader/LCDR Paul Dexter, M.S.

C. CC Block

cc: Field Copy

Following this page, 4 pages withheld in full (b)(4)

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/s/

Helen Ngai
1/13/2009 11:04:16 AM
MICROBIOLOGIST

Mark Anderson
1/13/2009 11:05:21 AM
MICROBIOLOGIST

checked for correct file and submission link; both OK

Neal Sweeney
1/23/2009 10:01:47 PM
MICROBIOLOGIST

Paul Dexter
1/26/2009 09:35:56 AM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090358Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Tandalja, Vadodara - 390 020, INDIA.
Tel. : 91- 265 - 6615500, 6615600, 6615700
Fax : 91- 265 - 2354897

ORIGINAL

SUN PHARMACEUTICAL INDUSTRIES LTD.

505(b)(2) O.K.
3 MAY 2008
90358

Date: 31' December, 07

Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 4 (MPN4) HFD-600
7519 Standish Place
Rockville, MD 20855

Re: ANDA Submission for Sumatriptan Succinate Injection, 6 mg/0.5 ml.

ORIGINAL ABBREVIATED NEW DRUG APPLICATION

Sun Pharmaceutical Industries Ltd. hereby submits this Original Abbreviated New Drug Application, which provides for **Sumatriptan Succinate Injection, 6 mg/0.5 ml** in accordance with section 505 (j) of the Federal Food Drug and Cosmetic Act. The subject drug is a prescription drug formulated as sterile solution for injection.

Sun Pharmaceutical Industries Ltd will manufacture the **Sumatriptan Succinate Injection, 6 mg/0.5 ml** in pre filled syringe assembled in autoinjector device as a final drug product at its manufacturing facility located at Sun Pharmaceutical Industries Ltd-Halol, Halol-Baroda Highway, Halol-389 350, Gujarat, India. (Formerly known as M.J. Pharmaceuticals Ltd). The Active Raw Material is manufactured by Sun Pharmaceutical Industries Ltd.-Panoli. Please refer to Drug Master File # 19372. For a full description of the facility and the Active raw material details.

Please refer to the accompanying Table of Contents for a list of the data supporting this submission. These data have been presented in 7 volumes for Module-3 and 1 volume each for Module-1 and Module-2, consistent with the Guidance's for Industry entitled "M4-Organization of an CTD" dated October 2001, "M4Q- The CTD quality", dated August 2001 and "ANDA checklist for CTD (updated 17 October, 07).

Sterility Assurance Information and Data has been provided in Section 3.2.P.3.5 which includes information for [redacted] (b)(4) manufacturing processes and its validation. This information is provided in Module-3, volume 2, 3 and 4.

RECEIVED

JAN 18 2008

OGD

Corporate Office : ACME PLAZA, Andheri Kurla Road, Andheri(E), Mumbai - 400 059 INDIA.
Tel. : (91 - 22) 28230102 / 28211260 / 28212143, Fax (91 - 22) 28212010, Website : www.sunpharma.com

Tandalja, Vadodara - 390 020, INDIA.
Tel. : 91- 265 - 6615500, 6615600, 6615700
Fax : 91- 265 - 2354897

SUN PHARMACEUTICAL INDUSTRIES LTD.

Sun Pharmaceutical Industries Ltd requests waiver from the requirements of submission of evidence demonstrating the *in-vivo* bioequivalence of its **Sumatriptan Succinate Injection, 6 mg/0.5 ml** to the listed drug, IMITREX® (sumatriptan succinate) Injection manufactured by GlaxoSmithKline, Research Triangle Park,, NC 27709, as the proposed product is a parenteral solution intended for subcutaneous administration and it contains the same amount of active ingredient and meets the same standards of strength, quality, purity and identity as the listed drug.

We are requesting (b) (4) months expiration dating for this product based on the 3 months accelerated stability and 3 month long term stability data enclosed herein in Module 3.2.P.8. At the FDA's request we will provide samples of the bulk drug substance and finished dosage form.

A copy of the Table of Contents has been provided in the front of each volume of the archival and review copies of this original abbreviated new drug application.

Following this letter is a letter authorizing Kendle International to act as the U.S. agent for this ANDA.

Thank you

Sincerely,

Dr. Abhay Muthal
General Manager, Regulatory Affairs

Corporate Office : ACME PLAZA, Andheri Kurla Road, Andheri(E), Mumbai - 400 059 INDIA.
Tel. : (91 - 22) 28230102 / 28211260 / 28212143, Fax (91 - 22) 28212010, Website : www.sunpharma.com

Kendle

Telephone Amendment

Hand Delivery

April 30, 2008

Attention: Ms. Rebekah Granger
Office of Generic Drug
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

RE: Telephone Amendment for ANDA 90-358, Sumatriptan Succinate Injection 6 mg/0.5 mL

Dear Ms. Granger,

As the appointed U.S. Agent for Sun Pharmaceutical Industries we submitting a telephone amendment providing a response to FDA's telephone request regarding ANDA 90-358, Sumatriptan Succinate Injection 6 mg/0.5 mL.

1. A completed form 3674. : Please find attached form 3674.

2. A revised 356h noting that the RLD is Imitrex stat dose and clarifying that this is pre-filled syringe.
Revised form 356h indicating "prefilled syringes" for RLD and Sun's product is attached.

3. Include exclusivity statement in certification, i.e. "there is no exclusivity".
Please note that in section 1.3.5.2 of module 1 the statement of exclusivity states that RLD is not entitled for marketing exclusivity. The copy of this page is attached for your ready reference.

4. Clarify under manufacturing process description, 3.2.P.3.3. whether the process is [redacted] (b) (4)
Please note that product is [redacted] (b) (4). It is mentioned in narrative summary of manufacturing process provided in section 3.2.P.3.3. Schematic diagram is revised to indicate the [redacted] (b) (4). The copy of this page is attached for your ready reference.

If you have any questions or need additional information, please let us know.

Sincerely,

Anthony Celeste
Senior, Vices President

Kendle Regulatory Affairs
7361 Calhoun Place
Suite 500
Rockville, MD 20855
Tel: +1 301 838 3120
Fax: +1 301 838 3182

Enclosures

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 90-358

Kendle International
US Agent for Sun Pharmaceutical Industries Ltd
Attention: Anthony Celeste
7361 Calhoun Celeste
Suite 500
Rockville, MD 20855-2765

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.

Reference is also made to the telephone conversation dated April 29, 2008 and your correspondence dated April 30, 2008.

NAME OF DRUG: Sumatriptan Succinate Injection,
6 mg/0.5 mL (pre-filled syringes)

DATE OF APPLICATION: December 31, 2007

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 18, 2007

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
5/2/2008 01:09:52 PM
Signing 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 #: 90-358 **FIRM NAME**: SUN PHARMACEUTICALS INDUSTRIES LTD.

PIV: NO **Electronic or Paper Submission:** PAPER (CTD FORMAT)

RELATED APPLICATION(S): SEE 78-295 FOR SUMATRIPTAN SUCCINATE TABLETS, 25 MG, 50 MG AND 100 MG FROM SUN PHARMACEUTICALS INDUSTRIES LTD. PN 7/6/2007 (RLD IMITREX)

Bio Assignments:		
☒ **BPH**	☐ **BCE**	☒ **Micro Review !!!Yes, MICRO Review NEEDED!!!**
☐ **BST**	☐ **BDI**	

First Generic Product Received? NO

DRUG NAME: SUMATRIPTAN SUCCINATE
DOSAGE FORM: INJECTION, 6 MG/0.5 ML

Random Queue: 9
Chem Team Leader: Smith, Glen J PM: Laura Longstaff Labeling Reviewer: Chan Park

Letter Date: JANUARY 18, 2008 **Received Date**: JANUARY 18, 2008

Comments: EC - 1 YES **On Cards:** YES
Therapeutic Code: 2011110 MIGRAINE

Archival copy: PAPER (CTD FORMAT) **Sections** I
Review copy: YES 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 Rebekah Granger
Date 4/28/2008

Recommendation:
☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: ____ **Date: ____**

ADDITIONAL COMMENTS REGARDING THE ANDA:
4/29/08 – Anthony Celeste (301) 838-3120. LM
Please submit FDA Form 3674
Revise FDA form 356h to include "STATDOSE" in name of RLD
Sponsor flip-flopped between the term (b) (4) **. Please clarify how was the product sterilized.** (b) (4)
(b) (4)
Per correspondence submitted by sponsor dated 4/30 the above is adequate for filing

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** YES (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: JANUARY 18, 2008 YES	☒
*	**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) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) 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)
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?
   b. Expiration of Pediatric Exclusivity?
4. Exclusivity Statement: YES

Patent and Exclusivity Search Results from query on Appl No 020080 Product 003 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
020080	003	5037845	Aug 6, 2008			U-72	
020080	003	5037845*PED	Feb 6, 2009				

Exclusivity Data

There is no unexpired exclusivity for this product.

Patent Use Codes

This page defines the patent use codes.

Code	Definition
U-72	TREATMENT OF MIGRAINE

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 YES
   b. Type III DMF authorization letter(s) for container closure YES
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 STATDOSE
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.) **HOW SUPPLIED** (NDC 62756-276-40) autoinjector containing 1 prefilled single-dose syringe	☒
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** **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** YES **3.2.S.1.2 Structure** YES **3.2.S.1.3 General Properties** YES	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (Includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers YES 2. Manufacturing Responsibilities YES 3. Type II DMF number for API YES – DMF #19372 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization** Refer to DMF #19372	☒
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 YES b. Same lot number(s) YES **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** YES	☒
3.2.S.5	**Reference Standards or Materials** YES	☒
3.2.S.6	**Container Closure Systems** Refer to DMF #19372	☒
3.2.S.7	**Stability** Refer to DMF #19372	☒

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 are appropriate per IIG YES – Q1Q2	☒
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) YES 2. CGMP Certification: YES 3. Function or Responsibility YES 4. CFN or FEI numbers **3.2.P.3.2 Batch Formula** Batch Formulation 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 YES 3. If sterile product: (b) (4) YES 4. Reprocessing Statement YES **3.2.P.3.4 Controls of Critical Steps and Intermediates** YES **3.2.P.3.5 Process Validation and/or Evaluation** 1. (b) (4) 2. **PROPOSED COMMERCIAL BATCH SIZE:** (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** USP/NF Testing **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

3.2.P.5	**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 YES 2. Same lot numbers YES **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form YES **3.2.P.5.5 Characterization of Impurities** YES **3.2.P.5.6 Justification of Specifications** YES	☒
3.2.P.7	**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 YES 4. Container/Closure Testing YES in Sec 3.2.P.3.5 5. Source of supply and suppliers address YES	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted YES 2. Expiration Dating Period YES – (b) (4) MONTHS **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 – Lot #JK70920	☒

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) NOT AVAILABLE** **3.2.R.2.S Comparability Protocols N/A** **3.2.R.3.S Methods Validation Package** YES 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 (b) (4) Actual Yield (b) (4) Packaged Yield **3.2.R.1.P.2 Information on Components** YES **3.2.R.2.P Comparability Protocols** N/A **3.2.R.3.P Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

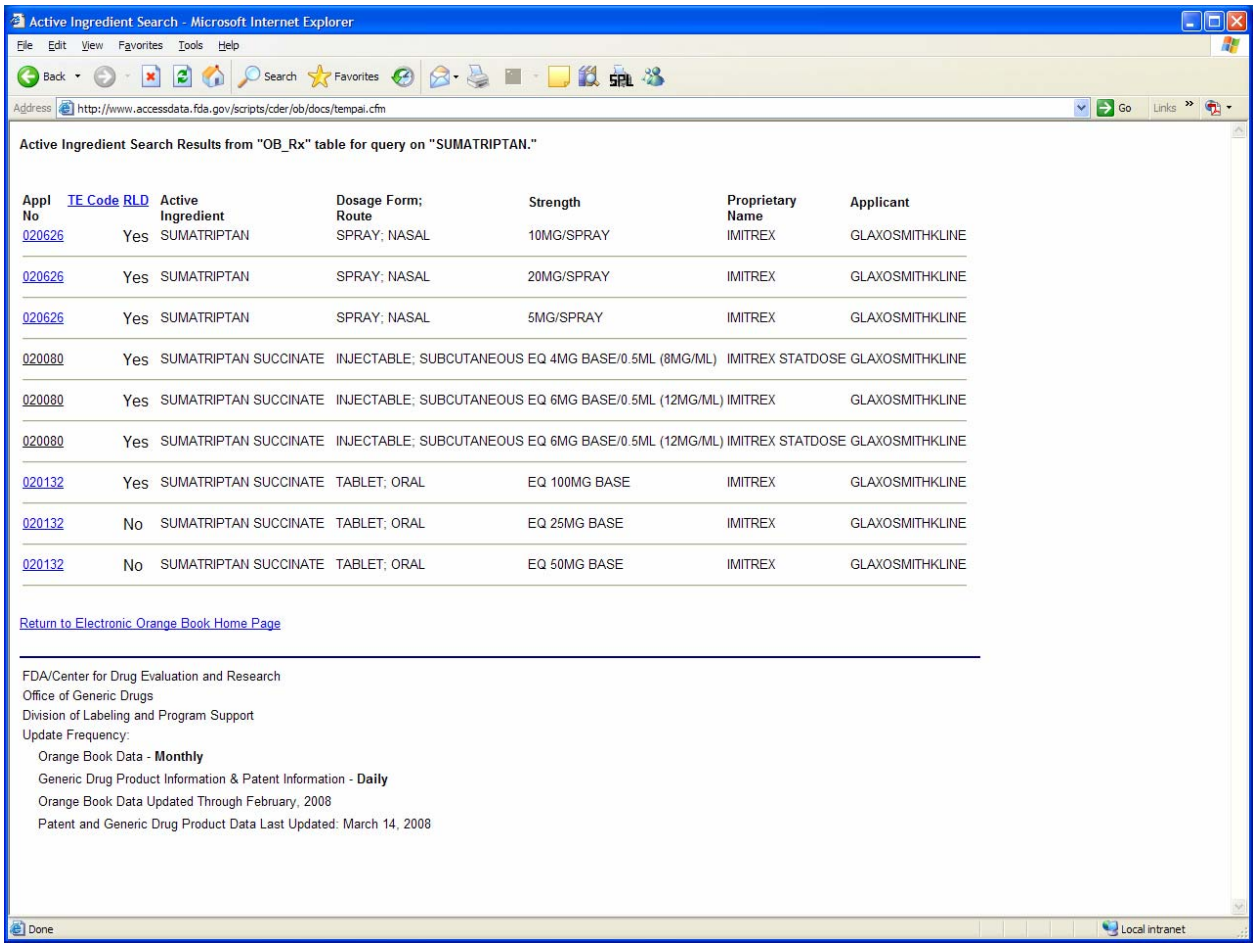
CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies N/A** **E-Submission: PDF** **Word Processed e.g., MS Word**	☐
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 PK STUDY(IES)** (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	☐

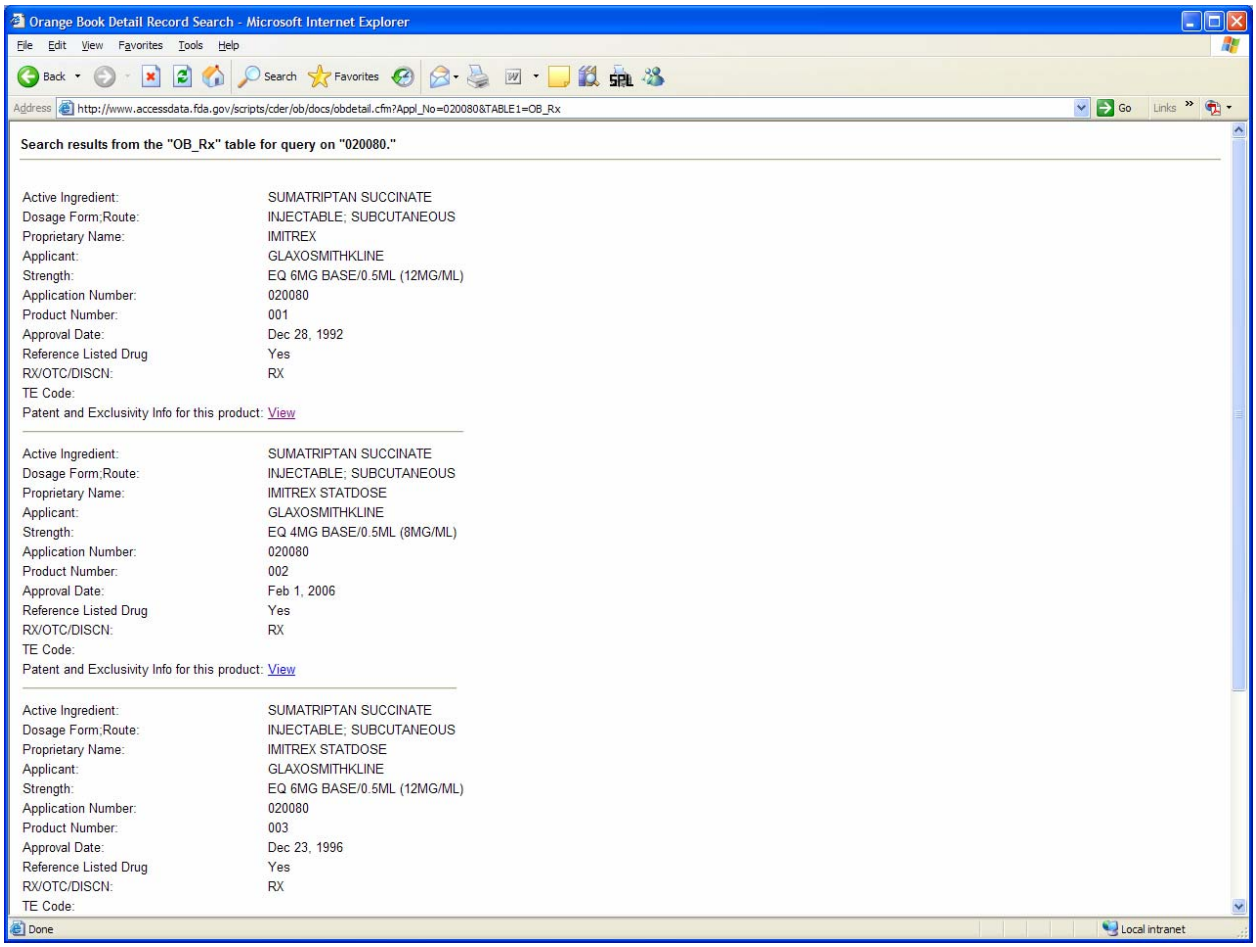


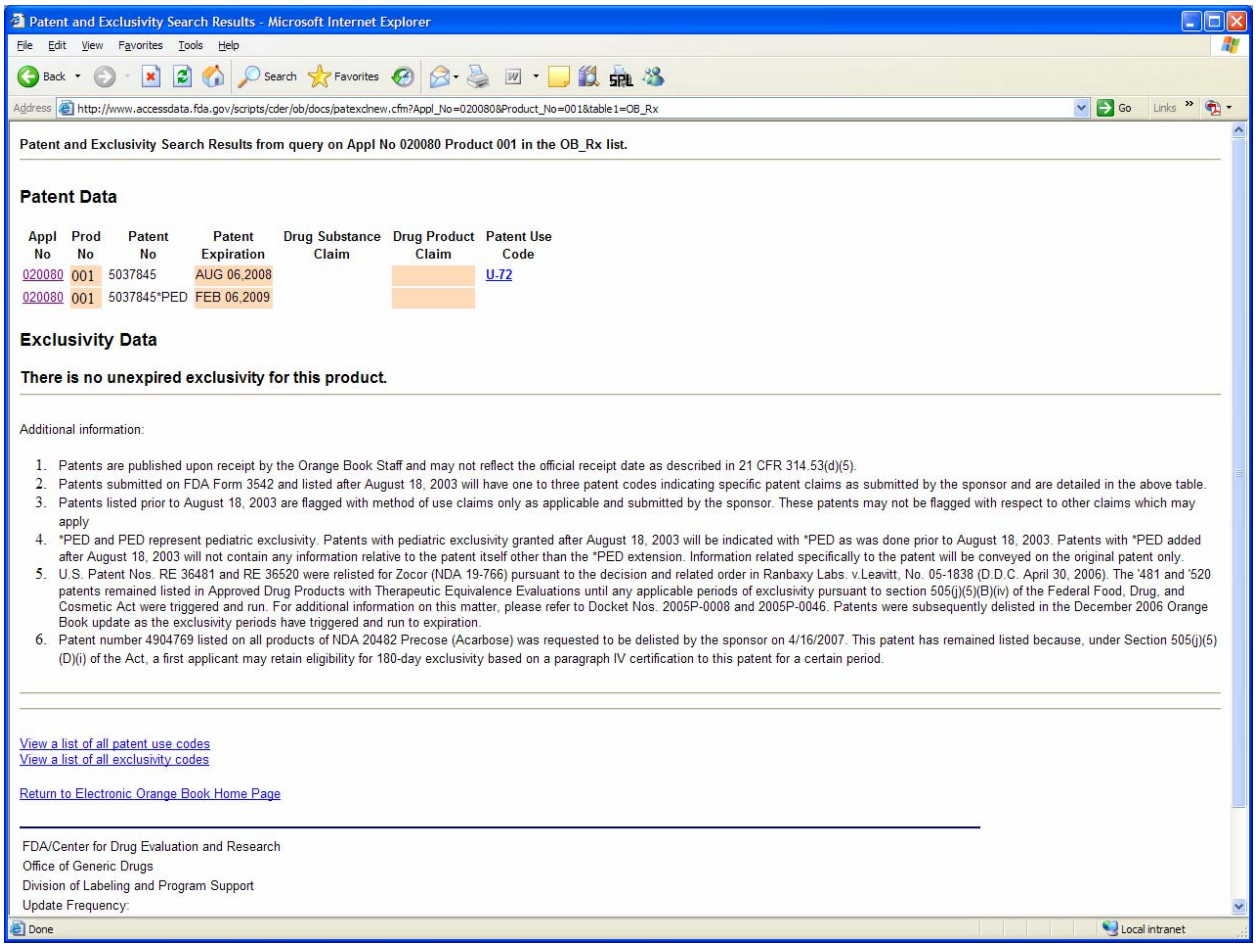
Active Ingredient Search Results from "OB_Rx" table for query on "SUMATRIPTAN."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
020626		Yes	SUMATRIPTAN	SPRAY; NASAL	10MG/SPRAY	IMITREX	GLAXOSMITHKLINE
020626		Yes	SUMATRIPTAN	SPRAY; NASAL	20MG/SPRAY	IMITREX	GLAXOSMITHKLINE
020626		Yes	SUMATRIPTAN	SPRAY; NASAL	5MG/SPRAY	IMITREX	GLAXOSMITHKLINE
020080		Yes	SUMATRIPTAN SUCCINATE	INJECTABLE; SUBCUTANEOUS	EQ 4MG BASE/0.5ML (8MG/ML)	IMITREX STATDOSE	GLAXOSMITHKLINE
020080		Yes	SUMATRIPTAN SUCCINATE	INJECTABLE; SUBCUTANEOUS	EQ 6MG BASE/0.5ML (12MG/ML)	IMITREX	GLAXOSMITHKLINE
020080		Yes	SUMATRIPTAN SUCCINATE	INJECTABLE; SUBCUTANEOUS	EQ 6MG BASE/0.5ML (12MG/ML)	IMITREX STATDOSE	GLAXOSMITHKLINE
020132		Yes	SUMATRIPTAN SUCCINATE	TABLET; ORAL	EQ 100MG BASE	IMITREX	GLAXOSMITHKLINE
020132		No	SUMATRIPTAN SUCCINATE	TABLET; ORAL	EQ 25MG BASE	IMITREX	GLAXOSMITHKLINE
020132		No	SUMATRIPTAN SUCCINATE	TABLET; ORAL	EQ 50MG BASE	IMITREX	GLAXOSMITHKLINE

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through February, 2008
Patent and Generic Drug Product Data Last Updated: March 14, 2008


Orange Book Detail Record Search - Microsoft Internet Explorer
File Edit View Favorites Tools Help
Back Search Favorites
Address http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=020080&TABLE1=OB_Rx
Go Links
Search results from the "OB_Rx" table for query on "020080."
Active Ingredient: SUMATRIPTAN SUCCINATE
Dosage Form;Route: INJECTABLE; SUBCUTANEOUS
Proprietary Name: IMITREX
Applicant: GLAXOSMITHKLINE
Strength: EQ 6MG BASE/0.5ML (12MG/ML)
Application Number: 020080
Product Number: 001
Approval Date: Dec 28, 1992
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Active Ingredient: SUMATRIPTAN SUCCINATE
Dosage Form;Route: INJECTABLE; SUBCUTANEOUS
Proprietary Name: IMITREX STATDOSE
Applicant: GLAXOSMITHKLINE
Strength: EQ 4MG BASE/0.5ML (8MG/ML)
Application Number: 020080
Product Number: 002
Approval Date: Feb 1, 2006
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Active Ingredient: SUMATRIPTAN SUCCINATE
Dosage Form;Route: INJECTABLE; SUBCUTANEOUS
Proprietary Name: IMITREX STATDOSE
Applicant: GLAXOSMITHKLINE
Strength: EQ 6MG BASE/0.5ML (12MG/ML)
Application Number: 020080
Product Number: 003
Approval Date: Dec 23, 1996
Reference Listed Drug Yes
RX/OTC/DISCN: RX
TE Code:
Done
Local intranet



Patent and Exclusivity Search Results from query on Appl No 020080 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020080	001	5037845	AUG 06,2008			U-72
020080	001	5037845*PED	FEB 06,2009			

Exclusivity Data

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply
4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.
5. U.S. Patent Nos. RE 36481 and RE 36520 were relisted for Zocor (NDA 19-766) pursuant to the decision and related order in Ranbaxy Labs. v.Leavitt, No. 05-1838 (D.D.C. April 30, 2006). The '481 and '520 patents remained listed in Approved Drug Products with Therapeutic Equivalence Evaluations until any applicable periods of exclusivity pursuant to section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act were triggered and run. For additional information on this matter, please refer to Docket Nos. 2005P-0008 and 2005P-0046. Patents were subsequently delisted in the December 2006 Orange Book update as the exclusivity periods have triggered and run to expiration.
6. Patent number 4904769 listed on all products of NDA 20482 Precose (Acarbose) was requested to be delisted by the sponsor on 4/16/2007. This patent has remained listed because, under Section 505(j)(5)(D)(i) of the Act, a first applicant may retain eligibility for 180-day exclusivity based on a paragraph IV certification to this patent for a certain period.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

Composition:
In the finished dosage form, Sumatriptan Succinate Injection, 6 mg/0.5 ml contains the following:

Components	**mg/ml**
Sumatriptan Succinate, Ph. Eur.	(b) (4)[1]
Sodium Chloride, USP	7.00
Water for Injection, USP	q.s. to 1 ml
(b) (4)	*[2]

*[1] (b) (4)
*[2]

(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/

Martin Shimer

5/2/2008 01:10:06 PM

Labeling Amendment

Hand Delivery

September 5, 2008

Attention: Chan Park
Office of Generic Drug
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

N/A
ORIG AMENDMENT

RE: Labeling Amendment for ANDA 90-358, Sumatriptan Succinate Injection 6 mg/0.5 mL

Dear Dr. Park,

As the appointed U.S. Agent for Sun Pharmaceutical Industries we submitting a labeling amendment providing a response to FDA's request of June 3, 2008 regarding ANDA 90-358, Sumatriptan Succinate Injection 6 mg/0.5 mL.

Please note that a letter of Non-Repudiation has been submitted.

If you have any questions or need additional information, please let us know.

Sincerely,

Anthony Celeste
Senior, Vices President

Enclosures

Kendle Regulatory Affairs
7361 Calhoun Place
Suite 500
Rockville, MD 20855
Tel: +1 301 838 3120
Fax: +1 301 838 3182

www.kendle.com

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: Anthony C, Celeste		**FROM:** Bonnie McNeal
U.S. Agent: Sun Pharmaceutical Industries Ltd.		Microbiology Project Manager
PHONE: 301-838-3120		**PHONE:** (240) 276-8831
FAX: 301-838-3182		**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 90-358 for Sumatriptan Succinate Injection. The submission reviewed was submitted on January 18, 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 Bonnie McNeal or Mark Anderson.

LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 90-358 APPLICANT: Sun Pharmaceutical Industries

DRUG PRODUCT: Sumatriptan Succinate Injection

Microbiology Deficiencies:

1. Please describe [redacted (b) (4)].

2. Please indicate how [redacted (b) (4)].

3. In regard to validation o [redacted (b) (4)]:

   a) [redacted (b) (4)]

   b) [redacted]

4. Please provide an updated Letter of Authorization from DMF (b) (4) [redacted].

5. Please provide the dilution of the drug product that will be used to test for endotoxins during routine production.

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

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

/s/

Paul Dexter

12/18/2008 01:55:22 PM

Kendle

Minor Amendment –
Response to Microbiology Deficiencies

Hand Delivery

December 29, 2008

Attention: Bonnie McNeal
Office of Generic Drug
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

RE: Minor Amendment – Response to Microbiology Deficiencies for ANDA 90-358, Sumatriptan Succinate Injection 6 mg/0.5 mL

Dear Dr. McNeal,

As the appointed U.S. Agent for Sun Pharmaceutical Industries we submitting a **Minor Amendment – Response to Microbiology Deficiencies** amendment providing a response to FDA's request of December 18, 2008 regarding ANDA 90-358, Sumatriptan Succinate Injection 6 mg/0.5 mL.

Please note that a letter of Non-Repudiation has been submitted.

If you have any questions or need additional information, please let us know.

Sincerely,

Anthony Celeste
Senior, Vices President

Enclosures

Kendle Regulatory Affairs
7361 Calhoun Place
Suite 500
Rockville, MD 20855
Tel: +1 301 838 3120
Fax: +1 301 838 3182

www.kendle.com

COMPLETE RESPONSE -- MINOR

ANDA 90-358

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: Sun Pharmaceutical Industries Ltd.
U.S. Agent: Kendle Regulatory

TEL: 301-838-3120

FAX: 301-838-3182

ATTN: Anthony C, Celeste

FDA CONTACT PHONE: (240) 276-8566

FROM: Laura Longstaff

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 31, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sumatriptan Succinate Injection, 6 mg/0.5 mL.

Reference is also made to your amendment dated September 5, and December 29, 2008.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (__**3**__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. 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. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

III. List of Deficiencies to Be Communicated to the Applicant

ANDA: 90-358 APPLICANT: Sun Pharmaceuticals, India

.

DRUG PRODUCT: Sumatriptan Succinate Injection 6 mg/0.5 mL (Auto-Injector)

A. Deficiencies

The deficiencies presented below represent MINOR deficiencies.

1. Regarding the Sumatriptan Succinate API:
   a. Since the drug substance is the subject of a USP monograph, please provide justifications based on USP in addition to Ph. Eur.
   b. The chemical name for all impurities should be specified in the list of specifications.
2. Please establish a time from the start of manufacture to packaging in the proposed market container. If applicable, proposed hold time periods should be supported be adequate data.
3. Regarding the controls for release of the finished drug product:
   a. Effective July 1, 2008, all Abbreviated New Drug Applications must demonstrate that the subject drug product is in compliance with USP Residual Solvents <467> prior to receiving Approval or Tentative Approval. Please refer to the information posted on the Office of Generic Drugs website for guidance on the required documentation.
   b. Chemical names for impurities should be specified in the list of specifications.
4. [redacted] (b) (4) Please provide pertinent revised documentation modified accordingly.
5. Regarding data provided for the glass barrel:
   a. We acknowledge the test procedures, specification and data for the glass barrel. We note that the test procedures do not correspond to the specifications and CoA. Please submit revised documentation showing agreement.
   b. [redacted] (b) (4)
   c. A CoA from the syringe manufacturer should be included. Please submit.
   d. The "Conformity Certificate" provided on page 95 of section 3.2.P.7 is not readable. Please submit a readable copy.

6. Regarding data provided for the plunger stopper:
    a. (b) (4)
    b.
    c.
    d.
7. Regarding the information provided for the auto-injector:
    a. A statement is included indicating that the device quality failures observed during the qualification of assembly process, are to be corrected and re-validation performed prior to regular production (p. 269). No additional studies are included within the ANDA. Please submit.
    b. Please indicate if the manufacturing package for the proposed auto-injector has been previously submitted to CDRH for review. Pertinent documentation should be submitted if applicable.
8. Please submit updated stability data.

B. In addition to the deficiencies noted above, please note and acknowledge the following comments in your response

Samples of the auto-injector should be provided. Please submit samples of your autoinjector (placebo filled) product along with samples of the RLD directly to:

Office of Generic Drugs
Attention: Mayra Pineiro-Sanchez/Glen Smith
HFD-640
Division of Chemistry II
7500 Standish Place
Rockville, MD 20855

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

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

/s/

Glen Smith

1/12/2009 12:45:47 PM

Minor Amendment

Kendle
Real people. Real results.

Hand Delivery

January 21, 2009

Attention: Ms. Laura Longstaff
Office of Generic Drug
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

RE: Minor Amendment for ANDA 90-358, Sumatriptan Succinate Injection 6 mg/0.5 mL

Dear Ms. Longstaff,

As the appointed U.S. Agent for Sun Pharmaceutical Industries we submitting a minor amendment amendment providing a response to FDA's letter dated January 12, 2009 regarding ANDA 90-358, Sumatriptan Succinate Injection 6 mg/0.5 mL.

Please note that a letter of Non-Repudiation has been submitted.

If you have any questions or need additional information, please let us know.

Sincerely,

Anthony Celeste
Senior, Vices President

Enclosures

7361 Calhoun Place
Suite 500
Rockville, MD 20855
United States

T +1 301 838 3120
F +1 301 838 3182

www.kendle.com

General Correspondence

Kendle
Real people. Real results.

Hand Delivery

June 1, 2009

Attention: Ms. Laura Longstaff
Office of Generic Drug
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

RE: General Correspondence for ANDA 90-358, Sumatriptan Succinate Injection 6 mg/0.5 mL

Dear Ms. Longstaff,

As the appointed U.S. Agent for Sun Pharmaceutical Industries we submitting general correspondence enclosing a copy of Sun's letter summarizing the evaluation of the information provided in ANDA 90-358, Sumatriptan Succinate Injection 6 mg/0.5 mL with respect to FDA's Draft Guidance for Industry and FDA Staff: "Technical Considerations Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products" dated April 24, 2009.

Based on Sun's evaluation all relevant information has been provided as suggested in this guidance either in ANDA or as a part of 510(K) submission which has been incorporated in the ANDA by reference.

Please note that a letter of Non-Repudiation has been submitted.

If you have any questions or need additional information, please let us know.

Sincerely,

Anthony Celeste
Senior, Vices President

Enclosures

7361 Calhoun Place
Suite 500
Rockville, MD 20855
United States

T +1 301 838 3120
F +1 301 838 3182

www.kendle.com

Labeling Amendment

Kendle
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September 1, 2009

Attention: Ms. Laura Longstaff
Office of Generic Drug
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

RE: Labeling Amendment for ANDA 90-358, Sumatriptan Succinate Injection 6 mg/0.5 mL

Dear Ms. Longstaff,

As the appointed U.S. Agent for Sun Pharmaceutical Industries we submitting a labeling amendment providing revised labeling with regards to ANDA 90-358, Sumatriptan Succinate Injection 6 mg/0.5 mL.

Please note that a letter of Non-Repudiation has been submitted.

If you have any questions or need additional information, please let us know.

Sincerely,

Anthony Celeste
Senior Vices President

Enclosures

7361 Calhoun Place
Suite 500
Rockville, MD 20855
United States

T +1 301 838 3120
F +1 301 838 3182

www.kendle.com

Tandalja, Vadodara - 390 020, INDIA.
Tel. : 91- 265 - 6615500, 6615600, 6615700
Fax : 91- 265 - 2354897

SUN
PHARMACEUTICAL
INDUSTRIES LTD.

Date: September 14, 2009

9-2
SUN-8

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

Subject: Change in US Agent Designation, for ANDA of Sumatriptan Succinate Injection, 6 mg (base)/0.5 mL (ANDA # 90-358)

Dear Sir/Madam

For the subject ANDA, Kendle International, 7361, Calhoun Place, Suite 500, Rockville, MD 20855-2765, U.S.A is currently acting as an US agent for Sun Pharmaceutical Industries Ltd.

This is to inform you for change in US agent, effective from September 20, 2009, our new US agent shall be as follows.

Sun Pharmaceutical Industries, Inc.
270 Prospect Plains Road
Cranbury, NJ 08512

Telephone : 609-495-2823
Fax : 609-495-2711

Contact person: Ms. Anne Toland

We hereby authorize Sun Pharmaceutical Industries, Inc.- Cranbury to submit and receive all correspondence on technical and administrative matters pertaining to our submissions in support of firms application for a drug product and any supplement thereafter and for scheduling the planned inspection of our plant. We request that all communications to be sent through Sun Pharmaceutical Industries, Inc.- Cranbury and we will in turn respond to FDA through them as well.

We also request you to make necessary updation in your records for the designated US agent for the subject ANDA.

Sincerely yours,

Dr. Abhay Muthal
General Manager, Regulatory Affairs
Sun Pharmaceutical Industries Ltd.

RECEIVED
OCT 19 2009
OGD

SUN
PHARMACEUTICAL
INDUSTRIES, INC.

December 21, 2009

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park, North II
7500 Standish Place, Room 150
Rockville, MD 20855-2733

TELEPHONE AMENDMENT

Re: Sumatriptan Succinate Injection,
6 mg/0.5 mL (Auto-Injector)
ANDA# 90-358
Telephone Amendment

Dear Mr. Buehler,

As the US Agent for Sun Pharmaceutical Industries Ltd., we are submitting this Telephone Amendment in duplicate for the above referenced ANDA. A true copy of this amendment has been faxed to the reviewer Dr. Mayra L. Pineiro-Sanchez, Ph.D. An electronic copy of this amendment is provided on CD in .pdf format.

A copy of this cover letter is enclosed in a self-addressed, stamped envelope. Please stamp the copy as 'Received' with the appropriate date of receipt and kindly return it to Sun Pharmaceutical Industries, Inc. as acknowledgment of receipt of this amendment.

During the course of the review of this amendment, if there are any questions or comments, please do not hesitate to contact me via telephone at (609) 495-2823, via facsimile at (609) 495-2711 or e-mail: anne.toland@sunpharmausa.com.

Sincerely,

Anne Toland

Anne Toland
Director, Regulatory Affairs
Sun Pharmaceutical Industries, Inc.

Enclosures

270 Prospect Plains Road, Cranbury, NJ 08512 • Phone: (609) 495 2823 • FAX: (609) 495 2711

BIOEQUIVALENCE AMENDMENT

ANDA 090358

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: Sun Pharmaceutical Industries Ltd. TEL: (301) 838-3120

ATTN: Anthony Celeste FAX: (301) 838-3182

FROM: Diane Nhu FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on January 18, 2008, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sumatriptan Injection (Prefilled Syringe), 6 mg/0.5 mL.

The Division of Bioequivalence 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.

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 Other
Bioequivalence Response to Information Request

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, 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:

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 090358

APPLICANT: Sun Pharmaceutical Industries Ltd.

DRUG PRODUCT: Sumatriptan Succinate Injection
EQ 6 mg base/0.5 mL (pre-filled syringe with auto-injector)

The Division of Bioequivalence (DBE) has completed its review of your submission and the following deficiencies have been identified:

1. The DBE does not agree that the information submitted by you demonstrates that Sumatriptan Succinate Injection, EQ 6 mg base/0.5 mL, pre-filled syringe with auto-injector meets the requirements of Section 21 CFR § 320.22(b)(1).

2. Because differences in injection time and other differences in device performance and design, such as the difference in needle gauge, might affect the plasma concentration profile for sumatriptan, and Cmax in particular, we recommend that an in vivo study with pharmacokinetic (PK) endpoints be conducted to demonstrate bioequivalence. Therefore, the DBE recommends that you conduct a single-dose two-way crossover fasting bioequivalence study in healthy subjects. The study subjects should inject themselves both the test and reference products using the respective auto-device.

3. Please also conduct comparative in vitro testings on 1) drug volume delivered, 2) injection time, and 3) force to fire. These in vitro tests should be conducted on the biobatch lot and the reference listed drug (RLD). Please submit an EXCEL spreadsheet of individual data, mean, and %CV for these data on the test product versus Imitrex® STATDOSE Injectable

4. In addition to the in vitro testing above, to address the large fluctuation in injection times observed in stability testing, the DBE recommends that you conduct additional in vitro testing on 1) drug volume delivered, 2) injection time, and 3) force to fire stability lots. These data should be compared to data from the RLD. Please submit an EXCEL spreadsheet of individual data, mean, and %CV for these data on the test products bio- and stability lots.

5. Considering the warning – among others - on the reference listed drug, "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 (cardiac artery disease), and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug", the DBE recommends adequate safety monitoring be in place during the bioequivalence study. You may also submit a protocol for the BE study.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90358	ORIG-1	SUN PHARMACEUTICAL INDUSTRIES LTD	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/

BARBARA M DAVIT
01/14/2010

Telephone Fax

ANDA 090358

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8951

TO: Sun Pharmaceuticals Industries LTD

TEL: 301-838-3120

FAX: 301-838-3182

ATTN: Anthony Celeste

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): 4

SPECIAL INSTRUCTIONS:

Please send an email at chan.park@fda.hhs.gov to confirm that you received this labeling comment.

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

ANDA Number: 090358 Date of Submission: September 5, 2008 and September 1, 2009

Applicant's Name: Sun Pharmaceutical Industries Ltd.

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

Labeling Deficiencies:

1. CONTAINER - 0.5 mL Single-dose Prefilled Syringe

   a. Please ensure that all text appears sufficiently legible.

   b. Please enhance the prominence of the route of administration by increasing the font size and/or by any other means. If space is a concern, you may delete text "Accme Plaza, Andheri-Kurla Road" from the manufacturer's address to free up space. We refer you to 21 CFR 201.1(h)(6)(i) for guidance.

2. BLISTER - 1 Single-dose Prefilled Syringe

   Satisfactory in FPL as of 9/5/08 submission

3. CARTON - 1 x 1 Single-dose Prefilled Syringe

   Satisfactory in FPL as of 9/5/08 submission

4. INSERT - PRECAUTIONS, Information for Patients:

   We acknowledge that you (b) (4) the depth of penetration to "4 to 7 mm" (b) (4) (b) (4). The change in the depth of penetration may potentially affect Tmax and in turn Cmax as well. The acceptability of this change is currently being reviewed by the CMC and Bioequivalence divisions. We defer comment pending completion of review by these divisions.

5. INFORMATION FOR THE PATIENT

   We acknowledge that you will provide one PPI (with "Instructions for Use" printed on another side) for each Autoinjector with a prefilled single dose system. We recommend that you include the following statement in a prominent manner in your patient information leaflet, preferably at the beginning of the leaflet.

   See the other side for "Instructions for Use" for Autoinjector.

6. INSTRUCTIONS FOR USE

   a. The currently proposed labeling for the operation and directions for use of the proposed device are not expected to raise clinical safety concerns for this generic product. However, we may need to further review your proposed language to ensure that the patients understand the instructions and appropriately follow the directions for use.

   b. We acknowledge that you revised the injection time, which is reflected in the revised Figure. 5 and associated instruction. This revision is currently being reviewed by the Bioequivalence division. We will defer the comment for the "Instructions for Use" pending the completion of your proposed device.

   c. We will not request the final printed labeling until all issues associated with your proposed device is resolved.

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

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90358	ORIG-1	SUN PHARMACEUTICAL INDUSTRIES LTD	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/

LILLIE D GOLSON
01/29/2010
for Wm. Peter Rickman

Tandalja , Vadodara-390 020 India
Tele : 91-265-6615500, 6615600,6615700
Fax: 91-265-2354897

SUN
PHARMACEUTICAL
INDUSTRIES LTD.

February 16 2010

Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Subject: Bioequivalence Response to Information Request - Sumatriptan Succinate Injection, 6 mg (base)/0.5 mL (ANDA # 90-358)

Dear Sir/Madam:

This is with reference to your letter dated 14' January, 10, regarding ANDA # 90-358 Sumatriptan Succinate Injection, 6 mg (base)/0.5 mL submitted on January 18, 2008. Please find enclosed herewith diskette containing electronic copy of our response to FDA's correspondence. The question and responses follows in the same order as in the letter.

Please note that fasted bioequivalence studies has been performed on Sumatriptan Succinate Injection, 6 mg (base)/0.5 mL for responding to the above mentioned bioequivalence deficiency.

Copy of FDA's Bioequivalence amendment letter is also provided in diskette for your ready reference.

Hope you find the responses in order. Kindly let us know if further information is required on the subject ANDA.

Please also note that Letter of Non-Repudiation (dated March 20, 2008) has been submitted to FDA on March 25, 2008.

Sincerely,

N·M·Daptasdae

for Dr. Abhay Muthal
General Manager, Regulatory Affairs

SUN
PHARMACEUTICAL
INDUSTRIES, INC.

March 1, 2010

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park, North II
7500 Standish Place, Room 150
Rockville, MD 20855-2733

LABELING AMENDMENT

Re: Sumatriptan Succinate Injection,
6 mg (base)/0.5 mL
ANDA# 90-358
Labeling Amendment

Dear Mr. Buehler,

As the US Agent for Sun Pharmaceutical Industries Ltd., we are submitting this Labeling Amendment in duplicate for the above referenced ANDA. An electronic copy of this amendment is provided on CD in .pdf format.

A copy of this cover letter is enclosed in a self-addressed, stamped envelope. Please stamp the copy as 'Received' with the appropriate date of receipt and kindly return it to Sun Pharmaceutical Industries, Inc. as acknowledgment of receipt of this amendment.

During the course of the review of this amendment, if there are any questions or comments, please do not hesitate to contact me via telephone at (609) 495-2823, via facsimile at (609) 495-2711 or e-mail: anne.toland@sunpharmausa.com.

Sincerely,

for

Anne Toland
Director, Regulatory Affairs
Sun Pharmaceutical Industries, Inc.

Enclosures

270 Prospect Plains Road, Cranbury, NJ 08512 • Phone: (609) 495 2823 • FAX: (609) 495 2711

SUN
PHARMACEUTICAL
INDUSTRIES, INC.

March 12, 2010

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park, North II
7500 Standish Place, Room 150
Rockville, MD 20855-2733

**BIOEQUIVALENCE AMENDMENT –
ADDITIONAL BIOEQUIVALENCE STUDIES**

**Re: Sumatriptan Succinate Injection,
EQ 6 mg (base)/0.5 mL (Pre-filled Syringe with Auto-Injector)
ANDA# 90-358
Bioequivalence Amendment – Additional Bioequivalence Studies**

Dear Mr. Buehler,

As the US Agent for Sun Pharmaceutical Industries Ltd., we are submitting this Bioequivalence Amendment – Additional Bioequivalence Studies in duplicate for the above referenced ANDA. This is in response to the deficiency letter (copy enclosed) dated January 14, 2010. An electronic copy of this amendment is provided on a CD in .pdf format. Please note that this amendment is not in the eCTD format.

A copy of this cover letter is enclosed in a self-addressed, stamped envelope. Please stamp the copy as 'Received' with the appropriate date of receipt and kindly return it to Sun Pharmaceutical Industries, Inc. as acknowledgment of receipt of this amendment.

During the course of the review of this amendment, if there are any questions or comments, please do not hesitate to contact me via telephone at (609) 495-2823, via facsimile at (609) 495-2711 or e-mail: anne.toland@sunpharmausa.com.

Sincerely,

Anne Toland

Anne Toland
Director, Regulatory Affairs
Sun Pharmaceutical Industries, Inc.

Enclosures

270 Prospect Plains Road, Cranbury, NJ 08512 • Phone: (609) 495 2823 • FAX: (609) 495 2711

BIOEQUIVALENCE AMENDMENT

ANDA 090358

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: Sun Pharmaceutical Industries Ltd. TEL: (609) 495-2823

ATTN: Anne Toland FAX: (609) 495-2711

FROM: Diane Nhu FDA CONTACT PHONE: (240) 276-8782

Dear Madam:

This facsimile is in reference to the bioequivalence data submitted on January 18, 2008, February 22, 2010, and March 12, 2010, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Sumatriptan Succinate Injection Prefilled Syringe with Auto-injector, EQ 6 mg base/0.5 mL.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **1** page. 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 Other
Bioequivalence Response to Information Request

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, 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:

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCIES

ANDA:	090358
APPLICANT:	Sun Pharmaceutical Industries, Ltd.
DRUG PRODUCT:	Sumatriptan Succinate Pre-filled Syringe with Auto-injector, EQ 6 mg base/0.5 mL

The Division of Bioequivalence (DBE) has completed its review and the following deficiency has been identified:

The clinical reports for bioequivalence studies PKD_10_033 and PKD_10_048 state that the injection was to be held firmly against the skin up to second click sound/approximately 15 seconds. Please explain why the auto-injector should be held for 15 seconds while the injection time is ≤ 5 seconds in your BE study design, and your proposed label states *"To start the injection (1) Press the Blue Button(first click will sound), (2)immediately release your thumb. …Once you hear the second click, lift the autoinjector straight up from the injection site… The injection is finished…If you did not remove your thumb from the blue button, the second 'click' cannot be heard. If this happens, slowly count to 5 before lifting the autoinjector from the injection site."*

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90358	ORIG-1	SUN PHARMACEUTICAL INDUSTRIES LTD	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/

ETHAN M STIER on behalf of BARBARA M DAVIT
05/20/2010

SUN
PHARMACEUTICAL
INDUSTRIES, INC.

June 1, 2010

Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park, North II
7500 Standish Place, Room 150
Rockville, MD 20855-2733

Bioequivalence Response to Information Request

Re: Sumatriptan Succinate Injection
6 mg (base)/0.5 mL
ANDA# 90-358
Bioequivalence Response to Information Request

Dear Mr. Buehler,

As the US Agent for Sun Pharmaceutical Industries Ltd., we are submitting this Bioequivalence Response to Information Request in duplicate for the above referenced ANDA. This is in response to the fax deficiency letter (copy enclosed) dated May 20, 2010. An electronic copy of this amendment is provided on CD in .pdf format.

A copy of this cover letter is enclosed in a self-addressed, stamped envelope. Please stamp the copy as 'Received' with the appropriate date of receipt and kindly return it to Sun Pharmaceutical Industries, Inc. as acknowledgment of receipt of this amendment.

During the course of the review of this amendment, if there are any questions or comments, please do not hesitate to contact me via telephone at (609) 495-2823, via facsimile at (609) 495-2711 or e-mail: anne.toland@sunpharmausa.com.

Sincerely,

Anne Toland
Director, Regulatory Affairs
Sun Pharmaceutical Industries, Inc.

Enclosures

270 Prospect Plains Road, Cranbury, NJ 08512 • Phone: (609) 495 2823 • FAX: (609) 495 2711

Tandalja, Vadodara - 390 020, INDIA.
Tel. : 91 - 265 - 6615500, 6615600, 6615700
Fax : 91 - 265 - 2354897

SUN
PHARMACEUTICAL
INDUSTRIES LTD.

Date: 28 June, 2010

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

Subject: Transfer of ownership of Sumatriptan Succinate Injection, 6 mg (base)/0.5 mL (ANDA # 90-358) from Sun Pharmaceutical Industries Ltd. to Sun Pharma Global FZE.

Dear Sir/Madam,

In accordance with the provisions of CFR 314.72, we are notifying you transfer of ownership of subject ANDA from Sun Pharmaceutical Industries Ltd. to Sun Pharma Global FZE.

We hereby request FDA to transfer ownership of subject ANDA to Sun Pharma Global FZE, Sharjah, UAE, having its registered office at Office # 43, Block Y, SAIF Zone, P.O.Box # 122304, Sharjah, U.A.E

We shall be pleased to furnish you any information/details you need for the above.

Sincerely yours,

Dr. Abhay. Muthal
General Manager, Regulatory Affairs
Sun Pharmaceutical Industries Ltd.

Registered Office :
Office # 43,
Block Y, SAIF Zone,
P.O.Box# 122304,
Sharjah,
United Arab Emirates
Tel / Fax : +971 4 3997569

SUN PHARMA GLOBAL FZE

Date: 28 June, 2010

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

Subject: Transfer of ownership of Sumatriptan Succinate Injection, 6 mg (base)/0.5 mL (ANDA # 90-358) from Sun Pharmaceutical Industries Ltd. to Sun Pharma Global FZE.

Dear Sir/Madam,

In accordance with the provisions of CFR 314.72, We hereby request you to transfer ownership of the subject ANDA from Sun Pharmaceutical Industries Ltd. to Sun Pharma Global FZE.

We hereby confirm that we are agreeable to all the terms and conditions of the above said ANDA.

We request you to send us all your correspondence, queries, comments etc. at following address of our US agent

Sun Pharmaceutical Industries, Inc.,
270 Prospect Plains Road,
Cranbury, NJ 08512.

We shall be pleased to furnish you any information/details you need for the above.

Sincerely yours,

Vishwanath Kenkare
Manager,
Sun Pharma Global FZE

Registered Office :
Office # 43,
Block Y, SAIF Zone,
P.O.Box# 122304,
Sharjah,
United Arab Emirates
Tel / Fax : +971 4 3997569

15 July, 2010

Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II , HFD-640
7500 Standish Place
Rockville, MD 20855

Subject: Amendment for Sumatriptan Succinate Injection, 6 mg (base)/ 0.5 mL (ANDA # 90-358)

Dear Sir/Madam:

We are submitting this amendment to propose (b) (4) in expiration dating period for the drug product (b) (4) to 18 months. Please note that drug product ANDA exhibit batch (batch # JK70920A) is conforming to stability specification upto (b) (4) months at long term storage condition (data provided in Telephone Amendment dated 18 December, 09) and upto 3 months at accelerated storage condition, however looking at (b) (4) we are proposing (b) (4) 18 months.

Revised post-approval stability studies protocol indicating reduced expiration dating period has been provide herewith in ***Attachment-1*.**

Based on stability evaluation of three commercial scale batches we shall subsequently establish (b) (4) months expiration dating period.

Hope you find the above information in order. Kindly let us know if further information is required on the subject ANDA.

Please also note that Letter of Non-Repudiation (dated May 21, 2009) has been submitted to FDA on May 26, 2009.

Sincerely,

Mr Vishwanath Kenkare
Manager,
Sun Pharma Global FZE.

Tandalja , Vadodara-390 020 India
Tele : 91-265-6615500, 6615600,6615700
Fax: 91-265-2354897

SUN
PHARMACEUTICAL
INDUSTRIES LTD.

August 9, 2010

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20857

Re: Labeling Amendment for Sumatriptan Succinate Injection, 6 mg (base)/0.5 mL. (ANDA # 90-358)

Dear Sir/Madam,

We are submitting this labeling amendment to update Sun's proposed package insert in accordance with Innovator's revised labeling approved on July 21, 2010.

Additionally, following changes have been made in package insert:

1. Due to transfer of ownership of this ANDA from Sun Pharmaceutical Industries Ltd. to Sun Pharma Global FZE
   - Change in labeler code from "62756" to "47335" [Sun Pharma Global FZE's labeler code]
   - Change in barcode in accordance with NDC
2. USP claim has been included for a drug substance

Electronic copy of revised Package Insert (word & pdf); and Side-by side labeling comparison of the Sun's revised labeling with last submitted labeling (pdf) has been provided in ***Attachment 1*** & ***Attachment 2*** respectively.

Hope you find these revised labeling in order. Kindly let us know if further information is required.

Sincerely,

Dr. Abhay Muthal
General Manager, Regulatory Affairs

Corporate Office Acme Plaza, Andheri-Kurla Road Andheri (E), Mumbai 400 059, INDIA.
Tele (91-22)-28230102/28211260/28212143, Fax (91-22)- 28212010. Website :
www.sunpharma.com

** Please email me at chan.park@fda.hhs.gov to confirm that you have received this labeling comment.

Telephone Fax

ANDA 090358

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8951

TO: Sun Pharmaceuticals Industries Ltd.

TEL: 609-495-2823

FAX: 609-495-2711

ATTN: Anne Toland

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, 6 mg/0.5 mL.

Pages (including cover): 5

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents has become:*

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

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/

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

ANDA Number: 090358 Date of Submission: March 1, 2010

Applicant's Name: Sun Pharmaceutical Industries Ltd.

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

Labeling Deficiencies:

1. CONTAINER - 0.5 mL Single-dose Prefilled Syringe

   Satisfactory in FPL as of the **3/1/10** submission

2. BLISTER (AUTOINJECTOR LABEL) - 1 Single-dose Prefilled Syringe

   Satisfactory in FPL as of 9/5/08 submission

3. CARTON - 1 x 1 Single-dose Prefilled Syringe

   Satisfactory in FPL as of 9/5/08 submission

4. PACKAGE INSERT LABELING

   Please be advised that an updated innovator's labeling for Imitrex® Injection was approved July 21, 2010. Please revise your labeling accordingly as follows:

   a. PRECAUTIONS

      i. Information for Patients - Include the following text as the 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. Nursing Mothers - Revise tor read as follows:

         Sumatriptan is excreted in human breast milk following subcutaneous administration. Infant exposure to sumatriptan can be minimized by avoiding breastfeeding for 12 hours after treatment with sumatriptan succinate injection.

   b. ADVERSE REACTIONS [Postmarketing Experience (Reports for Subcutaneous or Oral Sumatriptan) - Neurological:

      …dysphasia, serotonin syndrome, subarachnoid hemorrhage. [added "serotonin syndrome"]

5. INFORMATION FOR THE PATIENT

   Satisfactory in FPL as of the 3/1/10 submission

6. INSTRUCTIONS FOR USE

   a. GENERAL

      If you have any assessment data regarding the ability of patients to understand and appropriately follow the directions for use of autoinjector, please submit.

b. CAUTIONS - 5th statement:

We believe that it is preferable to include the text "after injection" to read "…into the autoinjector after injection.".

c. HOW TO USE THE AUTOINJECTOR

i. Print the title in upper case letters to enhance the prominence.

ii. Please clearly separate each instruction including a figure by allowing space between instructions. It may help the patients better understand the instructions.

iii. We ask that you include a reference to the associated figure in each instruction. Please refer to the following as an example:

Identify the application area with an adequate fatty tissue layer on… bruised, red, or hard. (See Figure 2)

iv. Middle panel, last paragraph:

It is possible that the completion of injection may not be ensured by slowly counting to 5 as the speed of counting may vary patient to patient. The inspection window of your device turns blue when the injection is completed. Taking this into consideration, we strongly recommend that you relocate the statement "The inspection window will… before lifting the autoinjector." appearing after the figure 5 to appear immediately after the last paragraph of the middle panel to read as follows. Please revise accordingly and/or comment:

If you did not remove your thumb from the blue button, the second "click" cannot be heard. If this happens, slowly count to 5 before lifting the autoinjector from the injection site. The inspection window will be blue, confirming the injection is complete. Verify that the injection window is blue to ensure that the injection is complete before lifting the autoinjector (See Figure 5)..

7. STRUCTURED PRODUCT LABELING (SPL)

We note that you did not include SPL in your submission. Please include SPL in your next submission.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-90358	ORIG-1	SUN PHARMACEUTICAL INDUSTRIES LTD	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/

LILLIE D GOLSON
08/18/2010
for Wm. Peter Rickman

Tandalja , Vadodara-390 020 India
Tele : 91-265-6615500, 6615600,6615700
Fax: 91-265-2354897

SUN
PHARMACEUTICAL
INDUSTRIES LTD.

August 21, 2010

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

Re: Labeling Amendment for Sumatriptan Succinate Injection, 6 mg (base)/0.5 mL. (ANDA # 90-358)

Dear Sir/Madam,

This is with reference to your Fax to Sun Pharmaceutical Industries, Inc. (U.S. Agent for Sun Pharmaceutical Industries Limited) dated August 18, 2010 for the labeling deficiencies. Please find enclosed herewith electronic copy of our response to FDA's correspondence. The question and responses follows in the same order as in the letter.

Comment-1

1. **CONTAINER – 0.5 mL Single-dose Prefilled Syringe**
   Satisfactory in FPL as of the 3/1/10 submission

Response-1

We acknowledge that the Single-dose Prefilled Syringe Label is satisfactory in final printed form as of March 1, 2010 submission.

Comment-2

2. **BLISTER (AUTOINJECTOR LABEL) – 1 Single-dose Prefilled Syringe**
   Satisfactory in FPL as of 9/5/08 submission

Response-2

We acknowledge that the autoinjector label is satisfactory in final printed form as of September 5, 2008 submission.

Comment-3

3. **CARTON – 1 × 1 Single-dose Prefilled Syringe**
   Satisfactory in FPL as of 9/5/08 submission

Response-3

We acknowledge that the carton is satisfactory in final printed form as of September 5, 2008 submission.

Corporate Office Acme Plaza, Andheri-Kurla Road Andheri (E), Mumbai 400 059, INDIA.
Tele (91-22)-28230102/28211260/28212143, Fax (91-22)- 28212010. Website : www.sunpharma.com

Tandalja , Vadodara-390 020 India
Tele : 91-265-6615500, 6615600,6615700
Fax: 91-265-2354897

SUN
PHARMACEUTICAL
INDUSTRIES LTD.

Comment-4

4. INSERT

Please be advised that an updated innovator's labeling for Imitrex® Injection was approved July 21, 2010. Please revise your labeling accordingly as follows:

a. PRECAUTIONS

i. Information for Patients - Include the following text as the 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. Nursing Mothers - Revise for read as follows:

Sumatriptan is excreted in human breast milk following subcutaneous administration. Infant exposure to sumatriptan can be minimized by avoiding breastfeeding for 12 hours after treatment with sumatriptan succinate injection.

b. ADVERSE REACTIONS [Postmarketing Experience (Reports for Subcutaneous or Oral Sumatriptan) - Neurological:

...dysphasia, serotonin syndrome, subarachnoid hemorrhage. [added "serotonin syndrome"]

Response-4

Please note that Sun's revised package insert as per Innovator's revised labeling approved on July 21, 2010 has been already submitted to FDA (letter dated August 9, 2010). It includes the suggested changes for point 4. This revised package insert has been further provided herewith for your ready reference.

Comment-5

5. INFORMATION FOR THE PATIENT

Satisfactory in FPL as of the 3/1/10 submission

Response-5

We acknowledge that the Patient Information is satisfactory in final printed form as of March 1, 2010 submission.

Corporate Office Acme Plaza, Andheri-Kurla Road Andheri (E), Mumbai 400 059, INDIA.
Tele (91-22)-28230102/28211260/28212143, Fax (91-22)- 28212010. Website : www.sunpharma.com

Tandalja , Vadodara-390 020 India
Tele : 91-265-6615500, 6615600,6615700
Fax: 91-265-2354897

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Comment-6

6. INSTRUCTIONS FOR USE

a. GENERAL

If you have any assessment data regarding the ability of patients to understand and appropriately follow the directions for use of autoinjector, please submit.

b. CAUTIONS – 5th statement:
We believe that it is preferable to include the text "after injection" to read "... into the autoinjector after injection.".

c. HOW TO USE THE AUTOINJECTOR

i. Print the title in upper case letters to enhance the prominence.

ii. Please clearly separate each instruction including a figure by allowing space between instructions. It may help the patients better understand the instructions.

iii. We ask that you include a reference to the associated figure in each instruction. Please refer to the following as an example:

Identify the application area with an adequate fatty tissue layer on... bruised, red, or hard. (See Figure 2)

iv. Middle panel, last paragraph:

It is possible that the completion of injection may not be ensured by slowly counting to 5 as the speed of counting may vary patient to patient. The inspection window of your device turns blue when the injection is completed. Taking this into consideration, we strongly recommend that you relocate the statement "The inspection window will.....before lifting the autoinjector." appearing after the figure 5 to appear immediately after the last paragraph of the middle panel to read as follows. Please revise accordingly and/or comment:

If you did not remove your thumb from the blue button, the second "click" cannot be heard. If this happens, slowly count to 5 before lifting the autoinjector from the injection site. The inspection window will be blue, confirming the injection is complete. Verify that the injection window is blue to ensure that the injection is complete before lifting the autoinjector (See Figure 5).

Corporate Office Acme Plaza, Andheri-Kurla Road Andheri (E), Mumbai 400 059, INDIA.
Tele (91-22)-28230102/28211260/28212143, Fax (91-22)- 28212010. Website : www.sunpharma.com

Tandalja , Vadodara-390 020 India
Tele : 91-265-6615500, 6615600,6615700
Fax: 91-265-2354897

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Response-6

a. The assessment data regarding the ability of patients to understand and appropriately follow the directions for use of autoinjector has been provided herewith in **Attachment 2**.

Please note that the study to evaluate the ability of patients to understand and follow the directions for use of autoinjector has been performed in India with reference to instructions for use provided with product marketed in India. These instructions are similar to those proposed for U.S. market. The differences in Instructions for use of Autoinjector used in assessment study and proposed in ANDA are tabulated below. These minor differences in Instructions for use shall not have any impact on readability and understanding for use of autoinjector device.

Sr.	Suminat Autoinjection, 6 mg/0.5 mL with Autoinjector (For Domestic/ INDIA Market)	Sumatriptan Succinate Injection, 6 mg/0.5 mL with Autoinjector (For U.S. Market)
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		

Corporate Office Acme Plaza, Andheri-Kurla Road Andheri (E), Mumbai 400 059, INDIA.
Tele (91-22)-28230102/28211260/28212143, Fax (91-22)- 28212010. Website : www.sunpharma.com

Tandalja , Vadodara-390 020 India
Tele : 91-265-6615500, 6615600,6615700
Fax: 91-265-2354897

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b. Under Cautions – 5th statement: ".....into the autoinjector." has been revised to ".....into the autoinjector after injection.".

c. i. The title "How to use the autoinjector" has been made uppercase.

ii. For better understanding the instructions by patients, each instruction including a figure has been clearly separated by allowing space between instructions.

iii. Please note that the associated figure reference for each instruction has been included.

iv. The statement "The inspection window will be blue, confirming the injection is complete. Verify that the injection window is blue to ensure that the injection is complete before lifting the autoinjector (See Figure 5)." has been relocated immediately after the last paragraph of the middle panel.

Comment-7

7. STRUCTURED PRODUCT LABELING (SPL)
We note that you did not include SPL in your submission. Please include SPL in your next submission.

Response-7

The Structured Product Labeling (SPL R4) has been provided herewith in folder named spl.

Electronic copy of revised package insert (word, pdf), Assessment Data for use of Autoinjector (pdf), revised Instructions for Use (word, pdf), and Side-by side labeling comparison of the Sun's revised Instructions for Use with the last submitted Instructions for Use has been provided in ***Attachment 1, Attachment 2, Attachment 3*** and ***Attachment 4*** respectively.

Hope you find these revised labeling in order. Kindly let us know if further information is required.

Sincerely,

Dr. Abhay Muthal
General Manager, Regulatory Affairs

Corporate Office Acme Plaza, Andheri-Kurla Road Andheri (E), Mumbai 400 059, INDIA.
Tele (91-22)-28230102/28211260/28212143, Fax (91-22)- 28212010. Website : www.sunpharma.com

SUN
PHARMACEUTICAL
INDUSTRIES, INC.

April 18, 2011

Dr. Keith Webber, Ph.D.
Deputy Director
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

Re: Change in US Agent contact person name

Dear Dr. Webber,

I am currently acting as the US Agent for the attached list of ANDA's submitted by Sun Pharma Global FZE (SPGFZE), replacing Ms. Anne Toland, who recently left Sun Pharmaceutical Industries, Inc. Please find attached the individual letter of authorization from SPGFZE along with 356h form for the products referenced in the attached list. An electronic copy of this correspondence is provided on a CD in .pdf format.

A copy of the cover letter is enclosed in a self-addressed, stamped envelope. Please stamp the copy as 'Received" with the appropriate date of receipt and kindly return it to Sun Pharmaceutical Industries, Inc. as acknowledgement of receipt of this correspondence.

Should you have any questions or require additional information, please contact the undersigned by phone at (609) 495-2808, via facsimile at (609) 495-2711 or e-mail: vincent.andolina@sunpharmausa.com

Sincerely,

Vincent P. Andolina

Vincent P. Andolina
Sr. Director, Regulatory Affairs
Sun Pharmaceutical Industries, Inc.

Enclosures

270 Prospect Plains Road, Cranbury, NJ 08512 • Phone: (609) 495 2808 • FAX: (609) 495 2711

ROUTING SHEET

☒ **APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **CGMP**

Division: II	**Team: 23**	**PM: Simon Eng**

Electronic ANDA: Yes ☐ No ☐

ANDA #:90358 First Generic Full Approval, NO REMS
Firm Name:Sun Pharma Global FZE
ANDA Name:Sumatriptan Succinate Injection, 6 mg (base)/0.5 mL, packaged in prefilled syringes.
RLD Name:Imitrex Statdose

Electronic AP Routing Summary Located:
vdrive: div II, team 23: 90358.AP.Routing Summary

AP/TA Letter Located:
vdrive: div II, team 23: 90358.AP.Letter

Project Manager Evaluation: **Date: 10-22-10 Initials:** se

☐ Previously reviewed and tentatively approved --- Date n/a
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date 12/31/2007	Date of Application _____	Date Acceptable for Filing 1/18/08
Patent Certification (type) II	Date Patent/Excl. expires	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: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☐ Date:	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☒ Pending ☐ Acceptable ☐ OAI *EES Date Acceptable:*_____ ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☒ Comment:
Date of Acceptable Quality (Chemistry) 10/13/10 Addendum Needed: Yes ☐ No ☒ Comment:
Date of Acceptable Bio 6/11/10 Bio reviews in DARRTS: Yes ☒ No ☐ (Volume location:)
Date of Acceptable Labeling 10/4/10 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) 1/26/09

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: _____ REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☐

☐ Regulatory Support

☐ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: _____

☐ Division

☐ 1st Generic Review

☐ Bob West / Peter Rickman
☐ Keith Webber

☐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: 27 OCT 2010**

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
Patent/Exclusivity Certification: Yes ☒ No ☐	Date Checked N/A
If Para. IV Certification- did applicant:	Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐	Written request issued ☐
Was applicant sued w/in 45 days:Yes ☐ No ☐	Study Submitted ☐
Has case been settled: Yes ☐ No ☐	
Date settled:	
Is applicant eligible for 180 day	
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 1/18/2008, BOS=Imitrex NDA 20-080, PII to '470, PIII to '845. Correspondence submitted on 4/30/2008-applicant clarified that they were seeking approval of a pre-filled autoinjector syringe. ANDA ack for filing on 1/18/2007 (LO dated 5/2/2008). There are no remaining unexpired patents or exclusivities that preclude approval of this ANDA. This approval will represent the first approval of an ANDA for an auto-injector configuration of Sumatriptan Injection. As such this ANDA has been subject to considerable scrutiny that wouldn't be considered customary for an injectable product. This ANDA was consulted to OGD's clinical division who recommended that in-vivo BE studies be conducted comparing the proposed product to the RLD. These studies in addition to further in-vitro studies were completed by Sun, reviewed by DBE and found acceptable for approval. It was also the clinical reviewer's opinion that while the proposed auto-injector was not identical in function characteristics to the RLD, it was similar enough not to cause any significant safety concerns.	

2. ***Labeling Endorsement***

Reviewer, :

Date_____

Initials_____

Labeling Team Leader, :

Date 6/21/11

Initials rlw/for

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☐n/a

Comments:

From: Park, Chan H
Sent: Tuesday, June 21, 2011 9:43 AM
To: West, Robert L
Cc: Eng, Simon; Vezza, Adolph E
Subject: RE: SUN'S ANDA 90-358 FOR SUMATRIPTAN SUCCINATE INJECTION (AUTO INJECTOR)

Hi Bob,

As far as the labeling is concerned, the last AP summary I prepared is still good. Thanks,

Chan

From: West, Robert L
Sent: Tuesday, June 21, 2011 9:05 AM
To: Park, Chan H
Cc: Eng, Simon; Vezza, Adolph E
Subject: FW: SUN'S ANDA 90-358 FOR SUMATRIPTAN SUCCINATE INJECTION (AUTO INJECTOR)

Chan:

Please see below.

Thanks,

Bob

From: West, Robert L
Sent: Tuesday, June 21, 2011 8:59 AM
To: Vezza, Adolph E
Cc: Eng, Simon
Subject: SUN'S ANDA 90-358 FOR SUMATRIPTAN SUCCINATE INJECTION (AUTO INJECTOR)

Adolph:

Is Sun's FPL still satisfactory for approval of ANDA 90-358? The most recent labeling review in DARRTS is 10/4/10.

This ANDA is now ready for approval.

Thanks,

Bob

Thanks Chan and Lillie.
Have a nice day!!
Simon

From: Golson, Lillie D
Sent: Thursday, October 28, 2010 3:27 PM
To: Eng, Simon
Subject: RE: ViewDocument

Thanks Simon. Therefore, endorse the AP routing form on behalf of Chan and me.

Lillie

From: Eng, Simon
Sent: Thursday, October 28, 2010 3:02 PM
To: Golson, Lillie D
Subject: RE: ViewDocument

Hi Chan and Lillie,
I only used the AF dated August 21, 2010 b/c all other AF should have been addressed and the firm is aware on the 8/18/10 Labelings def fax.
Thanks,
Simon

From: Golson, Lillie D
Sent: Thursday, October 28, 2010 10:43 AM
To: Park, Chan H; Eng, Simon
Subject: RE: ViewDocument

Chan/Simon,

Should the amendment dates for labeling submissions be included in the letter?

Thanks

From: Park, Chan H
Sent: Thursday, October 28, 2010 8:31 AM
To: Eng, Simon
Cc: Golson, Lillie D
Subject: FW: ViewDocument

Good morning Simon,

Please endorse the ARS for me. Have a good day!

Chan

From: Eng, Simon
Sent: Thursday, October 28, 2010 7:17 AM
To: Park, Chan H
Cc: Golson, Lillie D
Subject: ViewDocument

<< File: 90358_AP_LETTER.DOC >> << File: ViewDocument.pdf >>

Hi Chan,
Please endorse.
Thanks,
Simon

3. ***Paragraph IV Evaluation*** **PIV's Only**

David Read **Date 6/21/11**
OGD Regulatory Counsel **Initials rlw/for**

Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments: There are no paragraph IV certifications associated with this ANDA.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 11/10/10**

Chemistry Div. **II (Fang)** **InitialsFF**

Comments:The (b) (4) syringe used in the application is a 1 mL fixed canula system with no provisions for attachment such as a luer lock. The filled syringe is placed in an autoinjector covered by (b) (4) and cannot be manipulated by the user - GJSmith. cmc ok

5. ***First Generic Evaluation*** **First Generics Only**

Frank Holcombe **Date 6/21/11**
Assoc. Dir. For Chemistry **Initials rlw/for**

Comments: (First generic drug review)
Multiple ANDAs providing for this drug product without the AutoInjector component have been approved. The use of this drug product in association with the AutoInjector has been thoroughly evaluated by DBE and DC II.

OGD Office Management Evaluation

6. Peter Rickman **Date 6/21/11**

Director, DLPS **Initials rlw/for**

Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes ☐ No ☐
Petition: Yes☐ No☐
Comments: Although the drug product's formulation is "Q&Q" to that of the RLD, the Division of Bioequivalence requested the applicant to perform additional in-vivo fasting pK studies and additional in-vitro studies (volume delivered, injection time, force to fire) to address potential safety/effectiveness issues raised by the OGD clinical team. These studies were submitted by the applicant, reviewed by DBE and found acceptable to satisfactorily address the issues raised by the clinical team. Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 6/11/10.

Final-printed labeling (FPL) found acceptable for approval 10/4/10, as endorsed 10/28/10. No REMS is required.

CMC found acceptable for approval (Chemistry Review #2d) 11/3/10.

AND/OR

7. Robert L. West **Date 6/21/11**
Deputy Director, OGD **Initials RLWest**

Para.IV Patent Cert: Yes☐ No☒
Pending Legal Action: Yes☐ No☒
Petition: Yes☐ No☒
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 6/20/11 (Verified 6/21/11). No "OAI" Alerts noted.

There are no patents or exclusivity listed in the current "Orange Book" for this drug product.

Note: The delay in approval of this ANDA following completion of the CMC, Micro, Bio and Labeling reviews was due to the scheduling and inspection of Sun's manufacturing site in Halol, Gujarat State, India.

This ANDA is recommended for approval.

8. ***OGD Director Evaluation***
Keith Webber
Deputy Director, OPS

Comments:RLWest for Keith Webber, Ph.D. 6/21/11.

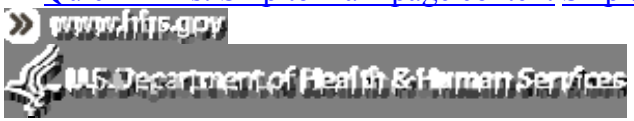
First-generic approval for this drug product packaged with an AutoInjector.
First Generic Approval ☒
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

Comments:

9. Project Manager
Date _____
Initials _____

Check Communication and Routing Summary into DARRTS

Orange Book Report:



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.

<>

There are no unexpired patents for this product in the Orange Book Database.

<>

There is no unexpired exclusivity for this product.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through May, 2011
Patent and Generic Drug Product Data Last Updated: June 20, 2011

-
-
-

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

/s/

SIMON S ENG
06/21/2011