

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022377Orig1s000

MEDICAL REVIEW(S)

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Eric Bastings, MD.
Subject	Deputy Division Director Summary Review
NDA/BLA #	22377
Supplement #	
Applicant Name	King Pharmaceuticals
Date of Submission	7/17/2008
PDUFA Goal Date	5/17/2009
Proprietary Name / Established (USAN) Name	(b) (4) sumatriptan succinate
Dosage Forms / Strength	Subcutaneous auto-injector / 6mg
Proposed Indication(s)	1. Acute treatment of migraine 2. Acute treatment of cluster headache
Action	Complete response

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Robert Harris, MD
Pharmacology Toxicology Review	D. Charles Thompson, R.Ph., Ph.D., D.A.B.T.
CMC Review/OBP Review	Patrick Marroum, Ph.D. and David J. Claffey, PhD
Microbiology Review	Stephen E. Langille, Ph.D.
Clinical Pharmacology Review	Jagan Mohan Parepally, Ph.D
OSE/DMEPA	Felicia Duffy RN, BSN, MSED
OSE/DRISK	LaShawn Griffiths, MSHS-PH, BSN, RN

1. Introduction

King Pharmaceuticals submitted a 505(b)(2) application for (b) (4) a new pre-filled, single-use disposable auto-injector product containing 6 mg of sumatriptan succinate delivered in a 0.5 mL subcutaneous dose (proposed proprietary name (b) (4) I will use the name “(b) (4) for the rest of this document, even though as noted below (b) (4) is not an acceptable proprietary name, and a new proprietary name will need to be proposed by the sponsor. (b) (4) is presented by the sponsor as similar to EpiPen, a marketed auto-injector.

The sponsor uses Imitrex Statdose NDA 20-080, approved 12/28/92, as the basis of reference for the safety and efficacy of (b) (4)

2. Background

As discussed by Dr. Harris, the Division of Neurology product agreed at a pre-IND meeting that this application was suitable for submission as a 505(b)(2) NDA, using Imitrex Statdose as a reference. Both Imitrex Statdose and (b) (4) contain 6 mg of sumatriptan succinate salt to be delivered as a 0.5 ml subcutaneous dose. However, Imitrex STATdose requires assembly of a prefilled cartridge with the non-disposable STATdose injector, and disassembly after use, while (b) (4) is a single-use device that is disposable. As (b) (4) differs from Imitrex STATdose with respect to design and operation, the division requested that the sponsor conduct a usability study during a migraine attack.

The sponsor requested FDA to waive the requirement for an in vivo bioequivalence/bioavailability study, based on the fact that the composition of the two products (active drug and inactive excipients) is identical. In order to support a biowaiver, the sponsor was required to establish that the delivery of drug from (b) (4) and from the reference product (Imitrex STATdose) is similar. Specifically, the sponsor was requested to provide evidence of similar needle penetration depth, dispensing time, dispensed volume, and injection force.

3. CMC/Device

I concur with the conclusions reached by Dr. Claffey regarding the acceptability of the manufacturing of the drug product and drug substance, and the comparability of the performance of the proposed drug product to the reference drug product.

I also concur with Dr. Marroum that an in vivo bioavailability/bioequivalence waiver is appropriate. I noted that Dr. Marroum’s comment that “since these two auto injectors are different with respect to design and operating principles, the amount of drug as well as the site of injection can be different between the 2 systems potentially leading to different absorption profile of the drug from the subcutaneous site of injection”.

In terms of design and operating principles, the usability study established that migraine patients are able to use the device during a migraine attack. As both products have a similar needle gage, needle penetration depth, dispensing time and dispensed volume, there is no scientific reason to believe that the absorption profile would be different. In terms of sites of injection, the labeling of Imitrex Statdose states that “patients should be directed to use injection sites with an adequate skin and subcutaneous thickness to accommodate the length of the needle”. As labeling for (b) (4) will be identical in that regard, there is no difference between the products in terms of recommended injection sites, and in terms of expected absorption in various injection sites.

Manufacturing site inspections (under DMF (b) (4)) were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by Dr. Thompson that there are no outstanding nonclinical pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by Dr. Parepally that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

I concur with the conclusions reached by Langille that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

As noted above, the sponsor used NDA 20-080 as the basis of reference for the efficacy of (b) (4) which is acceptable. The sponsor was required to conduct a usability study, which established that the product can be used by migraine patients during a migraine attack.

8. Safety

The sponsor also used NDA 20-080 as the basis of reference for the safety of (b) (4) which is acceptable. There was no significant new safety findings in the small usability study conducted by King Pharmaceuticals. There is no need for a REMS for this product.

9. Advisory Committee Meeting

An advisory committee meeting is not needed for this product, as there are no new safety issues compared to already approved similar sumatriptan auto-injectors.

10. Pediatrics

PREA was not triggered, as this application is not for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues. The application was cleared from a (b)(2) perspective by the Regulatory Affairs Team of OND and OCC.

12. Labeling

This application included conversion of the referenced drug (Imitrex Statdose) labeling to the physician labeling rule (PLR) format. FDA-approved patient labeling was reviewed by the Division of Risk Management (DRISK), and their recommendations are included in the labeling forwarded to the sponsor.

The original proposed proprietary name, (b) (4) was rejected by the Division of Medication Error Prevention and Analysis (DMEPA) because it is overly fanciful, and implies that the drug may be tailored to the specific patient taking the product.

The sponsor then proposed a new proprietary name, (b) (4) that was also rejected by DMEPA, because it contains the USAN stem, “-aj-”. DMEPA advises that the USAN stem “-aj-”, which is defined by the USAN council as “antiarrhythmics”, is not appropriate for use in the proprietary name, (b) (4).

The sponsor was asked on March 26, 2009 to propose a new proprietary name. No additional name has been submitted during this review cycle.

Carton and container deficiencies were communicated to the sponsor during the review cycle, and the sponsor agreed to the proposed labeling changes.

13. Decision/Action/Risk Benefit Assessment

I believe that a proprietary name is necessary to assure safe and effective use of this new product, and prevent medication errors. This new sumatriptan auto-injector differs from the previously approved Imitrex (sumatriptan) auto-injector in that this new product, among other things, is a preassembled single use disposable auto-injector. It is operated by grasping the device in the middle and applying pressure to push the needle end against the injection site.

By contrast, the Imitrex auto-injector is a reusable device that must be individually loaded before each use. It operates by pushing a button at the end of the device. The sponsor's proposed labeling, and the approved labeling of the Imitrex auto-injector, include statements directing prescribers to instruct patients on the proper use of the product prior to first use in a medically unsupervised situation. Given that patients instructed on the use of another sumatriptan auto-injector may be unable to use the product without prior training, inadvertent substitution may lead to failed use of the product during a migraine attack, or to a safety risk to the patient.

As communicated to the sponsor during the review cycle, both proposed proprietary names were found unacceptable by the Agency. As the sponsor has not proposed an alternative acceptable proprietary name, or evidence that the new sumatriptan auto-injector product is safe for use without a proprietary name, the application can not be approved.

Therefore, we are issuing a complete response letter, requesting a tradename for the product, or evidence that the product can be safely used without a tradename.

No Postmarketing Risk Management Activity is required.

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/s/

Eric Bastings
5/15/2009 02:46:31 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type sNDA
Application Number(s) 22-377
Priority or Standard S

Submit Date(s) 7/16/08
Received Date(s)
PDUFA Goal Date 5/19/09
Division / Office DNP/ODE 1

Reviewer Name(s) Rob Harris, M.D.
Review Completion Date 4/28/09

Established Name Sumatriptan Injectable
(Proposed) Trade Name
Therapeutic Class Triptan
Applicant King Pharma

Formulation(s) Sumatriptan Succinate
Dosing Regimen 6 mgs single sub-cutaneous
injection
Indication(s) Migraine
Intended Population(s) Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The [Tradename] (sumatriptan succinate) Auto-Injector, manufactured by King Pharma should be approved for a single, 6.0 mg subcutaneous injection, with a repeat in one hour and no more than two injections in 24 hours.

1.2 Risk Benefit Assessment

There are no apparent risks exceeding the Imitrex Injection RLD product.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

The sponsor seeks approval of a new pre-filled, fully-assembled single-use disposable auto-injector product containing 6 mg of sumatriptan (base) as the succinate salt delivered in a 0.5 mL subcutaneous dose. King Pharmaceuticals, Inc. proposes to market this product as [Tradename] (sumatriptan succinate) Auto-Injector which will follow the established dosing of Imitrex. The approved product name has yet to be definitively established.

The application is submitted in accordance with Section 505(b)(2) of the Food, Drug and Cosmetic Act. GlaxoSmithKline's NDA 20-080 for Imitrex (sumatriptan succinate) injection (approved 12/28/92) is the basis of reference for the safety and efficacy of [Tradename]. Approved within NDA 20-080 is a pre-filled auto-injector dosage form available as Imitrex (sumatriptan succinate) STATdose System. No controlled trials are submitted with the NDA, but a single clinical usability study is provided.

Because the sponsor has developed a new sumatriptan injectable delivery system with this product and has submitted a single uncontrolled usability study, they are requesting 3 years of exclusivity. Study K644-07-3001, the only study submitted for this NDA, was a Phase 3, open-label trial conducted by King Pharmaceuticals, Inc. at 10 sites in the

US. The study was designed to evaluate the successful administration and user handling of the [Tradename] Auto-Injector during a migraine attack. All subjects received a single subcutaneous dose of 6 mg sumatriptan via the [Tradename] Auto-Injector.

The sponsor had met with the Division previously to discuss the requirements for a 505b application for their injector.

2.1 Product Information

Name:

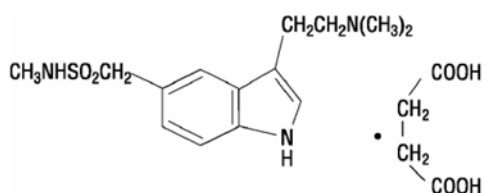
Chemical Name: 3-[2-(dimethylamino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate (1:1)

CAS Registry Number: [103628-48-4]

Formula:

Molecular Formula: $C_{14}H_{21}N_3O_2S \cdot C_4H_6O_4$

Structure:



Physical and Chemical Characteristics

Appearance: White or almost white powder.

Solubility: Freely soluble in water, 0.1N hydrochloric acid and 0.1N sodium hydroxide; sparingly soluble in methanol; practically in-soluble in organic solvents such as methylene chloride.

Molecular Weight: 413.5

Brief Historical Review of Sumatriptan Auto-injectors

The sumatriptan auto-injector reference listed product has been available for use in the US since 1992. The sponsor notes users of injectable sumatriptan tend to occupy the worse end of the migraine disease spectrum. The severity and symptoms of a migraine attack in this population can be distracting. Subjects may lack the capability to assemble a new auto-injector for use and must delegate the task to a relative or co-worker. This defeats the intent of self-administered subcutaneous acute therapy for migraine. Therefore, some migraineurs keep auto-injectors pre-assembled in their refrigerators with an unsealed needle inside the guard for later use, which violates labeled storage conditions. The sponsor believes their product addresses this issue.

The [Tradename] (sumatriptan succinate) Auto-Injector presented in this NDA is a pre-assembled, single-use drug delivery system designed for the subcutaneous injection of 6 mg sumatriptan for patients suffering a migraine. This product is similar to the EpiPen®, which is commonly used by patients for the intramuscular self-injection of epinephrine. The principal benefit of the [Tradename] Auto-Injector, the sponsor claims, is that it is pre-assembled and easy to use. Putatively it diminishes errors in assembly or the need for assistance in assembly in a patient suffering from a migraine.

2.2 Tables of Currently Available Treatments for Proposed Indications

The following table summarizes medications used to treat migraine. However, most are not FDA-approved for the indication.

Table 1: Migraine Acute Therapies in Current Use

Group 1 ^b	Group 2 ^c	Group 3 ^d	Group 4 ^e	Group 5 ^f
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^a Table adapted from: Silberstein, SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;55:754-762. Proven, pronounced statistical and clinical benefit (at least two double-blind, placebo-controlled studies and clinical impression of effect).

^b Moderate statistical and clinical benefit (one double-blind, placebo-controlled study and clinical impression of effect).

^c Statistically but not proven clinically or clinically but not proven statistically effective (conflicting or inconsistent evidence).

^d Proven to be statistically or clinically ineffective (failed efficacy versus placebo).

^e Clinical and statistical benefits unknown (insufficient evidence available).

The following are FDA-approved medications used for treating migraine:

Table 2: FDA Approved Migraine Medications

Brand Name	Generic Name	Manufacturer/Distributor	Indication for Adults*
Amerge tablets	naratriptan hydrochloride	GlaxoSmithKline	acute treatment of migraine attacks
Axert tablets	almotriptan malate	Ortho-McNeil Neurologics Inc.	acute treatment of migraine attacks
Frova tablets	frovatriptan succinate	Endo Pharmaceuticals	acute treatment of migraine attacks
Imitrex tablets, injection, nasal spray	sumatriptan succinate	GlaxoSmithKline	acute treatment of migraine attacks
Maxalt tablets and Maxalt-MLT orally disintegrating tablets	rizatriptan benzoate	Merck	acute treatment of migraine attacks
Zomig tablets, nasal spray; and Zomig-ZMT orally disintegrating tablets	zolmitriptan	AstraZeneca	acute treatment of migraine
Relpax tablets	eletriptan hydrobromide	Pfizer	acute treatment of migraine
Migranal nasal spray	dihydroergotamine mesylate	Valeant	acute treatment of migraine headache
Topamax tablets, sprinkle capsules	topiramate	Ortho-McNeil Neurologics Inc.	prevention of migraine headache
Depakote ER tablets	divalproex sodium	Abbott Laboratories	prevention of migraine headache
Blocadren tablets	timolol maleate	Merck	prevention of migraine headache
Inderal tablets, capsules	propranolol hydrochloride	AstraZeneca	prevention of migraine headache
Over-the-Counter Products			
Excedrin Migraine tablets, caplets	acetaminophen, aspirin, caffeine	Novartis Consumer Health	treatment of migraine
Advil Migraine capsules	ibuprofen	Wyeth Consumer Healthcare	treatment of migraine
Motrin Migraine Pain caplets	ibuprofen	McNeil Consumer & Specialty Pharmaceuticals	treatment of the pain of migraine headache

The majority of FDA-approved migraine products are the triptans, including Imitrex, (sumatriptan), the subject of this review. These are shown here in the Triptan Summary Table:

Table 3: Triptan Therapies Approved for Acute Migraine Rx in the US

Trade (generic) Name	NDA	Date of FDA Approval	Route of Delivery
IMITREX Injection (sumatriptan)	20-080	December 28, 1992	Subcutaneous injection
IMITREX [®] Tablets (sumatriptan)	20-132	June 1, 1995	Tablet
IMITREX [®] Nasal Spray (sumatriptan)	20-626	August 26, 1997	Nasal spray
Zomig [®] (zolmitriptan)	20-768	November 25, 1997	Tablet
Amerge [®] (naratriptan)	20-763	February 10, 1998	Tablet
Maxalt [®] / Maxalt-MLT [®] (rizatriptan)	20-864/20-865	June 29, 1998	Tablet/orally dissolving tablet
Zomig-ZMT [®] (zolmitriptan)	21-231	February 13, 2001	Orally dissolvable tablet
Axert [®] (almotriptan)	21-001	May 7, 2001	Tablet
Frova [®] (frovatriptan)	21-006	November 8, 2001	Tablet
Relpax [®] (eletriptan)	21-016	December 26, 2002	Tablet
Zomig [®] (zolmitriptan)	21-450	September 30, 2003	Nasal spray

2.3 Availability of Proposed Active Ingredient in the United States

Sumatriptan, the active ingredient, was first approved in 1992. The product is widely available in the US.

2.4 Important Safety Issues with Consideration to Related Drugs

The sumatriptan safety profile in adult patients with a clear diagnosis of migraine or cluster headache has been established and is summarized here.

While generally recognized as safe and effective, there have been concerns raised since sumatriptan's adult approval regarding, in particular, cardiac complaints. There have been fatalities within the triptan class due to cardiac causes. While perhaps vasospastic origin, the phenomenon remains pathologically undefined. Cerebrovascular events and fatalities have also been described, but this relationship is confounded by the presence of these complications in the migraine population in general. Other (non-coronary artery) vasospasm-type events have been described with triptan use including peripheral vascular and colonic ischemia and (rarely) transient and permanent blindness. A precise, clear relationship of these complications to the therapy, accompanied by an understanding of the pathophysiology, remains elusive, again reflecting the background migraine condition. The incidence of all of these disorders remains low, when the widespread use of triptans is considered.

Nevertheless because of the risk of myocardial ischemia and/or infarction and other adverse cardiac events, the sumatriptan label clearly states that it should not be given to patients with documented ischemic or vasospastic CAD. Similarly it should 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 reveals satisfactory clinical evidence that the

patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The current label acknowledges the sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. The conclusion is that 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, triptans should not be administered.

Still further, in patients whose risk factors predict CAD but who have a satisfactory cardiovascular evaluation, the sumatriptan label strongly recommends first administration of sumatriptan take place in the setting of a physician's office or similar medically staffed and equipped facility. As a further safeguard, acknowledging cardiac ischemia can occur in the absence of clinical symptoms, the label suggests consideration be given to obtaining an electrocardiogram (ECG) during the interval immediately following the first use of sumatriptan in these patients with risk factors.

The current label recommends 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 the drug. 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 development of a potentially life-threatening serotonin syndrome may occur with triptans, including sumatriptan, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs).

Other issues that have been described include Cerebrovascular Events and Fatalities With 5-HT₁ Agonists (cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events) which may be aggravated since migraine patients are already at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack). 5-HT₁ agonists 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 with 5-HT₁ agonists. Increases in blood pressure, including hypertensive crisis, have been reported on rare occasions in patients with and without a history of hypertension treated with other 5-HT₁ agonists. Problematic preclinical issues include binding to melanin-containing tissues and corneal opacities.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The sponsor submitted questions in a background information package submitted to the Division of Neurology Products dated 22 September 2006 to IND 75949. Upon review, DNP agreed that this application was suitable for submission as an application

described by section 505(b)(2) of the Act.” Only one open-label usability study was submitted by King Pharma. This information was discussed and agreed upon during a T-Con held with the sponsor on 10/24/06. The Division agreed no bioequivalence study was required and that a user handling study during an attack should be conducted. On 6/15/07 the firm was notified the Division’s formal review of the protocol was completed and the studies were allowed to proceed. There is no clinical review in DARRTS but the other disciplines’ archived reviews were studied, and all were in agreement that the product qualified for a 505b2 NDA without any hold issues identified. No other formal Division Comments to the Sponsor are in DARRTS.

2.6 Other Relevant Background Information

The sponsor filed a Citizen’s Petition (FDA-2009-P-0040-0001/CP) 2/02/09 to block approval of auto-injectors under 505(b)(2) or 505(j) unless a number of criteria are met. The petition is currently under review by the Agency.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission is of acceptable quality and integrity.

3.2 Compliance with Good Clinical Practices

This usability study (the only study submitted to the NDA) was conducted in accordance with Good Clinical Practice requirements described in the current revision of International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) Guidelines and all applicable regulations, including current United States (U.S.) Code of Federal Regulations, Title 21, Parts 11, 50, 54, 56, and 312 and Title 45, Part 164. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki.

3.3 Financial Disclosures

I reviewed the list of investigators. They all appear acceptable. None have any financial disclosures or conflicts-of-interest according to the firm’s accompanying affidavit.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see CMC Review.

4.2 Clinical Microbiology

This is a 505 (b) (2) application and no new clinical data was acquired to clinically evaluate these parameters. Please see Microbiology Consultative Review.

4.3 Preclinical Pharmacology/Toxicology

This is a 505 (b) (2) application, based on Imitrex Injectable, the referenced listed drug and no new clinical data was acquired to clinically evaluate these parameters,

4.4 Clinical Pharmacology

No new data was acquired for this 505(b)2 study.

4.4.1 Mechanism of Action

No new data was acquired for this 505(b)2 study.

4.4.2 Pharmacodynamics

No new data was acquired for this 505(b)2 study.

4.4.3 Pharmacokinetics

No new data was acquired for this 505(b)2 study.

The PK of sumatriptan was characterized by $t_{1/2}$ ~115 min, V_d ~ 50 L, C_{max} ~52-74 ng/mL (site- and injection technique-dependent), T_{max} ~12 min (independent of site and technique), and fb ~14-21%. Approximately 60% of SC dose eliminated in the urine, including 22% unchanged drug and 38% as inactive indole acetic acid metabolite. In vitro results showed that sumatriptan is primarily metabolized by monoamine oxidase (MAO), isoenzyme A.

5 Sources of Clinical Data

Only one uncontrolled, open-label, usability study with the product was submitted. The Division requested a study evaluation of user handling in migraine patients during an attack. This is the only new clinical data and this trial is briefly reviewed below in Sections 5 and 7.

5.1 Tables of Studies/Clinical Trials

The sponsor referenced the placebo-controlled Studies Referenced in the Clinical Trials Section of the Imitrex Injection Prescribing Information for this NDA.
The table for the single usability trial is reproduced from the submission here:

Table 4: Summary of the [Tradename] (Sumatriptan Succinate) Auto-Injector User Study – K644-07-3001

Study Identifier Phase Study Status Type of Report	Study Design	Type of Subjects	Treatments Administered	Disposition Demographics	Key Safety Results
K644-07-3001 Phase 3 Complete Final Clinical Study Report	Multicenter, open-label 2-week screening period Treatment of 1 migraine attack Follow-up evaluation within 72 hours	Males and females ≥18 and ≤60 years of age, with a history of migraines (with or without aura) according to IHS criteria, with prior effective use of SC injectable SUM on ≥2 occasions within the previous 2 months	SUM 6 mg, administered SC using the [Tradename] Auto-Injector Although not supplied per protocol, a second dose of SUM (any formulation) was permitted 2 hours after dosing Rescue medications were permitted at the discretion of the Investigator	Screened and enrolled: 66 Safety Population: 63 Age (mean): 45.4 years Gender: 19% M 81% F Race: 95% C 3% B 2% O	<u>Percentage of subjects with adverse events</u> 41% <u>Percentage of subjects with drug-related adverse events</u> 37% <u>Deaths</u> 0 <u>SAEs (in subjects exposed to study drug)</u> 0 <u>Discontinuations due to an adverse event</u> Subject 0002/0001 discontinued before being treated with study drug. Thirty-one of the reported adverse events were mild in intensity and 5 were moderate in intensity.

B = Black; C = Caucasian; F = female; IHS = International Headache Society; M = male; O = Other; SAE = serious adverse event; SC = subcutaneous; SUM = sumatriptan.
Source: K644-07-3001 CSR

5.2 Review Strategy

Only the above, uncontrolled usability study was reviewed for safety and the literature was relied upon to support safety where appropriate.

5.3 Discussion of Individual Studies/Clinical Trials

Please see Table 4: Summary of the [Tradename] (Sumatriptan Succinate) Auto-Injector User Study – K644-07-3001 above for an overview. Study K644-07-3001 is the only study and is a completed Phase III Usability Study. It was a multicenter, open-label design. It began with a 2 – week screening period followed by treatment of 1 migraine attack with the product and a single follow-up evaluation within 72 hours.

Males and females ≥ 18 and ≤ 60 years of age, with a history of migraines (with or without aura) according to IHS criteria, with prior effective use of SC injectable SUM on ≥ 2 occasions within the previous 2 months formed the subject population. 66 were screened and enrolled. The safety population was 63 subjects, the majority Caucasian and female, whose mean age was 45 years.

41% of subjects suffered adverse events and 37% were drug related. No deaths occurred and no SAEs occurred in subjects exposed to study drug. 31 of these were deemed mild and 5 were moderate in intensity.

This uncontrolled study is briefly discussed in section 7 Review of Safety.

5.3.1 Trial Objectives

Primary

- To assess the successful subcutaneous self-injection with a single 6-mg dose of sumatriptan succinate using the [Tradename] (sumatriptan succinate) Auto-Injector during a single migraine attack.

Secondary:

- To compare the subcutaneous self-injection with sumatriptan using the [Tradename] (sumatriptan succinate) Auto-Injector with the traditional self-injector device used to administer acute treatments for migraine.
- To assess the tolerability of the [Tradename] (sumatriptan succinate) Auto-Injector when used to treat a single migraine attack.

5.3.1 Design and Duration

The study design required that subjects have a single dose administered during a migraine attack using the [Tradename] (sumatriptan succinate) Auto-Injector. This was a multicenter, open-label study for adults who had prior effective use of subcutaneous

injectable sumatriptan for the treatment of migraines to assess subcutaneous self-injection with a single dose of sumatriptan using the [Tradename] (sumatriptan succinate) Auto-Injector during a single migraine attack.

Numbers of Subjects:

- Screened and enrolled: 66;
- evaluable for safety: 63;
- included in intent-to-treat (ITT) analysis: 63;
- included in per protocol (PP) analysis: 61

The subjects were adults 18 to 60 years of age who had prior effective use of subcutaneous injectable sumatriptan on at least 2 occasions within the prior 2 months for treatment of migraines with or without aura according to International Headache Society Classification 1.1 or 1.2. Subjects were instructed not to use the study drug until they sustained a migraine with a pain score of 2 (moderate) or 3 (severe) on the pain scale.

All subjects were to receive a single dose of 6 mg sumatriptan via the [Tradename] Auto-Injector. Subjects were instructed not to use the study drug until they sustained a migraine with a pain score of 2 (moderate) or 3 (severe) on the pain scale.

At the Baseline visit (Visit 1), subjects who met all inclusion/exclusion criteria were trained on the proper use of the [Tradename] Auto-Injector by video instruction and a question and answer session with the study coordinator or Principal Investigator, then each subject demonstrated proper administration of the auto-injector by using an active [Tradename] Auto-Injector on a paper towel roll. Once administered into the paper towel roll, the study coordinator marked the auto-injector as "TESTER" using a pre-printed label provided to the clinical site. Then the subject was sent home with another [Tradename] Auto-Injector for treatment at the onset of a migraine. In some instances, the investigational site combined the Screening visit and the Baseline visit, in which case all procedures were the same except that the site had to notify the subject by telephone once the laboratory results were received if the subject was eligible to participate in the study.

Rescue medication of any type, except ergot-containing compounds and MAOIs, were permitted at the discretion of the Principal Investigator. According to the protocol, subjects were permitted to take a second dose of sumatriptan if needed to treat a migraine. However, since only one dose was provided, if a second dose of sumatriptan was required, subjects had to use their own medication and were expected to wait at least 2 hours after administration of study drug.

5.3.2 Inclusion/Exclusion Criteria:

These were standard ones for migraine trials. The sponsor adhered to the following exclusionary criteria, specifically:

- Use of monoamine oxidase inhibitors (MAOIs) within the past 14 days.
- Any use of ergot-containing compounds within prior 30 days.
- Use of migraine prophylaxis headache medication (including but not limited to tricyclics, tramadol, trazodone, barbiturates, anti-epileptic drugs and selective serotonin receptor (5-HT₁) agonists, unless the dose had been stable for at least three months and the subject still fulfilled the attack frequency criterion above).
- Use of herbal or non-drug xenobiotic therapies (e.g., St. John's Wort).
- Basilar or hemiplegic migraine.
- Seizure disorders.
- Coronary artery disease (CAD), including ischemic cardiac or vasospastic CAD.
- Myocardial ischemia of any type, including, but not limited to, angina pectoris of any type, all forms of myocardial infarction, and silent myocardial ischemia.
- Cerebrovascular syndromes including, but not limited to, strokes of any kind, as well as transient ischemic attacks.
- Peripheral vascular disease including, but was not limited to, ischemic bowel disease, intermittent claudication, jaw claudication.
- Two or more major risk factors for CAD (i.e., hypertension, dyslipidemia, smoking, diabetes, and family history of CAD), as interpreted according to the sumatriptan labeling.
- Pathological cardiac dysrhythmia or pacemaker.
- Severe or uncontrolled high blood pressure (i.e., >160 mmHg systolic or >100 mmHg diastolic).

Subjects provided informed consent and were screened for eligibility within 14 days of the Baseline visit (Visit 1). At Visit 1, subject eligibility was confirmed, and subjects received training on the proper use of the [Tradename] (sumatriptan succinate) Auto-Injector (hereafter referred to as [Tradename] Auto-Injector). Eligible subjects were enrolled and dispensed the [Tradename] Auto-Injector filled with a 6-mg dose of sumatriptan (base) as the succinate salt. Subjects were provided with take-home questionnaires to record pre- and 2-hour postdose pain scores, and to provide an assessment of the [Tradename] Auto-Injector.

Subjects continued their normal behavior until they experienced a moderate to severe migraine attack. After a migraine attack occurred, subjects administered (or attempted to administer) a 6-mg dose of sumatriptan using the [Tradename] Auto-Injector. Subjects returned to the study site within 72 hours of the migraine for the Treatment Visit (Visit 2). At Visit 2, the Investigator performed safety assessments, examined the injection site, confirmed successful administration of the sumatriptan through review of the subject diary, and reviewed the subject pain and [Tradename]

Auto-Injector use questionnaires. A telephone follow-up visit (Visit 3) was conducted 7 to 10 days post-treatment to record the use of any concomitant medications or any adverse events (AEs) that had occurred since Visit 2.

5.3.3 Test Product, Dose and Mode of Administration

A pre-assembled, single-use 0.5 mL [Tradename] (sumatriptan succinate) Auto-Injector containing 6 mg of sumatriptan (as sumatriptan succinate), a clear, colorless to pale yellow, sterile, non-pyrogenic solution.

5.3.4 Evaluation Criteria

Efficacy:

Primary:

Successful subcutaneous administration of a 6-mg dose of sumatriptan using the [Tradename] Auto-Injector as demonstrated by: (1) subject questionnaire responses indicating injection into the arm or thigh during a migraine attack, and (2) confirmation of [Tradename] Auto-Injector use through inspection by the Sponsor of the used [Tradename] Auto-Injector.

Secondary:

- Comparison of pain scores predose and 2 hours postdose (where 0 = no pain; 1 = mild pain; 2 = moderate pain; and 3 = severe pain).
- Preference by 5-point scale of new [Tradename] (sumatriptan succinate) Auto-Injector experience compared to subject's traditional self-injector device for administration of sumatriptan.

Safety:

Tolerability was assessed based on adverse events (AEs), electrocardiograms (ECGs), physical examinations, and vital signs.

5.3.5 Schedule of Events

Table 5: Overall Time and Events Schedule

Study Procedure	Screening Visit [Visit 0/0 –14 days Before Baseline Visit]	Baseline Visit [Visit 1/ Dispensing of Study Drug]	Subject Treatment of Migraine	Treatment Visit [Visit 2/Within 72 hours after Drug Administration]	Follow-up Visit [Phone Screen/7 –10 days after Administration of Study Drug]
Informed Consent	X				
Inclusion/Exclusion Criteria	X				
Medical/Surgical History	X				
Clinical Laboratory	X				
Physical Examination	X	X		X	
Pregnancy Test	X (serum)	X (urine)		X (urine)	
Enrollment		X			
12-lead Electrocardiogram	X			X	
Vital Signs	X	X		X	
[Tradename] Auto-Injector Training		X			
Dispense Study Drug		X			
Adverse Event Assessment ¹	X ²	X ²		X	X
Concomitant Medication Review	X	X		X	X
Administer Study Drug			X		
Subject Questionnaire Completion			X		
Subject Questionnaire Collection				X	
Endpoint Assessment ³				X	
Drug Accountability				X	

¹Including any accidental injections

²Study-related procedures/SAEs only

³Includes successful administration and pain assessed predose and 2 hours postdose

6 Review of Efficacy

Efficacy Summary

No new data was acquired for this 505(b)2 study. The “efficacy results” regarding migraine symptoms that the sponsor obtained were uncontrolled and hence not reviewed here. The usability study is discussed in detail in section 7. The sponsor reports 63 subjects used the pre-assembled, single-use [Tradename] Auto-Injector, and 62 (98%) subjects successfully administered their injections ($p < 0.0001$). The status of the one remaining subject’s injection was counted as unsuccessful, despite the subject’s report of a successful injection, because the Auto-Injector was not returned and could not be confirmed by sponsor inspection as a success.

King Pharmaceuticals, Inc. relied upon the information submitted within the Imitrex (sumatriptan succinate) Injection NDA (NDA 20-080) as the basis for information pertaining to controlled clinical studies for this 505(b)(2) application, for [Tradename] (sumatriptan succinate) Auto-Injector. The reference product is Imitrex STATdose System.

6.1 Indication

Acute Migraine.

6.1.1 Methods

No new controlled data was acquired for this 505(b)2 study.

6.1.2 Demographics

No new controlled data was acquired for this 505(b)2 study. The demographic data from this uncontrolled trial is shown in Table 6 from the submission. It displays the typical demography encountered in migraine trials. Of the 63 subjects, 51 (81%) were female and 60 (95%) were Caucasian. The mean age was 45.4 years (range, 19 to 61 years). The mean Baseline Migraine Pain Score was 2.3 (standard deviation, 0.6), with 36 (57%) subjects reporting moderate pain and 24 (38%) subjects reporting severe pain. Subjects reported an average of 2 to 20 migraine episodes per month

Table 6: Subject Demographics and Baseline Migraine Pain Score – Study K644-07-3001 ITT Population

Characteristic	Overall (N = 63)
Age (years)	
N	63
Mean (standard deviation)	45.4 (10.0)
Median	48.0
Minimum, Maximum	19, 61
Gender, n (%)	
Female	51 (81)
Male	12 (19)
Race, n (%)	
Caucasian	60 (95)
Black	2 (3)
Asian	0
American Indian/Alaskan Native	0
Native Hawaiian/Pacific Islander	0
Other	1 (2)
Ethnicity, n (%)	
Hispanic or Latino	3 (5)
Not Hispanic or Latino	60 (95)
Baseline Pain Score, n (%) ¹	
No pain	0
Mild pain	3 (5)
Moderate pain	36 (57)
Severe pain	24 (38)
Mean (standard deviation) ²	2.3 (0.6)

¹ Baseline pain score was reported immediately before using the [Tradename] Auto-Injector.

² For calculations, baseline pain scores were assigned to the response categories as follows: no pain = 0; mild pain = 1, moderate pain = 2, and severe pain = 3.

Note: Percentages were based on the number of intent-to-treat subjects with non-missing data.

Source: K644-07-3001 CSR Post-text Table 10.1.3

6.1.3 Subject Disposition

No new controlled data was acquired for this 505(b)2 study.

In total, 66 subjects were screened and enrolled in this study. Enrolled subjects were those who signed an informed consent, completed Visit 1, and were dispensed an auto-injector for home use. Of these, 63 subjects were included in the safety population. Three subjects were excluded from the safety analysis due to an adverse event, not meeting inclusion/exclusion criteria, and lost to follow-up.

The following table from the submission displays the subject disposition:

Table 7: Subject Disposition – Study K644-07-3001 – All Enrolled Patients

Disposition	Overall n
Screened and enrolled ¹ Subjects	66
ITT population ²	63
Safety population ²	63
Discontinued	3
Adverse event	1
Did not meet inclusion/exclusion criteria	1
Subject lost to follow-up	1

¹ Enrolled: All subjects who signed an informed consent, completed Visit 1, and were dispensed an Auto-Injector for home use.

² Three subjects were excluded from both the ITT and Safety analyses. Subject 0002/0001 was discontinued for the SAE of cholecystitis; this subject was removed from the study before being treated with study drug. Subject 0007/0002 was discontinued at the request of the investigator for a clinically significant ECG abnormality at Screening; this subject was removed from the study before being treated with study drug. Subject 0001/0006 was lost to follow-up with no verifiable information available as to whether this subject had used the Auto-Injector.

Note: Percentages for the reason for discontinuation were based on the number of subjects discontinued (did not complete Visit 2).

ECG = electrocardiogram; ITT = intent-to-treat; SAE = serious adverse event.

Sources: K644-07-3001 CSR Section 6.1 and Post-text Table 10.1.2

6.1.4 Analysis of Primary Endpoint(s)

No new controlled data was acquired for this 505(b)2 study. As noted above, the 63 subjects who used the pre-assembled, single-use [Tradename] Auto-Injector, 62 (98%) subjects successfully administered their injections. The sponsor counted one remaining subject's injection unsuccessful, despite the subject's report of a successful injection, because the Auto-Injector was not returned and its status could not be confirmed by sponsor inspection.

6.1.5 Analysis of Secondary Endpoints(s)

No new controlled data was acquired for this 505(b)2 study. Despite this imposing limitation, for the secondary endpoints, the sponsor reports:

- All 63 (100%) subjects in the ITT population agreed that the written instructions were clear and easy to follow, 60 (95%) agreed or strongly agreed the [Tradename] Auto-Injector was easy to use, and all 63 (100%) were able to self-administer the study treatment according to subject diary reports. The one subject deemed as having an unsuccessful injection did report diary information indicating success, but failed to return the Auto-Injector.
- Sixty-two of 63 (98%) subjects reported a decrease in migraine pain from pre- to post-treatment. One subject's pain intensity (moderate) remained unchanged. This was uncontrolled and no clinical efficacy conclusions can be drawn.

- Two hours after treatment, 59 subjects (94%) reported either no pain or mild pain, and 4 (6%) subjects had moderate pain, in direct contrast to the 60 (95%) subjects who reported moderate or severe pain pretreatment. This was uncontrolled and no efficacy conclusions can be drawn.
- Overall, 41 (65%) subjects preferred the new [Tradename] (sumatriptan succinate) Auto-Injector, 14 (22%) expressed no preference, and 8 (13%) preferred the traditional self-injector device.

6.1.6 Other Endpoints

No new controlled efficacy data was acquired for this 505(b)2 study.

6.1.7 Subpopulations

No new controlled efficacy data was acquired for this 505(b)2 study.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No new controlled data was acquired for this 505(b)2 study.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No new controlled data was acquired for this 505(b)2 study.

6.1.10 Additional Efficacy Issues/Analyses

No new controlled data was acquired for this 505(b)2 study.

7 Review of Safety

Safety Summary

The only NDA trial was an open-label, multicenter study to assess safety, tolerability and efficacy of a single treatment with sumatriptan self-administered via a [Tradename] (Sumatriptan Succinate) Auto-Injector conducted at 10 United States' sites per agreement with the Division. The sponsor reports:

- The majority of AEs reported during this study reflected the mode of administration and were considered related to study drug.
- Twenty-six (41%) subjects reported AEs, with 10 subjects reporting injection site bruising, the single most frequently reported AE.
- Thirty-one of the 36 AEs reported were mild in intensity, and the remaining 5 events were moderate in intensity.

- There were no deaths.
- No subjects who were exposed to treatment with [Tradename] (sumatriptan succinate) Auto-Injector experienced a serious AE (SAE).
- No subjects reported AEs indicative of abnormal vital signs or abnormal ECG results.
- The [Tradename] (sumatriptan succinate) Auto-Injector was well tolerated by the study subjects.

7.1 Methods

See section 5.3. The data sources are adequate and appropriate for this 505 (b) (2) sNDA.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See Review Section 5.3.

7.1.2 Categorization of Adverse Events

AEs were coded to the MedDRA (v10) System Organ Class, principally General Disorders and Administration Site Conditions (which formed the largest AE category). See Table 10, below.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

No study pooling was conducted.

7.2 Adequacy of Safety Assessments

I believe the drug exposure and safety assessments were adequate and appropriate and included all tests reasonably applicable to assess the drug/device combination of the sNDA. The firm had reached agreement on their development plan with the Division prior to conducting the study.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 8 displays the exposure data. An adequate number of patients were exposed to the product to determine satisfactory usability during a migraine attack. The study was appropriately designed as open-label for this purpose. Detailed monitoring for known class side effects was not performed for this single injection study in subjects who have used injectable sumatriptan in the past.

Sixty-six subjects were enrolled, and 63 subjects self-administered a 6 mg dose of sumatriptan using the [Tradename] Auto-Injector. Data for all 63 treated subjects were included in the analyses of safety.

A second dose of sumatriptan (any formulation) was permitted per protocol, though not supplied to the subjects as study drug. Subject 0002/0010 reported use of a 100 mg oral dose of sumatriptan on 23 October 2007, which was the same day as administration of study drug via the [Tradename] Auto-Injector. No information regarding the timing of this other dose relative to study drug dosing was collected.

Table 8: Exposure to Study Drug – Study K644-07-3001

Subjects	Overall (N = 66) n (%)
Number of subjects exposed to the study drug	63 (95)
Number of non-subjects exposed to the study drug	0
Number of subjects with unused study drug	2 (3)
Number of subjects lost to follow-up	1 (2)

Note: Percentages are based on the number of enrolled subjects.

Source: K644-07-3001 CSR Post-text Table 10.2.1

Demographic data is displayed in Table 6, above.

7.2.2 Explorations for Dose Response

No new data acquired for this sNDA.

7.2.3 Special Animal and/or In Vitro Testing

No new data acquired for this sNDA.

7.2.4 Routine Clinical Testing

Routine clinical testing consisted, as noted above in Table 5, of an assessment upon screening for all subjects. At the baseline visit, these were again determined save for the ECG and blood work. These were repeated at Treatment Visit 2, within 72 hours of drug administration. This was adequate and appropriate for this usability study.

7.2.5 Metabolic, Clearance, and Interaction Workup

No new data acquired for this sNDA.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

No new data acquired for this sNDA, and no specific exploration for triptan class effects were conducted in the trial.. The major safety results are presented next.

7.3 Major Safety Results

An overview of the adverse events described in this section is displayed in Table 9. Twenty-six (41%) subjects reported an adverse event. Twenty-three (37%) subjects reported adverse events that were considered by the investigators to be related to study drug. Of the 36 adverse events that occurred during the study, 31(86%) were mild and 5 (14%) were moderate in intensity. There were no severe adverse events.

No subject died during this study. No subject exposed to study drug reported an SAE or discontinued due to an adverse event; however, 1 subject (Subject 0002/0001) experienced the SAE of cholecystitis, and discontinued without ever being treated with study drug.

Table 9: Overview of Adverse Events – Study K644-07-3001 – Safety Population

Criteria	Overall (N = 63) n (%)
Total number of adverse events ¹	36
Subjects with at least 1 adverse event	26 (41)
Subjects with at least 1 adverse event related to study drug	23 (37)
Subjects with SAEs	0 ²
Maximum intensity of adverse events	
Mild	31
Moderate	5
Severe	0
Discontinuations due to an adverse event	0 ²
Deaths	0

¹ Total number of adverse events counts all adverse events for subjects.

² No subjects exposed to study drug reported an SAE, but Subject 0002/0001 discontinued the study before being treated due to the SAE of cholecystitis.

SAE = serious adverse event.

Sources: K644-07-3001 CSR Post-text Tables 10.8.1 through 10.8.3 and Data Listings 12.2.7.1 through 12.2.7.5.

Table 10, shows the AEs by incidence. As can be seen, most were associated with the injection site (22/66). Injection site bruising occurred in 10/66 subjects, followed by pain in 4, injection site hemorrhage in 3, erythema in 2, and site swelling in 2.

7.3.1 Deaths

None.

7.3.2 Nonfatal Serious Adverse Events

None.

7.3.3 Dropouts and/or Discontinuations

None. One patient, as noted above, discontinued before being treated due to an SAE of cholecystitis.

7.3.4 Significant Adverse Events

None. The only SAE was the patient mentioned just above who had an attack of cholecystitis after screening but before taking study drug.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

The sponsor indicates no adverse events indicative of abnormal vital signs. Nearly all physical abnormalities detected were either present at screening or baseline. Subject 0002/0004 was noted to have a circular bruise at the injection site on her right thigh, which was reported as an adverse event.

No subjects included in the Safety Population had clinically significant ECG changes, with one exception. Subject 0007/0002 was discontinued from the study at the request of the Investigator before being treated with the [Tradename] Auto-Injector because her screening ECG result was deemed clinically significant (results were not reviewed by a study staff member until after the subject was enrolled in the study).

As mentioned, clinical laboratory values were only assessed at screening; therefore, no changes over time were evaluated.

7.4.1 Common Adverse Events

Table 10 summarizes the incidence of adverse events by system organ class and preferred term. Twenty-six (41%) subjects reported at least one adverse event. Adverse events were most commonly reported in the system organ class of general disorders and administration site conditions (22 [35%]).

The most commonly reported adverse events were injection site bruising (10 [16%]), injection site pain (4 [6%]), and injection site hemorrhage (3 [5%]). All other adverse events were reported by ≤3% of subjects.

Other adverse events commonly observed with the subcutaneous administration of sumatriptan 6 mg included dizziness or vertigo, throat tightness, flushing, nausea or vomiting, and warm or hot sensations. During this study, adverse events of these types were reported by 1 subject each.

Table 10: Adverse Events by Incidence – Study K644-07-3001 – Safety Population

System Organ Class Preferred Term	Overall (N = 63) n (%)
Subjects with at least 1 adverse event	26 (41)
General Disorders and Administration Site Conditions	22 (35)
Injection site bruising	10 (16)
Injection site pain	4 (6)
Injection site hemorrhage	3 (5)
Injection site erythema	2 (3)
Injection site irritation	2 (3)
Injection site swelling	2 (3)
Feeling hot	1 (2)
Flushing	1 (2)
Injection site pruritus	1 (2)
Injection site rash	1 (2)
Gastrointestinal Disorders	2 (3)
Diarrhea	1 (2)
Nausea	1 (2)
Infections and Infestations	2 (3)
Gastroenteritis viral	1 (2)
Urinary tract infection	1 (2)
Nervous System Disorders	2 (3)
Dizziness	1 (2)
Tremor	1 (2)
Cardiac Disorders	1 (2)
Palpitations	1 (2)
Injury, Poisoning and Procedural Complications	1 (2)
Joint sprain	1 (2)
Respiratory, Thoracic and Mediastinal Disorders	1 (2)
Throat tightness	1 (2)

Note: Subjects may have reported more than one adverse event per system organ class and preferred term. At each level of subject summarization, a subject was counted once if he/she reported one or more events. Percentages were based on the number of subjects in the Safety Population. MedDRA 10.0 was used for coding.

MedDRA = Medical Dictionary for Regulatory Activities.

Source: K644-07-3001 CSR Post-text Table 10.8.1

Table 11 presents adverse events by relationship to study drug. Twenty-three (37%) subjects reported a drug-related adverse event. Adverse events were most commonly reported in the system organ class of general disorders and administration site conditions (22 [35%]). The most commonly reported drug-related adverse events

included injection site bruising reported by 10 (16%) subjects, injection site pain reported by 4 (6%) subjects, and injection site hemorrhage reported by 3 (5%) subjects.

Table 11: Adverse Events by Relationship to Study Drug

System Organ Class Preferred Term	Relationship (N = 63)	
	Related n (%)	Not Related n (%)
Subjects with at least 1 adverse event	23 (37)	3 (5)
General Disorders and Administration Site Conditions	22 (35)	0
Injection site bruising	10 (16)	0
Injection site pain	4 (6)	0
Injection site hemorrhage	3 (5)	0
Injection site erythema	2 (3)	0
Injection site irritation	2 (3)	0
Injection site swelling	2 (3)	0
Feeling hot	1 (2)	0
Flushing	1 (2)	0
Injection site pruritus	1 (2)	0
Injection site rash	1 (2)	0
Gastrointestinal Disorders	1 (2)	1 (2)
Diarrhea	0	1 (2)
Nausea	1 (2)	0
Infections and Infestations	0	2 (3)
Gastroenteritis viral	0	1 (2)
Urinary tract infection	0	1 (2)
Nervous System Disorders	0	2 (3)
Dizziness	0	1 (2)
Tremor	0	1 (2)
Cardiac Disorders	1 (2)	0
Palpitations	1 (2)	0
Injury, Poisoning and Procedural Complications	0	1 (2)
Joint sprain	0	1 (2)
Respiratory, Thoracic and Mediastinal Disorders	1 (2)	0
Throat tightness	1 (2)	0

Note: The total number of adverse events counts all adverse events for subjects. Subjects may have had more than one adverse event per body system and preferred term. At each level of subject summarization, a subject was counted once under the most related event if he/she reported one or more events. Percentages are based on the number of subjects in the Safety population. MedDRA 10.0 was used for coding.

MedDRA = Medical Dictionary for Regulatory Activities.

Source: K644-07-3001 CSR Post-text Table 10.8.3

7.4.2 Laboratory Findings

Clinical laboratory values were only assessed at screening; therefore, no changes over time were evaluated.

7.4.3 Vital Signs

Vital signs were recorded at screening, at dosing, and within 72 hours of dosing at the final visit. No abnormalities were detected.

7.4.4 Electrocardiograms (ECGs)

In the study, ECGs were performed at the screening visit and following treatment. One subject was discontinued from the study at the request of the investigator for a clinically significant ECG taken at the screening visit. The ECG was not reviewed until after the subject was enrolled in the study and the subject did not receive study drug prior to discontinuation. From the Safety population, 13 (21%) subjects had abnormal ECGs at screening – none were considered clinically significant. Following treatment, no subject in the Safety Population had clinically significant ECG changes.

These results appear comparable to previous literature reports as well as results included in the Imitrex injection labeling information.

7.4.5 Special Safety Studies/Clinical Trials

No new data was acquired for this sNDA; the sponsor relies on the Imitrex Injectable RLD for their product. Other than the injection site reactions, no notable additional physical findings accompanied or followed the single injection.

7.4.6 Immunogenicity

No new data was acquired for this sNDA; the sponsor relies on the Imitrex Injectable RLD for their product. The product is not immunogenic.

7.5 Other Safety Explorations

No new data was acquired for this sNDA.

7.5.1 Dose Dependency for Adverse Events

No new data was acquired for this sNDA.

7.5.2 Time Dependency for Adverse Events

No new data was acquired for this sNDA.

7.5.3 Drug-Demographic Interactions

No new data was acquired for this sNDA.

7.5.4 Drug-Disease Interactions

No new data was acquired for this sNDA.

7.5.5 Drug-Drug Interactions

No new data was acquired for this sNDA.

7.6 Additional Safety Evaluations

No new data was acquired for this sNDA.

7.6.1 Human Carcinogenicity

No new data was acquired for this sNDA.

7.6.2 Human Reproduction and Pregnancy Data

No new data was acquired for this sNDA. Sumatriptan carries a Pregnancy Category C rating. Therefore pregnant or breast-feeding females were excluded from participating in the study.

7.6.3 Pediatrics and Assessment of Effects on Growth

No new data was acquired for this sNDA. Safety and effectiveness of sumatriptan in pediatric patients under age 18 years of age is not established at the time of this writing. No explorations for the pediatric population were conducted for this 505 (b) (2) indication.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In this sNDA open-label study each subject received only one [Tradename] Auto-Injector to be used for the treatment of a single migraine attack. Therefore specific assessments for drug-seeking behavior were not performed during the study. Diversion of the dispensed [Tradename] Auto-Injectors was not noted in study K644-07-3001, because all but one subject returned the [Tradename] Auto-Injector dispensed to them after use.

No other studies were conducted, the sponsor relying on the RLD information. That information is quoted here:

Subjects (N = 269) have received single 8 to 12 mg injections of sumatriptan without significant adverse effects. Volunteers (N = 47) have received single

subcutaneous doses of up to 16 mg of sumatriptan without serious adverse events.

No gross overdoses in clinical practice have been reported. Coronary vasospasm was observed after intravenous administration of subcutaneous sumatriptan. 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, and therefore monitoring of subjects after overdose with sumatriptan 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

7.7 Additional Submissions / Safety Issues

Not required, nor conducted for this sNDA. No new data acquired.

8 Postmarketing Experience

There is no post-market experience with this auto-injector product at this time. No new data was acquired and the sponsor refers to the RLD sumatriptan post-marketing experience.

9 Appendices

9.1 Literature Review/References

I reviewed the various literature citations submitted by the sponsor for this sNDA and find them to be appropriate with no data contraindicating use of this product in adult migraineurs. The literature cited is appropriate for their study and product. No additional, independent literature review was conducted.

9.2 Labeling Recommendations

Labeling for this product will follow the established labeling for Imitrex Injectable. The Dosage and Administration Section states:

- *For subcutaneous use only (2)*
- *Single 6 mg dose administered to the (b) (4) (2)*
- *(b) (4) (2)*
- *The maximum recommended dose that may be given in 24 hours is two doses separated by at least 1 hour (2)*
- *Benefit of second dose in patients who have failed to respond to a first dose has not been established (2)*
- *(b) (4)*

9.3 Advisory Committee Meeting

None required.

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this page is the manifestation of the electronic signature.**

/s/

Robert D. Harris
5/6/2009 03:54:45 PM
MEDICAL OFFICER

Eric Bastings
5/12/2009 02:56:00 PM
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