# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**22-239**

# MEDICAL REVIEW(S)

**MEMORANDUM**

DATE: July 14, 2009

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-239

SUBJECT: Action Memo for NDA 22-239, for Sumavel DosePro (sumatriptan injection)

NDA 22-239, for Sumavel DosePro (sumatriptan injection), was submitted by Zogenix, Inc., on 12/28/07 as a 505(b)(2) application with Imitrex injection as the reference listed drug. The division issued a Complete Response (CR) letter on 10/31/08. In that letter, the division noted there had been a positive finding in the in vitro chromosomal aberration assay in human lymphocytes, raising the possibility that one or more impurities (referred to as Impurities 1 and 3) might be genotoxic. However, the conditions of the assay suggested that the finding might have been spurious, and we asked the sponsor to repeat the genetox studies to determine if one or both of the impurities were, in fact, genotoxic (the sponsor had proposed specifications for these two impurities that exceeded the threshold for qualification). If one or the other impurity was found to be genotoxic, the sponsor would have to limit the specification for these impurities to below a total of 1.5 mcg/day. In addition, the sponsor had submitted an oral toxicity study in the rat and an embryo-fetal study in the rabbit to qualify the impurities, but because these studies had been submitted late in the review cycle, they had not been reviewed. In addition, we conveyed numerous comments related to the carton and container labels

The sponsor responded to the CR letter with a complete response dated 1/14/09. This response has been reviewed by Dr. Charles Thompson, pharmacologist, Dr. Lois Freed, supervisory pharmacologist, Felicia Duffy, Division of Medication Error Prevention and Analysis (DMEPA), LaShawn Griffiths, DRISK, Jeanine Best, Pediatric and Maternal Health Staff, Dr. David Claffey, chemist, and Dr. Eric Bastings, Deputy Director, DNP. The review team recommends that the application should be approved.

I agree.

Specifically, Drs. Thompson and Freed have concluded that the sponsor has submitted data that establish that neither Impurity 1 nor 3 is genotoxic, and, taken together with the results of the 90 day toxicity study in rats and the embryo-fetal study in rabbits, support the sponsor's proposed specifications for both impurities.

We have reached agreement with the sponsor on the language for the package insert and patient instructions for use, as well as the carton and container labeling. Further, as explained by Dr. Bastings, although Ms. Best of the Pediatric and Maternal Health Staff has recommended that we require the sponsor to establish a pregnancy registry, we do not feel that this is necessary.

For the reasons stated above, then, I will issue the attached Approval letter with the appended, agreed-upon labeling.

Russell Katz, M.D.

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/s/
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Russell Katz
7/15/2009 09:41:57 AM
MEDICAL OFFICER

# MEMORANDUM

**DEPARTMENT OF HEALTH & HUMAN SERVICES**
**Public Health Service**
**Food and Drug Administration**

| | |
|---|---|
| **Date:** | June 26, 2009 |
| **From:** | Eric Bastings, MD. |
| **To:** | File |
| **Subject:** | NDA 22-239 (from Zogenix) approval |

In a Citizen's petition dated 9/26/07, King Pharmaceuticals requested that FDA:

(1) refuse to designate any drug product containing an auto-injector approved under 505(b)(2) or (j) as therapeutically equivalent to an RLD [reference listed drug] containing an auto-injector unless it has been demonstrated that the auto injector is pharmaceutically equivalent to, bioequivalent to, and has the same labeling as the auto-injector contained in the RLD, and

(2) require that sponsors of new drug products containing auto-injectors conduct appropriate clinical studies in patients under the conditions for which the auto-injector is indicated if sponsors seek approval for a drug product containing an auto-injector under 505(b)(2) and the auto-injector is not the "same" as the auto-injector contained in the RLD.

A second petition from King Pharmaceuticals, dated 1/29/09, asked the Agency to take specific actions on abbreviated new drug applications for sumatriptan succinate injection containing an auto-injector. While the second petition did not specifically make any requests with regard to 505(b)(2) applications, it incorporated the earlier 2007 petition by reference.

The Division of Neurology Products (DNP) has reviewed NDA 22-239 from Zogenix, a 505(b)(2) application, and has concluded that the issues raised in King Pharmaceuticals 9/26/07 petition do not preclude approval of NDA 22-239.

First, the division is not designating the Zogenix product as therapeutically equivalent to the RLD. The sponsor has provided an adequate "bridge" to the RLD, by documenting bioequivalence between the Zogenix product and Imitrex STATdose 6 mg (RLD) when injected in the abdomen or thigh. The products however have a different labeling, as the instructions for use are not the same as those of the RLD.

Second, as the auto-injector used in NDA 22-239 and the RLD have different instructions for use, the sponsor was requested to conduct an appropriate clinical study in patients during a migraine attack, to show that patients are able to understand and implement the instruction for use during an attack. That study provided acceptable results.

For these reasons, the division is planning to approve the 505(b)(2) NDA 22-239.

Eric P. Bastings, M.D.
Deputy Director, DNP

epb
cc:
HFD-120

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/s/
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Eric Bastings
7/14/2009 03:38:55 PM
MEDICAL OFFICER

Russell Katz
7/15/2009 09:43:51 AM
MEDICAL OFFICER

# CLINICAL REVIEW

| | |
|---|---|
| Application Type | NDA |
| Submission Number | 022239 |
| Submission Code | |
| | |
| Letter Date | 12/28/07 |
| Stamp Date | 1/7/08 |
| PDUFA Goal Date | 10/31/08 |
| | |
| Reviewer Name | Rob Harris, M.D. |
| Review Completion Date | 10/31/08 |
| | |
| Established Name | sumatriptan injection |
| (Proposed) Trade Name | SUMAVEL DosePro |
| Therapeutic Class | 5HT1B/1D agonist (triptan) |
| Applicant | Zogenix, Inc. |
| | |
| Priority Designation | S |
| | |
| Formulation | needleless device for subcutaneous injection |
| Dosing Regimen | single dose of 6 mg |
| Indication | Acute Migraine & Cluster HA |
| Intended Population | Adult patients with migraine or cluster headache |

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

The OCP review indicates the sponsor has established bioequivalence of the needle-free injector, Sumavel DosePro (6 mgs/0.5 ml), with the Reference Listed Drug, Imitrex Statdose/Imigran MKII Injector (0.6mgs/0.5 ml). No new safety issues are raised. The indications are exactly the same as those of the RLD. The sponsor has satisfied all requirements of a 505 (b) (2) new drug application.

As noted in the Pharmacology/Toxicology Review, there are 2 pending impurity issues that have not been resolved. I recommend a complete response until these are resolved.

## 1.2 Risk Benefit Assessment

The product appears safe for its intended use as recommended in labeling by all tests reasonably applicable to this product's safety assessment. There are no additional safety concerns with this product than with the RLD. Treatment emergent adverse events associated with administration appear transient and mild and restricted to local site reactions to the needle-free injection.

## 1.3 Recommendations for Postmarketing Risk Management Activities

None

## 1.4 Recommendations for other Post Marketing Study Commitments

None

# 2 Introduction and Regulatory Background

Zogenix, Inc. submits a 505(b) (2) application for a new dosage form of sumatriptan. The sponsor is using as a reference IMITREX STATdose, which is approved for the acute treatment of migraine and cluster headache, under NDA 20-080.

By prior agreement with the Division, the clinical efficacy for this new product, Sumavel DosePro (also called Intraject sumatriptan during the development program), would be primarily based on the establishment of its bioequivalence to the reference product, IMITREX STATdose.

The device, described below, uses a needle-free delivery system for injecting sumatriptan succinate into the subcutaneous tissue using high pressure compressed nitrogen gas. The product has been evaluated in 4 active-controlled and 2 single-arm clinical studies (see Table 9, below). 195 subjects were enrolled into these studies with 194 of those subjects (including 53 migraine subjects and 141 healthy volunteers) receiving a total of 452 injections to one or more of 3 anatomical sites: the abdomen, the thigh, or the arm. The 6 clinical trials, 5 – in healthy subjects, and 1 – in migraineurs, are grouped as follows:

- Healthy Volunteers (123 subjects, 243 injections) –
  - SUM-04-0l (pilot PK/BE single-dose 4-way crossover study, at 3 injection sites)
  - ARD-2l 00-0501 (BE self-administration study at 2/3 injection sites),
  - ARD2100-0504 (BE self-administration study at each of 3 sites) and
  - ZX001-0601 (pivotal PK/BE Trial of Imitrex and Sumavel injections)
  - ZX001-0703 (repeat use study)
- Migraineurs (70 subjects total, 52 migraineurs)
  - ZX001-0701 (usability study)

## 2.1 Product Information

### 2.1.1 Description of the product

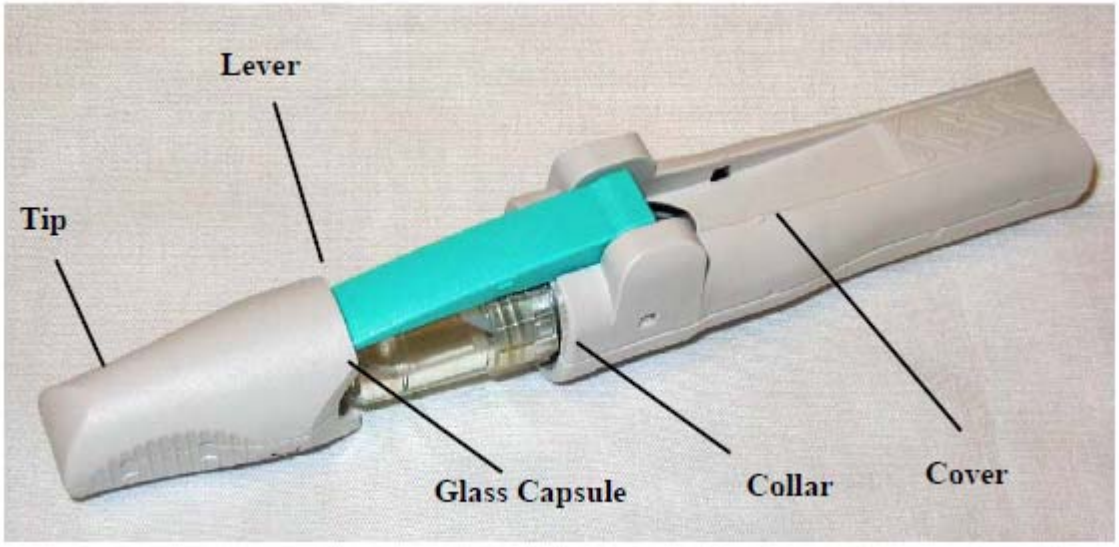
Intraject sumatriptan drug product (Figure 1) is a pre-filled, single-use disposable, needle-free drug delivery system (DDS) designed to deliver 0.5 mL (6 mg of sumatriptan as the succinate salt) in a sterile aqueous formulation into the subcutaneous tissue. Sumatriptan is delivered subcutaneously from the Intraject DDS without a needle in three steps. To use, the patient

- snaps off a plastic tip,
- flips back a 1.5 inch lever, and
- presses the end of the device to the skin of the abdomen or thigh.

Under the pressure of a small amount of compressed nitrogen gas, the aqueous formulation of sumatriptan is forced out of a very small hole in the device, and a thin jet of the medication is propelled through the skin into the subcutaneous tissue. This happens in less than 1/10th of a second.

The Device is pictured here:

**Figure 1: Intraject Sumatriptan Drug Product**




The sponsor suggests the Needle-Free-Injector offers the following advantages over the traditional needle-and-syringe injection devices:

- Eliminates the risk of cross-contamination from needle-stick injury
- Eliminates the costs of sharps disposal
- Eliminates needle-phobia (reportedly up to 15% of people are clinically needle-phobic, and the sponsor indicates most people are apprehensive about receiving injections)
- Improves compliance by overcoming apprehension of needles, especially for treatment of chronic conditions
- Reduces or eliminates under-dosing resulting for poor injection technique
- Reduces healthcare costs associated with patients needing to visit a clinic to receive injections

### 2.1.2 Established name and proposed trade name

The working name used in the IND, CMC, and non-clinical and clinical reports within the application is “Intraject sumatriptan” or Intraject drug delivery system. The proposed trade name is SUMAVEL™ DosePro™, which was submitted to IND 71275 (018) in July 2007.

### 2.1.3 Chemical class: New combination product

This is a new combination product delivering 6 mg of sumatriptan succinate subcutaneously using a needle-free system. The formulation and indications are the same as the RLD injectable triptan, Imitrex for injection.

There are several needle-free products marketed or under development, according to the sponsor. These products ostensibly diminish the possibility of needle injuries and cross-contamination. The devices can be used with either reconstituted lyophilized powder or liquid formulations, but the formulation must be loaded into the device prior to injection. Zogenix concludes needle-free injectors have yet to gain wide acceptability, because of cumbersome preparations and inconvenient use when compared to a needle and syringe or a pen-injector.

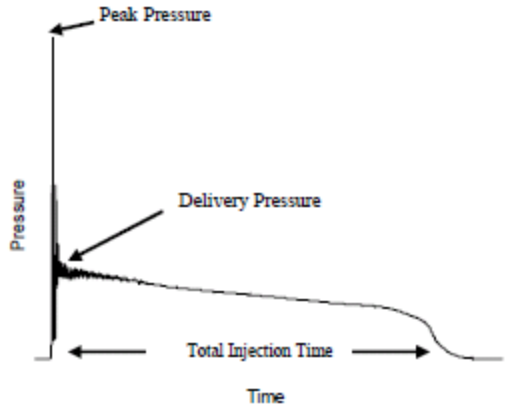
Pre-filled systems, comprising of a combination of drug and device, have therefore been developed to increase ease and intuitiveness of use. The sponsors have selected Intraject Drug Delivery System (IntrajectDDS), a sterile, pre-filled, single-use drug delivery system to deliver sumatriptan. This needle-free or jet injection propels the drug formulation as a liquid jet with sufficient intensity to pierce the skin. The sponsor states most NFI technologies pressurize the drug formulation container in order to force the aqueous formulation through a small orifice in the device, resulting in a high velocity liquid jet stream. Power sources are typically chemical, gas, or a mechanical spring. For a successful NFI there are two key physical requirements:

- The injection must penetrate the skin and
- Maintain a jet velocity sufficient to deliver the drug formulation into the intended space without unintended tissue damage or pain.

The sponsor believes, the liquid jet discharge characteristics of the Intraject DDS are uniquely described by a large ratio of peak pressure: average delivery pressure with a ratio between the two of approximately 6. This pressure profile has been previously determined to be optimal for injection performance in a large study in healthy subjects evaluating both system and subject parameters published by Linn, et al, in Pharm. Res. 2007; 24:1501-7.

The following figure describes the pressure profile as a function of time following actuation of the Intraject NFI system. The total injection time is only 50 ms.

**Figure 2: Pressure Profile as a function of time following actuation of the Intraject NFI Device**




As can be seen, the delivery profile is biphasic, a profile unlike other commercially available NFI systems such as Bioject, the sponsor claims. In these other systems, the peak : delivery pressure ratio is only 2, in contrast to Intraject's ratio of 6.

Similar to a needle injection, Intraject's skin penetration occurs only during the initial stages of injection by Intraject (approx.1 ms) since the high pressure phase is promptly followed by a lower pressure during the delivery of the bulk (>99%) of the injection solution. The actual pressure in the delivery phase for Intraject is lower than the minimum pressure required for piercing tissue. Zogenix cites literature evidence that the physical mechanism of the liquid penetration through the skin has been demonstrated to be similar to a needle from two recent literature reports by Shergold, et al in the Journal of Biomechanical Engineering.

In summary, the sponsor believes this new combination product has the potential to improve patient compliance and clinical outcomes in migraine. They believe a potential exists for this device to be used for large-scale immunization programs and other disorders where chronic parenteral administration of drugs may be of value.

Here is a summary table, prepared by Zogenix, describing the other NFI products marketed or under development.

**Table 1: Needle Free Injection Products, Marketed or Under Development**

| Developer | Technology | Power Source | Prefilled / Patient Filled | Variable Fixed Dose | Single / Multiple Use | Route of Delivery | Max. Volume (mL) | Comment |
|---|---|---|---|---|---|---|---|---|
| Activa | Advantajet | Spring | Patient | Variable | Multiple | SC | 0.5 | For insulin. (b) (4) |
| Anesiva (previously Corgentech) | Zingo | Gas | Pre-filled | Fixed | Single | ID | - | Powder delivery of lidocaine as topical local anesthetic. PowderJect technology NDA approval August 2007 |
| Antares | Medijector Vision | Spring | Patient | Variable | Multiple | SC | 0.5 | For insulin and growth hormone. Specific interchangeable capsules with different jet orifices per skin type |
| Avant Medical | Avant Guardian 101 | Spring | Patient | Variable | Multiple | SC | 1.0 | (b) (4) |
| Bioject | 1. Biojector 2000<br>2. Serojet / Coolclick<br>3. Iject | 1. Gas<br>2. Spring<br>3. Gas | 1. Patient<br>2. Patient<br>3. Pre-filled | Variable<br>Variable<br>Fixed | 1.Multiple<br>2. Multiple<br>3. Single | 1. All<br>2. SC<br>3. All | 1.0 | 1 & 2. 510(k) cleared. Biojector for immunization and other drugs. Serojet and Coolclick for somatropin<br>3. Iject in development |
| Crossject | Crossject System | Spring that energizes a chemical gas generator | Pre-filled | Fixed | Single | All | - | Multi-nozzle design.<br>Development stage |
| Felton / Pulse Needle Free Systems | HSI 500 | Gas | Large volume reservoir physician administered | Fixed | Multiple | SC | 0.5 | Mass vaccination High workload. |
| Injex-Equidyne | Injex | Spring | Patient | Variable | Multiple | SC | 0.3 – 0.5 | 510(k) cleared. Insulin delivery |
| National Medical Products | J-Tip | Gas | Patient | Variable | Single | SC | 0.02 – 0.25 | (b) (4)<br>Used for insulin delivery |

| Developer | Technology | Power Source | Prefilled / Patient Filled | Variable Fixed Dose | Single / Multiple Use | Route of Delivery | Max. Volume (mL) | Comment |
|---|---|---|---|---|---|---|---|---|
| PowderMed / Pfizer | PMED | Gas | Prefilled with powder particle dosage form | Fixed | Single | ID | - | Propels vaccine into epidermis. PowderJect technology. Development stage |
| The Medical House | 1. SQ Pen<br>(b) (4) | Spring | Patient | Variable | Multiple<br>(b) (4) | SC | 0.5 | In early development |
| Valeritas (Biovalve) | Mini-ject | Chemical gas creation | Patient | Fixed if prefilled. Variable if patient filled | Single | All | 1.3 | IM and ID capable to lower volumes<br>Development stage |
| Zogenix | Intraject | Gas | Pre-filled | Fixed | Single | SC | 0.5 | Technology used in Intraject sumatriptan |

Abbreviation: SC: subcutaneous; ID: intra-dermal

## 2.1.4 Pharmacological class

Triptan

### 2.1.5 Applicant's proposed indications, dosing regimens, age groups

The proposed indications are exactly the same as for Imitrex injection, namely:

- the acute treatment of migraine attacks, with or without aura, and
- the acute treatment of cluster headache episodes.

The adult dosing regimen for this pre-filled, single-dose, needle-free subcutaneous delivery system delivering 0.5 mL of sterile solution containing 6 mg sumatriptan (as the succinate salt) is:

- A single subcutaneous doses not exceeding 6 mg, and no more than two 6 mg doses to be given in 24 hours, separated by at least 1 hour

The safety and effectiveness of the product has not been established in patients less than 18 years and its use in that population is not recommended.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Migraine, a common, chronic, and often incapacitating genetically-based neurovascular disorder, occurs in approximately 18% of women and 6% of men. The peak prevalence of migraine occurs between 35 and 45 years of age and the total number of migraine sufferers in the United States is about 30 million. Typically attacks are disabling and last 15 to 20 hours, even as long as 48-72 hours. Characteristics are a moderate or severe headache, autonomic nervous system dysfunction, nausea or other gastrointestinal symptoms, photophobia or phonophobia, and, in some patients, can be associated with aura involving neurologic sequelae. Migraine attacks are associated with activation of the trigeminal-vascular system.

The disorder is treated either acutely (to stop an attack after it has started) or prophylactically (to prevent one). Acute therapy is divided into:

- migraine-specific therapies (i.e., cerebral vasoconstrictor agents) and
- non-specific migraine therapies (i.e., nonvasoconstrictive agents).

Migraine-specific acute medications are usually the treatment of choice by headache specialists for moderate to severe migraine, whereas nonspecific migraine treatments that include both over-the-counter (OTC) and prescription products are frequently used for milder migraine. Contemporary management authorities generally describe migraine-specific agent use (triptans, dihydroergotamine [DHE]) for patients with moderate or severe migraine or whose mild-to-moderate headaches respond poorly to nonsteroidal anti-inflammatory drugs (NSAIDs) or combinations such as aspirin plus acetaminophen plus caffeine.

The migraine-specific acute agents for with shown statistical and clinical benefit are the triptans and ergot alkaloids/ergotamine preparations (see tables below). Non-specific migraine acute agents include NSAIDs such as ibuprofen, naproxen, diclofenac, aspirin or aspirin-combination products (e.g., aspirin with acetaminophen and caffeine, available as Excedrin® Migraine), and opioids (particularly codeine) or opioid combinations, butalbital combinations and anti-

nausea/antiemetic medications (e.g., prochlorperazine, metoclopramide). The non-specific acute agents show varying degrees of statistical and/or clinical benefit depending on their pharmacologic class and route of delivery and are also summarized below. The following tables summarize currently available treatments for migraine:

**Table 2: Migraine Acute Therapies**

Copyright

[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).

## 2.3 Availability of Proposed Active Ingredient in the United States

Sumatriptan is the active ingredient in this NDA is and was first approved in the USA in 1992 as injectable Imitrex (NDA 20-080). It was the first of 7 triptan class migraine products that were developed and marketed for both migraines and cluster headaches. Triptans can be administered

- *subcutaneously* by self-injection,
- *orally* (including by quick-dissolving oral melts) or
- *nasally* as a spray.

IMITREX Injection remains the only injectable triptan available to patients. A list of approved triptans and their approval dates is provided in the following table.

**Table 3: Triptan Therapies Approved for Acute Migraine Treatment 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 |

Triptans are agonists at 5-hydroxytryptamine1 receptor subtypes (primarily at 5-HT1B and 5-HT1D receptors), having:

- weaker affinity for 5-HT1A, 5-HT5A, and 5-HT7 receptors and
- no significant affinity (as measured using standard radio-ligand binding assays) or pharmacologic activity at 5-HT2, 5-HT3, or 5-HT4 receptor subtypes or at alpha1-, alpha2-, or beta-adrenergic; dopamine1; dopamine2; muscarinic; or benzodiazepine receptors.

The 5-HT1 receptor subtypes activated by triptans mediate vasoconstriction in cranial arteries and in the vasculature of human dura mater. In addition to their vasoconstrictor effects, triptans also stimulate 5-HT1 receptors on the peripheral terminals of the trigeminal neurons innervating cranial blood vessels where they induce peripheral neuronal inhibition through second-order neurons of the trigeminocervical complex. These actions appear to inhibit the effects of activated nociceptive trigeminal afferents and, in this way, may contribute to the anti-migraine effect of triptans in humans.

As noted above, the RLD for this application is sumatriptan succinate for subcutaneous injection (6 mg/0.5 mL). The RLD is marketed by GlaxoSmithKline (Middlesex, UK) in the U.S. as IMITREX Injection (using the STATdose drug delivery system) and outside of the U.S. as Imigran Injection. IMITREX Injection STAT dose 6 mg auto-injector drug delivery system administers, per dose, 0.5 mL of an aqueous formulation of sumatriptan succinate, equivalent to 6 mg of sumatriptan as the base.

Efficacy of IMITREX Injection was demonstrated in two pivotal US placebo-controlled clinical trials in 1,104 migraine patients with moderate or severe migraine pain. Onset of relief was rapid (<10 minutes) with IMITREX Injection. 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 IMITREX Injection. Headache relief was

achieved in approximately 82% of patients within 2 hours, and 65% of all patients were pain free within 2 hours.

Sumatriptan delivered via subcutaneous (needle-based) injection has a $T_{max}$ of approximately 12 minutes compared to oral administration, which has a time-to-peak plasma level of 2-3 hours. $C_{max}$ after a 6 mg injection is approximately 74 ng/mL and the bioavailability of subcutaneous sumatriptan is approximately 97%.

## 2.4 Important Safety Issues with Consideration to Related Drugs

Sumatriptan's safety profile in patients with a clear diagnosis of migraine or cluster headache has been established. While generally safe and effective, there have been concerns raised since approval regarding, in particular, cardiac complaints with fatalities. These appear to have a vasospastic origin that is not clearly defined. 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 sumatriptan 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, considering the widespread use of triptans.

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

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 some cases, cerebrovascular events may have been primary, with sumatriptan being administered erroneously, presuming the symptoms experienced were due to migraine when they were not.

The potentially life-threatening serotonin syndrome, occurring with combined use of triptans and selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors

(SNRIs), is described and is noted in the Imitrex label. These and other CNS events such as seizures are also known.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Development of the Intraject drug product was performed under IND No. 71,275 in conjunction with the Division of Neurologic Products. Several meetings were held (and documented with Division Meeting Minutes) on:

28 June 2005: Pre-IND meeting
21 May 2007: Pre-NDA CMC meeting
11 June 2007: Pre-NDA clinical meeting

On 20 November 2007, the Division indicated submitting clinical usability and repeat use studies ZX001-0701 and ZX001-0703 within 60 days of NDA submission would be acceptable.

In the pre-NDA meetings, there was discussion on a number of questions pertaining to the NDA submission for Intraject sumatriptan. The sponsor prepared a large tabulated overview (pp 4 – 12 of the Cover Letter) in submission summarizing in detail the discussion points and agreements that arose from the pre-NDA meetings with the Agency. These points are hyperlinked to the location in the NDA eCTD where this information is located. This information was reviewed and appears to be accurate. The sponsor has complied with Division concerns as summarized next.

During development, FDA and Zogenix agreed that in support of a 505(b)(2) NDA application, the safety and efficacy of the drug product could be established via clinical pharmacokinetics / bioequivalence to the approved reference listed product IMITREX STATdose Injection (see 25 June 2005 pre-IND meeting). In response, Zogenix conducted the Pivotal PKBE study of Intraject sumatriptan versus IMITREX STATdose System, 6 mg (ZX001-0601). FDA also indicated in the pre-NDA meeting minutes that a usability study in migraine patients (subsequently referred to as Study ZXOO1-0701) could be submitted after NDA filing. Zogenix has submitted both:

- clinical study ZX001-0701, which addresses the usability of Intraject sumatriptan by patients, and
- a repeat injection clinical study ZX001-00703 (to address Agency questions about local site safety / tolerability associated with repeat injections to the same site). Local site injection signs have been followed in both of these studies to further FDA's understanding that local site injection signs following Intraject delivery are similar to those seen with conventional needle injection, as was established in the Pivotal PKBE study with IMITREX STATdose.

## 2.6 Other Relevant Background Information

None submitted and none required.

# 3 Ethics and Good Clinical Practices

## 3.1 Submission Quality and Integrity

The quality of this submission is good and was submitted in eCTD format. The information was well-organized and complete not necessitating additional queries for additional data to perform the review. A major amendment, the usability study, was submitted in accordance with previous agreements with the Division.

## 3.2 Compliance with Good Clinical Practices

The sponsor has properly addressed informed consent, protocol violations, and acceptable ethical standards for clinical investigations for their studies. The pivotal study was conducted at COVANCE, a single site in Dallas, TX.

Zogenix certified it did not use, in any capacity, the services of any person debarred under Section 306(a) or (b) with this NDA in a communication dated September 2007.

## 3.3 Financial Disclosures

The sponsor certified, in July 2007, that none of the clinical investigators or sub-investigators for the pivotal bioequivalence study, ZX001-0601, had neither financial arrangements nor any financial interests that required disclosure. Therefore no FDA Forms 3455 were submitted. This arrangement provides assurance as to the integrity of the data

The following table lists Protocol ZX001-00601's 4 clinical investigators and their professional affiliations:

**Table 4: Clinical Investigator List, Study ZX001-0601**

| Clinical Investigator/ Subinvestigators | Institution | Full or Part Time Employee of Zogenix (Yes/No) |
|---|---|---|
| Patricia A. Chandler, MD (Primary Investigator) | Covance Clinical Research Unit, Inc.<br>1341 W. Mockingbird Lane<br>Suite 400 E<br>Dallas, TX 75247 | No |

(b) (4)

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

This is a 505 (b) (2) application, based on bioequivalence to a referenced listed drug and no new efficacy clinical data was acquired to clinically evaluate these parameters. The safety profile of the product, as reviewed in detail below, appears benign. There were no drop-outs or deaths. The reader is referred to the specific discipline's review of this NDA for more information regarding these topics in this NDA.

## 4.1 Chemistry Manufacturing and Controls

This is a 505 (b) (2) application, based on bioequivalence to a referenced listed drug and no new clinical data was acquired to clinically evaluate these parameters. The following summary from Chemistry gives an overview of the CMC issues for this product. Details, particularly of the impurity issues, can be found in the Chemistry Review conducted by Dr. David Claffey.

The proposed drug product, SUMAVEL™ DosePro™ (sumatriptan injection) is a drug-device combination product. It is a sterile, pre-filled, disposable, needle-free delivery system, designed to deliver 6 mg/0.5 mL aqueous dose of sumatriptan (as the succinate salt) into the patient's subcutaneous tissue. It is the same dose and concentration as the existing marketed injectable formulation (IMITREX® Injection 6 mg).

The drug substance sumatriptan succinate is a white water-soluble compound whose CMC details were cross referenced to DMF (b) (4) This DMF was initially found to be deficient by Dr. Claffey, however all outstanding issues were

resolved in this review cycle. Drug substance specifications generally complied with those described in the recent USP monograph for sumatriptan succinate.

The administered drug product solution is simply composed of 0.5 ml of 12 mg/ml drug substance in an isotonic saline solution. The solution is (b) (4) during manufacture (b) (4) The drug product is manufactured by Patheon UK Ltd.

The manufacturing process involves several distinct operations - (b) (4) The drug product solution does not contain a preservative. Its sterility is assured by the (b) (4) operations and the (b) (4) .

The drug product container closure (capsule sub-assembly) is designed to protect the integrity of the drug formulation solution by preventing microbial contamination. Further assurance of acceptable microbial quality is provided by the testing of each drug product lot at release for sterility and bacterial endotoxins. Studies demonstrated that the drug product contact components did not significantly impact product quality through adsorption, leachables or extractables. No changes were made to the formulation during development nor were any changes made to the device that would significantly affect its performance across the pivotal clinical studies. Real time stability data supported the proposed 24-month drug product expiry period.

Chemistry recommends approval of the NDA, subject to the acceptance of the pharm/tox reviewer of the proposed acceptance criteria for drug product impurities 1 and 3. If lower limits for these impurities are deemed necessary, a reevaluation of the drug product expiry period will be required. All other outstanding CMC issues have been resolved.

Please see CMC Review and Pharm/Tox Review for detailed evaluation and discussion of the impurity issues.

## 4.2 Clinical Microbiology

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

leachables and impurities. However drug product impurities 1 and 3 acceptance criteria may be problematic. Please see the Pharm/Tox Review for any additional comments.

## 4.4 Clinical Pharmacology

The pharmacokinetics and bioequivalence of sumatriptan injection following subcutaneous administration using the Intraject DDS and IMITREX/Imigran auto-injector were evaluated in 4 clinical studies in healthy adult subjects. Please see the Biopharmaceutics review for details. Briefly, prior to the submission of the US IND and the conduct of the Pivotal Pharmacokinetic/Bioequivalence (PK/BE) Study ZX001-0601, three non-IND active-controlled pharmacokinetic studies ("Pilot PK Studies") were conducted in Australia in accordance with Good Clinical Practices under Protocol Nos. SUM-04-01, ARD-2100-0501, and ARD-2100-0504.

These 4 studies were designed to compare the safety, tolerability, pharmacokinetics, and bioequivalence of Intraject sumatriptan (6 mg/0.5 mL) to the reference product, sumatriptan injection as Imigran Injection (using the MK II Injector; 6 mg/0.5 mL) at three potential injection sites:

- abdomen,
- arm, and
- thigh.

Imigran Injection marketed in Australia employs the Mk II auto-injector that is the same device as the auto-injector (called STATdose System) used for IMITREX Injection in the U.S. All four studies evaluated single doses of 6 mg sumatriptan/0.5 mL when administered by the Intraject Drug Delivery System (DDS) or the IMITREX/Imigran drug delivery system (i.e., STATdose System or Mk II Injector).

After concluding study -504, which only evaluated arm injections, the sponsor determined the lateral arm injection sites were unsuitable due to the high incidence of wet or incomplete injections which then failed to establish bioequivalence with Imitrex injections. The wet injections were not due to device failure, rather to the inability to position and maintain the device so a complete injection of the drug is assured.

Therefore the following summary focuses primarily on the Pivotal PK/BE study (ZX001-0601) and two remaining Pilot PK studies (SUM-04-01, ARD-2100-0501), which evaluated all three possible injections sites. However, because the arm was an integral part of the design and statistical analysis of the Pivotal PK/BE Study and the two remaining Pilot PK Studies, results for the arm injection site have been retained in the following sections for each study.

The following table summarizes the 3 pivotal and pilot PK/BE clinical studies but excludes Study -504, where the arm was shown to be an unsatisfactory injection site.

**Table 5: Summary of Pivotal and Pilot Pharmacokinetic/Bioequivalence Clinical Studies of Single-Dose Subcutaneous Injection, Intraject Sumatriptan (6 mg/0.5ml vs. Imitrex Statdose/Imigran MK II Injector (6mg/0.5 ml)**

| Study | Country | Study Population | Injection / Sites | Study Design | Nominal No. Injections Per Injection Site[a] | Total Nominal No. of Injections[a] |
|---|---|---|---|---|---|---|
| **Pivotal PK/BE Study ZX001-0601** | U.S. (IND) | N=54 healthy adult M/F subjects. | Clinician injected to abdomen, arm, and/or thigh. | 4-way crossover, incomplete block. | N=36 | N=108 |
| **Pilot PK Study SUM-04-01** | Australia | N=18 healthy adult M/F subjects. | Clinician injected to abdomen, arm, and/or thigh. | 4-way crossover, incomplete block. | N=12 | N=36 |
| **Pilot Self-injection PK Study ARD-2100-0501** | Australia | N=24 healthy adult M/F subjects. | Self-injected to abdomen, arm, and/or thigh. | 4-way crossover, incomplete block. | N=16 | N=48 |
| **Total N=96 Subjects** | | | **Total nominal no. of Intraject injections[a] N=192** | | | |

[a] The number of nominal injections represent the number of planned injections per product Intraject sumatriptan or IMITREX/Imigran Mk II, per injection site and may have differed from the actual number of injections administered during the 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

The reader is referred to the Office of Clinical Pharmaceutics review for details of the PK study used to determine bioequivalence.

Briefly, from their review, a pivotal bioequivalence Study ZX001-0601 was conducted to assess the relative bioavailability of the Intraject® sumatriptan compared to the approved Imitrex® STATdose System. This study was a randomized, open-label, single-dose, 4-way crossover in an incomplete-block treatment design in 54 healthy adult male and female subjects between the ages of 18 and 55. Each subject received the **TEST** (Intraject® sumatriptan, 6 mg) and the **REFERENCE**, (Imitrex® STATdose System, 6 mg) in two of the three possible injection sites (i.e., abdomen, arm, and/or thigh). The injections were made by a clinician. Each subject was randomly assigned to receive four of six treatment sequences.

The statistical analysis showed that the Intraject® sumatriptan was bioequivalent to the Imitrex® STATdose System at the abdomen and the thigh sites, but was not bioequivalent at the arm site. The arm will not be recommended as a site of injection because injection into the lateral arm was

associated with wet or incomplete injections, which resulted in a failure to establish bioequivalence. The abdomen and the thigh will be recommended as injection sites.

# 5 Sources of Clinical Data

The sources of Clinical Data within this marketing application are listed in the Tables of Clinical Studies below. There were no other sources of data external to the NDA such as other trials conducted by the sponsor, their designees, NIH, literature reports, or foreign marketing safety data. This is a 505 (b) (2) application, based on bioequivalence to a referenced listed drug and no migraine efficacy studies were performed as noted.

Consultations were obtained from Microbiology, CDRH, OSE and DDMAC as part of the review and the reader is referred to their specific reviews for details.

In 2005, the Division and the sponsor agreed that the clinical efficacy for Intraject sumatriptan would be primarily based on the establishment of its bioequivalence to the US marketed reference product, IMITREX STATdose at the outset of the IND. At the pre-NDA meeting with the sponsor on 11 June 2007, the Agency agreed to submission of a usability study in migraine patients, Clinical Study Report (CSR) ZX001-0701, as an amendment to the NDA. The Division had questions about local site safety/tolerability associated with repeat injections to the same site. Therefore Zogenix initiated the repeat injection safety study, Clinical Study ZX001-0703, to address these concerns of safety and tolerability. The latter two studies were submitted as an amendment to the NDA within 60 days of filing as per agreements reached at the pre-NDA meeting.

An adequate number of subjects appear exposed to the drug, including adequate numbers of various demographic subsets and people with migraine for a 505 (b) (2) application. The doses and durations of exposure were adequate to assess safety for acute treatment of migraine. Study designs were adequate, noting some design differences described in the review section 5.1.1, Summary of Study Design Differences, below. Relevant safety assessments (e.g., diabetics, people over 75, people with recent myocardial infarction, people with renal or hepatic functional impairment, or people on other therapy) were not a part of this 505 (b) (2) application.

## 5.1 Tables of Clinical Studies

The tables are presented here. All told, 11 studies (including non-IND and legacy studies) with the device and/or device-drug combination were conducted over development. However, only 6 were used by the sponsor to support the NDA. The first 4 were in healthy volunteers. One pivotal PK/BE study, ZX001-0601, was done with 3 non-IND PK/BE studies having been done prior to the IND. Except for 3 clinical studies (ZX001-0601, ZX001-0701 and ZX001-0703), all of the remaining clinical studies conducted by Zogenix in support of this NDA are legacy studies.

The clinical safety data analysis, reviewed below, is based on a fully integrated dataset from all clinical trials (5 studies in healthy volunteers and 1 study in migraine subjects). The database

includes demographic and adverse event data from all 6 clinical trials and local injection site assessment data from 5 of the 6 trials, excluding Usability Study ZX001-0701, the local injection site assessment data, which had differences in study design. Design differences are discussed below.

The studies, again, are:

- Healthy Volunteers (123 subjects, 243 injections) –
  - SUM-04-0l (pilot PK/BE single-dose 4-way crossover study, at 3 injection sites)
  - ARD-2l 00-0501 (BE self-administration study at 2/3 injection sites),
  - ARD2100-0504 (BE self-administration study at each of 3 sites) and
  - ZX001-0601 (pivotal PK/BE Trial of Imitrex and Sumavel injections)
  - ZX001-0703 (repeat use study) and
- Migraineurs (70 subjects total, 52 migraineurs)
  - ZX001-0701 (usability study)

**Table 6: Clinical Studies Completed for the Intraject Sumatriptan NDA**

| Type of Study | Study Identifier | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Subject Participation | Total Intraject Injections | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|---|
| Safety Study | ZX001-0703 | Module 5, Section 5.3.5.2 | To evaluate the extent, persistence, and any cumulative effects on skin tissue by assessing local injection site reactions (bleeding, swelling, erythema, bruising) following repeated administrations of Intraject sumatriptan to the same anatomic site | Single-center, open-label, repeat-dose, single-arm, in-clinic study in 18 healthy adult subjects. | Intraject® needle-free injector using sumatriptan | 18 planned, 18 enrolled, 18 completed | Healthy adult subjects | 5 days, total | 54 | Completed; Full CSR |
| Usability Study | ZX001-0701 | Module 5, Section 5.3.5.2 | Primary: To evaluate the usability of sumatriptan delivered subcutaneously via the Intraject system in adult patients during acute migraine attack. Secondary: 1) to evaluate the reasons for incorrect use of the Intraject system during acute migraine attack; 2) to evaluate the adequacy of instructional materials on the use of the Intraject system; 3) to evaluate the frequency of occurrence and persistence of local injection site reactions (swelling, erythema, bruising, bleeding). | Multi-center, open-label, single-dose, single-arm study of the usability of Intraject sumatriptan (6 mg/0.5 mL) in 50 adult patients during acute migraine attack. | Intraject needle-free injector using sumatriptan | 50 planned, 54 enrolled, 52 completed | Migraine patients | Until the treatment of 3 migraines or until a maximum of 30 days, whichever was shortest | 155 | Completed; Full CSR |
| PK/BE (Pivotal Active controlled study) | ZX001-0601 | Module 5, Section 5.3.1.2 | To evaluate the pharmacokinetics and bioequivalence of Intraject sumatriptan vs. IMITREX Injection at three injection sites in healthy adult subjects | Single center, randomized, single-dose, open-label, four-way cross-over study at 2 of 3 injection sites (abdomen, arm, thigh) | Intraject needle-free injector using sumatriptan vs. marketed reference product, IMITREX; 2 Intraject and 2 IMITREX; physician administered; subcutaneous | 54 planned and randomized, 48 completed and evaluable | Healthy adult subjects | 6 days, total | 111 | Completed; Full CSR |
| Clinical performance assessment (Device evaluation with saline injection) | P095-002 | Module 5, Section 5.3.3.1 | To establish best design configuration of Intraject by evaluating injection performance of different design configurations in a large group of subjects. | Single-group study of subjects receiving 12 saline injections to the abdomen at multiple injection sites | Different design configurations of a needle-free injector (Intraject) using saline; 12 saline injections; subcutaneous | 300 planned, 300 completed (100 subjects received injections with "near-final device) | Generally healthy male and female adults aged 18-80 years | 10 days, total | 102 in near-final device (total exposure =3612) | Completed; Full CSR |

| Type of Study | Study Identifier | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Subject Participation | Total Intraject Injections | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|---|
| Clinical performance verification (CPV); (Device evaluation with saline injection) | ARDM-02A00-0104 | Module 5, Section 5.3.3.1 | To verify device design by evaluating injection performance in a large group of subjects | Single-group study of subjects receiving saline injections to the abdomen at multiple (6) injection sites | Intraject needle-free injector using saline; 4 saline injections; subcutaneous | 200 planned, 191completed | Generally healthy male and female adults | 4 days, total | 764 | Completed; Full CSR |
| Pilot PK (Active controlled study) | SUM-04-01 | Module 5, Section 5.3.3.1 | Pilot study to evaluate the pharmacokinetics and bio-equivalence of Intraject suma-triptan vs. marketed reference product at 3 injection sites | Single-dose, open-label, 4-way crossover PK study using a balanced incomplete block design | Intraject needle-free injector using sumatriptan vs. marketed reference product, Imigran MkII®; 2 Intraject and 2 Imigran physician administered; subcutaneous | 18 planned, 18 completed | Generally healthy male and female adult subjects | 4 days, total | 36 | Completed; Full CSR |
| PK (Active controlled study) | ARD-2100-0501 | Module 5, Section 5.3.3.1 | To establish the bioequivalence of subjects who self-administer Intraject sumatriptan in compari-son to self-administered marketed reference product at each of three injection sites | Single center, random-ized, single-dose, open-label, four-way cross-over study at 2 of 3 injection sites (abdomen, arm, thigh) | Intraject needle-free in-jector using sumatriptan vs. marketed reference product, Imigran Mk II; 2 Intraject and 2 Imigran self-injections; subcutane-ous | 24 planned, 24 completed | Healthy adult subjects | 6 days, total | 48 | Completed; Full CSR |
| PK (Active controlled study) | ARD-2100-0504 | Module 5, Section 5.3.3.1 | To establish the bioequivalence of subjects who self-administer Intraject sumatriptan in compari-son to self-administered marketed reference product at each of three injection sites | Single center, random-ized, single-dose, open-label, three-way cross-over study | Intraject needle-free in-jector using sumatriptan vs. marketed reference product Imigran Mk II; 2 Intraject and 1 Imigran; self-injections; subcutane-ous | 24 planned, 24 completed | Healthy adult subjects | 5 days, total | 48 | Completed; Full CSR |
| In Vitro/In Vivo Correlation (ZED Trial) | P/N 8800-1137 | Module 5, Section 5.3.5.4 | To further understand if certain skin attributes affect the performance of the Intraject | Single center study of the skin characteristics of subjects that previously participated in study P095-002 | N/A; no test material used | 40 planned, 40 completed | Healthy adult subjects | 1 day, total | 0 | Completed; Report |
| Naïve User Study | ARDM-02A00-0204 | Module 1, Section 1.14.1.4 | To evaluate the experience of naïve users as they were exposed to a progressive iteration of instruction followed by the opportunity to snap off the cap, prime and actuate the Intraject configured with the priming mechanism and snap-off cap | Single center, three-group, open-label study of subjects using instructional material to complete an injection into a foam pad | Intraject needle-free injector filled with sterile saline; 2 injections per subject; 2 subjects injected a third time | 102 planned, 102 completed | Healthy adult subjects | 1 day, total | 0* | Completed; Report |

| Type of Study | Study Identifier | Location of Study Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Subject Participation | Total Intraject Injections | Study Status; Type of Report |
|---|---|---|---|---|---|---|---|---|---|---|
| Pilot Usability Study | ZX000-0702 | Module 1, Section 1.14.1.4 | To create instructions for use for Intraject sumatriptan simple enough to be understood by patients experiencing a migraine attack. | Single center, two-group, open-label study of subjects using only the test instructional material as a guide to complete an injection into a foam pad | Intraject needle-free injector filled with non-sterile saline; 1 injection per subject | 20 planned, 19 completed | Healthy adult subjects | 1 day, total | 0* | Completed; Report |

*20 injections into a foam pad were completed during the Observational study (ZX000-0702). 206 injections into a foam pad were completed during the Naïve User study (ARDM-02A00-0204).

### 5.1.1 Summary of Study Design Differences

There are 4 differences noted between the 6 PK/BE and usability studies which are considered in this review. Apart from minor variations in the selection criteria, which did not change the study population significantly, the main differences between the studies are:

- Firstly, the *dosing regimen*: in study SUM-04-01 the 4 doses were given at intervals of 2 days or more; in studies ARD-2100-0501, ARD-2100-0504 and ZX001-0601, the doses were given on consecutive days; in study ZX001-0701 the doses were self-administered in response to migraine attacks outside of a clinical setting and per the approved label instructions for sumatriptan injection; and in study ZX001-0703, 3 doses were given within 25.5 hours (i.e., the first and second doses were given 1.5 hours apart on study Day 1, and the third dose was administered on study Day 2 at 24 hours following the second injection).
- The second difference between the 6 studies is in *administration*, Doses were either administered by *a clinician or self-administered by the subjects*:
    - in studies SUM-04-01, ZX001-0601 and ZX001-0703 the injections were administered by a *clinician*, while
    - in studies ARD-2100-0501, ARD-2100-0504 and ZX001-0701, the injections were *self-administere*d.
- Thirdly, *only one study* ZX001-0701 was conducted in *migraine subject*s, while all other studies were conducted in healthy subjects.
- Fourthly, there were *differences in injection site locations*. The 4 studies included in the original NDA submission studied the arm, abdomen and thigh as injection sites while the additional 2 studies added via the amendment only evaluated the abdomen and thigh injection sites as discussed previously.

## 5.2 Review Strategy

For this review the 6 PK/BE and usability clinical studies were reviewed for safety (see Table 9: Clinical Studies Included in the Intraject Sumatriptan NDA Safety Summary). The review's focus is on the pivotal PK/BE study, ZX001-601 and on the 2 usability studies (ZX001-701 and -703, submitted in the NDA amendment). The literature was relied upon to support safety where appropriate.

The following Reviewers from other disciplines contributed to the review:

- Lois Freed (PT),
- Martha Heimann (Chem),
- Ramana Uppoor (OCP),
- Andrea Powell (PT),
- Jagan Parepally (OCP),
- Daniel Brounstein (OSE),
- Amy Toscano (DDMAC), and
- Brian Pendleton (ORP/DRPI).

## 5.3 Discussion of Individual Studies

Please see the appendix for detailed summaries of the 6 trials conducted for this NDA. Here I briefly summarize the various studies for an overview. They are broken into 2 groups: Usability and PK/BE.

### 5.3.1 Usability

Intraject DDS usability was tested in 3 Studies (only one -0701, was used to support the NDA):

> Study (1): ARDM-02A00-0204 (**Naïve User Study Report**), a study in healthy subjects (N=102) conducted in November 2004 for Zogenix by (b) (4);
>
> Study (2): Study ZX000-0702 (**Pilot Usability Study**) a study conducted primarily in migraineurs (N=20) in July-August 2007 for Zogenix by the (b) (4)
>
> Study (3) ZX001-0701 (**Usability Study**), a clinical non-efficacy assessment study of the use of Intraject sumatriptan by migraine subjects during acute migraine attacks conducted in September-October 2007.

Subjects in the first two usability studies (ARDM-02A00-0204 and ZX000-0702) used Intraject DDS filled with normal saline to simulate injection into foam pads without any actual self-administration of formulation.

Subjects in the ZX001-0701 Usability Study used Intraject DDS filled with 6 mg sumatriptan succinate. Injection performance endpoints, i.e.,

- the proportion of subjects able to correctly complete each step to simulate delivering a successful injection, and
- subject ratings and other ratings were obtained and summarized in all three studies.

Usability Study 1's (ARDM-02A00-0204) focus (primarily evaluated in Intraject-naïve subjects), was ease and intuitiveness of use of the final Intraject configuration. Up to three levels of user instructions (User Guide, video, and/or demonstration) were evaluated in relation to a subject's ability to simulate an injection. The final Intraject configuration is comprised of the core device (combined glass-capsule and actuator subassemblies) encased by the setting mechanism. The setting mechanism comprised a snap-off cap (tip), setting lever (also referred to as the priming mechanism), and a plastic housing which formed a handle and encased the actuator subassembly.

Usability Study 2 (the Pilot Usability Study ZX000-0702) recruited primarily (80%) migraineurs with the central goal of refining the patient Instructions for Use (IFU) to facilitate specifically understanding and use of the Intraject DDS from the perspective of a migraine patient who would potentially use Intraject sumatriptan drug product during an acute attack. Note: the study was not intended to be conducted during acute migraine attack. The (b) (4) Study Investigators specialize in the optimization of human-device interfaces. The study's key

outcome: a substantially revised single-page Intraject IFU incorporating improvements to the original instructions used when the study began. Three successive revisions to the original user instructions were made by the (b) (4). Based on an evaluation of self-report and observational data, these revisions maximized the likelihood that the patient correctly enabled, positioned, and actuated the Intraject DDS at an appropriate injection site.

Finally, Usability Study 3 (ZX001-0701), a multi-center, open-label, single-dose, single-arm, outpatient study, evaluated usability of Intraject sumatriptan during an acute migraine attack outside the clinic. It probed reasons for any incorrect use of Intraject sumatriptan as well as the adequacy of written instructions and the occurrence and persistence of any local Intraject injection site reactions following injection. Injections were administered to either the abdomen or thigh, according to subject preference. Subjects were instructed to contact a call center between 2 and 24 hours following the use or attempted use of Intraject sumatriptan and were interviewed. Subjects were asked if they were able to correctly use Intraject sumatriptan during an acute migraine attack based on whether they were able to perform a defined sequence of steps needed to deliver the treatment dose. Subjects were asked by call center staff for information on any local injection site reactions that were present at the time of the call, including bleeding, swelling, erythema, and bruising. They were also asked about the adequacy of the Intraject sumatriptan instructional material. Subjects had one follow-up visit to confirm the collected data, to be interviewed for any adverse events or persistent local site reactions experienced since their last migraine attack, and to return both used and unused Intraject systems for study accountability.

### 5.3.2 PK/BE Studies

There were 3 PK/BE studies used for the NDA, one pivotal (ZX001-601) and two pilot (SUM 04-01 – a pilot PK/BE investigation and ARD-2100-0501 – a pilot self-injection PK study). The sponsor's system of naming and numbering the studies is confusing, For this review, the PK/BE Study 1 refers to Pivotal Study ZX001-601, PK/BE Study 2 refers to Pilot Study 04-01, and the pilot self-injection PK study ARD-2100-0501 is named PK/BE Study 3.

Another study, for the intended use of Intraject sumatriptan (Pilot PK Study ARD-2100-0504) which only evaluated arm injections and were found to be ineffective as discussed above not included in the NDA PK/BE sections.

The summary of the 3 trials' essential information is provided in this table:

**Table 7: Summary of Pivotal and Pilot Pharmacokinetic/Bioequivalence Clinical Studies of Single-Dose Subcutaneous Injection, Intraject Sumatriptan (6 mg/0.5ml) vs. IMITREX STATdose/Imigran Mk II Injector (6mg/0.5ml)**

| Study | Country | Study Population | Injection / Sites | Study Design | Nominal No. Injections Per Injection Site[a] | Total Nominal No. of Injections[a] |
|---|---|---|---|---|---|---|
| **Pivotal PK/BE Study ZX001-0601** | U.S. (IND) | N=54 healthy adult M/F subjects. | Clinician injected to abdomen, arm, and/or thigh. | 4-way crossover, incomplete block. | N=36 | N=108 |
| **Pilot PK Study SUM-04-01** | Australia | N=18 healthy adult M/F subjects. | Clinician injected to abdomen, arm, and/or thigh. | 4-way crossover, incomplete block. | N=12 | N=36 |
| **Pilot Self-injection PK Study ARD-2100-0501** | Australia | N=24 healthy adult M/F subjects. | Self-injected to abdomen, arm, and/or thigh. | 4-way crossover, incomplete block. | N=16 | N=48 |
| **Total N=96 Subjects** | | | **Total nominal no. of Intraject injections[a] N=192** | | | |

[a] The number of nominal injections represent the number of planned injections per product Intraject sumatriptan or IMITREX/Imigran Mk II, per injection site and may have differed from the actual number of injections administered during the study.

It can be seen Study designs were similar across all three studies and each had the same primary objective: evaluate the bioequivalence of sumatriptan (6 mg/0.5 mL) delivered subcutaneously via the Intraject system (test), compared to sumatriptan (6 mg/0.5 mL) delivered subcutaneously as IMITREX STATdose / Imigran Mk II (reference) at each of the three anatomical sites.

Studies were single-center (conducted in Phase 1 units), randomized, open-label, single-dose, and employed an *incomplete-block treatment design* in which each subject received both an Intraject sumatriptan injection and an IMITREX/Imigran Injection to two of the three possible injection sites (i.e., abdomen, arm, and/or thigh).

Each study also recruited healthy adult male and female subjects but differed principally in terms of whether injections were clinician-injected or self-injected, and the sample size. In addition, subjects in Study 4, the Pivotal PK/BE Study ZX001-0601, were approximately 13 to 15 years older than subjects in the two Pilot PK studies. However, it has been previously established that the pharmacokinetics of sumatriptan in healthy male subjects are similar to that in much older subjects, i.e., in the elderly. This is documented in the IMITREX Injection Prescribing Information.

Similarly, although target enrollment for the Study 4 (Pivotal PK/BE Study ZX001-0601) called for a diverse ethnic/racial study population, the systemic clearance and $C_{max}$ of sumatriptan have been established to be similar in Black and Caucasian healthy subjects as also reported in the IMITREX Injection Prescribing Information.

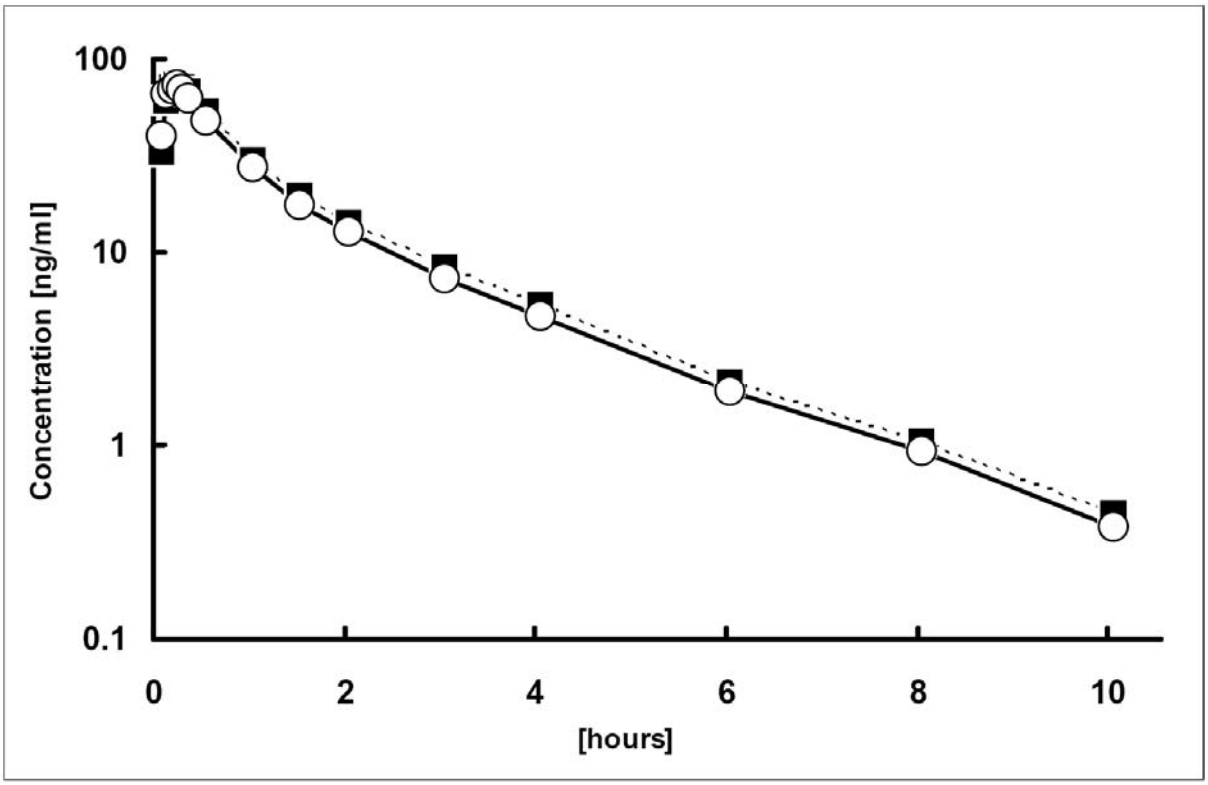
Plasma sumatriptan was assayed over 8 to 10 hours following each injection with an intervening washout period of 24 hours between dosing. Standard single-dose pharmacokinetic parameters

were determined from plasma concentration data. Conventional methods for the determination of bioequivalence were applied and bioequivalence between Intraject sumatriptan (test) and IMITREX/Imigran Injection (reference) was declared if the 90% confidence intervals of the mean ratios of the two systems for the log-transformed $AUC_t$, $AUC_{inf}$, and $C_{max}$ data were within 80–125%.

In addition, a partial AUC parameter was calculated, $AUC_{0\text{-}15}$, to evaluate the control of early drug exposure and absorption into the systemic circulation by truncating AUC at the approximate population median of $T_{max}$ based on data from the Pilot PK studies. This is an important PK marker for medications such as sumatriptan for which a rapid onset of action is intended. Please see the OCP review for evaluation of this calculation and plan.

Pharmacokinetic profiles for all three studies displayed a high degree of similarity between Intraject sumatriptan and IMITREX/Imigran Injection. The concentration-time profile for the Pivotal PK/BE Study ZX001-0601 shown in Figure 3 is representative of the pharmacokinetics following single-dose injected sumatriptan for Intraject versus IMITREX/Imigran Injection. Sumatriptan was absorbed rapidly as evidenced by the early $T_{max}$ and was followed by rapid distribution and slower elimination phases.

**Figure 3: Geometric Mean Concentration-Time Profile for Intraject Sumatriptan (O – O) vs. IMITREXSTAT Dose (■·····■) in Plasma following Single-Dose Injection. Mean of Pooled Abdomen and Thigh Data from Pivotal Study 4 (ZX001-0601). (N=54; N = 35 for Abdomen and N = 32 for Thigh) Per Protocol Analytic Population**




Intraject sumatriptan was found to be bioequivalent to IMITREX/Imigran Injection at the abdomen injection site across all three studies and at the thigh injection site in Study 4, the Pivotal PK/BE Study ZX001-0601 and Study 6, Pilot PK Self-injection Study ARD-2100-0501 but not for Study 5, the Pilot PK Study SUM-04-01 (the lower limit of the 90% confidence interval for the mean ratio of $AUC_t$ for sumatriptan of 79% was slightly less than the lower bioequivalence acceptance criteria of 80%), See (Table 8). Comparing bioequivalence results from Pilot PK Self-injection Study ARD-2100-0501 to the other two studies (ZX001-0601 and SUM- 04-01) suggests that there is no difference when subjects self-inject versus when they receive a clinician-injected dose.

**Table 8: Summary of Bioequivalence Evaluation Results Across Pivotal and Pilot PK/BE Studies. Intraject Sumatriptan vs. IMITREX/Imigran by Injection Site (Abdomen and Thigh Injection Sites)**

| Injection Site | Pivotal PK/BE Study ZX001-0601 (N=54) | Pilot PK Study SUM-04-01 (N=18) | Pilot Self-injection Study 0501 (N=24) |
|---|---|---|---|
| **Abdomen** | Bioequivalence demonstrated | Bioequivalence demonstrated | Bioequivalence demonstrated |
| **Thigh** | Bioequivalent demonstrated | Bioequivalence not demonstrated: [$AUC_t$ 90% CI 79.3 – 94.2%] | Bioequivalence demonstrated |

# 6 Review of Efficacy

## Efficacy Summary

This is a 505 (b) (2) application, based on bioequivalence to a referenced listed drug and no new data was acquired to evaluate efficacy parameters. Therefore this section is not applicable.

# 7 Review of Safety

The safety review is focused only on Intraject sumatriptan drug product with comparison to IMITREX/Imigran Injection.

## Safety Summary

This 505 (b) (2) application's clinical data is limited in scope as it was principally a bioequivalence study with additional support from a usability study indicating that migraineurs could use the product in a migraine attack without difficulty. No new safety signals emerged from this study. There were no deaths, no drop-outs and only one SAE in a patient required medical treatment due to a severe migraine attack that prompted hospitalization. All AEs were transient, resolved without sequelae and no modifications to the dosing were required. The emphasis of the safety review is comparison of local site reactions (erythema, swelling, bleeding, and bruising) as well as injection and puncture site pain reports in this product when compared to the RLD.

An adequate number of subjects were exposed: 194 total (53 migraineurs and 141 healthy volunteers) received a total of 452 doses of the product, Intraject 6 mgs. A subset of these subjects (130 total: 9 migraineurs and 121 normals) also received a total of 226 doses of Imitrex/Imigran (the European marketed Imitrex) 6 mgs. The data are presented below.

No additional information (further studies or analyses) is required. The product appears to have a similar safety profile to the RLD, but the transitory incidence of pain, swelling, bruising, erythema, and bleeding are higher with the needle-free system as compared to the RLD. But the

effects were all transient and resolved without sequellae. No risk management program is required.

## 7.1 Methods

This section reviews the integrated data (design, demographics) and safety data (AEs, laboratory measurements, vital signs, ECG data and local site injection signs) from the 6 studies shown in Table 9 (i.e., the 4 PK/BE studies included in the original NDA for Intraject sumatriptan and 2 additional studies completed for the amendment). Additionally, a comparison of the local site reaction (LSR) data from the self-injected studies (ARD-2100-0501 and ARD-2100-0504) versus the clinician-injected studies (SUM-04-01, ZX001-0601 and ZX001-0703), are reviewed. The 2 additional studies (ZX001-0701 and ZX001-0703) added to this NDA amendment did not include the arm as an injection site for Intraject sumatriptan. The sponsor explains the bioequivalence between Intraject sumatriptan and IMITREX STATdose was not established in the pivotal PK/BE study ZX001-0601. As a result, the arm was excluded as a recommended injection site in the draft labeling text.

### 7.1.1 Clinical Studies Used to Evaluate Safety

The safety of sumatriptan delivered by the Intraject DDS has been evaluated in 4 active-controlled and 2 single-arm clinical studies (see Table 9, below). 195 subjects were enrolled into these studies with 194 of those subjects (including 53 migraine subjects and 141 healthy volunteers) receiving a total of 452 injections to one or more of 3 anatomical sites: the abdomen, the thigh, or the arm. One subject enrolled (Subject 204 in Study ZX001-0701) did not use or attempt to use Intraject sumatriptan during that study.

**Table 9: Clinical Studies Included in the Intraject Sumatriptan NDA Safety Summary**

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Subjects | Duration of Subject Participation | Total Intraject Injections |
|---|---|---|---|---|---|---|---|---|
| Pilot PK (Active controlled study) | SUM-04-01 | Pilot study to evaluate the pharmacokinetics and bioequivalence of Intraject sumatriptan vs. marketed reference product at 3 injection sites | Single-dose, open-label, 4-way crossover PK study using a balanced incomplete block design | Intraject needle-free injector using sumatriptan vs. marketed reference product, Imigran Mk II®; 2 Intraject and 2 Imigran clinician administered; subcutaneous | 18 planned, 18 enrolled, 18 completed | Generally healthy male and female adult subjects | 4 days, total | 36 |
| PK (Active controlled study) | ARD-2100-0501 | To establish the bioequivalence of subjects who self-administer Intraject sumatriptan in comparison to self-administered marketed reference product at each of three injection sites | Single center, randomized, single-dose, open-label, four-way crossover study at 2 of 3 injection sites (abdomen, arm, thigh) | Intraject needle-free injector using sumatriptan vs. marketed reference product, Imigran Mk II; 2 Intraject and 2 Imigran self-injections; subcutaneous | 24 planned, 24 enrolled, 24 completed | Healthy adult subjects | 6 days, total | 48 |
| PK (Active controlled study) | ARD-2100-0504 | To establish the bioequivalence of subjects who self-administer Intraject sumatriptan in comparison to self-administered marketed reference product at each of three injection sites | Single center, randomized, single-dose, open-label, three-way crossover study | Intraject needle-free injector using sumatriptan vs. marketed reference product Imigran Mk II; 2 Intraject and 1 Imigran; self-injections; subcutaneous | 24 planned, 24 enrolled, 24 completed | Healthy adult subjects | 5 days, total | 48 |
| PK/BE (Pivotal Active controlled study) | ZX001-0601 | To evaluate the pharmacokinetics and bioequivalence of Intraject sumatriptan vs. IMITREX Injection at three injection sites in healthy adult subjects | Single center, randomized, single-dose, open-label, four-way crossover study at 2 of 3 injection sites (abdomen, arm, thigh) | Intraject needle-free injector using sumatriptan vs. marketed reference product, IMITREX; 2 Intraject and 2 IMITREX; clinician administered; subcutaneous | 54 planned, 57 enrolled, 54 completed | Healthy adult subjects | 6 days, total | 111 |

| Type of Study | Study Identifier | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage Regimen; Route of Administration | Number of Subjects | Healthy Subjects or Diagnosis of Subjects | Duration of Subject Participation | Total Intraject Injections |
|---|---|---|---|---|---|---|---|---|
| Usability Study | ZX001-0701 | Primary: To evaluate the usability of sumatriptan delivered subcutaneously via the Intraject system in adult subjects during acute migraine attack.<br>Secondary: 1) to evaluate the reasons for incorrect use of the Intraject system during acute migraine attack; 2) to evaluate the adequacy of instructional materials on the use of the Intraject system; 3) to evaluate the frequency of occurrence and persistence of local injection site reactions (swelling, erythema, bruising, bleeding). | Multi-center, open-label, single-dose, single-arm study of the usability of Intraject sumatriptan (6 mg/0.5 mL) in 50 adult subjects during acute migraine attack. | Intraject needle-free injector using sumatriptan | 50 planned, 54 enrolled, 52 completed | Migraine subjects | Until the treatment of 3 migraines or until a maximum of 30 days, whichever was shortest | 155 |
| Safety Study | ZX001-0703 | To evaluate the extent, persistence, and any cumulative effects on skin tissue by assessing local injection site reactions (bleeding, swelling, erythema, bruising) following repeated administrations of Intraject sumatriptan to the same anatomic site | Single-center, open-label, repeat-dose, single-arm, in-clinic study in 18 healthy adult subjects. | Intraject® needle-free injector using sumatriptan | 18 planned, 18 enrolled, 18 completed | Healthy adult subjects | 5 days, total | 54 |

### 7.1.2 Adequacy of Data

After entry into the electronic database, each AE was coded from the verbatim text to a preferred term using a thesaurus based on the Medical Dictionary for Regulatory Activities (MedDRA) v 10.0. Appropriate Safety Coding appears to be used and selected comparisons of verbatim terms to preferred terms were conducted as part of this review. Note the few numbers of drop-outs or treatment changes in these studies.

### 7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

The pooled clinical safety database is comprised of the 193 subjects that received at least one dose of Intraject sumatriptan and for which there are reported dose/safety information (i.e., the per-protocol safety population) It does not include Subject 103 from Study ZX001-0701 since they did not report, per protocol, into the call center about the use or attempted use of the drug product. The sponsor notes, however, the subject, during the interview at the end of study visit, returned 3 used Intraject sumatriptan systems and also reported the absence of adverse events.

The pooling allowed more precise analysis for the small number of subjects in the trials.

## 7.2 Adequacy of Safety Assessments

I believe the drug exposure and the safety evaluations performed as part of the development program are adequate and appear to include “all tests reasonably applicable” to assess the safety of sumatriptan delivered by the Intraject device for this 505(b) (2) bioequivalence application. The sponsor had reached agreements with the Division for all safety evaluations and conducted

thorough studies to evaluate the safety parameters within the scope of these agreements. The assessments appear complete and are of good quality.

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

An adequate number of patients were exposed to Sumavel for a bioequivalence NDA submission. The studies were single dose and appropriately designed to establish bioequivalence. *A total of 194 subjects (53 migraine subjects and 141 healthy volunteers) received a total of 452 doses of Intraject sumatriptan 6 mg.* A subset of these subjects (n = 130; 9 migraine subjects and 121 healthy volunteers) also received a total of 226 doses of IMITREX/Imigran Injection, 6 mg.

The pooled study database demographics are shown in this table:

**Table 10: Demographic Data from the Pooled Study Database (SUM-04-01, ARD-2100-0501, ARD-2100-0504, ZX001-0601, ZX001-0701, and ZX001-0703)**

| | | SUM-04-01 (N=18) | ARD-2100-0501 (N=24) | ARD-2100-0504 (N=24) | ZX001-0601 (N=57) | ZX001-0701 (N=54) | ZX001-0703 (N=18) | Overall (N=195) |
|---|---|---|---|---|---|---|---|---|
| Race | White | 12 (66.7%) | 22 (91.7%) | 21 (87.5%) | 38 (66.7%) | 51 (96.2%) | 11 (61.1%) | 155 (79.9%) |
| | Black | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 19 (33.3%) | 2 ( 3.8%) | 6 (33.3%) | 27 (13.9%) |
| | Asian | 3 (16.7%) | 2 ( 8.3%) | 1 ( 4.2%) | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 5.6%) | 7 ( 3.6%) |
| | Indian | 3 (16.7%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 3 ( 1.5%) |
| | Other | 0 ( 0.0%) | 0 ( 0.0%) | 2 ( 8.3%) | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 2 ( 1.0%) |
| Sex | Female | 5 (27.8%) | 13 (54.2%) | 12 (50.0%) | 36 (63.2%) | 45 (84.9%) | 13 (72.2%) | 124 (63.9%) |
| | Male | 13 (72.2%) | 11 (45.8%) | 12 (50.0%) | 21 (36.8%) | 8 (15.1%) | 5 (27.8%) | 70 (36.1%) |

N is the number of subjects enrolled in the study.
In study ZX001-0701 two subjects did not report treatment use. One of the subjects did not use the product. The other subject was found to have used the product but did not provide safety information.
Program: \Skt001\k\I S I\Analysis\Zogenix\SAS Programs\Tables\Table 1.sas Source: dmres1.sas7bdat

The summary demographic data table from all the studies combined is shown in Table 11 below:

**Table 11: Demographic Data: Pooled Data (n=194) a From all Intraject Sumatriptan Studies (SUM-04-01, ARD-2100-0501, ARD 2100-0504, ZX001-701, and ZX001-0703)**

| Variable | | All Studies |
|---|---|---|
| Age (yr) | Mean | 32 |
| | SD | 12 |
| | Minimum | 18 |
| | Maximum | 65 |
| Height (cm) | Mean | 170 |
| | SD | 9.1 |
| | Minimum | 150 |
| | Maximum | 197 |
| Weight (kg) | Mean | 74.5 |
| | SD | 14.3 |
| | Minimum | 44.9 |
| | Maximum | 127.0 |
| Sex (n[%]) | Female | 124 (64 %) |
| | Male | 70 (36 %) |
| Race (n[%])[b] | Asian | 7 (3.6 %) |
| | Black | 27 (14 %) |
| | Indian | 3 (1.5 %) |
| | Other | 2 (1.0 %) |
| | White | 155 (80 %) |

[a] These data include Subject 103 from Study ZX001-0701 who used 3 Intraject sumatriptan, but did not call into the call center. These data do not include Subject 204 from Study ZX001-0701 who was enrolled but did not use or attempt to use any Intraject sumatriptan during the study.

[b] In study ZX001-0601, "Hispanic" subjects self-reported their race as "Other" during the screening process; however, due to the FDA guidance on race and ethnicity reporting, their race was recorded in the database as either black or white, with ethnicity recorded as "Hispanic" verses "non-Hispanic".

As often seen in migraine studies, most patients were white and female. The *average age* of the 194 subjects was 32 years (range, 18-65 years) with an *average height* of 170 cm (range,150-197 cm). The *average weight* of the subjects was 74.5 kg (range, 44.9-127.0 kg).

In the overall study population, 64% of the subjects were female and 36% were male. In terms of race, 80% of the subjects were Caucasian/white, 14% were black or African-American and 6% were considered as 'other.'

The total extent of exposure per subject to Intraject sumatriptan during the 6 studies is provided in Table 12. The median total exposure to Intraject sumatriptan in the 6 clinical trials was 2 doses (i.e., a total of 12 mg sumatriptan).

**Table 12: Maximum Exposure to Intraject Sumatriptan Received by Subjects in Each Study (6 mg/injection)**

| Study | Injection Dose | | | | | Total |
|---|---|---|---|---|---|---|
| | 6 mg | 12 mg | 18 mg | 24 mg | 30 mg | |
| SUM-04-01 | 0 | 18 | 0 | 0 | 0 | 18 |
| ARD-2100-0501[a] | 0 | 24 | 0 | 0 | 0 | 24 |
| ARD-2100-0504[a] | 0 | 24 | 0 | 0 | 0 | 24 |
| ZX001-0601 | 3 | 54 | 0 | 0 | 0 | 57 |
| ZX001-0701[a,b] | 6 | 10 | 21 | 14 | 2 | 53 |
| ZX001-0703 | 0 | 0 | 18 | 0 | 0 | 18 |
| **Total** | **9** | **130** | **39** | **14** | **2** | **194** |

N= Number of Subjects
[a] Self-injection study
[b] Migraine subject study

The total extent of exposure per subject to sumatriptan from Intraject sumatriptan and IMITREX/Imigran Injection during the 6 studies is provided in Table 13. The median total exposure to sumatriptan in the 6 clinical trials was 4 doses (i.e., a total of 24 mg sumatriptan).

**Table 13: Maximum Doses of Sumatriptan (Intraject sumatriptan plus IMITREX/Imigran Injection Received by Subjects in each Study (6mg/Injection)**

| Study | Injection Dose | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | 6 mg | 12 mg | 18 mg | 24 mg | 30 mg | 36 mg | |
| SUM-04-01[c] | 0 | 0 | 0 | 18 | 0 | 0 | 18 |
| ARD-2100-0501[a, c] | 0 | 0 | 0 | 24 | 0 | 0 | 24 |
| ARD-2100-0504[a, c] | 0 | 0 | 24 | 0 | 0 | 0 | 24 |
| ZX001-0601[c, d] | 2 | 1 | 0 | 54 | 0 | 0 | 57 |
| ZX001-0701[a, b, d] | 4 | 9 | 23 | 13 | 3 | 1 | 53 |
| ZX001-0703 | 0 | 0 | 18 | 0 | 0 | 0 | 18 |
| **Total** | **6** | **10** | **65** | **109** | **3** | **1** | **194** |

N= Number of Subjects
[a] Self-injection study
[b] Migraine subject study
[c] Study used Imigran Mk II
[d] Study used IMITREX STATdose

Local injection site signs of bleeding, swelling, erythema and bruising were assessed in each of the treatment periods at 15 minutes before dosing, immediately after dosing, at 5, 15 and 30 minutes and at 1, 2, 3, 4, 8, and 24 to 32 hours after dosing in the three Pilot PK studies.

In Pilot PK Study SUM-04-01, assessments were also made at 10 minutes after injection and at 5, 6 and 7 hours after injection. Injection site pain was also assessed after dosing in the three Pilot PK studies.

The Pivotal PK Study ZX001-0601 assessed local injections sites signs in each of the treatment periods at 15 minutes before dosing, immediately after dosing, and at 1, 8, and 24 to 32 hours after dosing.

The Safety Study ZX001-0703 assessed local injection site signs for each of the three injections at 15 minutes before dosing, immediately after dosing, and at 1, 4, 8 and 24 hours after dosing. Additional assessments at 48 and 72 hours were also performed, if indicated.

In each of the studies above (i.e., excludes ZX001-0701), a medical technician or physician investigator assessed the local site signs of erythema, swelling and bruising and measured in millimeters across the longest dimension of the reaction. Bleeding was recorded as either present or absent (Yes/No).

The Usability Study ZX001-0701 had subjects self-report the presence (Yes/No) of local injection site signs at two time points (between 2-24 after dosing and between 24-32 hours after dosing) by calling a central call center and answering a questionnaire.

### 7.2.2 Explorations for Dose Response

This is a 505 (b) (2) application, based on bioequivalence to a referenced listed drug and no new data exploring a dose response was acquired.

### 7.2.3 Special Animal and/or In Vitro Testing

Not applicable to this 505 (b) (2) application.

### 7.2.4 Routine Clinical Testing

Routine clinical testing and the assessment frequency of study subjects, including efforts to elicit adverse event data and monitor laboratory parameters, vital signs, and ECGs was adequate and appropriate for this 505 (b) (2) application .

### 7.2.5 Metabolic, Clearance, and Interaction Workup

This is a 505 (b) (2) application, based on bioequivalence to a referenced listed drug, sumatriptan, no new biopharmaceutical investigations were conducted, beyond those to establish bioequivalence. Please see the OCP review for details.

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

This is a 505 (b) (2) application, based on bioequivalence to a referenced listed drug, sumatriptan. No new specific explorations for potential adverse events for the triptan class were conducted.

## 7.3 Major Safety Results

In the 6 clinical studies involving Intraject sumatriptan and among the 194 subjects who received 452 subcutaneous injections of 6 mg sumatriptan administered in the arm, thigh, and/or abdomen by the Intraject DDS, the AEs do not appear concerning. The clinical safety database includes data from 193 safety population subjects (i.e., does not include subjects 103 and 204 from ZX001-0701).

There were 366 reported treatment-related adverse events after Intraject sumatriptan reported by 105 subjects, and 251 treatment-related AEs reported by 85 subjects after administration of IMITREX/Imigran Injection. Most AEs were considered to be study treatment-related, which appears consistent with the established AE profile of subcutaneously administered sumatriptan.

Most AEs in both treatment groups across all studies were evaluated as mild or moderate in intensity and recovered without sequelae and without modification of study dosing. No major differences were apparent in the observed types of AEs between Intraject sumatriptan and IMITREX/Imigran Injection.

The sponsor prepared the following summary table from the ISS according to severity, relatedness, seriousness, and outcome. The degrees of severity and relatedness appear similar for Intraject sumatriptan and IMITREX/Imigran Injection. No major differences were observed in the frequency of AEs between the two sumatriptan delivery systems.

The average number of reported AEs per subject was 2.1 (409/193) in the Intraject sumatriptan group compared to 2.3 (281/121) in the IMITREX/Imigran Injection group. The percentage of subjects reporting AEs was 58% (112/193) in the Intraject sumatriptan group compared to 76% (92/121) in the IMITREX/Imigran Injection group.

**Table 14: Number of Adverse Events (Number of Distinct Subjects) by Sumatriptan Delivery System in all 6 Studies (Sum-04-01, ARD-2100-0501, ARD-2100-0504, ZX001-0701, and ZX001-0703)**

| Population Description | Number of AEs (Number of Distinct Subjects) | | |
|---|---|---|---|
| | Intraject sumatriptan (n=193) [a] | IMITREX/Imigran Injection (n=121) | Overall (n=193) |
| **Any Event** | 409 (112) | 281 (92) | 690 (124) |
| **Severity** | | | |
| Mild | 336 (108) | 235 (87) | 571 (121) |
| Moderate | 67 (34) | 46 (28) | 113 (42) |
| Severe | 6 (3) | 0 (0) | 6 (3) |
| **Relatedness** | | | |
| Related [b] | 366 (105) | 251 (85) | 617 (115) |
| Not Related [c] | 43 (35) | 30 (22) | 73 (48) |
| **Discontinuation due to AEs** | 0 (0) | 0 (0) | 0 (0) |
| **Serious Adverse Events** | 1 (1) | 0 (0) | 1 (1) |
| **Deaths** | 0 (0) | 0 (0) | 0 (0) |

[a] This table includes data from subjects in the pooled safety database 2.7.4.1.1.1 (i.e., excludes subjects 103 and 204 from Study ZX001-0701)

[b] Possibly, probably or definitely related adverse events

[c] Unlikely or not related adverse events

All Adverse Events resolved without sequelae and without modification to study dosing. Most of the AEs were mild or moderate in severity, not requiring additional treatment.

### 7.3.1 Deaths

None in any of the 6 studies.

### 7.3.2 Nonfatal Serious Adverse Events

Only one serious AE was reported in the 6 clinical studies, for a hospitalization for migraine and reported in Study ZX001-0701. It was assessed as not related to Intraject sumatriptan and resolved after 24 hours. I reviewed the narrative for that case and concur.

### 7.3.3 Dropouts and/or Discontinuations

None.

### 7.3.4 Significant Adverse Events

There were 6 severe Adverse Events reported: 4 of these were injection site pain reported by the same subject (Subject 202 in Study ZX001-0701) after each of 4 self-administered Intraject sumatriptan injections. Another severe AE was catheter site pain reported by Subject 001 in Study ARD-2100-0504 that was considered not related to study medication. The last severe AE was also a Serious Adverse Event because the AE (migraine) required hospitalization. This occurred on Study ZX001-0701 and was assessed as not related to Intraject sumatriptan and resolved 24 hours after hospitalization.

### 7.3.5 Submission Specific Primary Safety Concerns

None.

## 7.4 Supportive Safety Results

In addition to the local site physical reactions reviewed in Section 7.4.5 (signs), this review analyzes injection site pain (symptoms) as reported in the pooled safety data of the Sumavel clinical trials and the post-marketing reports for Imitrex injection. Injection site pain is reported as an adverse event presented in Section 7.4.1, whereas the sponsor considered the local signs of erythema, swelling, bleeding, and bruising to be expected in delivering the sumatriptan by Imitrex or the needle-free system they wish to market.

### 7.4.1 Common Adverse Events

#### 7.4.1.1 Adverse Event Overview

There were no significant adverse events in the trials. As can be seen the principal AEs are relatively benign in both event and intensity. Injection site pain is analyzed separately in Section 7.4.1.2 and compared to post-marketing reports to the FDA.

The overall trial comparative incidence of related adverse events in the pooled study database is presented in the following table:

**Table 15: Incidence of Related Adverse Events in the Pooled Study Database (SUM-04-01, ARD-2100-0501, ARD-2100-0504, ZX001-0601, ZX001-0701, and ZX001-0703, By Treatment**

| System Organ Class<br>Preferred Term | Intraject<br>(N=193)<br>n (%) | IMITREX<br>(N=121)<br>n (%) |
|---|---|---|
| NERVOUS SYSTEM DISORDERS | 84 ( 43.5) | 66 ( 54.5) |
| PARAESTHESIA | 35 ( 18.1) | 23 ( 19.0) |
| HEADACHE | 32 ( 16.6) | 22 ( 18.2) |
| DIZZINESS | 22 ( 11.4) | 13 ( 10.7) |
| TENSION HEADACHE | 17 ( 8.8) | 17 ( 14.0) |
| BURNING SENSATION | 6 ( 3.1) | 4 ( 3.3) |
| HEAD DISCOMFORT | 6 ( 3.1) | 3 ( 2.5) |
| HYPOAESTHESIA | 3 ( 1.6) | 4 ( 3.3) |
| SENSORY DISTURBANCE | 2 ( 1.0) | 2 ( 1.7) |
| LETHARGY | 2 ( 1.0) | 0 ( 0.0) |
| SOMNOLENCE | 2 ( 1.0) | 0 ( 0.0) |
| DYSGEUSIA | 1 ( 0.5) | 0 ( 0.0) |

Related = possibly, probably or definitely related to study medication
N is the number of treated subjects.
n (%) is the number (percentage) of subjects experiencing each adverse event.
All studies were coded with MedDRA version 10.0 except ZX001-0703, which was coded with MedDRA version 10.1.
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| System Organ Class<br>Preferred Term | Intraject<br>(N=193)<br>n (%) | IMITREX<br>(N=121)<br>n (%) |
|---|---|---|
| GASTROINTESTINAL DISORDERS | 27 ( 14.0) | 21 ( 17.4) |
| NAUSEA | 26 ( 13.5) | 20 ( 16.5) |
| HYPOAESTHESIA ORAL | 3 ( 1.6) | 1 ( 0.8) |
| VOMITING | 3 ( 1.6) | 1 ( 0.8) |
| DIARRHOEA | 1 ( 0.5) | 0 ( 0.0) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 25 ( 13.0) | 25 ( 20.7) |
| MUSCLE TIGHTNESS | 17 ( 8.8) | 21 ( 17.4) |
| NECK PAIN | 4 ( 2.1) | 0 ( 0.0) |
| MUSCULOSKELETAL STIFFNESS | 3 ( 1.6) | 2 ( 1.7) |
| PAIN IN EXTREMITY | 3 ( 1.6) | 1 ( 0.8) |
| MUSCULOSKELETAL DISCOMFORT | 1 ( 0.5) | 2 ( 1.7) |
| JOINT STIFFNESS | 1 ( 0.5) | 0 ( 0.0) |

Related = possibly, probably or definitely related to study medication
N is the number of treated subjects.
n (%) is the number (percentage) of subjects experiencing each adverse event.
All studies were coded with MedDRA version 10.0 except ZX001-0703, which was coded with MedDRA version 10.1.
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| System Organ Class<br>Preferred Term | Intraject<br>(N=193)<br>n (%) | IMITREX<br>(N=121)<br>n (%) |
|---|---|---|
| MUSCLE SPASMS | 1 ( 0.5) | 0 ( 0.0) |
| SENSATION OF HEAVINESS | 1 ( 0.5) | 0 ( 0.0) |
| ARTHRALGIA | 0 ( 0.0) | 1 ( 0.8) |
| BACK PAIN | 0 ( 0.0) | 1 ( 0.8) |
| MUSCULOSKELETAL PAIN | 0 ( 0.0) | 1 ( 0.8) |
| PAIN IN JAW | 0 ( 0.0) | 1 ( 0.8) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 24 ( 12.4) | 19 ( 15.7) |
| THROAT TIGHTNESS | 16 ( 8.3) | 12 ( 9.9) |
| NASAL DISCOMFORT | 3 ( 1.6) | 3 ( 2.5) |
| PHARYNGOLARYNGEAL PAIN | 3 ( 1.6) | 3 ( 2.5) |
| THROAT IRRITATION | 2 ( 1.0) | 2 ( 1.7) |
| DYSPNOEA | 1 ( 0.5) | 2 ( 1.7) |

Related = possibly, probably or definitely related to study medication
N is the number of treated subjects.
n (%) is the number (percentage) of subjects experiencing each adverse event.
All studies were coded with MedDRA version 10.0 except ZX001-0703, which was coded with MedDRA version 10.1.
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| System Organ Class<br>Preferred Term | Intraject<br>(N=193)<br>n (%) | IMITREX<br>(N=121)<br>n (%) |
|---|---|---|
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 21 ( 10.9) | 12 ( 9.9) |
| CHEST DISCOMFORT | 6 ( 3.1) | 6 ( 5.0) |
| INJECTION SITE PAIN | 5 ( 2.6) | 1 ( 0.8) |
| FEELING HOT | 3 ( 1.6) | 1 ( 0.8) |
| FATIGUE | 2 ( 1.0) | 0 ( 0.0) |
| INJECTION SITE EXTRAVASATION | 2 ( 1.0) | 0 ( 0.0) |
| NON-CARDIAC CHEST PAIN | 1 ( 0.5) | 4 ( 3.3) |
| INJECTION SITE PRURITUS | 1 ( 0.5) | 1 ( 0.8) |
| MALAISE | 1 ( 0.5) | 1 ( 0.8) |
| INJECTION SITE HAEMORRHAGE | 1 ( 0.5) | 0 ( 0.0) |
| INJECTION SITE SWELLING | 1 ( 0.5) | 0 ( 0.0) |
| PERIPHERAL COLDNESS | 1 ( 0.5) | 0 ( 0.0) |
| TEMPERATURE INTOLERANCE | 1 ( 0.5) | 0 ( 0.0) |

Related = possibly, probably or definitely related to study medication
N is the number of treated subjects.
n (%) is the number (percentage) of subjects experiencing each adverse event.
All studies were coded with MedDRA version 10.0 except ZX001-0703, which was coded with MedDRA version 10.1.
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| System Organ Class<br>Preferred Term | Intraject<br>(N=193)<br>n (%) | IMITREX<br>(N=121)<br>n (%) |
|---|---|---|
| VASCULAR DISORDERS | 10 ( 5.2) | 16 ( 13.2) |
| FLUSHING | 10 ( 5.2) | 16 ( 13.2) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 7 ( 3.6) | 5 ( 4.1) |
| SKIN TIGHTNESS | 3 ( 1.6) | 2 ( 1.7) |
| HYPERHIDROSIS | 2 ( 1.0) | 0 ( 0.0) |
| HYPOAESTHESIA FACIAL | 1 ( 0.5) | 1 ( 0.8) |
| PRURITUS | 1 ( 0.5) | 1 ( 0.8) |
| RASH MACULAR | 1 ( 0.5) | 0 ( 0.0) |
| COLD SWEAT | 0 ( 0.0) | 1 ( 0.8) |
| EAR AND LABYRINTH DISORDERS | 3 ( 1.6) | 2 ( 1.7) |
| VERTIGO | 3 ( 1.6) | 2 ( 1.7) |

Related = possibly, probably or definitely related to study medication
N is the number of treated subjects.
n (%) is the number (percentage) of subjects experiencing each adverse event.
All studies were coded with MedDRA version 10.0 except ZX001-0703, which was coded with MedDRA version 10.1.
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| System Organ Class<br>Preferred Term | Intraject<br>(N=193)<br>n (%) | IMITREX<br>(N=121)<br>n (%) |
|---|---|---|
| EYE DISORDERS | 2 ( 1.0) | 2 ( 1.7) |
| EYE PAIN | 1 ( 0.5) | 1 ( 0.8) |
| VISION BLURRED | 1 ( 0.5) | 0 ( 0.0) |
| VISUAL DISTURBANCE | 0 ( 0.0) | 1 ( 0.8) |
| CARDIAC DISORDERS | 2 ( 1.0) | 1 ( 0.8) |
| SINUS ARRHYTHMIA | 1 ( 0.5) | 0 ( 0.0) |
| VENTRICULAR EXTRASYSTOLES | 1 ( 0.5) | 0 ( 0.0) |
| PALPITATIONS | 0 ( 0.0) | 1 ( 0.8) |
| METABOLISM AND NUTRITION DISORDERS | 1 ( 0.5) | 0 ( 0.0) |
| HYPONATRAEMIA | 1 ( 0.5) | 0 ( 0.0) |
| PSYCHIATRIC DISORDERS | 1 ( 0.5) | 0 ( 0.0) |
| ANXIETY | 1 ( 0.5) | 0 ( 0.0) |

Related = possibly, probably or definitely related to study medication
N is the number of treated subjects.
n (%) is the number (percentage) of subjects experiencing each adverse event.
All studies were coded with MedDRA version 10.0 except ZX001-0703, which was coded with MedDRA version 10.1.
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#### 7.4.1.2 Injection site pain analysis

In the Safety Amendment to the NDA, the sponsor provided a table with the 20 most common sumatriptan injection adverse events in the FDA's SRS (965 reports) and AERS (528 reports) Post-marketing Databases reported from 1969 to 2007 as shown below. Pain and injection site reactions are the two most common AEs in the database. The following table summarizes the data:

**Table 16: A Summary of Injection Site Reaction Adverse Events by Database Reported in Association with Sumatriptan as the Suspect Drug During FDA's Post-Marketing Experience (1969 – 2007)**

| Injection Site Reaction Term; SRS Database (COSTART Data) 1969 to 31 October 1997 | Count | Injection Site Reaction Term AERS Database (MedDRA Data) November 1997 to March 2007 | Count |
|---|---|---|---|
| Injection site pain | 308 | Injection site pain | 150 |
| | | Injection site burning | 29 |
| | | Injection site discomfort | 3 |
| | | Injection site irritation | 32 |
| | | Injection site stinging | 10 |
| Injection site reaction | 259 | Injection site reaction | 12 |
| | | Injection site reaction NOS | 21 |
| Injection site hypersensitivity | 134 | -- | |

| Injection Site Reaction Term; SRS Database (COSTART Data) 1969 to 31 October 1997 | Count | Injection Site Reaction Term AERS Database (MedDRA Data) November 1997 to March 2007 | Count |
|---|---|---|---|
| | | Injection site erythema | 32 |
| | | Injection site pruritus | 8 |
| | | Injection site rash | 4 |
| | | Injection site urticaria | 24 |
| | | Injection site vesicles | 2 |
| Injection site hemorrhage | 103 | Injection site hemorrhage | 83 |
| | | Injection site bruising | 50 |
| Injection site edema | 80 | Injection site edema | 11 |
| | | Injection site swelling | 15 |
| Injection site mass | 39 | Injection site mass | 12 |
| Injection site inflammation | 26 | Injection site inflammation | 3 |
| Injection site abscess | 7 | -- | -- |
| Injection site atrophy | 5 | Injection site atrophy | 2 |
| Injection site necrosis | 4 | Injection site necrosis | 3 |
| Injection site anesthesia | 2 | Injection site paresthesia | 1 |
| | | Injection site cyst | 1 |
| | | Injection site dermatitis | 4 |
| | | Injection site discoloration | 1 |
| | | Injection site extravasation | 1 |
| | | Injection site granuloma | 1 |
| | | Injection site hypertrophy | 3 |
| | | Injection site induration | 6 |
| | | Injection site warmth | 2 |

For the sponsor's Trial pooled safety database, pain is reported for the pivotal PK/BE Study (ZX001-0601), and the Active –Controlled Trials (ZX001-0601, SUM-04-01, ARD – 21 – 0504), by treatment group. This is displayed below:

**Table 17: Summary of Number (%) of Adverse Events in the Pivotal PK/BE Study (ZX001-0601) and in the Pooled Active-Controlled Trial Database (ZX-001-0601, SUM – 04 – 01, ARD – 2100 – 0504) by Treatment Group.**

| MedDRA System Organ Class<br>MedDRA preferred Term | Study ZX001-0601<br>Intraject sumatriptan (N=57)<br>Subjects with related AEs | Study ZX001-0601<br>IMITREX (N=55)<br>Subjects with related AEs | All Studies<br>Intraject sumatriptan (N=123)<br>Subjects with related AEs | All Studies<br>IMITREX (N=121)<br>Subjects with related AEs |
|---|---|---|---|---|
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 7 (12.3%) | 9 (16.4%) | 20 (16.3%) | 24 (19.8%) |
| ASTHENIA | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.8%) |
| CATHETER RELATED COMPLICATION | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.8%) | 0 ( 0.0%) |
| CATHETER SITE HAEMATOMA | 0 ( 0.0%) | 1 ( 1.8%) | 0 ( 0.0%) | 2 ( 1.7%) |
| CATHETER SITE HAEMORRHAGE | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.8%) | 3 ( 2.5%) |
| CATHETER SITE PAIN | 0 ( 0.0%) | 0 ( 0.0%) | 2 ( 1.6%) | 2 ( 1.7%) |
| CHEST DISCOMFORT | 2 ( 3.5%) | 3 ( 5.5%) | 5 ( 4.1%) | 7 ( 5.8%) |
| FATIGUE | 1 ( 1.8%) | 0 ( 0.0%) | 3 ( 2.4%) | 1 ( 0.8%) |
| FEELING HOT | 0 ( 0.0%) | 0 ( 0.0%) | 3 ( 2.4%) | 1 ( 0.8%) |
| INJECTION SITE PAIN | 2 ( 3.5%) | 0 ( 0.0%) | 5 ( 4.1%) | 1 ( 0.8%) |
| INJECTION SITE PRURITUS | 1 ( 1.8%) | 0 ( 0.0%) | 1 ( 0.8%) | 1 ( 0.8%) |
| MALAISE | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.8%) | 1 ( 0.8%) |
| NON-CARDIAC CHEST PAIN | 1 ( 1.8%) | 4 ( 7.3%) | 1 ( 0.8%) | 4 ( 3.3%) |
| PAIN | 0 ( 0.0%) | 1 ( 1.8%) | 0 ( 0.0%) | 1 ( 0.8%) |
| PERIPHERAL COLDNESS | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.8%) | 0 ( 0.0%) |
| VESSEL PUNCTURE SITE PAIN | 2 ( 3.5%) | 4 ( 7.3%) | 2 ( 1.6%) | 5 ( 4.1%) |
| INFECTIONS AND INFESTATIONS | 0 ( 0.0%) | 1 ( 1.8%) | 0 ( 0.0%) | 4 ( 3.3%) |
| UPPER RESPIRATORY TRACT INFECTION | 0 ( 0.0%) | 1 ( 1.8%) | 0 ( 0.0%) | 4 ( 3.3%) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.8%) |
| CONTUSION | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.8%) |

It can be seen that the number of complaints of injection site pain and "vessel puncture site pain" is significantly higher in the Sumavel recipients than in the Imitrex recipients. "Vessel puncture site pain" refers to pain at the site of venipuncture or vein cannulation for the studies.

The sponsor then presented the following table describing the incidence of related adverse events in their Pivotal Study ZX – 001 – 0601, as well as from the pooled active-controlled trials listed above. This shows again the incidence of site pain for Sumavel recipients is twice that for Imitrex recipients. Both of these analyses are somewhat compromised by the small numbers involved.

**Table 18: Incidence of Related Adverse Events in the Pivotal PK/BE Study and Active-Controlled Trial Database**

| MedDRA System Organ Class<br>MedDRA preferred Term | Study ZX001-0601<br>Intraject sumatriptan (N=57)<br>Subjects with related AEs | Study ZX001-0601<br>IMITREX (N=55)<br>Subjects with related AEs | All Studies<br>Intraject sumatriptan (N=123)<br>Subjects with related AEs | All Studies<br>IMITREX (N=121)<br>Subjects with related AEs |
|---|---|---|---|---|
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 5 ( 8.8%) | 5 ( 9.1%) | 14 (11.4%) | 12 ( 9.9%) |
| CHEST DISCOMFORT | 2 ( 3.5%) | 3 ( 5.5%) | 5 ( 4.1%) | 6 ( 5.0%) |
| FATIGUE | 1 ( 1.8%) | 0 ( 0.0%) | 2 ( 1.6%) | 0 ( 0.0%) |
| FEELING HOT | 0 ( 0.0%) | 0 ( 0.0%) | 3 ( 2.4%) | 1 ( 0.8%) |
| INJECTION SITE PAIN | 0 ( 0.0%) | 0 ( 0.0%) | 2 ( 1.6%) | 1 ( 0.8%) |
| INJECTION SITE PRURITUS | 1 ( 1.8%) | 0 ( 0.0%) | 1 ( 0.8%) | 1 ( 0.8%) |
| MALAISE | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.8%) | 1 ( 0.8%) |
| NON-CARDIAC CHEST PAIN | 1 ( 1.8%) | 4 ( 7.3%) | 1 ( 0.8%) | 4 ( 3.3%) |
| PERIPHERAL COLDNESS | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.8%) | 0 ( 0.0%) |
| METABOLISM AND NUTRITION DISORDERS | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.8%) | 0 ( 0.0%) |
| HYPONATRAEMIA | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.8%) | 0 ( 0.0%) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 4 ( 7.0%) | 8 (14.5%) | 24 (19.5%) | 25 (20.7%) |
| ARTHRALGIA | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.8%) |
| BACK PAIN | 0 ( 0.0%) | 1 ( 1.8%) | 0 ( 0.0%) | 1 ( 0.8%) |
| JOINT STIFFNESS | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.8%) | 0 ( 0.0%) |
| MUSCLE SPASMS | 1 ( 1.8%) | 0 ( 0.0%) | 1 ( 0.8%) | 0 ( 0.0%) |
| MUSCLE TIGHTNESS | 2 ( 3.5%) | 7 (12.7%) | 17 (13.8%) | 21 (17.4%) |
| MUSCULOSKELETAL DISCOMFORT | 0 ( 0.0%) | 1 ( 1.8%) | 1 ( 0.8%) | 2 ( 1.7%) |
| MUSCULOSKELETAL PAIN | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.8%) |
| MUSCULOSKELETAL STIFFNESS | 0 ( 0.0%) | 0 ( 0.0%) | 3 ( 2.4%) | 2 ( 1.7%) |
| NECK PAIN | 0 ( 0.0%) | 0 ( 0.0%) | 4 ( 3.3%) | 0 ( 0.0%) |
| PAIN IN EXTREMITY | 1 ( 1.8%) | 1 ( 1.8%) | 3 ( 2.4%) | 1 ( 0.8%) |
| PAIN IN JAW | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.8%) |

Here, in the pivotal trial, there were no reports of injection site pain in either group, but when all studies with Sumavel were compared to Imitrex injection, Sumavel had an incidence of 1.6% compared to Imitrex 0.8%. The term “puncture site pain” relates to venipuncture site pain for lab tests.

It appears on the basis of this somewhat truncated data that there is more pain associated with needle-free Sumavel, than Imitrex injection.

### 7.4.2 Laboratory Findings

No consistent or clinically significant abnormalities in the 6 clinical studies at baseline, or changes from baseline, in the biochemistry, hematology or urinalysis tests performed appear to be related to the administration of either Intraject sumatriptan or IMITREX/Imigran.

In the 6 clinical studies, nearly all laboratory values out of range that were considered to be clinically significant were repeated and evaluated by the sponsor. All repeat laboratory values were considered to be not clinically significant.

One subject (Subject 002 in Study ARD-2100-0501) had *transient hyponatremia* possibly related to treatment. Hyponatremia was detected by the clinical laboratory evaluation 8 hours after dosing in Period 3 (Intraject abdomen) and sodium levels had returned to normal when laboratory testing was repeated 8 hours after Period 4 on the following day (Intraject thigh).

One pre-dose laboratory abnormality was considered clinically significant; this was a marked *elevation of creatine kinase* for Subject 1003 in Study ZX001-0601 at Screening, with a value of 1174 U/L (normal range 0-270 U/L). Subsequent creatine kinase values for this subject, although still elevated, were not considered to be clinically significant.

Several subjects had transient treatment-emergent abnormalities in chemistry, hematology, or urinalysis values at end of study evaluations. However, none of these abnormalities were considered to be clinically significant by the principal investigators. I reviewed these and concur that they were not clinically significant.

No notable trends between end of study and pre-dose values in chemistry, hematology, or urinalysis values are reported.

### 7.4.3 Vital Signs

No unexpected observable trends in measurements obtained from baseline (Screening) through to the Exit Evaluation in any of the 6 clinical trials are recorded. Mean systolic and diastolic blood pressures did increase moderately (i.e., 5-10 mmHg) at 15 minutes post-dose, then rapidly returned to pre-dose values. This is consistent with the established pharmacodynamic effects of sumatriptan injection (see *Prescribing Information for IMITREX Injection NDA 20-080*). Mean heart rate was lowest at 4 hours post-dose, increased at 6 hours post-dose, then returned to earlier levels. There were no other trends or abnormalities of note in the vital signs data.

All vital sign measurements taken during the 6 clinical trials were deemed to be acceptable by the Principal Investigators except one. This individual had a vital sign abnormality that was reported as an AE. Subject 1025 in Study ZX001-0601 had an increase of heart rate 22 hours after administration of Intraject sumatriptan to the arm. This treatment-emergent adverse event, which was further monitored with a 12-lead ECG and vital signs measurements, resolved within a few minutes, and was considered mild and unrelated to study treatment by the investigator.

### 7.4.4 Electrocardiograms (ECGs)

All subjects in the 6 clinical trials had ECGs at screening with the exception of 45 of the 54 subjects in Study ZX001-0701 who were migraine subjects already experienced with sumatriptan injection (12-lead ECGs were only performed at baseline on the 9 subjects naïve to sumatriptan injection). Most subjects also had continuous ECGs during in clinic study drug administration. All ECGs were reviewed by the medical investigators and were interpreted as either normal or abnormal but not clinically significant for all subjects at the times recorded.

One subject, (013 in Study ARD-2100-0501) had a sinus arrhythmia detected at Screening. It was detected in Period 2 during monitoring and a 12 lead was performed and found to be not different and clinically insignificant. There were no other ECG abnormalities in the studies.

### 7.4.5 Physical Findings Associated with, and Safety of, the Intraject Drug Delivery System for Subcutaneous Administration of Sumatriptan, Special Safety Studies

To develop an understanding of the frequency, extent and duration of potential injection site reactions following Intraject sumatriptan injection, the sponsor collected local site reactions (LSR) prospectively and separately from AEs. LSRs were comprised of bleeding, swelling, erythema, and bruising.

Secondarily they wished to compare injection signs after Intraject sumatriptan injections to IMITREX/Imigran injections as they were unable to find data in the published literature concerning the frequency, extent and duration of potential injection site reactions following IMITREX/Imigran injections. In my Google search for "Imitrex Injection Local Site Reaction", I found anecdotal reports of injection site reaction (59%) in some cases, including pain, redness, stinging, induration, swelling, contusion, subcutaneous bleeding, lipoatrophy, and lipohypertrophy from subcutaneous administration that have occurred post-marketing with Imitrex Injectable. These would not permit an evidence-based comparison.

Finally the sponsor wished to assess injection site signs under "actual use conditions" with subjects during an acute migraine attack outside of a clinic setting (Study ZX001-0701) and to assess a theoretical "worst case scenario" for injection site signs in which subjects received repeated injections of Intraject sumatriptan in close anatomical proximity over a short time period (Study ZX001-0703).

The sponsor states the most common time points for analysis in the clinical program were pre-dose, immediately after dosing, and at 1, 8 and 24 hours after dosing although additional time points were also obtained in individual studies. For example:

- in the three pilot PK studies (SUM-04-01, ARD-2100-0501 and ARD-2100-0504), the injection site signs of bleeding, swelling, erythema and bruising were also assessed at 5, 15 and 30 minutes and at 2, 3, 4 and 5 hours after dosing in each of the treatment periods.
- In Pilot PK Study SUM-04-01, assessments were also made at 10 minutes, 5, 6 and 7 hours.
- In Pivotal PK/BE Study ZX001-0601, assessments were made 15 minutes before dosing, immediately after dosing, and at 1, 8, and 24 to 32 hours after dosing.
- In Usability Study ZX001-0701, local injection site signs were self-reported by the subjects via the call center at 2-24 hours after dosing and 24-32 hours after dosing.
- In the Safety Study ZX001-0703, local site signs were prospectively assessed for each of the three injections at 15 minutes before dosing, immediately after dosing, and at 1, 4, 8 and 24 hours after dosing.

Additional assessments at 48 and 72 hours were also performed, as indicated per protocol. In addition, photographs of the injection sites were taken at specified time points in Safety Study ZX001-0703 to document possible injection site signs following repeated injections to the same

anatomic site. Each photograph included the same L-shaped centimeter ruler to provide horizontal and vertical perspective of scale.

Medical technicians and/or clinicians performed the local site assessments in five of the 6 studies (the exception being Study ZX001-0701 in migraine subjects). In those five studies, each subject (healthy volunteer) may have been assessed by multiple technicians and/or investigators throughout the course of a study. The medical technicians and/or clinicians were trained on the measurement in millimeters, using a ruler, of three injection signs (swelling, erythema and bruising). Measurements were made of the longest dimension (diameter) of each local site sign. By contrast, bleeding was noted only as “yes” or “no” (i.e., present or absent). Since these local signs were regarded as medically common, there was no specific training provided on the definition or characterization of the four anticipated local site signs. By contrast, in Usability Study ZX001-0701, subjects self-reported to a call center only the presence or absence of LSRs in response to a scripted interview soliciting LSR information.

To compare the data between the studies, the time points that were most commonly used for injection site assessments across studies were selected for cumulative analysis (i.e. immediately after dosing and at 1, 8, and 24 to 32 hours after dosing) (Table 19: Pooled Injection Site Signs Associated With Administration Site Reactions in Studies SUM-04-01, ARD-2100-0501, ARD-2100 0504, ZX001-0601 and ZX001-0703). Since migraine subjects were studied in Usability Study ZX001-0701, they did not self-report LSR data at these time points (nor were their reports of injection site signs confirmed by an investigator), the data from this Study are not included in this summary analysis. However, a summary of the LSR data from Usability Study ZX001-0701 are presented separately at the end of this section.

Following the table presentation, an analysis of the each of the 4 LSR findings is discussed.

**Table 19: Pooled Injection Site Signs Associated With Administration Site Reactions in Studies SUM-04-01, ARD-2100-0501, ARD-2100 0504, ZX001-0601 and ZX001-0703**

| Injection Site Sign & Diameter | Time Post-Injection | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Immediately after | | 1 Hour | | 8 Hours | | 24 – 32 Hours | |
| | Intraject sumatriptan | IMITREX/ Imigran | Intraject sumatriptan | IMITREX/ Imigran | Intraject sumatriptan | IMITREX/ Imigran | Intraject sumatriptan | IMITREX/ Imigran |
| N (# of Injections) | 297 | 217 | 297 | 217 | 297 | 217 | 297 | 217 |
| **Bleeding** | | | | | | | | |
| No (%) [a] | 144 (48.6) | 169 (77.9) | 279 (94.6) | 217 (100) | 295 (100) | 217 (100) | 261 (100) | 180 (100) |
| Yes (%) | 152 (51.4) | 48 (22.1) | 16 (5.4) | 0 | 0 | 0 | 0 | 0 |
| Not done | 1 | 0 | 2 | 0 | 2 | 0 | 36 | 37 |
| **Swelling** | | | | | | | | |
| No (%) | 48 (16.2) | 216 (99.5) | 104 (35.0) | 185 (85.3) | 281(95.3) | 217 (100) | 258 (99.2) | 179 (99.4) |
| Yes (%) | 249 (83.8) | 1 (0.5) | 193 (65.0) | 32 (14.7) | 14 (4.7) | 0 | 2 (0.8) | 1 (0.6) |
| Not done | 0 | 0 | 0 | 0 | 2 | 0 | 37 | 37 |
| Mean (SD) | 7.6 (5.9) | 6.0 (-) | 15.9 (8.6) | 8.8 (7.8) | 10.9 (8.6) | N/A | 3.5 (2.1) | 2.0 (-) |
| Median | 6 | 6 | 15 | 5 | 10 | N/A | 4 | 2 |
| **Erythema** | | | | | | | | |
| No (%) | 244 (82.2) | 209 (96.3) | 130 (43.8) | 162 (74.7) | 230 (78.0) | 209 (96.3) | 229 (88.1) | 175 (97.2) |
| Yes (%) | 53 (17.8) | 8 (3.7) | 167 (56.2) | 55 (25.3) | 65 (22.0) | 8 (3.7) | 31 (11.9) | 5 (2.8) |
| Not done | 0 | 0 | 0 | 0 | 2 | 0 | 37 | 37 |
| Mean (SD) | 15.4 (16.2) | 12.6 (8.3) | 30.1 (19.3) | 28.7 (17.5) | 5.0 (5.5) | 2.9 (3.2) | 5.3 (7.4) | 3.0 (1.2) |
| Median | 10 | 10 | 30 | 30 | 3 | 2 | 3 | 3 |

| Injection Site Sign & Diameter | Time Post-Injection | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Immediately after | | 1 Hour | | 8 Hours | | 24 – 32 Hours | |
| | Intraject sumatriptan | IMITREX/ Imigran | Intraject sumatriptan | IMITREX/ Imigran | Intraject sumatriptan | IMITREX/ Imigran | Intraject sumatriptan | IMITREX/ Imigran |
| **Bruising** | | | | | | | | |
| No (%) | 271 (91.3) | 216 (99.5) | 289 (97.3) | 210 (96.8) | 284 (96.3) | 207 (95.4) | 245 (94.2) | 170 (94.4) |
| Yes (%) | 26 (8.8) | 1 (0.5) | 8 (2.7) | 7 (3.2) | 11 (3.7) | 10 (4.6) | 15 (5.8) | 10 (5.6) |
| Not done | 0 | 0 | 0 | 0 | 2 | 0 | 37 | 37 |
| Mean (SD) | 19.7 (6.4) | 1.0 (N/A) | 26.9 (8.4) | 12.1 (9.9) | 19.3 (10.3) | 14.9 (12.9) | 21.4 (12.9) | 15.4 (12.3) |
| Median | 20 | 1 | 27 | 10 | 20 | 9 | 25 | 11 |

Note: Study ZX001-0701 data is not included due to difference in study design related to LSR collection time points.

[a] Percentages were calculated on total number of assessments performed. The total number did not include any assessments that were recorded as "Not Done".

#### 7.4.5.1 Bleeding

The data reveal a higher incidence of bleeding immediately following Intraject sumatriptan (i.e., 51%; 152/296) relative to IMITREX/Imigran injection (i.e., 22%; 48/217) (Table 19). For both injection methods, however, bleeding at the injection site spontaneously resolved within an hour for all but 5.4% (16/295) of the Intraject sumatriptan subjects. There was no persistent bleeding beyond this time point and there were no additional or new incidences of bleeding beyond this time point in any of the subjects.

None of the incidences of bleeding for either Intraject sumatriptan or IMITREX/Imigran Injection were reported as AEs in the studies included in the sponsor's integrated analysis of LSRs. No evidence of a cumulative effect in terms of bleeding was observed in Safety Study ZX001-0703 following three injections of Intraject sumatriptan in close anatomical proximity over a short time period. However, in Study ZX001-0701, there was one AE reported for injection site bleeding following administration of Intraject sumatriptan; as discussed separately below in the Injection Site Signs for this study.

#### 7.4.5.2 Swelling

The incidence of swelling observed and the magnitude of the responses following Intraject sumatriptan and IMITREX/Imigran injection is also provided in Table 19 above. "Swelling" response was described as a small area of circumscribed dermal edema at the location of the injection site.

Swelling at the injection site was observed immediately after the majority of injections with Intraject sumatriptan (84%; 249/297; median size = 6 mm) but in only 0.5% (1/217; size = 6 mm) of IMITREX/Imigran injections. The sponsor concludes the more frequent presence of "swelling" following Intraject sumatriptan than IMITREX/Imigran is most likely due to Intraject's delivery characteristic of depositing injectate in the subcutaneous space more proximal to the dermal surface relative to conventional needle injection.

Swelling incidence diminished to 65% (193/297) at 1 hour after Intraject sumatriptan although the median size increased to 15 mm, most likely as a result of the diffusion of the injected formulation into the surrounding subcutaneous space. The sponsor provided color photographs in the submission demonstrating all of the local site reaction findings. By contrast, the incidence of swelling after IMITREX/Imigran increased at 1 hour to 15% (32/217; median size = 5 mm).

The data show the incidence of swelling decreased to 4.7% (14/295) of all Intraject sumatriptan injections at 8 hours with a median size of 10 mm compared to no reports of swelling at 8 hours after IMITREX/Imigran injections. By 24 hours after injection, the observed swelling was extremely minor and similar for the two injection systems and was restricted to two subjects (0.8%) for Intraject sumatriptan (2 mm and 5 mm in size) and one subject for IMITREX/Imigran injection (0.5%; 2 mm in size).

No incidences of swelling for either Intraject sumatriptan or IMITREX/Imigran Injection were reported as AEs in the studies included in this integrated analysis of LSRs. However, in Study ZX001-0701, one AE for injection site swelling was reported following administration of Intraject sumatriptan; this is discussed below in the "Injection Site Signs in Study ZX001-0701" discussion. No evidence of a cumulative effect in terms of swelling was observed in Safety Study ZX001-0703 following three injections of Intraject sumatriptan in close anatomical proximity over a short time period.

#### 7.4.5.3 Erythema

The number of observed erythematous reactions and the magnitude of the responses following Intraject sumatriptan and IMITREX/Imigran injection are displayed in Table 19. The peak incidence of erythema appeared at 1 hour after injection for both Intraject sumatriptan (56%; 167/297) and IMITREX/Imigran (25%; 55/217) (median size = 30 mm for both injection systems).

The sponsor included representative photographic evidence of an erythematous reaction (15 mm) where a typical erythematous reaction reveals a light reddish area of skin around the abdominal injection site. Injection sites #1 and #2 in this same subject, shown in the photograph at 25 and 26.5 hours after the injections, show no evidence of erythema, as was typical of the vast majority of erythematous reactions at the later time points.

The incidence of erythema at 8 hours was reduced relative to the incidence noted immediately after injection for both Intraject sumatriptan (22%; 65/295) and IMITREX/Imigran (3.7%; 8/217). The median size of erythema also decreased substantially by 8 hours when the median size was only 3 mm for Intraject sumatriptan and 2 mm for IMITREX/Imigran.

The incidence of erythema was further reduced at the 24 hour observation compared to the earlier time points for both Intraject sumatriptan (12%; 31/260) and IMITREX/Imigran (2.8%; 5/180).

No AEs were reported for injection site erythema during the study for either Intraject sumatriptan or IMITREX/Imigran around the injection site injection. No evidence of a cumulative effect in terms of erythema was observed in Safety Study ZX001-0703 following three injections of Intraject sumatriptan in close anatomical proximity over a short time period.

#### 7.4.5.4 Bruising

The number of observed bruising reactions following Intraject sumatriptan and IMITREX/Imigran Injection is also displayed in Table 19. An unexpected number (8.8%; 26/297 injections) of observations of "immediate" bruising was recorded after Intraject sumatriptan injections compared to only 1 of 217 (0.5%) after IMITREX/Imigran Injection. The sponsor reports the higher incidence of "immediate" bruising following Intraject sumatriptan administration was not anticipated for two major reasons:

- First, immediate bruising that resolves within an hour is not consistent with any known pathophysiological mechanism, since bruising is not an immediate and very transient response to tissue insult, but typically develops over time and may persist for a week or more. Thus, an "immediate" observation of a bruise is inconsistent with the typical and expected clinical presentation of a subcutaneous hematoma following tissue insult.
- Second, 23 of the 26 "immediate" bruises were observed in a single study out of a total of 111 Intraject sumatriptan administrations (Pivotal PK/BE Study ZX001-0601).

In the other 4 clinical studies using investigator observers (SUM-04-01, ARD-2100-0501, ARD-2100-0504 and Study ZX001-0703), only 3 "immediate" bruises were observed out of a total of 186 Intraject sumatriptan injections. Thus, the sponsor concludes the medical technicians who recorded this observation in Pivotal PK/BE Study ZX001-0601 may have incorrectly interpreted localized swelling, erythema and/or some other factor as a "bruise."

Consistent with this interpretation of the results is the fact that both the incidence and size of the bruising response following Intraject sumatriptan and IMITREX/Imigran injections is very similar for the two delivery methods at all time points except the "immediate evaluation" in this single study. There was a low and nearly identical frequency (i.e., 3-6%) of bruising at the time points of 1, 8 and 24 hours for both delivery systems (Table 19). Specifically, the incidence of observed bruising following Intraject sumatriptan vs. IMITREX/Imigran was as follows: 2.7% (8/297) vs. 3.2% (7/217) at 1 hour; 3.7% (11/295) vs. 4.6% (10/217) at 8 hours; 5.8% (15/260) vs. 5.6% (10/180) at 24-32 hours.

Photographs provided by the sponsor in Safety Study ZX001-0703, demonstrated few bruises observed after 24 or more hours displaying clearly demarcated boundaries and the dark purplish coloring characteristic of subcutaneous blood. The majority of the late onset LSRs recorded as bruises consisted of very diffuse areas of light yellow-purple discoloration of the skin. The sponsor attributes this to slight subcutaneous plasma and/or blood leakage leading to mild, evolving subcutaneous tissue changes. Overall, the low frequency of bruises after either delivery system is consistent with known and expected sequelae of subcutaneous injections. The sponsor indicates the vast majority of subjects had no evidence of even minor bruising at the 24 hour time point, even under the "worst case scenario" conditions of this Study involving three administrations of Intraject sumatriptan in close anatomical proximity over a short time period. No AEs were reported for injection site bruising during any study for either Intraject sumatriptan or IMITREX/Imigran injection.

#### 7.4.5.5 Injection Site Signs for Usability Study ZX001-0701

Usability Study ZX001-0701 differed significantly from the other 5 clinical trials in three major ways:

- First, migraine subjects during an acute migraine attack (not healthy volunteers in a clinic setting) were studied in Usability Study ZX001-0701.
- Second, injection site signs were collected at only 2 times after dosing and the time duration allowed for reporting was longer (between 2-24 hours and between 24-32 hours post dose).

- Third, their reports of local site signs were self-reported by subjects and not confirmed by a trained investigator.

For these reasons, the data from this Study were not included in the integrated data summary above and have been summarized separately.

Table 20 below summarizes the frequency and persistence of local injection site reactions reported by subjects on inbound and outbound calls, summarized comparatively. The 137 uses reported included initial doses of Intraject sumatriptan and any re-dosing that occurred prior to either the inbound or outbound calls.

Erythema was the most common (47%) injection site reaction reported between 2-24 hours after the use of Intraject sumatriptan, followed by swelling (18%) and bruising (11%). Erythema and swelling were reported more frequently during the 2-24 hour time point than between the 24-32 hour time point (47% vs. 30% and 18% vs. 6.6%, respectively), while bruising was reported more frequently between 24-32 hours (17% vs. 11%). No bleeding was reported at either time-point.

Two local injection site reactions (injection site swelling in subject 310 and injection site bleeding in subject 309) were reported to the study site as AEs by the subjects.

**Table 20: Descriptive Summary of the Frequency and Persistence of Local Injection Site Reactions, Inbound and Outbound Calls Summarized Comparatively (Safety Population)**

| Injection site reaction: | Call Summary (time post-injection) N=137 doses, including re-doses | |
|---|---|---|
| | Inbound (2 – 24 hours) n (%) | Outbound (24 – 32 hours) n (%) |
| Bleeding | | |
| None | 132 (96) | 130 (95) |
| Present | 0 (0.0) | 0 (0.0) |
| Not Done | 5 (3.6) | 7 (5.1) |
| Swelling | | |
| None | 108 (79) | 122 (89) |
| Present | 24 (18) | 9 (6.6) |
| Not Done | 5 (3.6) | 6 (4.4) |
| Erythema (redness) | | |
| None | 68 (50) | 90 (66) |
| Present | 64 (47) | 41 (30) |
| Not Done | 5 (3.6) | 6 (4.4) |
| Bruising | | |
| None | 117 (85) | 108 (79) |
| Present | 15 (11) | 23 (17) |
| Not Done | 5 (3.6) | 6 (4.4) |

#### 7.4.5.6 Pooled LSRs From Clinician-administered Studies (SUM-04-01, ZX001-0601, ZX001-0703) Compared with LSRS from Self-administered Injection Studies (ARD-2100-0501 and ARD-2100-0504)

The pooled injection site data from the 4 initial clinical studies submitted in the original NDA submission suggested slight differences in injection site signs according to who carried out the injection, i.e. self-administered versus clinician-administered. For example, erythema and bleeding occurred more frequently after self-injection than after clinician-administered injection. However, the addition of the NDA amendment data generated in Study ZX001-0703 failed to confirm any consistent pattern. For example, in the pooled data, while erythema was more common at the immediate and 1 hour time points after clinician-administered injections than after self-administration, the opposite pattern was observed at the 8 and 24 hour time points. Although bleeding was reported slightly more frequently after self-administration injection than after clinician-administered injections, no bleeding was observed after either injection method after the 1 hour time point. As a result, the sponsor concludes, the minor differences observed between clinician-administered injections and self-administration in the clinical trials have no known practical or clinical consequence.

### 7.4.6 Special Safety Studies

No other special safety studies were conducted for this 505 b 2 NDA using sumatriptan injectable as the RLD. The sponsor does review potential safety hazards with use of the needle-free Intraject system, however. These were assessed by an extensive hazards analysis and include:

- *late firing* of Intraject (which might cause injury because the device is lifted from the skin and fired inappropriately),
- *device malfunction* (which might cause injury if parts of the device are expelled at high speed), and
- *broken glass* (which could cause injury through abrasion of the skin).

Zogenix believes it has completed extensive development efforts and has implemented appropriate controls during manufacture to ensure the reliability and safety of the Intraject system. None of the above 3 events occurred during the course of any of the studies described in this summary. I defer to CDRH for assessment of the appropriateness, reliability and safety of the Intraject system. Please see their consult.

### 7.4.7 Immunogenicity

Not applicable.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Event

Not reported in these studies.

### 7.5.2 Time Dependency for Adverse Events

Not reported in these studies.

### 7.5.3 Drug-Demographic Interactions

No drug interactions were noted in subjects treated with any of the study drugs in any of the Zogenix studies.

### 7.5.4 Drug-Disease Interactions

No drug interactions were noted in subjects treated with any of the study drugs in any of the Zogenix studies.

### 7.5.5 Drug-Drug Interactions

No drug interactions were noted in subjects treated with any of the study drugs in any of the Zogenix studies.

## 7.6 Additional Safety Explorations

### 7.6.1 Human Carcinogenicity

This is a 505 (b) (2) application, based on bioequivalence to a referenced listed drug and no new data exploring carcinogenicity was acquired.

### 7.6.2 Human Reproduction and Pregnancy Data

Sumatriptan carries a Pregnancy Category C rating. Therefore, pregnant or breastfeeding females were excluded from participating in the Zogenix-sponsored studies.

### 7.6.3 Pediatrics and Effect on Growth

Safety and effectiveness of sumatriptan in pediatric patients under 18 years of age have not been established. No explorations for the pediatric population were conducted for this 505 (b) (2) indication.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No instances of overdose were reported in subjects treated in any of the Zogenix studies. No instances of drug abuse were reported in subjects treated in any of the Zogenix studies. No instances of withdrawal or rebound were reported in subjects treated in any of the Zogenix studies.

## 7.7 Additional Submissions

No additional submissions beyond the single amendment were submitted.

# 8 Postmarketing Experience

# 9 Appendices

## 9.1 Sponsor's Summary of Individual Studies

### 9.1.1 Pivotal PK/BE Study (ZX001-0601) (Study 4)

This was a randomized, open-label, single-dose, partial-block, four-period four-way crossover study to evaluate the pharmacokinetics and bioequivalence of sumatriptan delivered via the Intraject® system versus the IMITREX STATdose System® at three injection sites in healthy adult subjects, conducted by Covance for the sponsor at their CRC. Of the 57 subjects enrolled, all 57 were included in the safety analysis and 54 were included in the pharmacokinetic (PK) analysis.

**Key inclusion and exclusion criteria**:

*Inclusion:* Healthy men or women ≥18 to ≤55 years of age; BMI ≥20 and ≤33 kg/m2; sufficient subcutaneous thickness for injection into the abdomen, arm, and thigh.

*Exclusion:* evidence of clinically relevant oral, cardiovascular, hematologic, gastrointestinal, hepatic, renal, endocrine, pulmonary, neurologic, psychiatric or skin disorder; history of neurologic or cardiovascular disease; history of allergy, anaphylaxis, or hypersensitivity to sumatriptan or similar drugs including sulphonamides; history of any skin condition that could adversely affect the injection or absorption of subcutaneously administered medications; tattoos or other significant skin discoloration that could restrict injection site selection or evaluation.

**Test product, dose and mode of administration, lot number**:

Intraject sumatriptan; each injector delivers 0.5 mL of sterile, isotonic solution of 6 mg sumatriptan (base) as the succinate salt; subcutaneous administration; lot number PD05141.

**Duration of treatment**:

The total duration of the study was approximately 4 weeks for each subject: 3 weeks for screening and enrollment and approximately 1 week for treatment and follow-up.

**Reference therapy, dose and mode of administration, lot number**:

IMITREX STATdose System; each injector contained 0.5 mL of solution of 6 mg sumatriptan (base) as the succinate salt; subcutaneous administration; lot number C255698

**Criteria for evaluation**:

*Pharmacokinetics:* Blood samples for PK analysis were collected 15 minutes before dosing and at 3, 6, 9, 12, 15, 20, and 30 minutes and at 1, 1.5, 2, 3, 4, 6, 8, and 10 hours after dosing on each of 4 treatment days. Plasma sumatriptan concentrations were measured using a validated assay method. Areas under the plasma concentration-time curve ($AUC_t$, partial $AUC_{(0-15)}$, $AUC_{inf}$, the maximum plasma concentration ($C_{max}$), time to maximum concentration ($T_{max}$), apparent terminal elimination phase half-life ($T_{half}$), and apparent terminal elimination rate constant ($K_{el}$) of sumatriptan were determined.

*Safety:* Safety was assessed throughout the study by monitoring adverse events (AEs), clinical laboratory tests, vital signs, electrocardiograms (ECGs), and physical examination findings. Injection sites were assessed prospectively for signs of erythema, swelling, bleeding, and bruising reactions immediately following injection and at 1, 8, and 24 hours following injection. These injection site assessments were performed separately from AE monitoring which was done throughout the study. Pretreatment safety procedures included urine and serum pregnancy tests and tests for human immunodeficiency virus, hepatitis B, and hepatitis C.

**Statistical methods**:

*Demographics and baseline characteristics:* Demographics and baseline characteristics were tabulated and summarized descriptively overall and by treatment sequence. Baseline physical examination and medical history data were listed.

*Pharmacokinetics/Bioequivalence*: The primary bioequivalence evaluation of Intraject sumatriptan relative to the reference IMITREX STATdose System was determined by computing the 90% confidence intervals of the mean ratios of the two systems for AUCt, AUCinf, and Cmax of sumatriptan for each injection administration site independently (abdomen, thigh, and arm). Point estimates for each of the mean ratios were obtained from the antilogs of the mean differences of the log-transformed data; similarly, the 90% confidence intervals were obtained from the antilogs of the lower and upper bounds of the 90% confidence intervals

for the differences in the means of the log-transformed data. Bioequivalence was declared for an injection site if the 90% confidence intervals of the mean ratios of the two systems for $AUC_t$, $AUC_{inf}$, and $C_{max}$ were within 80–125%. Secondary bioequivalence evaluations consisted of establishing the similarity in the early exposure of sumatriptan absorption between the two delivery systems based on the partial $AUC_{(0\text{-}15)}$ parameter, and comparing $T_{max}$ values non-parametrically between the two delivery systems. Similarity in early exposure between the two systems was declared if the 90% confidence interval of the mean ratio of Intraject and IMITREX STATdose for $AUC_{(0\text{-}15)}$ was within 80–125%.

A supportive analysis determined the bioequivalence of Intraject to IMITREX STATdose when sumatriptan concentration data were pooled across the three injection sites.

No sub-group analyses of PK or safety endpoints (e.g., by age group, gender, ethnicity) were planned or performed.

**Safety Analysis**:

Adverse events (AEs) were listed by system organ class and preferred term and were summarized by treatment, administration site, severity, and relationship to treatment. Laboratory values outside normal ranges, along with any associated repeat values, were listed separately and evaluated clinically. Vital signs (heart rate, respiratory rate, resting systolic/diastolic blood pressure) and 3-lead ECG parameters were listed, summarized, and evaluated clinically.

**Summary of results**:

*Pharmacokinetics/Bioequivalence Results:*

Based on mean ratio analyses of AUCt, AUCinf, and Cmax, Intraject sumatriptan was found bioequivalent to reference IMITREX STATdose at the abdomen and thigh injection sites, but not at the arm (deltoid). Lack of bioequivalence at the arm was associated with an increased incidence of incomplete injections for Intraject at this injection site, resulting in disproportionately low mean values and high variance estimates for Cmax, AUCt, and AUCinf sumatriptan PK parameters.

**Table 21: Primary Bioequivalence Results Analysis for Study Drugs at Abdomen, Thigh, and Arm Sites, Per Protocol Population**

| Injection Site | Parameter (units) | N Test | N Ref | Test Mean [a] (Intraject) | Reference Mean [a] (IMITREX) | Mean Ratio, Test/Ref (%) | 90% Confidence Interval |
|---|---|---|---|---|---|---|---|
| Abdomen | $C_{max}$ (ng/mL) | 35 | 35 | 76.9 | 85.3 | 90.1 | (83.92, 96.80) |
| | $AUC_t$ (ng*hr/mL) | 35 | 35 | 93.2 | 102 | 91.0 | (87.12, 94.97) |
| | $AUC_{inf}$ (ng*hr/mL) | 35 | 35 | 94.3 | 104 | 91.0 | (87.17, 94.99) |
| Thigh | $C_{max}$ (ng/mL) | 32 | 32 | 70.6 | 66.5 | 106 | (100.82, 112.01) |
| | $AUC_t$ (ng*hr/mL) | 32 | 32 | 91.0 | 98.5 | 92.3 | (90.93, 93.79) |
| | $AUC_{inf}$ (ng*hr/mL) | 32 | 32 | 92.1 | 99.8 | 92.3 | (90.91, 93.72) |
| Arm | $C_{max}$ (ng/mL) | 34 | 34 | 59.2 | 81.6 | 72.5 | (52.88, 99.49) |
| | $AUC_t$ (ng*hr/mL) | 34 | 34 | 51.7 | 97.4 | 53.0 | (34.28, 82.06) |
| | $AUC_{inf}$ (ng*hr/mL) | 32 | 32 | 72.7 | 98.5 | 73.8 | (58.69, 92.71) |

[a] Geometric means

Mean ratio analyses of AUC(0-15) demonstrated the bioequivalence of the early exposure to sumatriptan injection for Intraject relative to IMITREX STATdose at the abdomen and thigh injection sites but not at the arm (Table 21: Primary Bioequivalence Results Analysis for Study Drugs at Abdomen, Thigh, and Arm Sites, Per Protocol Population).

Non-parametric analysis of $T_{max}$ values showed a statistically significant difference between the two systems at the abdomen and thigh injection sites (median values for $T_{max}$ are shown in Table 22, with $T_{max}$ occurring slightly earlier (approximately 2 minutes) following Intraject administration.

The mean (SD) difference in $T_{max}$ (Intraject IMITREX) at the abdomen was -0.032 (0.031) hr, or -1.92 (1.84) min; the mean difference at the thigh was -0.039 (0.024) hr, or -2.34 (1.42) min.

Bioequivalence was not achieved at the arm for $AUC_{(0-15)}$, also likely due to the disproportionately distorting effect on both of these parameters resulting from the increased incidence of incomplete Intraject injections at this injection site.

**Table 22: Secondary Bioequivalence Analysis: Early Exposure and Tmax of Study Drugs, Abdomen and Thigh Sights. Per-Protocol PK Analytic Population**

| Injection Site/ Parameter (units) | N, Test | N, Ref | Test Mean/ Median[a] (Intraject) | Reference Mean/ Median[a] (IMITREX) | Mean Ratio, Test/Ref (%) | Difference, Test-Ref | 90% Confidence Interval | P-Value[b] |
|---|---|---|---|---|---|---|---|---|
| Abdomen | | | | | | | | |
| $AUC_{(0-15)}$ (ng*hr/mL) | 35 | 35 | 14.4 | 14.2 | 101 | — | (92.03, 111.43) | — |
| $T_{max}$ (hr) | 35 | 35 | 0.200 | 0.200 | — | 0.000 | (-0.150, 0.100) | 0.0355 |
| Thigh | | | | | | | | |
| $AUC_{(0-15)}$ (ng*hr/mL) | 32 | 32 | 13.1 | 11.4 | 115 | — | (105.55, 124.99) | — |
| $T_{max}$ (hr) | 32 | 32 | 0.200 | 0.225 | — | -0.050 | (-0.183, 0.150) | 0.0470 |
| Arm | | | | | | | | |
| $AUC_{(0-15)}$ (ng*hr/mL) | 34 | 34 | 11.0 | 14.9 | 74.0 | — | (52.42, 104.48) | — |
| $T_{max}$ (hr) | 34 | 34 | 0.150 | 0.175 | — | -0.050 | (-0.183, 0.050) | <0.0001 |

[a] Geometric means are given for $AUC_{(0-15)}$; medians are given for $T_{max}$.
[b] Wilcoxon's signed-rank test.

Sumatriptan concentration data for the arm were excluded from the planned supportive bioequivalence analysis of pooled injection site data based on the incidence of incomplete injections at this site. Bioequivalence was demonstrated for the Intraject system relative to IMITREX STATdose for pooled abdomen and thigh sumatriptan concentration data based on mean ratio analyses of $AUC_t$, $AUC_{inf}$, and $C_{max}$.

Supportive Bioequivalence Analysis supports these observations (Table 23)

**Table 23: Supportive Bioequivalence Analysis: Intraject vs. IMITREX STATdose Sumatriptan Concentration Data for Pooled Abdomen and Thigh Injection Sites PK Analytic Population**

| Parameter (units) | N, Test | N, Ref | Test Mean[a] (Intraject) | Reference Mean[a] (IMITREX) | Mean Ratio Test/Ref (%) | 90% Confidence Interval |
|---|---|---|---|---|---|---|
| $C_{max}$ (ng/mL) | 51 | 53 | 74.1 | 76.6 | 96.7 | (91.77, 101.99) |
| $AUC_t$ (ng*hr/mL) | 51 | 53 | 92.8 | 102 | 90.8 | (88.14, 93.49) |
| $AUC_{inf}$ (ng*hr/mL) | 51 | 53 | 93.9 | 103 | 90.8 | (88.19, 93.50) |

[a] Geometric means

*Safety Results:*

There were no deaths, SAEs, AEs leading to study discontinuation, or other significant AEs. Overall, treatment-emergent adverse events (TEAEs) were reported by 43 (75.4%) of the 57 randomized and treated subjects. A total of 95 TEAEs were reported following administration of Intraject, of which 82 (86.3%) were considered possibly or probably related to study treatment, and 100 TEAEs were reported following administration of IMITREX, of which 90 (90.0%) were considered possibly or probably related to study treatment. The *most frequently*

*reported TEAEs for either treatment (reported by ≥5% of subjects*, in order of decreasing frequency of overall incidence) were headache, dizziness, nausea, flushing, muscle tightness, burning sensation, puncture site pain, chest discomfort, hypoaesthesia, non-cardiac chest pain, paresthesia, vertigo, hypoaesthesia oral, and nasal discomfort. All TEAEs were mild and transient. There were no clinically meaningful differences in the respective incidences of TEAEs following Intraject vs. IMITREX administration.

*Non-study treatment was required for mild, non-cardiac chest pain for one subject* following IMITREX administration and for three subjects following Intraject administration, with one subject each reporting a mild heart rate increase, mild asthma, and dizziness. For both Intraject and IMITREX there were fewer TEAEs following administration to the thigh than administration to the abdomen or arm.

There were *no clinically significant differences between Intraject and IMITREX in clinical laboratory findings, vital signs, ECG findings, or other safety findings.*

*For local injection site signs, a higher incidence of swelling was observed for Intraject injection.* This is an expected response due to Intraject's delivery characteristic of depositing injectate into the subcutaneous space more proximal to the dermis relative to conventional needle-based injection. With the exception of the localized transient swelling, the prospectively collected information on local injection site signs demonstrated that the majority of injections by both delivery systems are not associated with local injection site signs. The local injection site signs that occurred were similar for both delivery systems in that they are mild, transient, resolved spontaneously, and do not suggest any safety or tolerability concerns for a chronic, intermittent dosing regimen. Moreover, of the four injection site signs assessed (bleeding, swelling, erythema, and bruising), none were reported as adverse events. No subject discontinued the study due to an injection site reaction.

**Conclusions:**

- Based on analyses of sumatriptan concentration data performed for each injection site independently, Intraject sumatriptan is bioequivalent to the reference product IMITREX STATdose at the abdomen and thigh injection sites, but not at the arm (deltoid).
- Based on pooled sumatriptan injection site data for the abdomen and thigh, bioequivalence was similarly demonstrated for the Intraject system relative to the reference IMITREX STATdose System.
- The early exposure to Intraject sumatriptan injection, an accepted measure of migraine pain relief as measured by AUC(0-15), was shown to be bioequivalent

to that of IMITREX STATdose at the abdomen and thigh injection sites but not at the arm.
- The arm is an unreliable site of administration for Intraject sumatriptan due to the incidence of incomplete injections, which can result in under-dosing.
- A slightly earlier but statistically significant difference in Tmax (by approximately 2 minutes) was found for Intraject relative to IMITREX STATdose. This mean difference was not deemed clinically relevant.
- While all injection sites (abdomen, thigh, and arm) showed similar sumatriptan exposure for the two delivery systems, in general, the greatest mean Cmax and AUCinf values were observed for the abdominal injection site.
- The subject population was representative of the intended patient population for Intraject sumatriptan.
- There were no serious or significant AEs during the study.
    - Intraject and IMITREX STATdose exhibited highly similar adverse event profiles representative of the CNS and neurovascular class effects of the triptans; there were no clinically meaningful differences in the respective incidences of TEAEs following Intraject vs. IMITREX administration.
    - All TEAEs were mild and transient for both treatment groups.
- There were no clinically significant differences between Intraject and IMITREX in laboratory values, vital signs, ECG findings, or other safety findings.
- No subjects were discontinued from the study for any injection site reaction, nor were there any AEs reported for the four prospectively assessed injection site signs of bleeding, swelling, erythema, or bruising.
- With exception of the localized transient swelling associated with the needle-free injection properties of Intraject, the majority of injections by both delivery systems were not associated with any local injection site signs, and most that did occur were mild, transient, resolved spontaneously, and do not suggest any safety or tolerability concerns for a chronic intermittent dosing regimen.

### 9.1.2 Usability Study (ZX001-0701)

This was a Phase 2 multi-center, open-label, single-dose, single-arm study to evaluate the usability of subcutaneously administered sumatriptan delivered via the Intraject® System in Adult patients during acute migraine attack outside the clinic. It was conducted by the sponsor at various individual sites in Tennessee, Missouri, and Illinois. It also evaluated the reasons for incorrect use of Intraject sumatriptan as well as the adequacy of written instructions and occurrence and persistence of any local injection site reactions following injection.

Subjects were instructed to contact a call center between 2 to 24 hours following the use or attempted use of Intraject sumatriptan and were interviewed. Subjects were queried to determine whether they were able to correctly use Intraject sumatriptan during an acute migraine attack based on whether they were able to perform a defined sequence of steps needed to deliver the treatment dose. If they were not, the reason(s) for incorrect use were noted.

Subjects were asked by call center staff to provide information on any local injection site reactions that were present at the time of the call, including bleeding, swelling, erythema, or bruising. In addition, subjects were queried on the adequacy of the Intraject sumatriptan instructional material. Subjects were contacted by the call center approximately 24-32 hours postdose to report new or persistent local site reactions. Subjects had one follow-up visit to confirm the collected data, be interviewed for any adverse events (AEs) or persistent local site reactions experienced since their last migraine attack, and to return both used and unused Intraject systems for study accountability.

**NUMBER OF SUBJECTS and DURATION:**

Fifty male and female adult migraine subjects were planned. Fifty-four subjects were enrolled, and 52 subjects were included in the safety population. Subjects treated up to three migraine attacks during a 30-day study period or until the study was terminated by the Sponsor.

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:**

Male or female subjects, ≥ 18 years of age, were eligible if they had a diagnosis of migraine with an average of ≥ 2 to ≤ 6 attacks/month. Subjects were ineligible if they had any skin condition that could adversely affect the injection or absorption of SC administered medications.

**TEST PRODUCT, REFERENCE THERAPY, DOSE, MODE OF ADMINISTRATION, AND BATCH NUMBER:**

Intraject sumatriptan; each injector contained 0.5 mL of a sterile, isotonic solution of 6 mg of sumatriptan (base) as the succinate salt, lot #PD05141.

**CRITERIA FOR EVALUATION:**

*Primary endpoint*: The primary study endpoint was the overall proportion of subjects who were able to correctly use Intraject sumatriptan for their first migraine attack outside of the clinic. Correct use of the Intraject sumatriptan was

defined as the subject performing all of the sequence of steps necessary to deliver a SC dose of sumatriptan without failure in the subject's ability to perform any individual step; failure in ability to perform any step resulted in overall incorrect use of the product.

*Secondary Endpoint*: Secondary study endpoints were failure (yes/no) using Intraject sumatriptan during an acute migraine attack at any of the following steps: snap off the end-cap (snap-off tip); enable the system by fully retracting the setting mechanism (lever); select the abdomen or thigh as the appropriate injection site; place and correctly orient the system perpendicular to the skin; depress the system against the skin until the sound of expelled gas is heard; other reason.

*Other Endpoints*: Additional study endpoints included the following: overall proportion of correct total number of uses of Intraject sumatriptan among all subjects for all acute migraine attacks (correct use was defined as described for the primary endpoint); subject finding of adequacy (yes/no) of the instructional materials on the use of the Intraject system; frequency of occurrence and persistence of local injection site signs (bleeding, swelling, erythema and bruising) following injection; side of abdomen or thigh chosen for injection (left/right); if contralateral injection sites for the abdomen and/or thigh were used during the study or a switch from the abdomen to the thigh (or vice-versa), the reason for changing sides or anatomic injection sites.

*Safety and Tolerability*: Safety and tolerability were assessed by reported AEs and prospectively collecting local injection site reactions data.

**STATISTICAL METHODS:**

*Screening, Demographics, and Baseline Characteristics*: Demographics, baseline characteristics and medical history were tabulated and summarized descriptively. Electrocardiogram (ECG) findings at baseline (normal/abnormal) were tabulated and summarized for sumatriptan injection naïve subjects required to undergo cardiovascular risk screening.

*System Usability*: The primary study analysis was the overall proportion of subjects who were able to correctly use Intraject sumatriptan for their first migraine attack outside of clinic; correct use was defined as performing all of the sequence of steps necessary to deliver a dose without a failure to perform any individual step. The proportion of subjects who correctly used Intraject sumatriptan was computed along with the 90% exact binomial confidence interval for the true probability of a correct use.

*Safety Data*: Adverse events were listed by subject and summarized by body system and preferred term. All AEs reported in this study were coded using MedDRA. Self-reported, solicited local injection site reaction data were listed for

each subject and summarized by type (bleeding, swelling, erythema, and bruising), frequency of occurrence and categorical duration of persistence.

**SUMMARY OF RESULTS:**

*Usability*: Fifty-one of 52 subjects (98.1%) used Intraject sumatriptan correctly on their first use during an acute migraine attack outside of the clinic. The 90% exact binomial confidence interval (CI) was 91.2-99.9%. Success rates were similarly high for second and third uses.

Nearly all reported uses of Intraject sumatriptan by the 52 subjects in the safety population were performed correctly (122/125 usability assessments, 97.6%). Three incorrect uses in three separate subjects were reported, each attributed to a different causative factor.

In 124 of 125 reported uses of Intraject sumatriptan (99.2%), subjects somewhat agreed, agreed, or strongly agreed with the following statement: "The Intraject sumatriptan instructional materials provided were adequate; meaning they were clear and easy to follow."

*Safety*: Thirty-one AEs were reported by 9 of the 52 safety population subjects. Twenty-eight of the 31 reported AEs (90.3%) were considered possibly or probably related to the drug or injection. The 3 unrelated events were mild bacterial infection (Subject 203), mild upper respiratory tract infection (Subject 412), and the serious AE (SAE) of severe migraine (Subject 408).

Local injection site skin reactions were prospectively collected via the subjects' responses to the call center interviews during the inbound and outbound calls. Subjects reported swelling, erythema, and bruising to the call center. No bleeding was reported to the call center although one subject did report a history of transient mild injection site bleeding to the study site.

The most commonly reported AEs by SOC and preferred term were general disorders and administration site conditions.

Of 31 reported AEs, 20 were assessed as mild, 6 as moderate, and 5 as severe. Of the 5 severe AEs, 4 were injection site pain reported by the same subject (Subject 202) after each of the subject's self-administered Intraject sumatriptan injections, and one was an unrelated SAE of migraine.

Use of Intraject sumatriptan was not associated with any deaths or other significant AEs.

All AEs reported in this study were treatment-emergent AEs (TEAEs); therefore, summaries of AEs and TEAEs are identical.

**CONCLUSIONS:**

- Intraject sumatriptan was used correctly outside the clinic setting by > 90% of subjects on their first use and subsequent uses of Intraject sumatriptan during an acute migraine attack. Success rates were similarly high for second and third uses.
- Subjects had little difficulty in performing any of the steps necessary to use Intraject sumatriptan.
- The incorrect use of Intraject sumatriptan by 3 subjects did not result in any AEs or safety issues.
- All 3 of these subjects were able to successfully use Intraject sumatriptan to treat subsequent migraines.
- Written Intraject sumatriptan instructions were adequate for use in the population of migraine subjects for treating a migraine attack.
- Most Intraject sumatriptan doses were self-administered to the thigh.
- Subjects changed injection site locations when re-dosing, and the reason for changing location was that subjects believed they had been instructed to administer the second dose to a different anatomical location than the first.
- Twenty-eight of 31 reported AEs were treatment-related. The only AE that occurred in more than 5% of subjects was injection site pain (3 subjects, 5.8%). No other AE occurred in more than 2 subjects. Twenty six of 31 reported AEs were mild or moderate in severity, and all that were assessed as severe resolved.
- Of 31 reported AEs, only 1 was an SAE. It resolved and was not related to Intraject sumatriptan.
- Use of Intraject sumatriptan was not associated with any deaths or other significant AEs.
- No subjects were discontinued from the study for injection site reactions. Only 2 AEs were related to injection site reactions (1 of bleeding and 1 of swelling), and both resolved.
- The AEs reported by more than a single subject (i.e., nausea, injection site extravasation and injection site pain) were assessed as related to study treatment and are consistent with AEs frequently reported with subcutaneous triptan use (based on marketed subcutaneous sumatriptan data).
- Intraject sumatriptan can be used successfully by migraine subjects during an acute migraine attack.

### 9.1.3 Repeat Use Safety Study (ZX001-0703)

This was a single-center, in-house, open-label, repeat-dose, single-arm study to evaluate the a) extent, b) persistence, and c) cumulative effects on skin tissue of local injection site reactions following subcutaneously administered sumatriptan delivered via the Intraject® system in *healthy adult subjects*, conducted for the sponsor by Covance. Local site reactions (LSRs) (bleeding, swelling, erythema, bruising) following repeated administrations of Intraject sumatriptan to the same anatomic site were studied.

**Number of Subjects and Duration:**

The study was conducted in 18 male and female subjects. They received two injections of Intraject sumatriptan 1.5 hours apart on the first day of treatment, followed by a third injection of Intraject sumatriptan 24 hours after the second injection on the second day of treatment. They were confined to the Unit for the 3 days of the Study.

**Design:**

Enrolled subjects were randomized in a 1:1 ratio to receive a total of 3 injections to either the abdomen or thigh. Per protocol, subjects were to choose their preferred side of treatment, left or right, and use that same side for administration of all three injections. During study orientation with the volunteers, this issue was discussed, and no subject had any preference as to the treatment side. Therefore, all injections were performed on the same side (right) to facilitate and standardize the photographic documentation of the injection sites.

On Study Day 1, the designated injection site was assessed by a physician investigator. Subjects were then administered the first injection of Intraject sumatriptan and the presence and extent (in millimeters diameter) of local injection site reactions (bleeding, swelling, erythema, and bruising) were assessed by the physician investigator, immediately post-injection, and at 1, 4, and 8 hours after administration. Photographs of the first injection site alone were taken at 15 minutes pre-injection, immediately after injection and at 1 hour after injection.

Subjects were administered a second injection of Intraject sumatriptan 1.5 hours following the first administration, approximately 1 inch away from the first injection. The second injection site was assessed separately in the same manner and at the same time points as the first injection. The injection sites were also photographed prior to the first injection and at specified time points post-injections. Photographs of the second injection site (in combination with the first injection site) were taken immediately after injection, at 1 hour post-injection and at 8 hours post-injection. Continuous 3-lead ECG monitoring was performed following every injection for at least 4 hours following the first and second injections (total of 5.5 hours). Vital signs were recorded at regularly scheduled intervals, including pre-injection. Adverse events were monitored throughout the study.

On Study Day 2, 24-hour assessments of each of the first two injection sites were made. A photograph of the first two injection sites was taken prior to the third injection, and then additional photographs were taken at specified time points following the third injection. Subjects were administered a third and final injection of Intraject sumatriptan at 24 hours following the second injection (i.e., t=25.5 hours) to the assigned administration site, and the third site was assessed separately in the same manner and at the same time points as for the other injection sites. The third injection was administered approximately 1 inch apart from the first two injections, with all injections in an equilateral triangular pattern. Photographs of the third injection site (also including the first and second injection sites) were taken immediately after injection, at 1 hour post-injection and at 8 hours post-injection.

On Study Day 3, a 24-hour assessment of the third injection site and 48-hour assessments of the first two injection sites were performed. A single photograph was taken of all three administration sites approximately 24 hours following the third injection (i.e., approximately 48 hours after the first and second injections). Following these assessments, all subjects were discharged from the research unit and were subjected to study Discharge procedures. If indicated and at the discretion of the investigator, subjects could be scheduled for additional follow-up assessment(s) of any persistent local injection site reactions or until resolution of such reaction(s) had occurred. The same standard assessments of bleeding, swelling, erythema, and bruising were to be performed including photography. If the local injection site reactions were considered to be adequately resolved or resolving by the investigator, the subject's involvement in the study ended and he or she was terminated from the study and discharged from the research unit. Upon discharge, safety laboratory tests including vital signs measurements were completed.

**Inclusion Criteria:**

There were 18 subjects, 2:1 females to males who were at least 18 years of age and fulfilled all entry criteria. It was a diverse ethnic and racial population consisting of approximately 60% Caucasians, 30% African-Americans, and 10% other ethnicities.

**Test product, reference therapy, dose, mode of administration, and batch number**:

Intraject sumatriptan; each injector contained 0.5 mL of a sterile, isotonic solution of 6 mg of sumatriptan (base) as the succinate salt, lot no. PD05141.

**Endpoints:**

*Co-Primary Endpoints:*

1) Measurement of the extent (diameter in millimeters) of swelling, erythema and bruising, and the presence (Yes or No) of bleeding after each of three administrations of Intraject sumatriptan delivered to the same anatomic location. Measurements were performed separately for each injection and for each reaction at all scheduled time points. From these data, the frequency of occurrence and the persistence of each reaction over time were determined.

2) Time to resolution of each local injection site reaction after each of three administrations of Intraject sumatriptan. This determination was performed separately for bleeding, swelling, erythema, and bruising for each injection.

*Secondary Endpoint:* Serial photographic documentation of local injection site reactions across specified time points, including any additional unscheduled time points.

*Other Endpoints:* Safety information, including adverse events (AEs), changes in clinical laboratory tests, vital signs, and changes in 12-lead ECG findings before and after treatment, if applicable.

*Local Injection Site Reactions (LSRs)*: The primary study analysis was a descriptive statistical summary of the extent (diameter in millimeters) and change over time (from immediately post-injection to 1, 4, 8, and 24 hours post-injection) in the extent and persistence of local injection site reactions after each of the three administrations of Intraject sumatriptan delivered approximately 1 inch apart to the same anatomic site.

Descriptive summaries were displayed separately for bleeding, swelling, erythema, and bruising for each injection. A secondary analysis was serial photographic documentation of local injection site reactions across specified time points including any unscheduled time points.

*Safety Data:*
Adverse events were listed by subject and summarized by body system and preferred term. All AEs reported in this study were coded using MedDRA (Version 10.1). Physician assessed local injection site reaction data were listed for each subject and summarized by type (bleeding, swelling, erythema, and bruising), frequency of occurrence and categorical duration of persistence. Concomitant medications were listed by individual subject. Vital signs were summarized using descriptive statistics for the Study Check-in visit and by time point before and following each injection at the scheduled assessment intervals. The 12-lead ECG at the Screening visit was evaluated clinically by the investigator to rule out subjects who were contraindicated to receive injectable sumatriptan. Continuous 3-lead ECG monitoring before, during, and after sumatriptan injection was evaluated to determine the emergence of any clinically significant cardiovascular findings or abnormalities. The continuous 3-lead ECG data were not maintained. In the event a pre-programmed alarm was indicated by the 3-lead ECG monitoring, the subject was assessed by the investigator and a 12-lead ECG was to be performed, if indicated. The results (normal, abnormal/clinically significant) of any 12-lead ECGs performed were to be recorded in the CRF, and changes in 12-lead ECG findings from baseline were to be summarized, if applicable. Clinical laboratory tests from the Screening Visit (hematology, biochemistry, urinalysis) were reviewed and evaluated clinically

prior to Study Check-in. Clinical laboratory test values outside the laboratory's normal ranges, along with any associated repeat values, were listed separately, and comments were provided to indicate their clinical significance. Clinical laboratory test values were summarized using descriptive statistics by visit (Screening and at Discharge) and compared and evaluated clinically to determine the presence of any clinically significant abnormal changes.

**Summary of Results:**

Use of Intraject sumatriptan was not associated with any deaths, serious AEs (SAEs), or other significant AEs. There were no AEs that required discontinuation of a subject from the study and there were no LSRs that were assessed as an AE. The local site reaction data obtained are shown in Table 24.

Overall, minor bleeding at the injection site immediately following injection was the most common injection site reaction reported (94% incidence of all injections), followed by swelling at +1 hour (72%), erythema at +1 hour (72%), and bruising at +24 hours (7%).

Expected minor bleeding accompanied almost all injections but resolved rapidly (i.e., it was absent at the 1 hour time point). There was no cumulative effect of multiple injections on the incidence or extent of bleeding observed. The bleeding that was observed in the study was typical of needle-based subcutaneous injection and was considered mild, not clinically significant, and did not require medical attention.

The incidence of swelling following the second and third injections was greater than following the first injection. Among subjects in whom swelling developed following injection, onset was rapid but resolved within several hours.

**Table 24: Local Site Reactions Following Injection**

| | Time Post-Injection[a] (N=18 subjects; N=54 Total Intraject sumatriptan injections) | | | | |
|---|---|---|---|---|---|
| **Injection Site Reaction** | **T(0)** [b] | **+1 Hr** | **+4 Hrs** | **+8 Hrs** | **+24 Hrs** |
| **Bleeding** | | | | | |
| None (% of injections) | 3 (6%) | 54 (100%) | 54 (100%) | 54 (100%) | 54 (100%) |
| Present (% of injections) | 51 (94%) | 0 | 0 | 0 | 0 |
| **Swelling** | | | | | |
| None (% of injections) | 15 (28%) | 36 (67%) | 54 (100%) | 54 (100%) | 54 (100%) |
| Present (% of injections) | 39 (72%) | 18 (33%) | 0 | 0 | 0 |
| Mean mm (SD) | 6 (4.0) | 17 (7.2) | NA | NA | NA |
| Median mm | 4 | 20 | NA | NA | NA |
| **Erythema** | | | | | |
| None (% of injections) | 45 (83%) | 15 (28%) | 17 (31%) | 36 (67%) | 41 (76%) |
| Present (% of injections) | 9 (17%) | 39 (72%) | 37 (69%) | 18 (33%) | 13 (24%) |
| Mean mm (SD) | 12 (7.2) | 13 (8.3) | 8 (5.9) | 9 (7.4) | 5 (8.1) |
| Median diameter (mm) | 10 | 12 | 8 | 6 | 3 |
| **Bruising** | | | | | |
| None (% of injections) | 54 (100%) | 54 (100%) | 53 (98%) | 51 (94%) | 50 (93%) |
| Present (% of injections) | 0 | 0 | 1 (2%) | 3 (6%) | 4 (7%) |
| Mean mm (SD) | NA | NA | 35 (NA) | 23 (15.3) | 27 (15.3) |
| Median mm | NA | NA | 35 | 20 | 27 |

[a] Mean values and standard deviations are calculated from non-zero data.
[b] Time is relative to injection. T(0) is immediately post-injection.
References: Table 14.3-12, Listing 16.2.9-10

When present, swelling immediately after injection was characterized as a small area of circumscribed dermal edema at the location of the injection site (4 mm median diameter across all injections). As the formulation diffused into the surrounding subcutaneous space, the incidence of swelling decreased at 1 hour (median diameter of 20 mm across injections) and was not observed at subsequent time points.

Although erythema was observed immediately following injection, peak onset and peak magnitude appeared at 1 hour after injection in 72% of subjects with significant resolution occurring by 24 hours in both the incidence and extent of the erythema. The observed incidence of erythema was greatest in the hour following the third injection compared to the hour following the first and second injections.

Bruising developed occasionally, as expected, as a delayed response to injection. The earliest onset of bruising occurred at approximately 4 hours following the third injection, with a peak incidence occurring at 24 hours or later. There were 4 observed bruises among the 54 injections (7%) at 24 hours post-injection (with diameters of 8, 24, 30 and 45 mm). Additional bruises were observed beyond the 24-hour evaluation, but the true incidence after 24 hours cannot be determined due to the limited number of subjects (3/18) who were evaluated beyond 24 hours after injection #3 (per protocol design). All bruises were deemed to be either resolved or adequately resolving with no clinical significance by the investigator at the time of the final evaluation (24 to 72 hours after the injections).

There were a total of 31 AEs (30 were TEAEs) reported by 10 of the 18 safety population subjects and all were assessed as mild.

The most commonly reported treatment-emergent AEs for Intraject sumatriptan were, by system/organ class (SOC), nervous system disorders which included paresthesia, headache, dizziness, postural dizziness, and somnolence. Other AEs by SOC included gastrointestinal disorders consisting of nausea and vomiting and general disorders and administration site conditions consisting of temperature intolerance. Twenty-six of 31 reported AEs (83.9%) were considered possibly or probably related to the study drug and the most frequently occurring, the nervous system disorders or gastrointestinal disorders, are known class effects of the triptan medications.

There were no clinically significant changes in clinical laboratory tests, vital signs, physical findings, or ECG results during the study or as a result of treatment.

**Conclusions:**

The results of this study demonstrate that injection site reactions following multiple injections of Intraject sumatriptan, when they occur, are mild, not clinically significant, and resolve rapidly. This study represented a “worst case” scenario in which a patient would ignore the package label instructions to avoid injecting the same site with repeated administrations of the product. There was no evidence of a significant cumulative effect of multiple injections to a single administration site on any injection site reaction nor do the results suggest any safety or tolerability concerns associated with the injection site for chronic intermittent dosing in the treatment of migraine and/or cluster headache.

These data demonstrate that Intraject sumatriptan can be used safely and without concern for any clinically significant cumulative tissue damage even if maximally allowed dosages (i.e., 3) are administered to the same anatomic site over a short time period.

### 9.1.4 PK/BE 3 Site Pilot Study (Sum-04-01)

A randomized, open-label, single-dose, four-way crossover study to evaluate the pharmacokinetics and bioequivalence of subcutaneously administered sumatriptan delivered via the Intraject® system versus the currently marketed Imigran™ Mk II Injection at three injection sites in healthy adult volunteers..

Conducted in Australia by (b) (4) there were 2 objectives:

- Primarily to evaluate the pharmacokinetics and bioequivalence of sumatriptan delivered subcutaneously via the Intraject® system (test) compared to sumatriptan delivered subcutaneously via the Imigran™ Mk II Injection (reference) at three injection sites (abdomen, thigh and arm (deltoid)) and
- Secondarily to evaluate the tolerability and subject preference compared to the currently marketed device.

**Number of Subjects and Duration:**

The study population was 18 healthy, non-smoking male and female volunteers, aged between 18 and 40 years. The study was conducted over approximately 18 days, including screening, four study periods and Exit evaluation. During each study period, subjects remained in-clinic for approximately 24 hours. Subjects Exit evaluations occurred 24-48 hours after the last dose in period 4.

**Design:**

This was a single centre, randomized, single-dose, open-label, four-period crossover study in 18 healthy adult subjects. Test treatment was the Intraject® system: each injector contained 0.5 mL of solution with 6 mg of sumatriptan (base) as the succinate salt. The reference treatment was Imigran™ Mk II injection: each injector contained 0.5 mL of solution with 6 mg of sumatriptan (base) as the succinate salt. All treatments were given subcutaneously.

Assessments included vital signs, tolerability, visual inspections of the injection sites, continuous ECG monitoring for at least 4 hours post-dosing, and clinical lab tests. Blood samples for pharmacokinetic assessment were collected at -15, +2, +5, +7, +10, +12, +15, +20, +30 minutes, +1, +1.5, +2, +3, +4, +5, +6, +7 and +8 hours post dose in each treatment period. A total of 72 blood samples for pharmacokinetic analysis were collected during the entire study.

Descriptive statistics were used for analysis and all AEs were coded using MedDRA.

**Endpoints:**

The concentrations of sumatriptan were measured in plasma samples from all subjects, using a validated assay method. The pharmacokinetic analysis included

collection of a concentration-time profile of sumatriptan following each dose. The area under the plasma concentration-time curve ($AUC_t$, $AUC_{inf}$), maximal plasma concentration ($C_{max}$), time to maximal concentration ($T_{max}$), terminal elimination half-life ($T_{half}$) and apparent terminal elimination rate ($K_{el}$) of sumatriptan were determined.

Assessment of bioequivalence was evaluated for three administration sites (abdomen vs. thigh vs. arm (deltoid)) for the Intraject® system and Imigran™ Mk II injection and between delivery methods (Intraject® vs. Imigran™ Mk II injection) for each administration site.

The two treatments being compared were deemed to be bioequivalent if the 90% confidence interval of the ratios of the test and reference means for log transformed AUCt and Cmax fell within the acceptance range of 80%-125% for sumatriptan.

**Results:**

*Safety and tolerability:*
Adverse events were experienced by 14 of 18 subjects. The most common Adverse Event was paresthesia experienced by 8 subjects (44%). This is a common, known adverse event associated with sumatriptan treatment. All possibly, probably or definitely related AEs were reported as either mild or moderate in severity.

There were no Serious Adverse Events. There were no obvious differences in reported AEs or frequency of AEs for subjects when treated with Intraject compared with treatment with Imigran™ Mk II injection.

For all injection sites, Intraject® injection caused more bleeding, erythema, swelling and bruising than the Imigran™ MK II injection, except for the arm where Imigran™ Mk II injection caused more bruising than Intraject® and for the abdomen where both treatments had the same incidence of erythema.

There were no significant differences in the pain score between Intraject® and Imigran™ Mk II injection. The average sensation score for pain was 3.8 for both treatments in the abdomen, 3.7 for both treatments in the arm, and 3.1 for Intraject® compared with 3.2 for Imigran™ Mk II when injected in the thigh. Out of 18 subjects completing the study, 7 (39%) preferred the Intraject® system to the Imigran™ Mk II injection, 5 (28%) preferred the Imigran™ Mk II injection and six subjects (33%) had no preference.

*Pharmacokinetics:*
The concentrations of sumatriptan were measured in plasma. Single-dose pharmacokinetic parameters were determined.

The major pharmacokinetic parameters, including area under the plasma concentration versus time curve from time zero to the time of last measurable concentration (AUCt), area under the plasma concentration versus time curve from time zero to infinite time ($AUC_{inf}$), maximum observed plasma concentration ($C_{max}$), time to reach maximum observed plasma concentration ($T_{max}$), apparent terminal plasma elimination rate constant ($K_{el}$) and half-life ($T_{half}$), were determined from the plasma concentration data. The pharmacokinetic parameters and observations were compared between treatments for all subjects who completed the study.

The least squares means of $C_{max}$, AUC and $AUC_{inf}$, back-transformed from the analysis of log-transformed parameters, and the least square means ratios, are shown in this table:

**Table 25: 3 Site PK Results**

| Dosing Site | PK Parameter | Number of subjects | Units | Test: 6 mg Intraject® system (Aradigm) | Reference: 6 mg Imigran™ Mk II injection (GlaxoSmithKline) | Least Squares Means Ratio (90% Confidence Interval) |
|---|---|---|---|---|---|---|
| Abdomen | Cmax | 12 | (ng/mL) | 66.67 | 71.69 | 93.0% (86.4 – 100.1%) |
| | AUCt | 12 | (ng*h/mL) | 69.64 | 78.16 | 89.1% (82.5 – 96.2%) |
| | AUCinf | 12 | (ng*h/mL) | 76.53 | 86.68 | 88.3% (82.5 – 94.5%) |
| Arm (013 not exptrapolable for Imigran dose) | Cmax | 12 | (ng/mL) | 82.99 | 82.29 | 100.8% (94.4 – 107.7%) |
| | AUCt | 12 | (ng*h/mL) | 72.55 | 80.86 | 89.7% (82.9 – 97.2%) |
| | AUCinf | 11 | (ng*h/mL) | 79.96 | 87.62 | 91.3% (84.4 – 98.7%) |
| Thigh (omitting 006 and 012) | Cmax | 10 | (ng/mL) | 60.46 | 58.95 | 102.6% (91.5 – 114.9)% |
| | AUCt | 10 | (ng*h/mL) | 64.55 | 74.68 | 86.4% (79.3 – 94.2)% |
| | AUCinf | 10 | (ng*h/mL) | 72.44 | 83.22 | 87.1% (80.6 – 94.0)% |

For the abdomen and arm (deltoid) injection sites, the 90% confidence intervals for the least squares means ratio of AUCt, AUCinf, Cmax, back-transformed following analysis on log-transformed parameters, all lie within the bioequivalence acceptance interval of 80%-125%.

For the thigh, two deviations with regards to dosing occurred: in Period 3, the Imigran™ MK II injection dose was not administered to subject 006 due to nurse error; in Period 2, Subject 012 did not receive a complete dose from the Imigran Mk II™ injection due to poor injection technique. Bioequivalence analysis was thus performed omitting subjects 006 and 012 (n=1 0). The 90% confidence interval for the least squares means ratio of $AUC_t$ extends slightly below 80%. The 90% confidence intervals for the least squares mean ratios of $AUC_{inf}$ and $C_{max}$ lie within the 80 - 125 % bioequivalence acceptance interval.

### 9.1.5 PK/BE Self-Administration at 2 of 3 Sites Study (ARD-2100-0501):

This was a randomized, open-label, single-dose, and four-way crossover study. It compared the pharmacokinetics, efficiency, ease, and tolerability of self-administered sumatriptan delivered to 2 of the 3 anatomical via the Intraject@ system versus the Imigran™ Mk II system in healthy adult subjects. The sequence of injections is shown in Table 26: Injection Site Sequence for Study -501 It was conducted by the Australian firm. (b) (4)

The objectives were primarily to evaluate the pharmacokinetics and bioequivalence of self-administered sumatriptan delivered subcutaneously via the Intraject system (test) compared to sumatriptan delivered subcutaneously via the Imigran™ Mk II system (reference) at each of 3 injection sites (abdomen, thigh or arm). Secondarily, the bioequivalence of self-administered sumatriptan delivered subcutaneously via the Intraject@ system (test) compared to sumatriptan delivered subcutaneously via the Imigran™ Mk II system (reference) pooled across 3 injection sites (abdomen, thigh and arm) was evaluated. Finally, the sponsor evaluated the tolerability and subject preference compared to the currently marketed device in this trial.

**Number of Subjects and Study Duration:**
For each study cohort, subjects were resident in the clinical facility overnight prior to Period 1 (Day 1) and until 24 hours post dosing in Period 4 (Day 4). Subjects returned to the clinical facility approximately 1 week later for a follow-up (end of study) visit.

The total duration of the study was approximately 7 weeks (3 weeks screening and enrollment and 3 weeks of treatment (1 week of treatment for each of the 3 cohorts) and follow-up).

The study population consisted of 24 generally healthy, non-smoking volunteers, male and female, aged between 18 and 40 years (inclusive), who fulfilled all the entry criteria. Approximately equal numbers of male and female subjects were enrolled.

**Design:**
This was a single center, randomized, single-dose, open-label, four-way crossover study in 24 healthy adult subjects.

The Study Treatments were:

- Test formulation: Intraject@ Sumatriptan: each injector will contain 0.5 mL of solution with 6 mg of sumatriptan (base) as the succinate salt and
- Reference formulation: Imigran™ Mk II Injection: each injector will contain 0.5 mL of solution with 6 mg of sumatriptan (base) as the succinate salt

Injection treatment sequences are shown in this table:

**Table 26: Injection Site Sequence for Study -501**

| Cohort (Study Week) | Sequence | Day -1 | Day 1 Period I | Day 2 Period II | Day 3 Period III | Day 4 Period IV | Day 5 |
|---|---|---|---|---|---|---|---|
| 1 | A1 | *PM Check-in* | Intraject Abdomen | Imigran Abdomen | Intraject Thigh | Imigran Thigh | *AM Check-out* |
| 1 | B1 | *PM Check-in* | Imigran Abdomen | Imigran Thigh | Intraject Abdomen | Intraject Thigh | *AM Check-out* |
| 1 | C1 | *PM Check-in* | Imigran Thigh | Intraject Thigh | Imigran Abdomen | Intraject Abdomen | *AM Check-out* |
| 1 | D1 | *PM Check-in* | Intraject Thigh | Intraject Abdomen | Imigran Thigh | Imigran Abdomen | *AM Check-out* |
| 2 | A2 | *PM Check-in* | Intraject Arm | Imigran Arm | Intraject Thigh | Imigran Thigh | *AM Check-out* |
| 2 | B2 | *PM Check-in* | Imigran Arm | Imigran Thigh | Intraject Arm | Intraject Thigh | *AM Check-out* |
| 2 | C2 | *PM Check-in* | Imigran Thigh | Intraject Thigh | Imigran Arm | Intraject Arm | *AM Check-out* |
| 2 | D2 | *PM Check-in* | Intraject Thigh | Intraject Arm | Imigran Thigh | Imigran Arm | *AM Check-out* |
| 3 | A3 | *PM Check-in* | Intraject Arm | Imigran Arm | Intraject Abdomen | Imigran Abdomen | *AM Check-out* |
| 3 | B3 | *PM Check-in* | Imigran Arm | Imigran Abdomen | Intraject Arm | Intraject Abdomen | *AM Check-out* |
| 3 | C3 | *PM Check-in* | Imigran Abdomen | Intraject Abdomen | Imigran Arm | Intraject Arm | *AM Check-out* |
| 3 | D3 | *PM Check-in* | Intraject Abdomen | Intraject Arm | Imigran Abdomen | Imigran Arm | *AM Check-out* |

Assessments included vital signs, tolerability (using a categorical sensation score and site inspection for erythema, swelling, bleeding, and bruising). A visual assessment, using a 5-point rating scale was used to estimate the amount of residual injectate for all Intraject injections. Subject preference for the 2 devices was studied through a subject's questionnaire. Continuous ECG monitoring occurred for at least 4 hours post dosing while clinical laboratory measures were performed during screening, check-in and in evenings prior to dosing on day 2, 3 and 4, and at exit evaluation. Fifteen blood samples for pharmacokinetic assessment were collected at -15, +2, +5, +10, +12, +15, +20, +30, +45 minutes, +1, +1.5, +2, +3, +4, and +8 hours post dose in each treatment period. A total of 60 blood samples for pharmacokinetic analysis were collected during the entire study.

**Data analysis:**

*Screening, Compliance, and Safety Data*

Demographics were tabulated and summarized. Physical examination and medical history data at baseline were listed. All clinical safety and tolerability data were listed for each subject. Laboratory values outside the laboratory's normal ranges were listed separately, with associated repeat values listed together with comments as to their clinical

significance. Vital signs (heart rate, respiratory rate, resting systolic/diastolic blood pressure) and ECG parameters were tabulated and summarized.

*Tolerability and Subject Preference Data*
Injection site pain scores and injection site signs (including swelling, erythema, bleeding and bruising) were tabulated and summarized per treatment. Treatment emergent adverse events were listed and summarized per treatment. All adverse events reported in this study were coded using MedDRA. Subject preference ratings were tabulated and summarized per treatment.

*Pharmacokinetic Data*
The concentrations of sumatriptan were measured in blood samples (plasma) from all subjects, using a validated assay method. The pharmacokinetic analysis included collection of a concentration-time profile of sumatriptan following each dose. The area under the plasma concentration-time curve ($AUC_t$, $AUC_{inf}$), maximal plasma concentration ($C_{max}$), time to maximal concentration ($T_{max}$), terminal elimination half-life ($T_{half}$) and apparent terminal elimination rate ($K_{el}$) of sumatriptan were determined.

*Statistical Comparisons - Bioequivalence assessment*
Assessment of bioequivalence was evaluated between delivery methods (Intraject vs. Imigran™ MKII Injection) for each administration site, and pooled across all administration sites. Bioequivalence was demonstrated if the 90% confidence intervals of the ratios of log-transformed $AUC_t$, $AUC_{inf}$, and $C_{max}$ lay within the acceptance range of 80%-125%. Comparability between administration sites (abdomen vs. thigh vs. arm (deltoid)) for both delivery methods was also assessed.

**Results:**
*Subject preference, safety and tolerability*
Adverse events were recorded for all 24 subjects. There were no Serious Adverse Events. All AEs were reported as either mild or moderate in severity. Most AEs were adverse events commonly associated with sumatriptan (head discomfort, nausea, paresthesia, throat tightness, and headache) and thus were deemed possibly, probably or definitely related to study medication.

All vital sign measurements taken during the study observation period were deemed to be acceptable by the Principal Investigator. There were no clinically significant observable trends in measurements obtained from baseline (Screening) through to the Exit Evaluation.

There were no clinically significant changes in physical findings or clinical laboratory diagnostic results for any of the subjects throughout the study that were considered to be related to either study treatment, from Screening through to the Exit Evaluation, except for one subject who had a short episode of hyponatremia which could possibly have been related.

There was little or no residual drug formulation at the injection site for all Intraject@ injections administered to the abdomen and thigh. For Intraject@ injections to the deltoid, 2 subjects had wet injections (notable splashback) with an unknown amount of injectate delivered, and 4 additional subjects had partial injections estimated to be 90-94% delivery of the injectate.

The incidence of bleeding was comparable for both devices. The incidence of erythema and swelling were higher when using the Intraject@ device than for the Imigran™ MK II injection, but this was less pronounced at the deltoid injection site. The mean pain scores were similar for the Intraject@ and Imigran™ Mk II devices at each site. There was very little bruising observed with either device. Out of 24 subjects in this study, twenty subjects (83%) preferred the Imigran™ Mk II injection, three subjects (13%) preferred the Intraject@ system, and one subject (4%) had no preference. Eleven subjects (46%) indicated they would be unwilling to use the Intraject@ system on a regular basis, compared with two subjects (8%) who would be unwilling to regularly use the Imigran™ Mk II injection.

Overall, Intraject@ injections appear to be as safe as the currently marketed Imigran™ Mk 1\ injection in healthy volunteers.

*Pharmacokinetics:*
The concentration of sumatriptan was measured in plasma at specified intervals. The single-dose pharmacokinetic parameters of sumatriptan determined from the plasma concentration data were: area under the plasma concentration-time curve ($AUC_t$, $AUC_{inf}$), maximum plasma concentration ($C_{max}$), time to maximal concentration ($T_{max}$), terminal elimination half-life ($T_{half}$) and apparent terminal elimination rate ($K_{el}$). The pharmacokinetic parameters and observations were compared between treatments and injection sites for all subjects who completed the study.

The least squares means of $C_{max}$, AUC and $AUC_{inf}$, back-transformed from the analysis of log-transformed parameters, and the least square means ratios, are shown in the following table:

**Table 27: Study PK Data from the 3 Sites**

| Dosing Site | PK Parameter | Number of subjects | Units | Test: 6 mg Intraject® system (Aradigm) | Reference: 6 mg Imigran™ Mk II injection (GlaxoSmithKline) | Least Squares Means Ratio (90% Confidence Interval) |
|---|---|---|---|---|---|---|
| Abdomen | Cmax | 16 | (ng/mL) | 82.49 | 84.47 | 97.7% (91.5 – 104.2)% |
| | AUCt | 16 | (ng*h/mL) | 76.24 | 79.54 | 95.9% (92.9 – 98.9)% |
| | AUCinf | 16 | (ng*h/mL) | 84.88 | 87.94 | 96.5% (93.1 – 100.1)% |
| Arm (omitting 018 and 026) | Cmax | 14 | (ng/mL) | 80.6 | 74.05 | 108.8% (92.2 – 128.5)% |
| | AUCt | 14 | (ng*h/mL) | 64.74 | 68.94 | 93.9% (84.7 – 104.1)% |
| | AUCinf | 14 | (ng*h/mL) | 74.15 | 78.67 | 94.3% (85.2 – 104.3)% |
| Thigh | Cmax | 16 | (ng/mL) | 76.6 | 72.03 | 106.3% (91.1 – 124.2)% |
| | AUCt | 16 | (ng*h/mL) | 72.26 | 77.07 | 93.8% (87.9 – 99.9)% |
| | AUCinf | 16 | (ng*h/mL) | 80.41 | 86.41 | 93.1% (87.7 – 98.8)% |
| All sites pooled (omitting 018 and 026 for Arm) | Cmax | 24 | (ng/mL) | 80.66 | 77.58 | 104.0% (96.1 – 112.5)% |
| | AUCt | 24 | (ng*h/mL) | 71.56 | 75.71 | 94.5% (90.6 – 98.6)% |
| | AUCinf | 24 | (ng*h/mL) | 80.25 | 84.81 | 94.6% (90.0 – 98.5)% |

*Bioequivalence Results:*
For the abdomen and thigh injection sites, and when pooled across all injection sites, the 90% confidence intervals for the least squares means ratio of AUCt, AUCinf, Cmax, back-transformed following analysis on log-transformed parameters, all lie within the bioequivalence acceptance interval of 80%-125%.

For the arm (deltoid) injection site, two subjects (018 and 026) failed to self-administer a measurable dose using the Intraject® device. Bioequivalence analysis was thus performed omitting subjects 018 and 026 (n=14).

The 90% confidence interval for the least squares means ratio of $C_{max}$ extends slightly above 125%. The 90% confidence intervals for the least squares mean ratios of AUC and $AUC_{inf}$ lie within the 80 - 125% bioequivalence acceptance interval. In a three-way comparison between sites of injection for each device, the $C_{max}$ values were more comparable between injection sites for the Intraject® System than for Imigran™ MK II injection.

### 9.1.6 PK/BE Self-Administration at Each of 3 Sites Study (ARD-2100-0504):

This was a randomized, open-label, single-dose, three-way crossover study comparing the pharmacokinetics, efficiency, ease, and tolerability of self-administered sumatriptan delivered via the Intraject® system versus the Imigran™ MKII system in healthy adult subjects at each of 3 sites.

It primarily studied the pharmacokinetics and bioequivalence of self-administered sumatriptan delivered subcutaneously via the Intraject "test" system (in the anterior and lateral arm) compared to sumatriptan delivered subcutaneously via the Imigran Mk II "reference" system (in the lateral arm only). Secondarily it evaluated the tolerability, ease of administration, and subject preference for injections given in the anterior vs. lateral arm.

**Number of Subjects and Duration:**
The study population consisted of 24 generally healthy, non-smoking volunteers, male and female, aged between 18 and 37 years (inclusive). Equal numbers of male and female subjects were enrolled..

The total duration of the study was approximately 5 weeks, comprising a four-week screening period, and then two consecutive groups of 12 subjects dosed daily for 3 days. Subjects were resident in the clinical facility for 4 nights, from the evening prior to the first dose until approximately 24 hours after the third dose, with an Exit evaluation at check-out.

**Design:**
This was a single centre, randomized, single-dose, open-label, three-way crossover study in 24 healthy adult subjects.

The study treatment for the Test System was : Intraject@ Needle-free Subcutaneous Injection System: each injector contained 0.5 mL of saline solution with 6 mg of sumatriptan (base) as the succinate salt. For the Reference System was: Imigran™ Mk II Injection: each injector contained 0.5 mL of saline solution with 6 mg of sumatriptan (base) as the succinate salt.

The 3-way Williams' square design randomization schedule shows the injection/site sequences:

**Table 28: Randomization Schedule**

(b) (4)

Key for Treatments:

R = Imigran™ MK II, Lateral arm (Reference), self-administered

L = Intraject®, Lateral arm, self-administered

A = Intraject®, Anterior arm, self-administered

Assessments included :

- Demographics, medical history, medication history, and physical examination data collected at screening. EGG was done at screening and continuous ECG monitoring occurred for at least 4 hours post dosing in each study period. Vital

signs were taken at screening, check-in, -15 minutes prior to treatment, at +15, +30 minutes, at +1, +2, +3, +4, and +8 hours following each dose, and at Exit. Clinical laboratory measures were performed during Screening, Check-in, at 4 hours post-dose on Days 1, 2, 3, and Exit Evaluation. Occurrence of adverse events and use of concomitant medications were monitored throughout the study period. At each vital signs collection time, subjects were questioned regarding adverse events.

• Tolerability of injections using several measures. Categorical sensation score for pain was assessed using an 11-point scale (0 = no pain, 10 = worst pain imaginable) immediately following the dosing. Injection sites were assessed for erythema, swelling, bleeding, and bruising, within 15 minutes pre-dose, immediately following dosing, then at +5, +15, +30 minutes, and at +1, +2, +3, +4, +8, and +24 hours post dose during each treatment period.

• A visual assessment, using a 5-point rating scale (Appendix 3 of Protocol), was used to evaluate the amount of residual injectate immediately after all Intraject injections.

• Ease of administration of Intraject treatment to the lateral versus anterior arm and subject preferences for the site of application for regular injections were collected using a questionnaire at Day 3 (Period 3) after all Dose Administrations were completed.

• Twelve blood samples for pharmacokinetic assessment were collected at -15, +2, +5, +10, +12, +15, +20, +30 minutes, +1, +2, +3, and +8 hours post dose in each treatment period. Up to 36 blood samples for pharmacokinetic analysis were collected from each subject during the study.

**Data Analysis:**

Demographics were tabulated and summarized. Physical examination and medical history data at baseline were listed. Laboratory values outside the laboratory's normal ranges were listed separately, with associated repeat values listed together with comments as to their clinical significance. Vital signs and ECG assessments were tabulated and summarized. All adverse events reported in this study were listed for each subject. Treatment-emergent adverse events were listed and summarized. All adverse events were coded for System Organ Class and Preferred Term, using MedDRA v 8.0. Injection site pain scores and injection site signs (including swelling, erythema, bleeding, and bruising) were listed for each subject and summarized per treatment and per dose administration site. Subject ratings of ease of administration for Intraject injections and regular dose administration site preferences were listed and summarized.

*Pharmacokinetic Data*

The pharmacokinetic analysis included collection of a concentration-time profile of sumatriptan following each dose. The area under the plasma concentration-time curve ($AUC_t$, $AUC_{inf}$), maximal plasma concentration ($C_{max}$), time to maximal concentration ($T_{max}$), terminal elimination half-life ($T_{half}$), and apparent terminal elimination rate ($K_{el}$) of sumatriptan were determined.

Assessment of bioequivalence was evaluated between each pair of treatments (Intraject at each administration site versus Imigran in lateral upper arm, anterior upper arm versus lateral upper arm for Intraject). Bioequivalence was demonstrated if the 90% confidence intervals of the ratios of $AUC_t$, $AUC_{inf}$, and $C_{max}$ lay within the acceptance range of 80%-125%.

**Results:**

*Safety, Tolerability, Ease of Administration, and Subject Preference*

Adverse events (AEs) were recorded for all 24 subjects. There were no serious adverse events. All AEs were reported as either mild or moderate in severity. Most AEs were adverse events commonly associated with sumatriptan (chest discomfort, dizziness, flushing, headache, head discomfort, nausea, paresthesia, muscle tightness, and throat tightness) and thus were deemed possibly or probably related to study medication. There was no obvious difference in type of AEs or frequency of AEs reported between treatments with the Intraject system and the Imigran MK \I injection.

All vital sign measurements taken during the study observation period were deemed to be acceptable by the Principal Investigator. There were no clinically significant observable trends in measurements obtained from baseline (Screening) through to the Exit Evaluation. All continuous ECG monitoring during the study was deemed to be not clinically significant by the Principal Investigator. There were no clinically significant changes in clinical laboratory diagnostic results for any of the subjects throughout the study that were considered to be related to either study treatment, from Screening through to the Exit Evaluation.

Some residual injectate after dosing with the Intraject device was observed in 4 subjects. One subject had considerable residual injectate (rated as 5-90% penetration) after dose administration to the lateral arm, with less residual (rated as at least 90% penetration) for the other 3 subjects.

Injection site assessments showed a higher incidence of erythema, swelling, and bleeding for dose administration with the Intraject system than the Imigran MKII injection. There was very little bruising with either device. The average and median pain score was higher for the Intraject device at both sites than for Imigran Mk II injection.
Subjects indicated that the anterior arm was an easier site to perform an injection using the Intraject device. However, there was no marked preference for either lateral arm or anterior arm as the site for regular injections using the Intraject device.

*Pharmacokinetics*

The pharmacokinetic parameters and observations were compared between treatments for all subjects who completed the study with evaluable pharmacokinetic profiles. Due to missing samples at critical kinetic time points, not all profiles were included in the evaluations of bioequivalence between each pair of treatments.

The least squares means of $C_{max}$, $AUC_t$, and $AUC_{inf}$, back-transformed from the analysis of log-transformed parameters, and untransformed Tmax, with the least squares means ratios for comparison between each pair of treatments, are in the table below.

**Table 29: Comparative PK Findings by Device and Arm Injection Site Location**

**Intraject (Lateral Arm) vs Imigran MK II (Lateral Arm) (n=21)**

| PK Parameter | Units | 6 mg Intraject system, Lateral Arm (Aradigm) | 6 mg Imigran Mk II injection, Lateral Arm (GlaxoSmithKline) | Least Squares Means Ratio (90% Confidence Interval) |
|---|---|---|---|---|
| Cmax | (ng/mL) | 99.13 | 95.43 | 103.9% (95.0 – 113.6)% |
| AUCt | (ng*h/mL) | 68.63 | 76.53 | 89.7% (81.6 – 98.6)% |
| AUCinf | (ng*h/mL) | 76.75 | 86.11 | 89.1% (80.9 – 98.2)% |
| Tmax | (h) | 0.16 | 0.17 | 95.2% (80.4 – 109.9)% |

**Intraject (Anterior Arm) vs Imigran MK II (Lateral Arm) (n=22)**

| PK Parameter | Units | 6 mg Intraject system, Anterior Arm (Aradigm) | 6 mg Imigran Mk II injection, Lateral Arm (GlaxoSmithKline) | Least Squares Means Ratio (90% Confidence Interval) |
|---|---|---|---|---|
| Cmax | (ng/mL) | 104.66 | 95.91 | 109.1% (101.5– 117.3)% |
| AUCt | (ng*h/mL) | 77.05 | 76.68 | 100.5% (96.8– 104.3)% |
| AUCinf | (ng*h/mL) | 85.48 | 86.13 | 99.2% (96.0 – 102.6)% |
| Tmax | (h) | 0.17 | 0.17 | 100.0% (85.6 – 114.4)% |

**Intraject (Anterior Arm) vs Intraject (Lateral Arm) (n=22)**

| PK Parameter | Units | 6 mg Intraject system, Anterior Arm (Aradigm) | 6 mg Intraject system, Lateral Arm (Aradigm) | Least Squares Means Ratio (90% Confidence Interval) |
|---|---|---|---|---|
| Cmax | (ng/mL) | 97.67 | 99.36 | 98.3% (82.8 – 116.7)% |
| AUCt | (ng*h/mL) | 70.74 | 69.01 | 102.5% (85.8 – 122.4)% |
| AUCinf | (ng*h/mL) | 79.23 | 77.27 | 102.5% (87.0 – 120.9)% |
| Tmax | (h) | 0.17 | 0.16 | 106.2% (91.3 – 121.1)% |

*Bioequivalence*

Bioequivalence was assessed for subcutaneous administration of sumatriptan delivered via the Intraject system (in the anterior and lateral arm) compared with the Imigran Mk II system (in the lateral arm only), and also between the two sites for administration via the Intraject system. For each pairwise comparison, the 90% confidence intervals for the least squares means ratio of $AUC_t$, $AUC_{inf}$, $C_{max}$, back-transformed following analysis on log-transformed parameters, all lie within the bioequivalence acceptance interval of 80%-125%, based on subjects with evaluable pharmacokinetic profiles for both treatments in the comparison. The 90% confidence intervals for the least squares means ratio of $T_{max}$, untransformed, also lie within the interval of 80%-125% for each pairwise comparison.

In summary, this study showed bioequivalence, based on $C_{max}$, $AUC_t$, $AUC_{inf}$, and $T_{max}$, for sumatriptan delivered subcutaneously via the Intraject system to the lateral upper lateral arm and anterior upper arm compared to sumatriptan delivered subcutaneously via the Imigran MK II injection to the lateral upper arm, and also showed bioequivalence

between sumatriptan delivered subcutaneously via the Intraject system to the anterior and lateral upper arm.

## 9.2 Literature Review/References

The sponsor performed an adequate search of the literature. Independently, I also searched for local site reaction comparators for the needle-free injector and Imitrex injection which yielded no information of scientific value.

## 9.3 Labeling Recommendations

The draft labeling submitted with this supplement is inadequate, because the annotated label is not accurate. Numerous changes to the last approved Imitrex Injection label are not identified in their annotated label. The sponsor was asked to carefully review their proposed labeling and Imitrex Injection last approved labeling (02/01/2006), and clearly identify ALL changes, including deletions.

## 9.4 Advisory Committee Meeting

None.

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/s/
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Robert D. Harris
10/31/2008 02:55:04 PM
MEDICAL OFFICER

Eric Bastings
10/31/2008 03:29:31 PM
MEDICAL OFFICER

# Cross-Discipline Team Leader Review

| | |
|---|---|
| **Date** | October 30, 2008 |
| **From** | Eric Bastings, MD. |
| **Subject** | Cross-Discipline Team Leader Review |
| **NDA/BLA #**<br>**Supplement#** | 22239 |
| **Applicant** | Zogenix |
| **Date of Submission** | December 28, 2007 |
| **PDUFA Goal Date** | October 31, 2008 |
| | |
| **Proprietary Name / Established (USAN) names** | Sumavel DosePro (sumatriptan injection) |
| **Dosage forms / Strength** | Injection (subcutaneous needle-free) |
| **Proposed Indication(s)** | 1. Acute treatment of migraine<br>2. Cluster headache |
| **Recommended:** | *Complete Response* |

## 1. Introduction

The sponsor, Zogenix, submitted a 505(b)(2) application for a drug (sumatriptan)/device combination product for the acute treatment of migraine attacks with or without aura and the acute treatment of cluster headache episodes.

The product is a pre-filled, single-use disposable, needle-free drug delivery system designed to deliver 0.5 mL (6 mg of sumatriptan as the succinate salt) into the subcutaneous tissue (Figure 1). To use Sumavel DosePro, the patient has to press the end of the device to the skin at the target area (i.e. abdomen or thigh), which triggers the propulsion of sumatriptan through a small hole in the device (under the pressure of compressed nitrogen), and through the skin into the subcutaneous tissue.

**Figure 1: Sumavel DosePro drug/device combination**

The sponsor is using as a reference NDA 20-080 for IMITREX injection (6 mg/ 0.5 mL) to support the safety and efficacy of the device. Sumavel DosePro (previously named “Intraject Sumatriptan) uses the same dose, concentration and volumes as the reference product, and is identical in composition. Therefore, the sponsor was not required to conduct any new efficacy trial or long-term safety trial.

The sponsor conducted several bioavailability and tolerability studies in healthy volunteers, as well as a usability study in migraine patients during an attack.

## 2. Background

Imitrex (sumatriptan) is approved under several formulations for the treatment of migraine: Imitrex Injection (NDA 20-080); Imitrex Tablets (NDA 20-132) ; and Imitrex Nasal Spray (NDA 20-626). The patent for sumatriptan expires on February 6, 2009.

This needleless mode of administration, according to the sponsor, eliminates needle-phobia, improves compliance, and reduces under-dosing resulting from poor injection technique, even though these hypotheses were not tested in the development program.

## 3. CMC/Device

Dr. David Claffey, from ONDQA, reviewed the CMC data. Dr. Claffey recommends an approval action from a CMC perspective, subject to the review by the nonclinical reviewer of the proposed acceptance criteria for drug product impurities 1 and 3. Dr. Claffey notes that the proposed limits for these impurities (impurity 1 at NMT (b) (4), and impurity 3 at NMT (b) (4)) are above the ICH Q3b recommended qualification limits (see discussion below). Dr. Claffey notes that should lower limits for these impurities be found to be necessary, a reevaluation of the drug product expiry period will be required.

Dr. Claffey also notes, in his review, an overall acceptable recommendation from the Office of Compliance.

Mr. William M. Burdick, from CDRH, concurred with Dr. Claffey that the device is acceptable.

## 4. Nonclinical Pharmacology/Toxicology

Dr. Andrea Powell conducted the nonclinical review (Dr. Lois Freed did the supervisory non clinical review). As noted by Dr. Powell, no nonclinical studies were required to assess the local toxicity and local distribution of sumatriptan administered with this device. Dr. Powell observes that the only nonclinical issues that needed to be addressed were impurities and leachables.

As discussed by Dr. Powell and Dr. Claffey, the proposed drug product specification limits for 2 of the impurities (#1 and #3) exceed the threshold for qualification. Dr. Powell further notes no additional nonclinical studies would be required if the sponsor had demonstrated that impurities 1 and 3 were present in the innovator product at levels greater than, or equal to, those in the proposed specifications limits. Dr. Powell discusses that the sponsor was not able to support the proposed specifications through that comparison with the innovator product.

Therefore, Dr. Powell believes that the sponsor needs to qualify the impurities with an appropriate battery of nonclinical tests using either the isolated impurities or the drug substance containing levels of the impurities that are at least equal to the proposed specification limits.

Dr. Powell notes that the sponsor submitted several studies support the qualification of drug product impurities 1 and 3. Dr Powell reviewed the studies submitted with the original NDA: Study 961610, an in vitro bacterial mutation assay (Ames test) using a “stressed” sumatriptan succinate formulation, and Study 961611, an in vitro chromosome aberration assay in human peripheral lymphocytes using a “stressed” sumatriptan succinate formulation.

Dr. Powell observes that the Ames test was negative, but that the in vitro chromosomal aberration assay in human peripheral lymphocytes was positive. Therefore, she recommends that the sponsor be required to further address this issue.

Dr. Freed agrees, and concludes that since impurities are unlikely to confer any clinical benefit, the presence of a genotoxic impurity would result in unacceptable risk. I concur.

## 5. Clinical Pharmacology/Biopharmaceutics

The sponsor is referring to NDA 20-080 for information on drug-drug interactions, pathway of elimination, and special populations.

The sponsor also submitted a pivotal BA/BE study conducted in the US (Study ZX001-0601) and three pilot studies conducted in Australia. Mrs. Carol Noory conducted the clinical pharmacology review. Mrs. Noory finds the clinical pharmacology information acceptable.

Mrs. Noory’s review focused on the pivotal bioequivalence study ZX001- 0601. Study ZX001-0601, was a Phase 1, randomized, open-label, single-dose, 4-way crossover in an incomplete-block treatment design in 54 healthy adult male and female subjects between the ages of 18 and 55. Each subject received the test (Sumavel DosePro 6 mg) and the reference, (Imitrex STATdose 6 mg) in two of the three possible injection sites (i.e., abdomen, arm, and/or thigh). Mrs. Noory concludes that the test and reference are bioequivalent at the abdomen and thigh sites, but not at the arm injection site, where AUC and Cmax were respectively 26% and 28% lower for Sumavel DosePro than for Imitrex STATdose.

## 6. Clinical/Statistical- Efficacy

For this 505(b)(2) application, the sponsor is using NDA 20-080 to support efficacy of the product. No new efficacy study was conducted.

## 7. Safety

Dr. Robert Harris reviewed the clinical safety data, and Ms. Felicia Duffy reviewed the usability data.

Dr. Harris notes that there are no new safety concerns from the clinical PK/PD and usability studies conducted by the sponsor. This is not unexpected, given that the product is bioequivalent to an already marketed product, Imitrex Injection, and that the development program was relatively limited (i.e. no new efficacy trial or long-term safety assessment). It is however noteworthy that local site reactions were markedly higher with Sumavel DosePro than with the reference product, Imitrex Injection (see table1). This information should be included in labeling.

Table 1: Local site reactions in Sumavel DosePro active-controlled studies

| | Sumavel DosePro | Imitrex Injection |
|---|---|---|
| **Bleeding** | | |
| *Immediately after* | 51% | 22% |
| *1 hour post-injection* | 5% | 0% |
| *8 hours post-injection* | 0% | 0% |
| *24 hours post-injection* | 0% | 0% |
| | | |
| **Swelling** | | |
| *Immediately after* | 84% | 1% |
| *1 hour post-injection* | 65% | 15% |
| *8 hours post-injection* | 5% | 0% |
| *24 hours post-injection* | 1% | 1% |
| | | |
| **Erythema** | | |
| *Immediately after* | 18% | 4% |
| *1 hour post-injection* | 56% | 25% |
| *8 hours post-injection* | 22% | 4% |
| *24 hours post-injection* | 12% | 3% |
| | | |
| **Bruising** | | |
| *Immediately after* | 9% | 1% |
| *1 hour post-injection* | 3% | 3% |

| | Sumavel DosePro | Imitrex Injection |
|---|---|---|
| *8 hours post-injection* | 4% | 5% |
| *24 hours post-injection* | 6% | 6% |

Ms. Duffy notes that the sponsor conducted three usability studies. In the first two studies, subjects performed simulated injections into a foam pad. The third usability study (ZX001-0701) was conducted with 52 migraineurs who actually injected themselves with the drug product during a migraine attack. Ms. Duffy comments that nearly all reported uses of Sumavel DosePro were performed correctly (122/125 usability assessments). Three incorrect uses in three separate subjects were reported, each attributed to a different causative factor. One subject failed to press the device straight down against the skin until the burst of air was heard. However, the subject used the device correctly in subsequent uses. The second subject felt that the device "bounced off her leg", and the third subject indicated that they "did not receive medication" and used another device. Ms. Duffy notes that in 124/125 reported uses of Sumavel DosePro, 99% of subjects somewhat agreed, agreed or strongly agreed that instructional materials were adequate.

## 8. Advisory Committee Meeting

No advisory meeting was needed for this 505(b)(2) application, because this product is bioequivalent to an already approved marketed product, the Imitrex STATdose System, for which there is sufficient safety experience.

## 9. Pediatrics

PREA was not triggered for this application.

## 10. Other Relevant Regulatory Issues

Patent: the referenced product's patent expires on February 6, 2009.

DSI conducted an audit of the clinical and analytical portions of the following bioequivalence study ZXOOl-601. DSI identified some minor deficiencies, which were evaluated by the OCB review team. OCB concluded that the issues found during the inspection do not to impact the bioequivalence evaluation of Intraject Sumatriptan in the abdomen and the thigh.

## 11. Labeling

Ms. Felicia Duffy, from the Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed proprietary name.

DMEPA concluded that the proposed name, Sumavel DosePro, is vulnerable to name confusion that could lead to medication errors with the name (b) (4)

(b) (4). According to DMEPA, the acceptability of the proprietary name is dependent upon which application is approved first. If Sumavel DosePro is approved first, DMEPA will recommend that the second product, (b) (4) seek an alternate name. DMEPA also notes that if the product approval is delayed beyond 90 days from the date of their review, the proposed name must be resubmitted for evaluation. Since the patent for the reference product only expires in February 2009, approval is not expected before that time, so that a new DMEPA review will very likely be needed.

This application included a conversion of the Imitrex labeling into PLR. Comments from the various review disciplines were integrated into the proposed labeling. A draft proposed labeling will be included in the action letter, but final labeling negotiations will take place in the next cycle.

DMEPA reviewed the carton and container labels, insert labeling, and postmarketing data for sumatriptan and identified areas of improvement that may minimize the potential for medication errors with Sumavel DosePro (sumatriptan) injection:

*Container Label and Carton Labeling*
1. Provide better color contrast with the background of the label for the font used to display the proprietary name, established name, and product strength.
2. Increase the prominence of the product strength. Revise the product strength to include the volume in each injection (e.g., 6 mg/0.5 mL).
3. Relocate “DosePro” so it appears immediately following “Sumavel” in order to minimize confusion that the proprietary name is Sumavel DosePro rather than “DosePro Sumavel”.
4. Include the route of administration statement “For Subcutaneous Use Only” on the principle display panel.

*Container Label*
1. Relocate the NDC number to the top third of the principle display panel in accordance with 21 CFR 207.35(3)(i).

*Carton Labeling*
1. On the sample 4-pack display carton, relocate the NDC number to the top third of the principle display panel in accordance with 21 CFR 207.35(3)(i) and increase the prominence of the NDC number.
2. Relocate the “See full prescribing information….” statement to the side panel.
3. Include the volume in the net quantity of the carton (e.g., 1 prefilled, 0.5 mL single-dose unit)

## 12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: I recommend a complete response action. The nonclinical issue (impurity 1 and impurity 3 qualification) described above must be resolved prior to approval.

Risk Benefit Assessment: this product is bioequivalent to an already approved and marketed product, Imitrex STATdose. This product has a higher rate of injection site adverse reactions, but has the theoretical benefit of having the potential to be used by patients with needle-phobia.

Recommendation for Postmarketing Risk Management Activities: none.

Recommendation for other Postmarketing Study Commitments: none.

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Eric Bastings
10/31/2008 06:03:26 PM
MEDICAL OFFICER

**MEMORANDUM**

DATE: October 30, 2008

FROM: Director
Division of Neurology Products/HFD0-120

TO: File, NDA 22-239

SUBJECT: Action Memo for NDA 22-239, for the use of Sumavel DosePro (sumatriptan Intraject) in the acute treatment of migraine

NDA 22-239, for the use of Sumavel DosePro (sumatriptan Intraject) in the acute treatment of migraine, was submitted by Zogenix, Inc., on 12/28/07. This product contains the equivalent of 6 mg of sumatriptan in a needle-less device that delivers the drug to the subcutaneous space under pressure of compressed nitrogen gas, and is designed for self-administration. The product is designed to be bioequivalent to marketed Sumatriptan injection (Imitrex), and the application is submitted under section 505(b)(2) of the FD&C Act, relying on safety and effectiveness of Imitrex Injection as the reference listed drug.

The application contains reports of several Phase 1 studies, including a definitive bioequivalence study comparing a single injection of Sumavel given in the arm, thigh, or abdomen to a single injection of Imitrex. In addition, the application includes reports of a study examining the usability of the product in patients with an acute migraine headache, as well as a study examining the safety of multiple uses of the product. The application also contains the requisite CMC information. Included in the initial submission were the results of an Ames test as well an in vitro Chromosomal Aberration test, and additional non-clinical studies have been submitted during the review cycle.

The application has been reviewed by Dr. Rob Harris, medical officer, Drs. David Claffey and Ramesh Sood, ONDQA, Dr. John Metcalfe, microbiology, William Burdick, CDRH, Dr. Hyojong Kwon, Division of Scientific Investigations, Felicia Duffy, Division of Medication Error Prevention and Analysis, Dr. Andrea Powell, pharmacology, and Dr. Eric Bastings, Deputy Director, DNP. The review team recommends that the sponsor be sent a Complete Response (CR) letter. I will very briefly review the relevant data, and offer the rationale for the division's action.

As noted above, the sponsor has performed a bioequivalence study comparing single 6 mg doses given with the Sumavel product in the arm, thigh, and abdomen to a single 6 mg dose of Imitrex. This study demonstrates the bioequivalence (with acceptably similar $T_{max}$ 's) of Sumavel (when given in the abdomen and thigh) and Imitrex.

Regarding safety, a total of 194 subjects/patients have received a total of 452 injections. Generally, the type and incidence of adverse reactions seen were similar to those seen with Imitrex. However, there was considerably more Bleeding, Swelling, Erythema, and Bruising at the injection site with the Sumavel product than with Imitrex. In the table below, abstracted from the sponsor's Table 19, reproduced in Dr. Harris's review, I give the incidence of these events immediately after each injection:

| Event | Sumavel (N=297) | Imitrex (N=217) |
|---|---|---|
| Bleeding | 51% | 22% |
| Swelling | 84% | 0.5% |
| Erythema | 18% | 4% |
| Bruising | 9% | 0.5% |

These reactions were all self-limited, and resolved over time without sequelae. The frequency of Injection Site Pain was greater after Sumavel injection than after Imitrex injection. Depending upon different pooling strategies employed, the rates varied from 3-4% vs 1% for Sumavel and Imitrex, respectively.

In addition, the usage study demonstrated that patients were able to successfully self-inject with the Sumavel product.

There are no outstanding chemistry or device deficiencies.

The sponsor has identified 2 impurities, designated as Impurity 1 and 3, that also appear in the marketed sumatriptan products. Dr. Powell has undertaken a detailed review of this and related non-clinical issues.

Specifically, the sponsor proposes to market the product with a 24 month expiry, with specifications o (b) (4) for Impurity 1 and 3, respectively. Because these are above the level of qualification, the sponsor was informed that these would need to be qualified, unless they could show that a marketed sumatriptan product had similar amounts of these impurities. The sponsor could not document that current sumatriptan products contained these levels of these impurities, so undertook to qualify them.

The initial submission included the results of 2 in vitro genotoxicity assays, the Ames test and a chromosomal aberration test. As described by Dr. Powell, the sponsor exposed the drug product used in these assays to "stressed" conditions, and added additional impurity to the product in an attempt to produce drug with sufficient amounts of these 2 impurities to support their proposed specifications. The resultant drug product used did not quite contain sufficient amounts of impurities to qualify their proposed specifications, but, in Dr. Powell's view, the levels achieved were acceptable. As she describes, the Ames test was negative,

but the chromosomal aberration test was positive (although the sponsor concluded that it was negative, Drs. Powell and Freed are convinced otherwise). This outcome is problematic for several reasons.

Although the study is positive, it is not clear how to interpret the result. As noted earlier, the sponsor exposed the product used in the studies to stressed conditions ($50^{o}$ C for 35 days prior to its use). Apparently, this maneuver can produce numerous impurities and substances that do not exist in the unstressed product, in addition to the 2 impurities of interest. As Dr. Powell points out, because the study did not include a sumatriptan control (numerous previous genotoxicity studies of other sumatriptan products have uniformly been negative in several genotoxicity assays), it is difficult to know what impurity/substance is responsible for the positive finding. Indeed, the positive finding might be as a result of a substance produced by the stressed conditions, and not either of the relevant impurities.

Agency policy dictates that the total daily intake of genotoxic impurities be no more than 1.5 micrograms/day. If we were willing to ignore the possibility that the positive result in the chromosomal aberration test could have been due to substances other than the 2 impurities, and conclude that this study did, in fact, establish that either or both of the two impurities of interest were genotoxic (again, we believe the study is positive), then the amount of these genotoxic impurities to which patients could be exposed if 1) they were given the maximum daily labeled dose of 12 mg (2 injections), ***and*** 2) we approved the sponsor's proposed specifications, would be about (b) (4) (Impurity 1) and (b) (4) (Impurity 3) times the maximum allowable total daily intake, which would clearly be unacceptable.

Further, Dr. Powell finds the study inadequate because the highest concentration used did not produce adequate cytotoxicity. This was related to the sponsor's choice to study product with the same concentration as the clinical formulation. Guidances set higher concentration limits for these sorts of compounds, which the sponsor could have achieved by producing product with a higher concentration than that of the clinical product.

For the reasons stated above, then, the sponsor will need to perform additional genotoxicity studies, either with adequate levels of the impurities alone or, failing that, with the drug "spiked" with adequate levels of the impurities. If either of the impurities is found, in an adequate assay, to be genotoxic, the specifications must be set so as to limit the total daily intake to be no more than 1.5 micrograms/day.

Also as noted by Dr. Powell, in addition to assessing the genotoxic potential of these impurities, adequate qualification of these impurities (assuming that the sponsor wishes to have specifications for them that are above the level of qualification) entails additional studies, including an adequate 90 day repeat dose

toxicity bridging study in rats and an adequate embryo-fetal development study in rabbits. The sponsor has submitted a 90 day toxicity study in rats and an embryo-fetal development study in rabbits (with dose ranging studies to support dosing in each definitive study), but late in the review process. As Dr. Powell describes, because these studies were submitted late, they have not yet been reviewed, though they will need to be reviewed and found to be acceptable prior to approval.

Staff of the Division of Medication Error Prevention and Analysis have found the name Sumavel DosePro acceptable at this time, but an application for (b) (4) [redacted], is under review at this time. As Ms. Duffy of DMEPA points out (b) (4) [redacted] For this reason, if Sumavel is approved before (b) (4) the sponsor of the latter product will be asked to propose a new name. Of course, if (b) (4) is approved first, we will ask that a new name be proposed for what is now Sumavel.

In addition, the staff of DEMPA has several recommendations for improving the carton and container labeling for this product.

Comments

For the reasons specified above (primarily related to issues related to further assessments of the toxicity and genotoxicity of Impurities 1 and 3), I will issue the attached Complete Response with draft labeling.

Russell Katz, M.D.

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/s/

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Russell Katz
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