CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

MEMORANDUM

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

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: January 14, 2013

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 202-278 Resubmission (received July 17, 2012), Zecuity™ (sumatriptan) Iontophoretic Transdermal system (NP101, Zelrix™)

Background

NDA 202-278 was originally submitted by NuPathe Inc. on October 29, 2012 to support approval of Zelrix Iontophoretic Transdermal System (now Zecuity™ TDS), a drug/device combination product for treatment of migraine, with or without aura, in adults. Upon review, it was determined that the application could not be approved due to numerous (CMC, Biopharmaceutics, CDRH, microbiology, clinical pharmacology, nonclinical, clinical) deficiencies. A Complete Response (CR) letter was issued on August 29, 2011.

The nonclinical deficiencies (*cf. Pharmacology/Toxicology NDA Review and Evaluation, NDA 202,278, D. Charles Thompson, R.Ph., Ph.D., D.A.B.T., 6/29/2011; Memorandum [NDA 202-278], Lois M. Freed, Ph.D., 8/10/2011*) were identified in the CR letter, as follows:

1. You have not adequately assessed the chronic dermal toxicity of the NP101 drug formulation since the 9-month dermal toxicity study in miniature swine (PROT-55-NP101-006/S08719) was inadequate by design and conduct. The study needs to be repeated using:
    a. A clinically relevant formulation and dosing regimen. Justification would need to be provided for less than daily dosing at the same site.
    b. A sufficient number of animals to allow for meaningful interpretation (4/sex/group).
    c. Untreated and vehicle control groups. It is possible that assessment of untreated skin could be conducted in animals from other groups, i.e., a separate group may not be needed.
    d. Three dose levels to allow assessment of the dose-dependent nature of any toxicity observed, up to a dose documented to be either a maximum tolerated or maximum feasible dose.
    e. Toxicokinetic analysis to document drug delivery through the skin.

2. You have not provided adequate justification to allow for a waiver of the requirement for conducting a dermal carcinogenicity study for NP101. We understand that the NP101 patch cannot be used to dose rodents. However, you have failed to address the feasibility of conducting a carcinogenicity study in which the components of the drug product are painted onto the skin. Unless the results of an adequately conducted chronic dermal toxicity study in non-rodent demonstrate the lack of any histopathological changes in locally exposed tissue, you will need to either conduct a dermal carcinogenicity study (preferably in mouse) or provide adequate justification for why a dermal painting carcinogenicity study is not feasible or would not provide data relevant to humans.
3. If substantial changes are made to the clinical product, additional nonclinical studies may be required.

An End-of-Review meeting was held with the sponsor on November 9, 2011 (*Memorandum of Meeting Minutes, 12/9/2011*). For that meeting, the sponsor posed two nonclinical questions:

- "Does the Agency concur that, although atypical, the completed chronic toxicity study, in conjunction with previous studies, is adequate to support approval of this product?"
- "Does the Agency concur that a waiver of the requirement for conducting a dermal carcinogenicity study is warranted?"

The division's preliminary responses and the meeting discussion were as follows (*Memorandum of Meeting Minutes, 12/9/2011*):

FDA Preliminary Comments:

The completed 9-month dermal toxicity study is not an adequate study and we do not concur that you have provided sufficient information to warrant a waiver of the need for a dermal carcinogenicity study, for the reasons given previously. However, if you can adequately document that a dermal carcinogenicity study is not feasible, you would not need to repeat the 9-month study, since the results of that study inform the decision as to whether or not a dermal carcinogenicity study is needed. If you determine that a meaningful dermal carcinogenicity study can be conducted, you may choose to conduct that study and not repeat the 9-month study.

If there is a substantial change in the drug product, then additional nonclinical studies may be needed.

Meeting Discussion:

The Sponsor questioned the need for a dermal carcinogenicity study since sumatriptan is not expected to penetrate the skin without iontophoresis. The division stated that the Sponsor will need to demonstrate that a meaningful study cannot be conducted using sumatriptan painted onto the skin, e.g., using a formulation designed to enhance dermal absorption. Data indicating a lack of absorption, such as toxicokinetic data demonstrating no systemic exposure, would need to be provided to document that a meaningful assessment of dermal carcinogenic potential is not feasible.

The sponsor submitted a Complete Response to the August 29, 2011 CR letter on July 16, 2012 (received July 17, 2012).

NDA Resubmission following Complete Response Letter

The nonclinical sections of the NDA resubmission provided the following:

- Summary document addressing the nonclinical deficiencies identified in the CR letter.
- Study 04-330-10-0-00036-00: Sumatriptan Iontophoretic Patch Formulation (b) (4) Statement on Skin Toxicity study (study dates not specified).
- Study NP101-PC001: Evaluation of Formulation and Electrode Designs on Skin Tolerability and Pharmacokinetics Using a Porcine Model (July 27, 2007).
- Labeling recommendations

This information was reviewed by Dr. Thompson (*Pharmacology/Toxicology NDA Review and Evaluation, D. Charles Thompson, R.Ph., Ph.D., D.A.B.T., 10/16/2012*). Based on that review, Dr. Thompson has concluded that "No new nonclinical data relevant to the nonclinical deficiencies identified in the CR letter were submitted" and, therefore, the NDA is "Not approvable."

Summary of resubmission: The sponsor provided a summary document addressing the three nonclinical deficiencies identified in the CR letter.

The sponsor maintained that the 9-month dermal toxicity study in minipig was adequate, based on a number of considerations, including the following:

- The clinical delivery system, with only two series of minor modifications, was used; none of the modifications affected any portion in contact with skin.
- Minipigs were dosed more frequently than "…typically required by humans with acute migraine."
- The study tested "…a sufficient number of animals to confirm the absence of systemic and local toxicity." Since two patches were applied to each minipig (i.e., two times the recommended daily dose in humans), the "number of pigs assessed for dermal response to the device was twice the actual number of pigs…"
- "…the abundance of untreated skin provided comparators to treated skin within the same animals, precluding the use of control pigs to provide untreated skin."
- The size of the patch (8 inches x 4 inches) precludes testing in rodent.
- Systemic toxicity was not anticipated. (Comment: The sponsor's discussion of data taken from the "Imitrex Summary Basis of Approval" was not considered since these data may not be used in support of the sponsor's application.)

The sponsor also maintained that sufficient data had been provided to document both the infeasibility of conducting a dermal carcinogenicity study and the lack of a need to assess carcinogenic potential via the dermal route, based on a number of considerations, including the following:

- NP101 (the clinical delivery system) is for acute, not chronic, use in adults with migraine.

- Sumatriptan is not genotoxic and there was no evidence of carcinogenicity when sumatriptan was administered by other routes in nonclinical studies or based on post-marketing experience in humans.
- There was no evidence of preneoplastic changes in the 9-month toxicity study in minipig.
- It is impossible to test the NP101 patch in rodent.
- Topical application without iontophoresis results in no systemic exposure, based on in vitro (bovine udder and human epidermis; with and without permeation enhancers) or in vivo (human) data. (Comment: the sponsor stated that "Bovine epidermis is much thinner on the udder…" but provided no information on the relevance of that to the question of feasibility.)
- No changes in metabolic profile with dermal application.

Two nonclinical study reports were provided in the resubmission. One clearly was not conducted in response to the CR letter; the report for Study NP101-PC001 (a non-GLP study in anesthetized female Yorkshire minipig) was dated July 27, 2007, prior to original submission of the NDA. The report for Study 04-330-10-0-00036-00 (non-GLP) was not dated, and, as noted by Dr. Thompson, "…is not actually a report of any original…study."

In response to nonclinical deficiency #3 (CR letter, 8/29/2011), the sponsor stated that no modifications made in response to the numerous drug product deficiencies conveyed in the CR letter raised additional safety concerns requiring nonclinical assessment.

Conclusion: The sponsor provided no new information to address the inadequacy of the 9-month toxicity study in minipig, the lack of an assessment of carcinogenic potential of sumatriptan administered dermally, or the feasibility of conducting a dermal carcinogenicity study. The CMC review team concurred with the sponsor's statement that no new modifications to the clinical product raised any safety issues that would require nonclinical assessment; therefore, this deficiency has been adequately addressed. The remaining deficiencies and the inadequacy of the sponsor's data have been discussed in previous reviews/memos and communications (*cited above*).

A Discipline Review (DR) letter was sent to the sponsor (12/21/2012), stating that nonclinical deficiencies #1 and #2 identified in the CR letter (August 29, 2011) have not been adequately addressed:

- No new data were submitted to document the adequacy of the 9-month chronic dermal toxicity study in miniature swine. We continue to believe that this study is inadequate to assess the dermal toxicity of the sumatriptan iontophoretic transdermal system (TDS) or to dermal application of sumatriptan. Deficiencies include, but are not necessarily limited to, the following:
    - Too few animals were used to test the chronic dermal toxicity of the sumatriptan iontophoretic TDS. Only four animals were treated for the entire 9-month dosing period, and the data from one of these four animals were "…excluded due to it's *[sic]* high rate of patch failure." In addition, two different strains (Yucatan and Hanford) of miniature swine were used (i.e., two animals/strain/group), and, as you note, the data documented notable differences between the strains (*cf. Toxicology Written Summary, page 49*).
    - The dosing regimen did not provide an adequate safety margin compared to the proposed clinical use. Animals were treated with two clinical TDS per week, each delivering (b)(4) mg over 4 hours, at two different application sites. The proposed maximum recommended daily dose in humans is two TDS, each delivering 6.5 mg of sumatriptan over four hours; the proposed label does not state a limit to the number of days per week that the sumatriptan iontophoretic TDS may be used. In addition, the study report did not fully describe how often the same application site was used in each animal during the 9-month dosing period.
    - The lack of a TDS control group or site. Although, as you note, untreated skin was examined in each animal, the lack of an assessment of the dermal toxicity of a control TDS precluded an evaluation of the dermal toxicity of sumatriptan itself. This is of particular importance when considering whether or not an assessment of dermal carcinogenicity may be necessary.
- No new data were submitted relevant to the feasibility of conducting an assessment of the carcinogenic potential of dermally applied sumatriptan. An *in vitro* test of the use of penetration enhancers was conducted only using bovine udder skin and human epidermis. No *in vitro* or *in vivo* assays were conducted to test the effect of various penetration enhancers on absorption of sumatriptan by rodent skin. Published literature suggests that rodent skin is more permeable to a variety of compounds than is human skin (e.g., Calabrese EJ *Drug Metab Rev* 15(5&6):1013-1032, 1984; Scott RC *et al. J Investig Dermatol* 96(6):921-925, 1991; van Ravenzwway B, Leibold E *Toxic in Vitro* 18:219-225, 2004; Williams AC, Barry BW *Adv Drug Deliv Rev* 56:603-618, 2004; Ross JH *et al. Reg Toxicol Pharm* 41:82-91, 2005). The relevance of the *in vitro* data provided to address the issue of the feasibility of assessing carcinogenic potential appears questionable.

The sponsor submitted a response (January 6, 2013 email communication) to the DR letter in preparation for a teleconference requested by the sponsor to discuss the issues conveyed in the DR letter. (It does not appear that this response has been officially submitted to the NDA.) The teleconference was held on January 8, 2013.

In the response to the DR letter, the sponsor re-stated many of the same points made in the NDA submission(s); additional comments based on the DR letter were as follows:

- Regarding the need for a placebo patch control, the sponsor noted that there is no need to assess an inactive TDS "…since humans would not be chronically wearing inactive TDS."

- Regarding the feasibility of conducting a dermal carcinogenicity study, the sponsor stated that:
    - the lack of passive delivery was confirmed in multiple models, including human (in vitro, in vivo), minipig (in vitro, in vivo), rat (in vivo), and bovine (in vitro). Also, published studies, including those cited in the DR letter, indicate that there are "many exceptions" to the "general assumption that the skin of rabbit, rats, mice, and guinea pigs is more permeable than the skin of humans and pigs…"
    - "…all permeation enhancers are toxic to the skin…this study [dermal (painting) carcinogenicity study] would be akin to a co-carcinogenicity study, uninformative for human risk assessment."

The sponsor's response to the DR letter provided no additional information or basis for accepting the adequacy of the data submitted. Regarding the 9-month minipig study, the sponsor's comment on the need for a placebo TDS group reflects an apparent lack of understanding of the purpose of such a control, i.e., to control for dermal effects due solely to application of the TDS. However, as the division stated in the End-of-Review meeting, a repeat 9-month minipig study is no longer needed to support clinical development of Zecuity TDS because sufficient clinical data are now available; a repeat study would only be useful in determining whether or not a dermal carcinogenicity study was warranted. At this stage, this issue is better addressed by conducting an appropriate feasibility study in rodent (mouse) and then, if possible, a dermal carcinogenicity study. Therefore, the 9-month study does not need to be repeated.

Regarding the feasibility issue, the sponsor did provide in vitro and in vivo data on skin permeability of sumatriptan with and without permeation enhancers and with and without iontophoresis. However, none of these data addressed the feasibility of conducting a dermal carcinogenicity study of sumatriptan painted onto the skin of rodent (preferably mouse, as previously recommended by the division), using an appropriate permeation enhancer. The purpose of the references to published literature given in the DR letter was to document that the skin of various animal species (including rodent) is generally considered to be more permeable than human. The fact that there are exceptions simply indicates that data are needed to evaluate the permeability of any particular compound. Although the sponsor continues to argue that a dermal study of Zecuity TDS cannot be conducted in mouse, it should be noted that in no communication did the Division suggest such a strategy.

The DR letter and the sponsor's response were discussed during the January 8, 2013 teleconference. Prior to the teleconference, what data constitute sufficient evidence of feasibility/infeasibility was discussed with the Division of Dermatology and Dental Products (DDDP). Based on the DDDP experience, a multiple-dose dermal (painting) study in mouse (with toxicokinetic confirmation of absorption), typically of 7-14 days duration, is a straightforward, acceptable approach. Apparently, compounds with no skin permeability following an acute dose may demonstrate substantial permeability with repeated daily doses of at least 7 days duration. This type of study was recommended to the sponsor during the teleconference. Also, it does not appear to be the case that all

permeation enhancers are toxic and would confound interpretation of a dermal carcinogenicity study, as stated by the sponsor. It is my understanding that certain permeation enhancers, e.g., PEG, can be successfully used as a vehicle in dermal (painting) carcinogenicity studies.

Recommendation

I concur with Dr. Thompson's conclusion that the sponsor has not provided sufficient nonclinical data to support approval of the NDA. However, it is my understanding that the clinical team has determined that the Zecuity TDS provides clinical benefit, particularly in migraine patients who cannot take sumatriptan orally (e.g., due to excessive nausea) or are injection-averse. If the NDA is approved at this time based on clinical considerations, the sponsor should be required to adequately address the remaining nonclinical deficiencies as Post-Marketing Requirements:

- An in vivo repeat-dose dermal painting study (with TK analysis) of sumatriptan succinate in an appropriate mouse model, and using various permeation enhancers.
- A dermal (painting) carcinogenicity study of sumatriptan succinate in mouse.

Labeling recommendations are provided in the following table. The "RDL" is Imitrex injection (NDA 20-080, label approved on 10/2/2012). Safety margins were removed since interspecies comparisons based on body surface area (mg/m^2) cannot be made when different routes of administration are involved.

RLD	SPONSOR'S PROPOSED (v. 1/3/2013)	RECOMMENDED
HIGHLIGHTS OF PRESCRIBING INFORMATION		
----------INDICATIONS AND USAGE----------	**----------INDICATIONS AND USAGE----------**	**----------INDICATIONS AND USAGE----------**
IMITREX is a serotonin (5-$HT_{1B/1D}$) receptor agonist (triptan) indicated for: • Acute treatment of migraine with or without aura in adults (1) • Acute treatment of cluster headache in adults (1) <u>Limitations of Use:</u> • Use only if a clear diagnosis of migraine or cluster headache has been established. (1) • Not indicated for the prevention of migraine attacks. (1)	(b) (4)	ZECUITY is an iontophoretic transdermal system (TDS) that delivers sumatriptan, a serotonin (5HT) 1b/1d receptor agonist (triptan), and is indicated for the acute treatment of migraine with or without aura in adults (1)
-------USE IN SPECIFIC POPULATIONS--------	**-------USE IN SPECIFIC POPULATIONS--------**	**-------USE IN SPECIFIC POPULATIONS--------**
• Pregnancy: Based on animal data, may cause fetal harm (8.1) • Geriatric use: A cardiovascular evaluation is recommended in those who have other cardiovascular risk factors prior to receiving IMITREX. (8.5)	• Pregnancy: Based on animal data, may cause fetal harm (8.1)	• Pregnancy: Based on animal data, may cause fetal harm (8.1)
FULL PRESCRIBING INFORMATION		
8 USE IN SPECIFIC POPULATIONS	**8 USE IN SPECIFIC POPULATIONS**	**8 USE IN SPECIFIC POPULATIONS**
8.1 Pregnancy	**8.1 Pregnancy**	**8.1 Pregnancy**
<u>Pregnancy Category C</u>: There are no adequate and well-controlled trials of IMITREX Injection in pregnant women. When sumatriptan was administered intravenously to pregnant rabbits daily throughout the period of organogenesis, embryolethality was observed at doses at or close to those producing	(b) (4)	<u>Pregnancy Category C</u>: There are no adequate and well-controlled studies in pregnant women. ZECUITY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. When sumatriptan was administered intravenously

maternal toxicity. These doses were less than the maximum recommended human dose (MRHD) of [redacted] mg/day on a mg/m^2 basis. Oral administration of [redacted] matriptan to rabbits during organogenesis was associated with increased incidences of fetal vascular and skeletal abnormalities. The highest no-effect dose for these effects was 15 mg/kg/day. The intravenous administration of sumatriptan to pregnant rats throughout organogenesis at doses that are approximately 10 times the MRHD on a mg/m^2 basis did not produce evidence of embryolethality. The subcutaneous administration of sumatriptan to pregnant rats prior to and throughout pregnancy did not produce evidence of embryolethality or teratogenicity.	[redacted]	to pregnant rabbits daily throughout the period of organogenesis, embryolethality was observed at doses at or close to those producing maternal toxicity. Oral administration of sumatriptan to rabbits during organogenesis was associated with increased incidences of fetal vascular and skeletal abnormalities; the highest no-effect dose for these effects was 15 mg/kg/day. The intravenous administration of sumatriptan to pregnant rats throughout organogenesis did not produce evidence of embryolethality. The subcutaneous administration of sumatriptan to pregnant rats prior to and throughout pregnancy did not produce evidence of embryolethality or teratogenicity.
8.3 Nursing Mothers	**8.3 Nursing Mothers**	**8.3 Nursing Mothers**
It is not known whether sumatriptan is excreted in human breast milk following subcutaneous administration. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from IMITREX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.	[redacted]	It is not know whether sumatriptan is excreted in human milk following transdermal administration. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ZECUITY, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
8.4 Pediatric Use	**8.4 Pediatric Use**	**8.4 Pediatric Use**
Safety and effectiveness of IMITREX Injection in pediatric patients under 18 years of age have not been established; therefore, IMITREX Injection is not recommended for use in patients under 18 years of age. Two controlled clinical trials evaluated IMITREX Nasal Spray (5 to 20 mg) in 1,248 adolescent migraineurs aged 12 to 17 years who	[redacted] Two controlled clinical trials evaluated sumatriptan nasal spray (5 to 20 mg) in 1,248 adolescent migraineurs aged 12 to 17 years who treated a	Safety and effectiveness in pediatric patients have not been established. *[No comments on the remaining portion of this section.]*

treated a single attack. The trials did not establish the efficacy of IMITREX Nasal Spray compared with placebo in the treatment of migraine in adolescents. Adverse reactions observed in these clinical trials were similar in nature to those reported in clinical trials in adults. Five controlled clinical trials (2 single-attack studies, 3 multiple-attack studies) evaluating oral IMITREX (25 to 100 mg) in pediatric patients aged 12 to 17 years enrolled a total of 701 adolescent migraineurs. These studies did not establish the efficacy of oral IMITREX compared to placebo in the treatment of migraine in adolescent. Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults. The frequency of all adverse events in these patients appeared to be both dose- and age dependent, with younger patients reporting events more commonly than older adolescents. Post-marketing experience documents that serious adverse events have occurred in the pediatric population after use of subcutaneous, oral, and/or intranasal IMITREX. These reports include events similar in nature to those reported rarely in adults, including stroke, visual loss, and death. A myocardial infarction has been reported in a 14-year-old male following the use of oral IMITREX; clinical signs occurred within 1 day of drug administration. Since clinical data to determine the frequency of serious adverse reactions in pediatric patients who might receive subcutaneous, oral, or intranasal IMITREX are not presently available, the use of IMITREX in patients under 18 years of age is not recommended.	single attack. The trials did not establish the efficacy of sumatriptan nasal spray compared with placebo in the treatment of migraine in adolescents. Adverse reactions observed in these clinical trials were similar in nature to those reported in clinical trials in adults. Five controlled clinical trials (2 single-attack studies, 3 multiple-attack studies) evaluating oral sumatriptan (25 to 100 mg) in pediatric patients aged 12 to 17 years enrolled a total of 701 adolescent migraineurs. These studies did not establish the efficacy of oral sumatriptan compared to placebo in the treatment of migraine in adolescent. Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults. The frequency of all adverse events in these patients appeared to be both dose- and age dependent, with younger patients reporting events more commonly than older adolescents. Post-marketing experience documents that serious adverse events have occurred in the pediatric population after use of subcutaneous, oral, and/or intranasal sumatriptan. These reports include events similar in nature to those reported rarely in adults, including stroke, visual loss, and death. A myocardial infarction has been reported in a 14-year-old male following the use of oral sumatriptan; clinical signs occurred within 1 day of drug administration. Since clinical data to determine the frequency of serious adverse reactions in pediatric patients who might receive subcutaneous, oral, or intranasal sumatriptan are not presently available, the use of ZECUITY in patients under 18 years of age is not recommended.	

12 CLINICAL PHARMACOLOGY		
12.1 Mechanism of Action	**12.1 Mechanism of Action**	**12.1 Mechanism of Action**
Sumatriptan binds with high affinity to human cloned 5-$HT_{1B/1D}$ receptors. IMITREX presumably exerts its therapeutic effects in the treatment of migraine headache by binding to 5-$HT_{1B/1D}$ receptors located on intracranial blood vessels and sensory nerves of the trigeminal system. Current theories proposed to explain the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of sensory neuropeptides (including substance P and calcitonin gene-related peptide) through nerve endings in the trigeminal system. The therapeutic activity of IMITREX for the treatment of migraine headaches is though to be due to the agonist effects at the 5-$HT_{1B/1D}$ receptors on intracranial blood vessels (including the arterio-venous anastomoses) and sensory nerves of the trigeminal system, which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.	(b) (4)	Sumatriptan is the active component of ZECUITY. Sumatriptan binds with high affinity to human cloned 5-$HT_{1B/1D}$ receptors. ZECUITY presumably exerts its therapeutic effects in the treatment of migraine headache by binding to 5-$HT_{1B/1D}$ receptors located on intracranial blood vessels and sensory nerves of the trigeminal system. Current theories proposed to explain the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of sensory neuropeptides (including substance P and calcitonin gene-related peptide) through nerve endings in the trigeminal system. The therapeutic activity of sumatriptan for the treatment of migraine headaches is though to be due to the agonist effects at the 5-$HT_{1B/1D}$ receptors on intracranial blood vessels (including the arterio-venous anastomoses) and sensory nerves of the trigeminal system, which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.
13 NONCLINICAL TOXICOLOGY		
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**
Carcinogenesis: In carcinogenicity studies, rats and mice were given sumatriptan by oral gavage. Mice were dosed for 78 weeks and rats were dosed for 104 weeks. Average exposures achieved in mice receiving the highest dose were approximately 110 times the exposure attained in humans after the maximum recommended single dose of (b) (4) mg. The highest dose to rats was approximately 260 times	(b) (4)	Carcinogenesis: In carcinogenicity studies, rats and mice were given sumatriptan by oral gavage. Mice were dosed for 78 weeks and rats were dosed for 104 weeks. There was no evidence of an increase in tumors in either species related to sumatriptan administration. Mutagenesis: Sumatriptan was not mutagenic in the

the maximum single dose of (b) (4) mg on a mg/m^2 basis. There was no evidence of an increase in tumors in either species related to sumatriptan administration. Mutagenesis: Sumatriptan was not mutagenic in the presence or absence of metabolic activation when tested in 2 gene mutation assays (the Ames test and the in vitro mammalian Chinese hamster V79/HGPRT assay). It was not clastogenic in 2 cytogenetics assays (the in vitro human lymphocyte assay and the in vivo rat micronucleus assay). Impairment of Fertility: A fertility study (Segment I) by the subcutaneous route, during which male and female rats were dosed daily with sumatriptan prior to and throughout the mating period, has shown no evidence of impaired fertility at doses equivalent to approximately 100 times the maximum recommended single human dose of (b) (4) mg on a mg/m^2 basis. However, following oral administration, a treatment-related decrease in fertility, secondary to a decrease in mating, was seen for rats treated with 50 and 500 mg/kg/day. The no-effect dose for this finding was approximately 8 times the maximum recommended single human dose of (b) (4) mg on a mg/m^2 basis. It is not clear whether the [redacted]oblem is associated with the treatment of males or females or both.	(b) (4)	presence or absence of metabolic activation when tested in two gene mutation assays (the Ames test and the in vitro mammalian Chinese hamster V79/HGPRT assay). It was not clastogenic in two cytogenetics assays (in vitro human lymphocyte assay and in vivo rat micronucleus assay). Impairment of Fertility: A fertility study by the subcutaneous route, during which male and female rats were dosed daily with sumatriptan prior to and throughout the mating period, has shown no evidence of impaired fertility. However, following oral administration, a treatment-related decrease in fertility, secondary to a decrease in mating, was seen for rats treated with 50 and 500 mg/kg/day. It is not clear whether the problem is associated with the treatment of males or females or both.
13.2 **Animal Toxicology and/or Pharmacology** Corneal Opacities: Dogs receiving oral sumatriptan developed corneal opacities and defects in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg/day, and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a 60-week study. Earlier examinations for these toxicities were	13.2 **Animal Toxicology and/or Pharmacology** (b) (4)	13.2 **Animal Toxicology and/or Pharmacology** Corneal Opacities: Dogs receiving oral sumatriptan developed corneal opacities and defects in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg/day, and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a 60-week study. Earlier examinations for these toxicities were not

not conducted and no-effect doses were not established; however, the relative exposure at the lowest dose tested was approximately 5 times the human exposure after a 100-mg oral dose or 3 times the human exposure after a 6-mg subcutaneous dose. Melanin Binding: In rats with a single subcutaneous dose (0.5 mg/kg) of radiolabeled sumatriptan, the elimination half-life of radioactivity from the eye was 15 days, suggesting that sumatriptan and its metabolites bind to the melanin of the eye. The clinical significance of this binding is unknown.	(b) (4) Melanin Binding: In rats with a single subcutaneous dose (0.5 mg/kg) of radiolabeled sumatriptan, the elimination half-life of radioactivity from the eye was 15 days, suggesting that sumatriptan and its metabolites bind to the melanin of the eye. The clinical significance of this binding is unknown.	conducted and no-effect doses were not established. Melanin Binding: In rats with a single subcutaneous dose (0.5 mg/kg/day) of radiolabeled sumatriptan, the elimination half-life of radioactivity from the eye was 15 days, suggesting that sumatriptan and its metabolites bind to the melanin of the eye. The clinical significance of this binding is unknown.

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/s/

LOIS M FREED
01/14/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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Applicant's letter date:	July 16, 2012
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Product:	Zecuity (formerly Zelrix/sumatriptan iontophoretic transdermal system
Indication:	Migraine
Applicant:	NuPathe Inc. 227 Washington Street Suite 200 Conshohocken, PA 19428
Review Division:	Neurology Products, HFD-120
Reviewer:	D. Charles Thompson, R.Ph., Ph.D., D.A.B.T.
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TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

NDA 202-278 was originally received on October 29, 2010, proposing registration of a drug/device combination product (Zecuity) that utilizes iontophoretic technology in a patch application to deliver sumatriptan transdermally for the acute treatment of migraine with or without aura in adults. Following review, a Complete Response (CR) letter was issued to the sponsor on August 29, 2011. The present submission constitutes the sponsor's response to the CR letter and resubmission of the original NDA.

1.2 Brief Discussion of Nonclinical Findings

No new nonclinical data relevant to the nonclinical deficiencies identified in the CR letter were submitted.

1.3 Recommendations

1.3.1 Approvability: Not approvable.

1.3.2 Additional Non Clinical Recommendations: The sponsor should provide definitive in vivo TK data from an appropriate rodent model for dermal carcinogenesis confirming an absence of systemic sumatriptan exposure following reasonable attempts at dosing via skin painting with various formulations of drug and known absorption enhancers. A final recommendation on the need for a full, two-year dermal carcinogenicity assay is deferred pending receipt and evaluation of the above-noted TK data.

1.3.3 Labeling: Deferred at this time.

2 Drug Information

2.1 Drug

CAS Registry Number: 103628-48-4

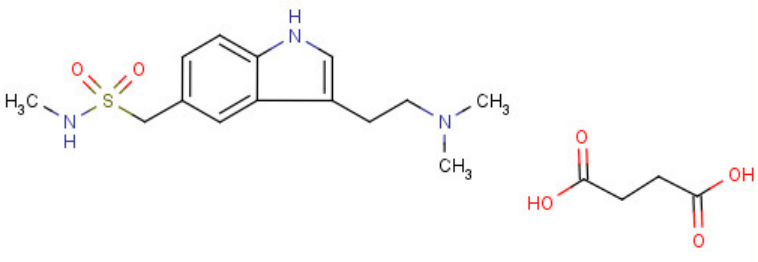
Generic Name: Sumatriptan succinate

Code Name: NP101

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

Molecular Formula/Molecular Weight: $C_{14}H_{21}N_3O_2S•C_4H_6O_4/413.5$

Structure or Biochemical Description:



Pharmacologic Class: Serotonin (5HT) 1B/1D Receptor Agonist (triptan)

2.2 Relevant INDs, NDAs, and DMFs

NDAs 20-080, 20-132, and 20-626; IND 74,877

2.3 Drug Formulation

Zecuity is a disposable, single-use, drug/device combination product that utilizes iontophoretic technology in a patch application to deliver sumatriptan transdermally for the acute treatment of migraine with or without aura in adults. The sponsor asserts that "no changes to the drug and salt formulations have been made" relative to that which was assessed in the original NDA submission (see previous nonclinical review: PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION, NDA 202-278, D. Charles Thompson, June 29, 2011); in addition, none of the other product modifications "...resulted in a change to materials that come in contact with the skin" and "...have not significantly changed the device tested in the nonclinical animal studies."

2.4 Comments on Novel Excipients

No change from original NDA submission (see previous nonclinical review: PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION, NDA 202-278, D. Charles Thompson, June 29, 2011).

2.5 Comments on Impurities/Degradants of Concern

No change from original NDA submission (see previous nonclinical review: PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION, NDA 202-278, D. Charles Thompson, June 29, 2011).

2.6 Proposed Clinical Population and Dosing Regimen

Dermal patch administration in adult migraineurs.

2.7 Regulatory Background

NDA 202-278 was originally received on October 29, 2010; a Complete Response (CR) letter was issued on August 29, 2011, which identified numerous deficiencies, most of which were related to product quality and/or device issues. An End of Review Meeting was held with the sponsor on November 9, 2011 to discuss the issues identified in the CR letter (see Meeting Minutes, December 9, 2011). The present submission constitutes the sponsor's response to the CR letter coupled with a resubmission of the original NDA.

3 Studies Submitted

3.1 Studies Reviewed

- 04-330-10-0-00036-00: Sumatriptan Iontophoretic Patch Formulation (b) (4) Statement on Skin Toxicity study
- NP101-PC001: Evaluation of Formulation and Electrode Designs on Skin Tolerability and Pharmacokinetics Using a Porcine Model

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

- PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION, NDA 202-278, D. Charles Thompson, June 29, 2011.

10 Special Toxicology Studies

Study title: Sumatriptan Iontophoretic Patch Formulation (b) (4) Statement on Skin Toxicity study

Study no.:	04-330-10-0-00036-00
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Not defined
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Not defined

Summary Description and Conclusions

This document is actually not a report of any original in vivo skin toxicity study. Rather, it is a brief discussion of and reference to the published literature on sumatriptan toxicity

data and to the sponsor's own clinical trials with the NP101 patch, combined with apparently original in vitro skin permeation data generated by (b) (4)

These in vitro studies employed a modified "Keshary-Chien diffusion cell" test system and evaluated transport (µg/cm^2) of sumatriptan succinate across both bovine udder skin and human epidermis. In the bovine udder skin experiment, sumatriptan succinate was dissolved (b) (4)% w/w) in three different vehicles (gelatin, HPMC, and polyamine) and applied with and without iontophoresis. In the human epidermis experiment, the sumatriptan succinate was dissolved at (b) (4)% w/w in each of four solvent systems (3% tylose in water; thylose/water plus DMSO; olive oil; and ethanol) and applied without iontophoresis only. The results from these two experiments are summarized in the sponsor's two tables reproduced below.

Table 1: *In vitro* permeation data of iontophoretic and passive sumatriptan succinate transport across **bovine udder skin**. The API concentration was 4% (w/w) for these experiments

		amounts in [µg/cm²] as succinate (mean n=3)			
no.	**Time [h]**	**0**	**1**	**2**	**3**
1	Gelatin with iontophoresis	0	10.9	91	214
2	HPMC with iontophoresis	0	28.9	136.0	358
3	Polyamine with iontophoresis	0	104	229	393
4	Gelatin reference passive diffusion	0	0.455	3.58	5.50
5	HPMC reference passive diffusion	0	9.37	30.8	54.8
6	Polyamine reference passive diffusion	0	2.49	8.80	16.8

Table 2: *In vitro* permeation profile of passive sumatriptan succinate across **human skin (epidermis)**. The API concentration was 2% (w/w) for these experiments.

		Amounts in [µg/cm²] as succinate (mean n=3)				
no.	**Time h**	**0**	**4**	**8**	**24**	**48**
1	3% Tylose in H_2O	0	0.075	0.142	0.338	0.647
2	Tylose/H_2O + DMSO	0	0.099	0.452	2.933	5.770
3	Olive Oil	0	0.165	0.701	1.993	3.908
4	Ethanol	0	0.190	0.779	2.531	5.357

The report concludes by saying that, "...a sufficient exposure of dermal cells to test dermal carcinogenicity is highly unlikely even with penetration enhancers with passive transdermal delivery" and that, as a result, "...the proposed skin painting study with passive transdermal administration, even with penetration enhancers, is unlikely to provide a valid assessment of the dermal carcinogenic potential of sumatriptan."

Study title: Evaluation of Formulation and Electrode Designs on Skin Tolerability and Pharmacokinetics Using a Porcine Model

Study no.:	NP101-PC001
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Report Date:	July 27, 2007
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Sumatriptan succinate, not further defined

Summary Description and Conclusions

Report NP101-PC001 describes investigations into the tolerability and PK in pigs (Yorkshire, female, anesthetized) of various formulations and patch designs for administration of sumatriptan via transdermal iontophoresis (single application; 4 patches/animal/application; 4-6 hr patch time). The sponsor's synopsis of the study design is reproduced below.

Name of Sponsor/Company: NuPathe Inc.

Name of Finished Products:
Study Drug: NP101 Sumatriptan Iontophoretic Transdermal Patch
Comparators: Sumatriptan 6 mg subcutaneous injection

Name of Active Ingredient:
Sumatriptan Succinate

Objectives:

The study is divided into six separate experiments, each with a specific primary objective:

Feasibility 1: To determine if the patch adhesive used in previous human trials would provide adequate adherence to porcine skin.

Feasibility 2: Using the same electrode (b) (4)) and patch formulation (b) (4) HPMC, (b) (4) sumatriptan succinate) used in previous human trials, to determine the number of milliamp (mA) minutes of current required to reliably produce erythema in the porcine model.

Phase 1A: To evaluate the skin tolerability of six patch formulations:

- (b) (4) HPMC, (b) (4) sumatriptan succinate
- HPMC (b) (4) sumatriptan succinate
- HPC, (b) (4) sumatriptan succinate
- HPC (b) (4) sumatriptan succinate
- polyamine, (b) (4) sumatriptan succinate
- gelatin, (b) % sumatriptan succinate

Using three electrode designs:

- (b) (4) lectrode
- electrode
- l electrode

The formulations and electrodes were used in all possible combinations, using the same number of mA minutes of current which reliably produced erythema as determined in Feasibility 2.

Phase 1B: The formulation in this experiment was (b) (4) HPMC. The electrode shape and size being evaluated was as follows:

- (b) (4) electrode
- (b) (4) electrode
- (b) (4) electrode

In addition, (b) (4)

Phase 2: To evaluate the pharmacokinetics of delivery of sumatriptan succinate from three of the electrode/formulation patch combinations previously studied, compared to a 6 mg sumatriptan subcutaneous injection. Five animals were treated with three patch formulations:

- (b) (4) HPMC, (b) (4) sumatriptan succinate
- (b) (4) HPC (b) (4) sumatriptan succinate
- polyamine, (b) (4) sumatriptan succinate

Using two electrode designs:

- (b) (4)
- (b) (4) electrode

The sponsor concludes the study with the following summation: "The PK results coupled with the erythema scores of the Phase 2 study support the decision to move forward with the (b) (4) HPC (b) (4) and polyamine formulations in the porcine acute toxicology study."

The sponsor's purpose for inclusion of report NP101-PC001 in the current response to CR submission is unclear. As noted, the date of the report is July 27, 2007, which predates the date of the original NDA submission (October 29, 2010) by more than three years. In addition, no overall conclusion is drawn from the study by the sponsor beyond that quoted above and the study report is not discussed or even referenced anywhere else in any of the sponsor's summary documents (e.g., Nonclinical Overview, Toxicology Written Summary) included in the current submission.

11 Integrated Summary and Safety Evaluation

NDA 202-278 was originally received on October 29, 2010. The application proposes a drug/device combination product (Zecuity) that utilizes iontophoretic technology in a patch application to deliver sumatriptan transdermally for the acute treatment of migraine with or without aura in adults. Review of the original application resulted in the issuance of a Complete Response (CR) letter to the sponsor on August 29, 2011, which identified numerous deficiencies in the application, most of which were related to product quality and/or device issues. An End of Review Meeting was held with the sponsor on November 9, 2011 to discuss the issues identified in the CR letter. The present submission constitutes the sponsor's response to the CR letter and resubmission of the original NDA.

Three nonclinical deficiencies/issues were identified in the CR letter, which are excerpted below.

> "1. You have not adequately assessed the chronic dermal toxicity of the NP101 drug formulation since the 9-month dermal toxicity study in miniature swine (PROT-55-NP101-006/S08719) was inadequate by design and conduct. The study needs to be repeated using:
> a. A clinically relevant formulation and dosing regimen. Justification would need to be provided for less than daily dosing at the same site.
> b. A sufficient number of animals to allow for meaningful interpretation (4/sex/group).
> c. Untreated and vehicle control groups. It is possible that assessment of untreated skin could be conducted in animals from other groups, i.e., a separate group may not be needed.
> d. Three dose levels to allow assessment of the dose-dependent nature of any toxicity observed, up to a dose documented to be either a maximum tolerated or maximum feasible dose.
> e. Toxicokinetic analysis to document drug delivery through the skin.
>
> 2. You have not provided adequate justification to allow for a waiver of the requirement for conducting a dermal carcinogenicity study for NP101. We understand that the NP101 patch cannot be used to dose rodents. However, you have failed to address the feasibility of conducting a carcinogenicity study in which the components of the drug product are painted onto the skin. Unless the results of an adequately conducted chronic dermal toxicity study in non-rodent demonstrate the lack of any histopathological changes in locally exposed tissue, you will need to either conduct a dermal carcinogenicity study (preferably in mouse) or provide adequate justification for why a dermal painting carcinogenicity study is not feasible or would not provide data relevant to humans.

> 3. If substantial changes are made to the clinical product, additional nonclinical studies may be required."

With the current submission, the sponsor has provided neither reports of GLP toxicity studies nor any new and relevant in vivo nonclinical data of any kind that directly address the nonclinical issues identified in the CR letter. Rather, the sponsor has provided two documents that summarize, one, in vitro studies of bovine and human skin permeation of sumatriptan succinate and, two, preliminary studies (conducted more than three years prior to the original NDA submission) of the tolerability and PK in pigs with various developmental NP101 drug formulations and patch designs. The sponsor has also provided a separate, summary document entitled "Guide for Complete Response Letter", which consists of the sponsor's itemized and specific responses to each of the deficiencies (i.e., Product Quality, Microbiology, Clinical Pharmacology, Clinical, as well as Nonclinical) identified in the CR letter. Each of the sponsor's responses to the identified nonclinical issues is addressed individually in the paragraphs that follow.

Sponsor Response: Nonclinical Issue #1

Relevant portions of the sponsor's response are excerpted below.

> "NuPathe believes that the 9-month dermal toxicity study was adequate to assess the potential risks from repeated human exposure, to demonstrate the absence of systemic toxicity not formerly identified in earlier nonclinical studies performed by the innovator firm, and to confirm the absence of proliferative or pre-neoplastic changes in any tissues, including the epidermis, dermis and subcutaneous tissues, that might indicate a possible risk for dermal carcinogenicity in humans....At the End of Review meeting on 09 November 2011, FDA provided preliminary comments regarding this issue in which they stated that if NuPathe can "adequately document that a dermal carcinogenicity study is not feasible, you would not need to repeat the 9-month study, since the results of that study inform the decision as to whether or not a dermal carcinogenicity study is needed."...As discussed below in Nonclinical Item #2, NuPathe is providing new data to support that a dermal carcinogenicity study is not feasible."

Reviewer Comments

For reasons previously discussed in this reviewer's review of the original NDA submission (PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION, NDA 202-278, D. Charles Thompson, June 29, 2011), the Division has provided clear communication to the sponsor—originally in the CR letter (Agency Letter, August 29, 2011) and reiterated in the End of Review Meeting Minutes (Meeting Minutes, December 9, 2011)—that the 9-month dermal toxicity study in miniature swine (PROT-55-NP101-006/S08719) is considered inadequate as an assessment of the chronic dermal toxicity of the proposed NP101 drug product.

The sponsor's current submission provides no new and/or relevant data nonclinical data that directly address this issue. Moreover, certain specific arguments provided by the sponsor in separate summary documents in the submission suggest a selective reading on their part of the published literature with respect to clinical behavior of the migraine patient population. For example, the sponsor argues that "...it has adequately assessed

the chronic dermal toxicity of the NP101 drug formulation in the 9-month dermal toxicity study in miniature swine..." because they assert that the study's dosing regimen "...employed the human clinical formulation and device (NP101), used a multiple of the human clinical dose, [and] provided doses more frequently than is typically required by humans with acute migraine, per the literature..." (see Section 2.6.1: Introduction and Statement of Nonclinical Issues).

However, this reviewer notes that the dosing regimen employed in the sponsor's 9-month toxicity study (i.e., two (b) (4) mg patches applied once per week) appears, on face, to be little, if any, exaggeration r ative to that recommended in current approved labeling for sumatriptan injection, where the MRDD is (b) (4) mg in 24 hours. Moreover a cursory search of the literature by this reviewer identified numerous reports that describe overuse or misuse of sumatriptan in a significant fraction of migraine patients.[1] This suggests that the dosing regimen employed in the sponsor's 9-month study may not adequately reflect actual migraine patient behavior in an uncontrolled clinical setting, much less provide any sort of exaggeration of even label-recommended dosing. Given that the proposed iontophoretic transdermal patch drug product represents a reformulation and alternative route of administration relative to approved sumatriptan drug product formulations, it is with respect to assessing the potential for local (i.e., 'under patch') toxicity under reasonably anticipated actual use conditions that this apparent lack of exaggeration is most concerning. Thus, for this and other reasons as described in the original NDA review, this reviewer reaffirms the original finding that the 9-month dermal toxicity study in miniature swine is inadequate. This reviewer also reaffirms the original recommendation that the study should be repeated as specified in the original NDA review, unless a 2-year rodent dermal carcinogenicity study is to be conducted or confirmed to be unfeasible (see below).

Sponsor Response: Nonclinical Issue #2

Relevant portions of the sponsor's response are excerpted below.

> "This was discussed with FDA at the End of Review meeting on 09 November 2011. FDA clarified that to demonstrate that a meaningful study cannot be conducted using sumatriptan painted onto the skin (e.g., using a formulation designed to enhance dermal absorption), data indicating a lack of absorption would need to be provided to document that a meaningful assessment of dermal carcinogenic potential is not feasible....NuPathe completed further work in a formal clinical study, NP101-024, to demonstrate that no passive delivery of sumatriptan occurs. Of note, despite the current drug formulation

[1] For example, see: Dobson CF, Tohyama Y, Diksic M, Hamel E. Effects of acute or chronic administration of anti-migraine drugs sumatriptan and zolmitriptan on serotonin synthesis in the rat brain. Cephalalgia. 2004 Jan;24(1):2-11; Gaist D, Tsiropoulos I, Sindrup SH, Hallas J, Rasmussen BK, Kragstrup J, Gram LF. Inappropriate use of sumatriptan: population based register and interview study. BMJ. 1998 May 2;316(7141):1352-3; Drucker P, Tepper S. Daily sumatriptan for detoxification from rebound. Headache. 1998 Oct;38(9):687-90; Ottervanger JP, Valkenburg HA, Grobbee DE, Stricker BH. Pattern of sumatriptan use and overuse in general practice. Eur J Clin Pharmacol. 1996;50(5):353-5; Dekker F, Wiendels NJ, de Valk V, van der Vliet C, Knuistingh Neven A, Assendelft WJ, Ferrari MD. Triptan overuse in the Dutch general population: a nationwide pharmaco-epidemiology database analysis in 6.7 million people. Cephalalgia. 2011 Jun;31(8):943-52; and Lionetto L, Negro A, Palmisani S, Gentile G, Fiore MR, Mercieri M, Simmaco M, Smith T, Al-Kaisy A, Arcioni R, Martelletti P. Emerging treatment for chronic migraine and refractory chronic migraine. Expert Opin Emerg Drugs. 2012 Sep;17(3):393-406.

> containing a well characterized (b) (4), the sumatriptan in NP101 is not passively absorbed. Furthermore, (b) (4)) conducted comprehensive in vitro testing in bovine, bladder, and human skin tissues to show that sumatriptan is not passively absorbed through the skin, even in the presence of one of the strongest enhancers, DMSO....Based on the data provided, a sufficient exposure of dermal cells to test dermal carcinogenicity is highly unlikely even with penetration enhancers with passive transdermal delivery. Moreover, general and subcutaneous toxicity of sumatriptan has been widely tested without critical findings....The FDA proposed a skin painting study employing a hairless mouse with passive transdermal administration; however, even with penetration enhancers it is unlikely to provide a valid assessment of the dermal carcinogenic potential of sumatriptan. In light of the low likelihood for sumatriptan to be a human carcinogen and the inability to test sumatriptan by passive absorption in a rodent dermal carcinogenicity study, NuPathe again requests a waiver for this requirement for this NP101 NDA...."

Reviewer Comments

The sponsor's comments appropriately reflect an understanding of the underlying objective of carcinogenicity assessment in drug development, which is to predict risk to exposed human patients. However, they seemingly overlook a fundamental first step of risk assessment—i.e., hazard identification—and the fact that rat and mouse are generally accepted to be the only viable and validated models for assessing carcinogenic hazard (ICH S1B). Thus, while the sponsor has provided both in vitro and in vivo human data that purportedly address the potential for sumatriptan succinate to permeate human skin in the presence and absence of an iontophoretic motive force, these data fail to address the fundamental question posed to the sponsor in the CR letter, which was, is a rodent skin painting study feasible? The data required of the sponsor were even more precisely and clearly defined in direct communication with the sponsor in the End-of-Review meeting (Meeting Minutes, December 9, 2011). The sponsor was specifically advised that, to support their assertion that a dermal carcinogenicity study in rodent is not feasible, they would need to provide in vivo TK data in an appropriate animal model confirming an absence of systemic drug exposure following skin painting with various formulations of sumatriptan combined with absorption enhancers. Absent provision of such data in the current submission, it is concluded that the sponsor's application remains inadequate and not approvable from a nonclinical perspective.

Sponsor Response: Nonclinical Issue #3

Relevant portions of the sponsor's response are excerpted below.

> "No changes to the drug and salt formulations have been made. Two series of minor modifications were made to the patch used in the porcine PROT-55-NP101-006/S08719 study. The first set of modifications included only a battery change from (b) (4) batteries to (b) (4) batteries, and the (b) (4) . None of these modifications resulted in a change to materials that come in contact with the skin....Changes to the

> device have not significantly changed the device tested in the nonclinical animal studies...."

Reviewer Comments

Based on the information above, the described changes to the clinical drug product do not appear to raise any new patient safety concerns that require evaluation from a nonclinical perspective. However, definitive recommendations on this issue are deferred pending availability of findings from CDER ONDQPA and CDRH evaluations of the current submission.

Overall Conclusions and Recommendations

The sponsor has failed to adequately address Nonclinical Issues #1 and #2, as originally enumerated in the CR letter. From a nonclinical perspective, it is concluded that approval of NDA 202-278 cannot be supported in its current form. The sponsor needs to provide definitive in vivo TK data from an appropriate rodent model for dermal carcinogenesis confirming an absence of systemic sumatriptan exposure following reasonable attempts at dosing via skin painting with various formulations of drug and known absorption enhancers. A final recommendation on the need for a full, two-year dermal carcinogenicity assay is deferred pending receipt and evaluation of the above-noted TK data.

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/s/

DONALD C THOMPSON
10/16/2012

LOIS M FREED
10/16/2012

MEMORANDUM

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

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: August 10, 2011

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 202-278 (received October 29, 2010), Zelrix™ (sumatriptan) Iontophoretic Transdermal System, NP101

NDA 202-278 was submitted by NuPathe Inc. on October 29, 2010 to support approval of Zelrix Iontophoretic Transdermal System (Zelrix TDS), a drug/devise combination product for treatment of migraine, with or without aura, in adults. NDA 202-278 is filed under 505(b)(2), with Imitrex (sumatriptan succinate; GlaxoSmithKline) as the Reference Listed Drug Product. Imitrex is approved for subcutaneous (NDA 20-080), oral (NDA 20-132), and intranasal (NDA 20-626) administration. Zelrix Iontophoretic TDS (aka NP101) was developed under IND 74,877.

The nonclinical studies conducted to support approval of Zelrix Iontophoretic TDS consist of PK, pilot local toxicity, and acute and repeat-dose dermal toxicity studies. The pivotal, GLP nonclinical study is a 9-month dermal toxicity study of NP101 conducted in pigmented and non-pigmented miniature swine. Theses studies were reviewed in detail by Dr. Thompson (*Pharmacology/Toxicology NDA Review and Evaluation, NDA 202,278, D. Charles Thompson, R.Ph., Ph.D., D.A.B.T, 6/29/2011*). Based on his review, Dr. Thompson has concluded that the nonclinical studies do not support approval, based on the following deficiencies:

- The lack of nonclinical data on the safety of the inotophoretic TDS. In particular, the 9-month dermal toxicity study in miniature (Hanford, Yucatan) swine is inadequate, due to:
    - lack of a control group,
    - testing of a single dose level (the only difference among groups was the duration of dosing),
    - an insufficient number of animals (2/breed/group),
    - use of weekly, rather than daily, dosing,
    - lack of an adequate description of sampling procedures for histopathological examination, and

    - lack of toxicokinetic data to document delivery through the dermal layers.
- The lack of nonclinical data demonstrating that the metabolic profile for sumatriptan following application of the inotophoretic TDS is similar to that of the RLD. (Dr. Thompson notes that "It will be a clinical review team decision as to whether any human clinical data provided by the sponsor are sufficient and adequate to address this issue.")
- The sponsor's justification for waiving the need for a dermal carcinogenicity study is inadequate.

To address these deficiencies, Dr. Thompson recommends that the sponsor provide the following:

- A repeat acute dermal toxicity study in an appropriate species, with the to-be-marketed drug product.
- A repeat 9-month toxicity study in non-rodent, using an appropriate study design.
- Metabolic profile data with the inotophoretic TDS unless, as noted above, there are sufficient clinical data to address this potential deficiency.
- Justification for "why a dermal painting carcinogenicity study is not relevant and not feasible", unless the results of an adequately conducted 9-month dermal study demonstrate a lack of any preneoplastic or neoplastic findings.

Dr. Thompson also notes that ONDQA has communicated to the sponsor (*Information Request, 16 May 2011*) numerous deficiencies regarding the "fundamental design of NP101", and that changes to the clinical formulation designed to address these deficiencies may require additional nonclinical studies.

Comments and Recommendation

I concur with Dr. Thompson's conclusion that the sponsor has not provided adequate nonclinical data to support approval of Zelrix, based on the lack of (1) an adequate chronic dermal toxicity study and (2) either a dermal carcinogenicity study in one species or sufficient justification for why such a study would not be feasible or informative.

The sponsor's proposed dosing regimen is two patches, separated by at least 2 hours, in one 24-hour period. As for all potential migraine therapies, it is assumed that patients may medicate daily. Therefore, two pivotal studies (a chronic dermal toxicity study in one species [typically minipig] and a 2-year dermal carcinogenicity study in one species [typically rat]) have been required to support approval of a product previously approved by a different route but reformulated for dermal delivery. (Currently, it has been suggested that the results of the chronic dermal toxicity study be taken into account when assessing the need for a carcinogenicity study.) The 9-month dermal toxicity in minipig was inadequate by design (e.g., no control group), and did not adequately cover the intended clinical dosing regimen. Therefore, there is no adequate assessment of the local effects of chronic administration and the results of the sponsor's minipig study cannot be taken into consideration when assessing whether or not a dermal carcinogenicity study is needed. And, as discussed by Dr. Thompson, the sponsor's reasons for why a dermal carcinogenicity study is not feasible were not compelling.

If the current formulation is pursued, I don't believe an acute dermal toxicity study (as Dr. Thompson recommends) would be needed; this assessment could be incorporated into the chronic toxicity study. However, if there are substantial changes to the clinical formulation, additional nonclinical studies may be required, depending on what specific changes are made. Additional nonclinical studies may also be needed if data in humans indicate a substantially different metabolic profile with the transdermal route compared to the route(s) of administration for the RLD. The sponsor should attempt to finalize the clinical formulation and address the metabolic profile issue prior to initiating new nonclinical studies.

Labeling: due to the numerous CMC deficiencies related to the design of NP101, no labeling recommendations are being made at this time.

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/s/

LOIS M FREED
08/10/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	202,278
Supporting document/s:	1
Applicant's letter date:	29 October 2010
CDER stamp date:	29 October 2010
Product:	Zelrix™ (sumatriptan) Iontophoretic Transdermal System
Indication:	Migraine
Applicant:	NuPathe Inc. 227 Washington Street Suite 200 Conshohocken, PA 19428
Review Division:	Neurology Products, HFD-120
Reviewer:	D. Charles Thompson, R.Ph., Ph.D., D.A.B.T.
Supervisor/Team Leader:	Lois M. Freed, Ph.D.
Division Director:	Russell G. Katz, M.D.
Project Manager:	Lana Y. Chen, R.Ph.

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 202,278 are owned by NuPathe Inc. or are data for which NuPathe Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 202,278 that NuPathe Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 202,278.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

NDA 202,278 is an original 505(b)(2) application from Nupathe, Inc. for a drug/device combination product incorporating iontophoretic technology to deliver sumatriptan transdermally for the treatment of acute migraine with and without aura. Developmental work for the application was conducted under IND 74,877. Sumatriptan (Imitrex®, GlaxoSmithKline) subcutaneous injection (NDA 20-080, approved 28 December 1992), oral tablets (NDA 20-132, approved 1 June 1995), and nasal spray (NDA 20-626, approved 26 August 1997) are identified as the Reference Listed Drugs (RLD). The sponsor is relying for nonclinical support of the current application on the Agency's determinations of safety and approved labeling for these RLDs; in addition, they have conducted nonclinical studies intended to assess local toxicity/tolerability of sumatriptan following dermal administration.

1.2 Brief Discussion of Nonclinical Findings

CDER/ONDQA has informed the sponsor that, "The fundamental design of NP101 is not acceptable." A single 4-hour patch administration with a prototype patch resulted in observations of "slight epidermal necrosis" and "severe erythema or injuries in depth" in miniature swine. A 9-month repeated-dose toxicity study in miniature swine is inadequate by design and fails to address the potential for the NP101 drug formulation—not only the sumatriptan API, but each of the excipients as well—to induce either local or systemic toxicity following repeated transdermal iontophoretic administration. The submission contains no nonclinical data to address whether sumatriptan administered via transdermal iontophoresis results in a metabolite profile comparable to that of the RLDs. The sponsor has not provided adequate justification for waiving the requirement for conducting a dermal carcinogenicity study with the proposed clinical drug product formulation. The potential issues of dermal sensitization and phototoxicity of the existing NP101 product appear to have been adequately addressed.

1.3 Recommendations

1.3.1 Approvability: Not approvable

1.3.2 Additional Non Clinical Recommendations: None at this time

1.3.3 Labeling: Deferred at this time

2 Drug Information

2.1 Drug

CAS Registry Number: 103628-48-4

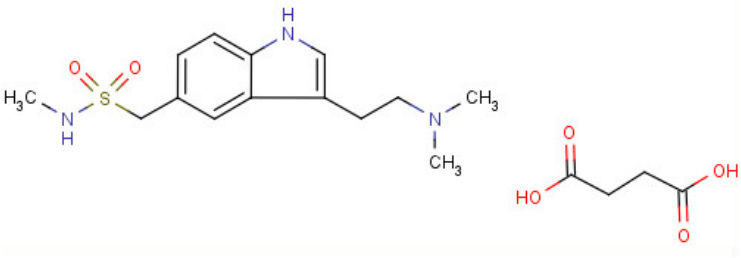
Generic Name: Sumatriptan succinate

Code Name: NP101

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

Molecular Formula/Molecular Weight: $C_{14}H_{21}N_3O_2S \cdot C_4H_6O_4$/413.5

Structure or Biochemical Description



Pharmacologic Class: N0000175764/ Serotonin 1d Receptor Agonist

2.2 Relevant INDs, NDAs, and DMFs

NDAs 20-080, 20-132, and 20-626

2.3 Drug Formulation

NP101 is a disposable, single-use, co-packaged drug/device combination product that utilizes iontophoretic technology to deliver sumatriptan transdermally. The drug product component of NP101 is contained within what is referred to as the reservoir card, comprised of two separate reservoirs. One reservoir contains a nonwoven pad (30 cm^2) imbibed with (b) (4) g of sumatriptan formulation ((b) (4) sumatriptan succinate containing 86 mg of sumatriptan). A second reservoir contains a similar nonwoven pad imbibed with (b) (4) g of salt formulation (b) (4) sodium chloride). Each reservoir is sealed separately (see sponsor's summary table and figure reproduced below).

Table 1: Reservoir Card Formulations

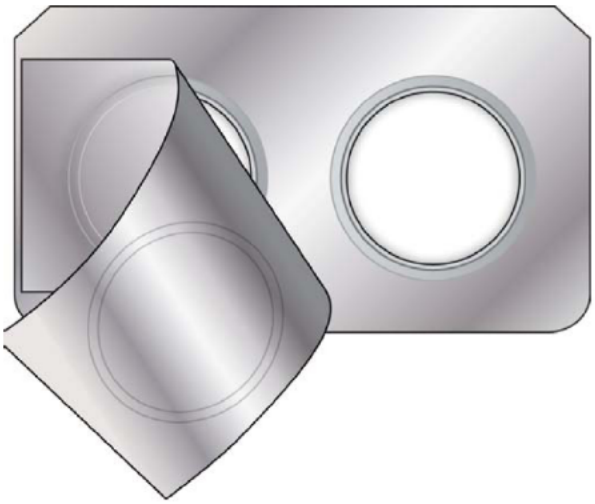
Component	Function	mg / 30 cm²	Reference to Quality Standards
Sumatriptan Formulation			
Sumatriptan Succinate	Active Pharmaceutical Ingredient (API)	(b) (4) (86 mg as sumatriptan)	United States Pharmacopoeia (USP)/ European Pharmacopoeia (EP)
Purified Water	(b) (4)		EP
Polyamine (b) (4) (b) (4)			EP
Lauric Acid			(b) (4)
Adipic Acid			USP/EP

Table 1: Reservoir Card Formulations (Continued)

Component	Function	mg / 30 cm²	Reference to Quality Standards
Methylparaben (b) (4) (b) (4)	(b) (4)		USP/EP
Salt Formulation			
Hydroxypropylcellulose (HPC)			USP/EP
Sodium Chloride			USP/EP
Methylparaben (b) (4) (b) (4)			USP/EP
Purified Water			EP

[1] cv = current version

Figure 1: Reservoir Card with Upper Foil Peeled Away to Expose Imbibed Pads



The device component consists of a dual-electrode patch (approximately 8 x 4 inches) as illustrated in the sponsor's figure reproduced below. The patch contains a positively charged (b) (4) electrode and a negatively charged (b) (4) electrode, both connected to a pre-programmed circuit that is powered by two small lithium batteries. A flexible tape material holds the patch to the skin once the imbibed pads have been aligned against the respective anode and cathode electrodes, such that the two pads, tape, and the foam ring come in direct contact with the patient's skin (upper arm or thigh). Pressing the button in the center of the cover dome activates current flow. The total time of current flow/drug delivery is approximately four hour (b) (4)), after which time the patch is automatically deactivated. Approximately (b) (4) mg of sumatriptan is delivered to the patient.

Figure 2: Electrode Patch (Top and Bottom View)

2.4 Comments on Novel Excipients

Of the proposed excipients, (b) (4) have been used previously in approved drug products administered via iontophoresis. However, the absolute amounts applied in the currently proposed patch application ((b) (4), respectively) appear to exceed anything previously approved, though both excipients have been used in various parenteral injection solutions approved previously. In the case of the other proposed excipients (i.e., polyamine/(b) (4), lauric acid, adipic acid, and hydroxypropyl cellulose), usage experience in previously approved drug products varies. The (b) (4) has only been used in approved (b) (4) drug product formulations. Lauric acid has not been used as an excipient in any approved drug product, (b) (4) Adipic acid has been used as an excipient in drug products approved for intramuscular injection and vaginal insertion. Hydroxypropyl cellulose has been used as

an excipient in drug products approved for oral and topical administration. Other than a discussion of the general theoretical principles underlying iontophoretic transdermal drug delivery, the sponsor has provided no specific support based on nonclinical data for use of the above-noted excipients in a drug product administered via transdermal iontophoresis. In particular, no attempt was made to assess whether any amount of any of these excipients was delivered to the systemic circulation via the iontophoretic administration process. The sponsor has submitted reports of nonclinical toxicity testing in which these excipients were included as constituents of the drug product test article evaluated; these reports are reviewed and their adequacy addressed in Sections 6 and 10 below.

2.5 Comments on Impurities/Degradants of Concern

All reported impurities/degradants for the drug product derive from those reported for the drug substance, as "no additional impurities are introduced by the excipients used in drug product manufacturing nor does the manufacturing process contribute to any additional impurities in the formulated drug product." The reported impurities are as shown in the sponsor's table reproduced below and are the same as those specified in the USP and EP monographs for sumatriptan. The sponsor states in their nonclinical overview that, "there are no impurities or degradants that require qualification by toxicology investigations." The sponsor acknowledges that only impurity (b) (4) was found at levels (b) (4) during the stability testing on the drug product.

Table 12: Potential Degradation Products and Release Limits for NP101 Reservoir Card (Drug Product)

Impurity	Release Limits	Chemical Name
(b) (4)		
Total degradation products	(b) (4)	N/A

[1] NMT - not more than

2.6 Proposed Clinical Population and Dosing Regimen

NP101 is proposed for the acute treatment of migraine headaches, with and without aura, in adult patients. Each patch is designed to deliver approximately (b) (4) mg of sumatriptan to the patient over a 4-hour period of iontophoresis. The proposed

maximum recommended daily dose (MRDD) is two patches (or approximately (b) (4) mg sumatriptan) in any 24-hour period.

2.7 Regulatory Background

The current submission is an original 505(b)(2) NDA for a drug/device combination product based on developmental work conducted under IND 74,877. The sponsor proposes to rely on prior Agency safety decisions and approved labeling from three (3) separate RLDs, comprised of three distinct formulations of sumatriptan (Imitrex®, GlaxoSmithKline): subcutaneous injection (NDA 20-080, approved 28 December 1992); oral tablets (NDA 20-132, approved 1 June 1995); and nasal spray (NDA 20-626, approved 26 August 1997). In addition, the sponsor has submitted their own data from nonclinical studies intended to assess the safety and tolerability of sumatriptan administered via transdermal iontophoresis.

3 Studies Submitted

3.1 Studies Reviewed

- NP101-PC003/SRCS07562: Acute Expanded Dermal and Systemic Toxicity of Sumatriptan in Miniature Swine
- PROT-55-NP101-006/S08719: Chronic (9 month), Weekly Local Dermal Tolerance Study of NP101-Sumatriptan Iontophoretic Transdermal Patch in Non-Pigmented and Pigmented Miniature Swine
- PROT-55-NP101-007/UKA00004: A Sensitization Study of Sumatriptan Administered by the Dermal Route to Guinea Pigs-Maximization Design
- PROT-55-NP101-009/UKA00005: A Sensitization Study of Sumatriptan Administered by the Dermal Route to Guinea Pigs-Maximization Design
- PROT-55-NP101-008/S10060: Phototoxicity of Sumatriptan when Administered by the NP101 Sumatriptan Iontophoretic Transdermal Patch in Hanford Miniature Swine
- PROT-55-NP101-012/118148: ISO Agarose Overlay Using L-929 Mouse Fibroblast Cells
- PROT-55-NP101-013/118149: Repeated Patch Dermal Sensitization Test (Buehler Method Modified for Medical Devices)
- PROT-55-NP101-014/118150: Primary Skin Irritation

3.2 Studies Not Reviewed

(b) (4)

(b) (4)

6 General Toxicology

6.1 Single-Dose Toxicity

Study title: Acute Expanded Dermal and Systemic Toxicity of Sumatriptan in Miniature Swine

Study no.:	S07562
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	31 May 2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Sumatriptan succinate, batch no. 10/a, purity 100.0% via HPLC

Study Design and Methodology Summary

The toxicity of sumatriptan was assessed following a single 4-hour dermal application with and without iontophoresis in Hanford Miniature Swine (6/sex/group; 11-15 months old and 27-52 kg at dosing initiation) followed by sacrifice at 3 or 15 days post dosing (see sponsor's study design summary reproduced below). Sumatriptan was administered to the dorsal trunk through iontophoresis while animals were anesthetized by inhalation of isoflurane (dosing was staggered over one week). The patches (5 x 4.5 inches) were connected to an external power source and computer with software that controlled th (b) (4) Sumatriptan was intended to be delivered at a dose of approximately (b) (4) mg/drug-containing patch over the 4-hour period of iontophoresis. Patches were removed after the 4-hour dosing period and the application sites were wiped clean.

Table 1 Details of Experimental Study Design

A) Day 3 Sacrifice Groups

Group	No. of Animals	Treatment	No. of Patches/ Animal
1	3 ♂/3 ♀	One Formulation A without iontophoresis plus a saline patch with iontophoresis	2
2	3 ♂/3 ♀	One Formulation A patch with iontophoresis	1
3	3 ♂/3 ♀	One Formulation B patch with iontophoresis	1

4	3 ♂/3 ♀	One Formulation A & one Formulation B patch with iontophoresis	2

B) Day 15 Sacrifice Groups

Group	No. of Animals	Treatment	No. of Patches/ Animal
1	3 ♂/3 ♀	One Formulation B without iontophoresis plus a saline patch with iontophoresis	2
2	3 ♂/3 ♀	One Formulation A patch with iontophoresis	1
3	3 ♂/3 ♀	One Formulation B patch with iontophoresis	1
4	3 ♂/3 ♀	One Formulation A and one Formulation B patch with iontophoresis	2

Note: Due to equipment required, the study animals were staggered over multiple days. The day of dose administration corresponds to study day 1 for each animal.

Total Number of Animals:	48 (24 males and 24 females)
Duration of the Study:	Acclimation Period: 7 to 14 days Exposure Period: 4 hours 3 and 15 days for Day 3 and Day 15 sacrifice groups, respectively.
Length of Exposure to Test Substance:	Animals were dosed once on Study Day 1 Dose administration was performed by dermal iontophoresis for 4 hours. The waveform of the patches was operated at (b) (4) (b) (4) mA minutes).
Randomization:	Animals were randomized based on gender and a body weight determined during acclimation period.
Recovery Period:	2 or 14 days following dose administration

Patch Reservoir Pads	Saline Patches	Patches with Formulation A	Patches with Formulation B
Anode	2% HPC + Salt	(b) (4)	
Cathode	2% HPC + Salt		
Anode Pad Batch Number:	8/21118/07		
Administration Route:	Dermal in patch with iontophoresis		
Ingredients of Formulations:	Refer to Appendix I		
Concentration of Dose Formulations:	0		
Dose/Patch	0		
Packaging	Gel pad in (b) (4) sealed pouch	Gel pad in (b) (4) sealed pouch	Gel pad in (b) (4) sealed pouch
Manufacturer:	(b) (4)		
Date of Manufacture:	May 14, 2007	May 14, 2007	May 14, 2007
Date of Expiration:	June 14, 2007	June 14, 2007	June 14, 2007
Storage Conditions:	Room Temperature	Room Temperature	Room Temperature

Note: HPC = Hydroxypropylcellulose

Certification of test article formulations provided by the sponsor to the test facility was as shown in the tables reproduced below. Though the patch A and patch B formulations do differ distinctly, the constituents of the patch formulations overall are largely consistent with that proposed for the clinical drug product formulation (see Section 2.3). Study parameters evaluated included dosing site observations (Draize dermal erythema scoring system-see sponsor's table below), clinical observations, body weights and feed consumption, clinical pathology assessments, toxicokinetics (blood collected at 0.5, 2,

4, 6, 8, and 10 hours post dosing initiation), organ weights, and gross/microscopic tissue observations.

Saline Control Patch

1. **Sample ID 8/21118/07**: Hydroxypropylcellulose or HPC and Salt. This formula contains:

Ingredient	Formula Weight	Formula %	Weight per Pad
Purified Water			
TOTAL	700.000 g	100.000 %	3000 mg

Formulation A Patch

3. **Sample ID 8/21117/07**: Polyamine drug formulation. This formula contains:

Ingredient	Formula Weight	Formula %	Weight Per Pad
Purified Water			
Sumatriptan succinate			
methacrylate copolymer or			
Lauric acid, CAS Number			
Adipic acid, CAS Number			
TOTAL			

Formulation B Patch

2. **Sample ID 8/21119/07:** (b) (4) hydroxypropylcellulose (HPC) drug formulation. This formula contains:

Ingredient	Formula Weight	Formula %	Weight per Pad
Purified Water			(b) (4)
Sumatriptan succinate, (b) (4) (b) (4)			
Hydroxypropylcellulose or (b) (4) (b) (4)			
(b) (4)			
(b) (4)			
TOTAL			

Draize scoring system

Category	Score	Description
Erythema	0	No erythema
	1	Slight erythema
	2	Well-defined erythema
	3	Moderate or severe erythema
	4	Severe erythema or slight eschar formation (injuries in depth)

Summary Results and Conclusions

All animals survived to scheduled necropsy and no treatment-related changes in clinical observations, body weight, feed consumption, clinical pathology parameters, or organ weights were reported. Estimated plasma TK parameters did not differ between male and female animals and were, therefore, pooled (see sponsor's summary table reproduced below). The reported values indicate that Formulation B patches resulted in a greater systemic sumatriptan exposure than Formulation A patches and that application of both patches (i.e., Formulation A and Formulation B) yielded systemic exposures that roughly approximated the sum from the individual patch exposures. For perspective, mean sumatriptan C_{max} values reported for humans in the RLD labeling were as follows: 18 ng/mL (range, 7-47 ng/mL) and 51 ng/mL (range, 28-100 ng/mL) following oral dosing with 25 and 100 mg of sumatriptan, respectively; 5 and 16 ng/mL following 5- and 20-mg intranasal doses, respectively; and 71 ng/mL (range, 49-110 ng/mL) following a 6-mg subcutaneous injection.

Table 11 Mean Sumatriptan Toxicokinetic Parameters in Miniature Swine Receiving Topical Sumatriptan Patches

Treatment Group	C_{max} (ng/mL)	T_{max} (hr)	$t_{½}$ (hr)	AUC_{last} (ng/mL*hr)	$AUC_{0-\infty}$ (ng/mL*hr)	CL (mL/hr/kg)
2; Formulation A + Iontophoresis	23.58	4.0	2.8	119.4	138.8	56884
3; Formulation B + Iontophoresis	36.69 [a]	4.3	2.7	195.1 [b]	225.7 [b]	35139 [b]
4; Formulation A & B + Iontophoresis	68.36 [c]	4.0	2.8	342.0 [c]	395.7 [c]	37130 [b]

Note: Pooled across gender. N = 12 (6 males and 6 females per group).
a t-Test: Compare to Group 2, $p < 0.05$.
b t-Test: Compare to Group 2, $p < 0.01$.
c t-Test: Compare to Group 2 or 3, $p < 0.01$.

In general, dosing site erythema scoring revealed that Formulation B was the more irritating of the two drug patch formulations, with several scores of '4' (i.e., severe erythema or injuries in depth) being reported (see tabular summary below). In contrast, saline control/cathode patches, as well the drug formulation patches without iontophoresis, all scored essentially zero at all timepoints.

Mean Anode Erythema Scores (with iontophoresis only)

Scoring Day (n)	Formulation A	Formulation B
1 (Patch removal) (24)	0.625	1.625
2 (24)	0.375	1.583
3 (24)	0.250	1.708
7 (12)	0.083	1.000
14 (12)	0.000	0.583

Microscopic examination of a full battery of organ tissues from all high dose (Group 4) and control animals at necropsy on Day 3 revealed no treatment-related effects in tissues other than skin and, thus, only skin was examined microscopically at the Day 15 necropsy. Treatment-related skin changes were confined almost exclusively to dosing sites patched with Formulations A and B with iontophoresis (see sponsor's summary table reproduced below). Crust, defined as "…accumulations of serum and/or cell infiltrates, usually neutrophils, on the epidermal surface", was observed in the greatest incidence at Day 3, with comparable incidences and severities between the two drug patch formulations. An observation of slight epidermal necrosis with Formulation B is consistent with the more severe erythema scores noted above for this formulation and is concerning, given the exposure duration was only a single, 4-hour patch. Similarly, crust formation observed on Day 15 was also more severe with Formulation B.

Table 1. Total Incidence and Mean Severity for Selected Findings in Dose Skin Sites

Groups	Saline Cont.	Formulation A with iontophoresis	Formulation A without iontophoresis	Formulation B with iontophoresis	Formulation B without iontophoresis
Day 3	n = 6	n = 12	n = 6	n = 12	n = 0
Crust	-	4 (1.3)	-	4 (1.3)	-
Infiltrate neutrophils, Superficial dermis	-	-	-	1 (1.0)	-
Necrosis, epidermis	-	-	-	1 (1.0)	-
Pustule	-	-	-	2 (1.0)	-
Day 15	n = 6	n = 12	n = 0	n = 12	n = 6
Crust	-	5 (1.0)	-	6 (1.8)	-
Parakeratosis	1 (1.0)	1 (1.0)	-	3 (1.0)	-
Pustule	2 (1.0)	-	-	-	-

n = sample number
- = no findings
( ) = sum of severities divided by number affected

In conclusion, systemic toxicity was not observed under the conditions of this study. However, local toxicity was observed in the form of a potentially clinically significant skin irritation response to the proposed drug formulation(s)—most notably Formulation B—when administered via a single patch application in the presence of iontophoresis. The more severe responses observed with the Formulation B patch may be due to the apparent greater delivery through the skin with this formulation, as evidenced by the higher plasma exposure.

6.2 Repeat-Dose Toxicity

Study title: Chronic (9 month), Weekly Local Dermal Tolerance Study of NP101-Sumatriptan Iontophoretic Transdermal Patch in Non-Pigmented and Pigmented Miniature Swine

Study no.:	PROT-55-NP101-006/S08719
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	21 August 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Sumatriptan succinate, (b) (4) patch formulation, lots 7027478, 7037628, and 7063718

Key Study Findings

- Inadequate Study by design
- Same dose level to all animals, distinguished only by duration
- No control group(s) included
- Only 16 female animals total on study; 2 different strains
- Animals dosed only once per week for 4 hours; dosing site variability unclear
- Only 4 animals received full, 36-patch treatment over 9 months

- TK analysis not performed
- Iontophoretic device current flow/control undefined
- Stability of test article for full study duration not confirmed

Methods

Doses:	See sponsor's summary table below
Frequency of dosing:	One 4-hour patch application per week*
Route of administration:	Dermal patch with iontophoresis (self-contained power source; current flow/control undefined)
Dose volume:	See sponsor's summary table below
Formulation/Vehicle:	See sponsor's summary table below
Species/Strain:	Female Hanford (non-pigmented) and Yucatan (pigmented) miniature swine
Number/Sex/Group:	See sponsor's summary table below
Age:	5.6-6.4 Months
Weight:	23-36 kg
Satellite groups:	None
Unique study design:	*Patches were left in place for 4 hours; however, iontophoretic current flow was subject to automatic shut-off design specification of device if approximately 1 hour of "suboptimal delivery performance" occurs (see results below); also, see below for additional unique aspects
Deviation from study protocol:	For Group 1 and 2 animals, dose site skin samples for histopathology were collected from only one patch site and not both sites

Table 1 Study Design

Group	Number of animals/group	Treatment[a]	Number of Active Patches/Animal[b]
1	2 Hanford 2 Yucatan	Dose 4 times approximately weekly[c]	2
2	2 Hanford 2 Yucatan	Dose 12 times approximately weekly[c]	2
3	2 Hanford 2 Yucatan	Dose 24 times approximately weekly[c]	2
4	2 Hanford 2 Yucatan	Dose 36 times approximately weekly[c]	2

[a] The patches were used as manufactured.
[b] Each animal theoretically received 12 mg sumatriptan/dose event delivered via two patches.
cApproximately weekly will be +/- 1 day.

2.2. Test Device Information

Test Device Item [a]	Description	Lot/Batch Nos.
Electrode Patch	NP101-Sumatriptan Iontophoretic Transdermal Patch	8/21046/08; 8/21047/08; MBR-75-NP101-001-0007; MBR-75-NP101-001-0008; MBR-75-NP101-001-0011
Anode/Cathode Pads	**Anode:** (b) (4) (b) (4) **Cathode:** (b) (4)	7027478; 7037628; 7063718

[a] The theoretical dose per NP101 patch was (b) (4) mg. Certificates of analysis and Certificates of Conformance are attached in Appendix II.

Reproduced below is the sponsor's description of the dosing (patch application) procedures, followed by the sponsor's summary of key study dates. Patches were applied to two shaved sites on the dorsal trunk of each animal. **NOTE**: Study methodology does not describe use of any sort of anesthesia and/or restraint during iontophoretic patch exposure (cf. single-dose study, #S07562, reviewed above).

"2.8. Dose Administration
The route of administration was topical patch. Day 1 corresponds to the first day of dosing. The actual method of dose administration was as follows:
1) The dose area was washed with soap, rinsed with water and allowed to air dry or gently dried with gauze and/or paper towel.
2) Two patches were applied at the same pre-designated site on each swine once weekly (+/- 1 day) irrespective of body weight. If the designated site had not fully recovered from previous treatments, then the patches were placed on an alternative site. The patches were placed directly on the skin and secured with Elastikon tape. The area around the patch was marked so future clinical assessments could be made.
3) The patches utilized a fully integrated power source. The patches were activated by pressing firmly on the center of the plastic dome of the integrated power source for approximately 5 seconds until the red LED light came on and remained solid. The initiation (device activated) and completion time of dose application was documented in the raw data.
4) Each patch was removed after the 4-hour wearing time."

2.6. Dates for the Key Study Events

Study Initiation	August 21, 2008
Acclimation Start	August 21, 2008
Randomization	September 02, 2008
Physical Examination	August 28, 2008
Body Weight Measurement	Pre-dose (August 22, 2008) and weekly thereafter and prior to termination
Dose Administration	Group 1: September 11, 2008 thru September 30, 2008 Group 2: September 11, 2008 thru November 25, 2008 Group 3: September 11, 2008 thru February 17, 2009 Group 4: September 11, 2008 thru May 12, 2009
TK Blood Collection	September 30, 2008
Clinical Pathology Blood Collection	Predose (August 27, 2008) and at sacrifice
Necropsy	Group 1: October 6, 2008 Group 2: December 02, 2008 Group 3: February 23, 2009 Group 4: May 19, 2009

Observations and Results

As noted above, maximum theoretical dose to any animal was (b) (4) mg/2-patch application, without regard to the individual animal's weight. Reproduced below is the sponsor's summary of nominal versus actual iontophoretic exposure duration to the animals during patch application. According to the sponsor, "These suboptimal delivery times are not thought to represent patch failures but higher skin resistance in [certain] pigs, causing these devices to cease delivery of sumatriptan after approximately 1 hour of suboptimal delivery performance, a design specification of each device." While iontophoretic current flow through the patches was less than nominal to the extent noted (e.g., Group 1: 4 patch applications x 2 patches/animal x 4 hours/patch application = 32 hours/animal nominal iontophoretic patch activation time), patches were left adherent in place to the animal's dermal dosing site for the full prescribed 4-hour duration of each patch application. It should be noted that the report fails to describe what current flow was during patch application or to what extent, if at all, it was controlled.

Table 5 Summary of Actual Dose Exposure Time

Group	Animal ID	Duration (months)	Nominal Exposure Hours	Actual Exposure Hours/Pig*	Percent Nominal (%)
Group 1	1F1:5582	1	32	32.0	100.0
	1F2:5557	1	32	28.9	90.3
	1F3:0330	1	32	32.0	100.0
	1F4:0289	1	32	32.0	100.0
Mean				31.2	97.6
SD				1.5	4.8
Group 2	2F1:5608	3	96	93.7	97.6
	2F2:5535	3	96	86.1	89.7
	2F3:0262	3	96	96.0	100.0
	2F4:0328	3	96	96.0	100.0
Mean				93.0	96.8
SD				4.7	4.9
Group 3	3F1:5558	6	192	192.0	100.0
	3F2:5555	6	192	176.7	92.0
	3F3:0329	6	192	192.0	100.0
	3F4:0303	6	192	188.9	98.4
Mean				187.4	97.6
SD				7.3	3.8
Group 4	4F1:5556	9	288	224.2	77.8
	4F2:5546	9	288	256.0	88.9
	4F3:0270	9	288	288.0	100.0
	4F4:0290	9	288	285.1	99.0
Mean				263.3	91.4
SD				29.8	10.4
Mean[a]				276.4	96.0
SD[a]				17.7	6.1

*The time was calculated with the last time point when the device was observed on for those premature devices. All patch treatments were made to the same site throughout the study.

[a] Mean and Standard Deviation presented with 4F1 data excluded. For this data 4F1 was excluded due to it's high rate of patch failure. This is only to illustrate the effect that this animal's high incidence of failure had on the Group 4 averages.

Mortality

Observed twice daily. All animals survived to scheduled necropsy.

Clinical Signs

Clinical observations performed prior to dosing and once weekly thereafter; in addition, dermal dosing site scoring was conducted prior to each dose (post-shaving), immediately following patch removal, and daily on non-dosing days until Draize score (see below) reached zero.

Table 2 Modified Draize Scoring System

Category	Score	Description
Erythema	0	No erythema
	1	Slight erythema
	2	Well-defined erythema
	3	Moderate or severe erythema
	4	Severe erythema or slight eschar formation (injuries in depth)
Edema	0	No edema
	1	Very slight edema
	2	Slight edema (well-defined edges)
	3	Moderate edema (raised > 1 mm)
	4	Severe edema (raised > 1 mm and extending beyond the area of exposure)

The study design employed (i.e., no untreated and/or vehicle-treated control groups included) precluded any ability to detect drug treatment-related effects on clinical observations. Results of Draize dermal erythema scoring are summarized in the sponsor's tables reproduced below, which indicates that the Yucatan strain (pigmented) appeared to be the more sensitive strain. However, no erythema score ever exceeded 2 (well-defined erythema) for either strain and no longer than 4 days until full resolution. Edema scores were uniformly zero (0) in the Hanford strain, but scores of 1 were observed in the Yucatan strain as early as Week 3 and as late as Week 18, resolving in every case by 2 days (data not shown).

Table 8 Summary of Maximum Draize Erythema Scores and Duration by Group and Time Point

A) Hanford

Week	Group 1Hanford		Group 2 Hanford		Group 3 Hanford		Group 4 Hanford	
	Max. Score	Duration*	Max. Score	Duration*	Max. Score	Duration*	Max. Score	Duration*
1	1	1	1	2	1	2	1	2
2	1	2	1	2	1	1	1	2
3	1	2	1	4	1	3	1	2
4	1	1	1	2	1	3	1	3
5	NA	NA	1	2	1	2	1	2
6	NA	NA	1	2	1	2	1	2
7	NA	NA	1	2	1	2	1	2
8	NA	NA	1	2	1	2	1	2
9	NA	NA	1	2	1	2	1	3
10	NA	NA	1	2	1	2	1	2
11	NA	NA	1	2	1	1	1	3
12	NA	NA	1	3	1	3	1	3
13	NA	NA	NA	NA	1	3	1	3
14	NA	NA	NA	NA	1	2	1	3
15	NA	NA	NA	NA	1	3	1	3
16	NA	NA	NA	NA	1	3	1	3
17	NA	NA	NA	NA	1	3	1	3
18	NA	NA	NA	NA	1	2	1	3
19	NA	NA	NA	NA	1	2	1	3
20	NA	NA	NA	NA	1	2	1	2
21	NA	NA	NA	NA	1	3	1	2
22	NA	NA	NA	NA	1	3	1	3
23	NA	NA	NA	NA	1	3	1	3
24	NA	NA	NA	NA	1	3	1	3
25	NA	NA	NA	NA	NA	NA	1	2
26	NA	NA	NA	NA	NA	NA	1	3
27	NA	NA	NA	NA	NA	NA	1	3
28	NA	NA	NA	NA	NA	NA	1	2
29	NA	NA	NA	NA	NA	NA	2	2
30	NA	NA	NA	NA	NA	NA	1	3
31	NA	NA	NA	NA	NA	NA	1	2
32	NA	NA	NA	NA	NA	NA	1	3
33	NA	NA	NA	NA	NA	NA	1	2
34	NA	NA	NA	NA	NA	NA	1	2
35	NA	NA	NA	NA	NA	NA	1	2
36	NA	NA	NA	NA	NA	NA	1	2

*Number of days to resolution (Draize erythema score = 0); NA = Not Applicable

B) Yucatan

Week	Group 1 Yucatan		Group 2 Yucatan		Group 3 Yucatan		Group 4 Yucatan	
	Max. Score	Duration*	Max. Score	Duration*	Max. Score	Duration*	Max. Score	Duration*
1	1	1	1	1	1	1	1	1
2	1	1	1	3	1	3	1	3
3	2	3	2	4	2	3	2	4
4	1	2	2	3	1	2	1	3
5	NA	NA	1	2	1	2	1	2
6	NA	NA	2	2	1	2	1	2
7	NA	NA	1	2	1	2	1	2
8	NA	NA	2	2	1	2	1	2
9	NA	NA	1	2	1	2	1	3
10	NA	NA	1	2	1	2	1	2
11	NA	NA	1	2	1	3	1	3
12	NA	NA	1	3	1	3	1	3
13	NA	NA	NA	NA	1	3	1	3
14	NA	NA	NA	NA	1	3	2	3
15	NA	NA	NA	NA	1	3	1	2
16	NA	NA	NA	NA	1	2	1	3
17	NA	NA	NA	NA	1	2	1	3
18	NA	NA	NA	NA	1	3	1	3
19	NA	NA	NA	NA	1	2	1	2
20	NA	NA	NA	NA	1	2	1	2
21	NA	NA	NA	NA	1	1	1	2
22	NA	NA	NA	NA	1	2	1	3
23	NA	NA	NA	NA	1	1	1	2
24	NA	NA	NA	NA	1	2	1	3
25	NA	NA	NA	NA	NA	NA	1	2
26	NA	NA	NA	NA	NA	NA	1	4
27	NA	NA	NA	NA	NA	NA	1	3
28	NA	NA	NA	NA	NA	NA	1	2
29	NA	NA	NA	NA	NA	NA	2	2
30	NA	NA	NA	NA	NA	NA	1	3
31	NA	NA	NA	NA	NA	NA	2	2
32	NA	NA	NA	NA	NA	NA	1	3
33	NA	NA	NA	NA	NA	NA	1	3
34	NA	NA	NA	NA	NA	NA	1	2
35	NA	NA	NA	NA	NA	NA	2	2
36	NA	NA	NA	NA	NA	NA	1	2

*Number of days to resolution (Draize erythema score = 0); NA = Not Applicable.

Body Weights

Measured weekly. The study design employed (i.e., no untreated and/or vehicle-treated control groups included) precluded any ability to detect drug treatment-related effects on body weight.

Feed Consumption

Feed provided to animals was described only as a daily “maintenance amount using a pre-measured scoop. Consumption results reported “by exception” only, indicated that only a single animal (1F1-5582) did not consume all the feed offered them; data provided as net amount of feed consumed (g). The absence of untreated and/or vehicle-treated control groups precluded any ability to detect drug treatment-related effects on feed consumption.

Ophthalmoscopy

Not performed.

ECG

Not performed.

Hematology

Pretest and at scheduled necropsy. The study design employed (i.e., no untreated and/or vehicle-treated control groups included) precluded any ability to detect drug treatment-related effects on hematological parameters.

Clinical Chemistry

Pretest and at scheduled necropsy. The study design employed (i.e., no untreated and/or vehicle-treated control groups included) precluded any ability to detect drug treatment-related effects on clinical chemistry parameters.

Urinalysis

Not performed.

Gross Pathology

Protocol-specified necropsy days were Days 31, 91, 181, and 271; actual necropsy days reported in the Pathology Report were "Days 26 ± 2, 81 ± 2, 165 ± 2, and 250 ± 2". Neither description appears to be entirely consistent with the information provided in the sponsor's summary of key study event dates reproduced above (2.6 Dates for the Key Study Events). No explanation for this apparent discrepancy was provided in the report. In addition, it is not possible, based on the information provided in the report, to define what the time difference was between removal of the final patch and terminal necropsy.

The sponsor states that "only a few gross findings were observed at necropsy", which are summarized in the table reproduced below. No further detail of gross necropsy findings is provided in the report.

Table 17 Summary of Gross Findings at Necropsy

Animal ID	Strain	Finding
1F2:5557	Hanford	Liver right and left median lobes, white depressed multiple foci on the surface; approximately 20%
2F3:0262	Yucatan	Multiple, less than 1 mm brown spots in the skin on left dose site
2F4:0328	Yucatan	Right treatment site superficial skin contains up to 2 mm diameter dark brown to black spots; left treatment site is similar but much less affected.

Organ Weights

Weights of the organs shown in the sponsor's table below were collected at necropsy. However, the study design employed (i.e., no untreated and/or vehicle-treated control groups included) precluded any ability to detect drug treatment-related effects on organ weights.

Table 4 Organs Weighed at Necropsy

Adrenal (2)	Pituitary
Brain	Salivary glands (2)
Cecum	Small intestine
Heart	Spleen
Kidney (2)	Stomach
Large intestine	Thymus
Liver with gall bladder	Thyroid (2 lobes) with parathyroid
Lung with mainstem bronchi	Uterus
Ovary with oviduct (2)	

Histopathology

Adequate Battery: Yes, an adequate battery of tissues was collected as shown in the sponsor's table reproduced below. In addition, as noted in the Pathology Report, "…dose site skin was only collected from sites where a superficial skin biopsy sample was not collected. Two samples of application site skin (one left and one right) were collected and received for histopathology from all Group 3 and 4 animals, however one sample of dose site skin (left only) was received from all Group 1 and 2 animals. Additionally, one sample of skin from an untreated portion of the pig from each animal on study was collected and received for histopathology."

Table 3 Tissues Collected at Necropsy

adrenal (2)	mammary gland
aorta	ovary (2)
bone (femur & sternum with marrow)	pancreas
brain (cerebellum, cerebrum, medulla & pons)	pituitary gland
bone marrow smear***	rectum
cecum	salivary gland [mandibular (2)]
cervix	sciatic nerve
colon	skeletal muscle (quadriceps femoris)
duodenum	dose site skin (2) + 1 from untreated area[1]
esophagus	skin on abdominal region
eyes with optic nerve (2)*	spinal cord (cervical, thoracic & lumbar)
heart	spleen
ileum	stomach
jejunum	thymus
kidney (2)	thyroid (2)
lacrimal gland	tongue
lesions**	trachea
liver with gall bladder	urinary bladder
lung with mainstem bronchi	uterus
lymph node (mandibular)	vagina
lymph node (mesenteric)	

* Tissues were fixed in Davidson's solution for at least 2-3 days prior to transfer to 70% ethanol.
** Gross lesions were collected at the discretion of pathologist conducting the necropsy.
*** Fixed with methanol
[1] dose site skin was only collected from sites where a superficial skin biopsy sample had not been collected.

Peer Review: Not performed

Histological Findings: The Pathology Report states that microscopic observations, which are described as "…few and sporadic", were confined to the skin and that "other microscopic changes in the tissues examined occurred sporadically and are incidental findings with no correlation to the test material." However, such a conclusion has no basis in fact. The study design employed (i.e., no untreated and/or vehicle-treated control groups included) precluded any ability to detect drug treatment-related effects and/or to differentiate between drug-related and procedural-related (i.e., iontophoretic patching alone) effects on tissue microscopic observations. One possible exception to this deficiency may relate to local effects (i.e., under patch) on the skin. Reported skin findings are summarized in the table below. The conclusions of the Study Pathologist were as follows:

> "Hyperkeratosis at the treated (anode) site appears to be associated with the protocol specified application of the test patch rather than with the test material. There is a slight increase in incidence of hyperkeratosis at the treated sites versus untreated sites, but the severity of the change is similar throughout the treatment period. The increased incidence of hyperkeratosis with an application of a NP101-Sumatriptan Iontophoretic dermal patch may indicate a slight irritating effect, but the occurrence of hyperkeratosis at untreated sites eliminates NP101 as the sole cause of the change."

From a regulatory review perspective, the study report provides confusing, if not contradictory, information on whether each animal was patched on the exact same two skin sites with each patch application. On the one hand, the sponsor's description of the dosing procedures (Methods Section above), indicates that "if the designated site had not fully recovered from previous treatments, then the patches were placed on an alternative site." However, the legend to the sponsor's 'Summary of Actual Dose Exposure Time' (Table 5 reproduced above) states that, "all patch treatments were made to the same site throughout the study", which seems to suggest that recovery was complete in all cases by the time of the next scheduled patch application. If, in fact, multiple dosing sites were employed, the report provides no information on which skin sites were collected for histopathology. The report also provides no explanation for the apparent distinction (see table below) between 'anode dose site' in Groups 1 and 2 and the 'dose skin right/left' of Groups 3 and 4. Similarly, the apparent distinction between untreated skin from Groups 1 and 2 and that from Groups 3 and 4 is also not explained. In conclusion, the various deficiencies in the overall study design identified throughout this review, in conjunction with the inconsistencies/inadequacies in the reporting of the histopathology findings noted above, preclude a meaningful evaluation of the reported histopathology findings.

Incidence of Skin Histopathology Findings

	Number of Patch Applications (n=4 animals/group)			
Finding/Grade*	4	12	24	36
Dose Site (anode) Mononuclear infiltrate	2	2		
Grade 1	2			
Grade 2		2		
Dose Skin (left) Mononuclear infiltrate			3	3
Grade 1			3	2
Grade 2				1
Dose Skin (right) Mononuclear infiltrate			2	3
Grade 1			2	2
Grade 2				1
Skin Untreated 1,2 Mononuclear infiltrate	-	1		
Grade 2		1		
Skin Untreated 3,4 Mononuclear infiltrate			1	3
Grade 1			1	3
Dose Site (anode) Hyperkeratosis	4	2		
Grade 1	4			
Grade 2		1		
Grade 3		1		
Dose Skin (left) Hyperkeratosis			1	2
Grade 1			1	2
Dose Skin (right) Hyperkeratosis			2	2
Grade 1			2	2
Skin Untreated 1,2 Hyperkeratosis	1	2		
Grade 1	1	1		
Grade 3		1		

*Grade 1 = minimal; 2 = slight; 3 = moderate

Special Evaluation: None

Toxicokinetics: Not performed; single blood samples were collected from each study animal at approximately 3.5 hours post dosing initiation on Day 20 (4th patch) solely to confirm systemic exposure. Results indicate that plasma sumatriptan concentrations ranged from 34 to 69 ng/mL (Yucatan mean: 61 ng/mL; Hanford mean: 46 ng/mL).

Dosing Formulation Analysis: Not performed, although letters of certification provided by the sponsor to the study test facility are included in the submission, purportedly to provide assurances of stability for the drug reservoir cards in the patches. However, the information provided in these letters indicates that the latest stability

dating for the relevant test article lots was February, 2009. As noted in the sponsor's table reproduced above (2.6 Dates for the Key Study Events), Group 4 animals received patch applications up through 12 May 2009.

10 Special Toxicology Studies

Study title: Phototoxicity of Sumatriptan when Administered by the NP101 Sumatriptan Iontophoretic Transdermal Patch in Hanford Miniature Swine

Study no.:	PROT-55-NP101-008/S10060
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	12 December 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Sumatriptan succinate in NP101 E-patches, reservoir card lot no. 7037628, purity not defined

Summary Description and Conclusions

The potential for sumatriptan to induce photoirritation was assessed in male miniature Hanford swine (7-8 months old and 34-43 kg) following a single, 4-hour NP101 iontophoretic patch application. Two groups of animals (3/group) were dosed with the NP101 patch (see sponsor's patch description below) or the positive control agent, 8-MOP (8-methoxypsoralen, 0.01% or 0.1% in methanol @ 2 µL/cm^2 and 10 µL/site), both in the presence and absence of UV irradiation (35 minutes @ 0.67 Minimal Erythema Dose/hour, equivalent to approximately 5 joule/cm^2 of UV-A over the time period) (see sponsor's summary diagrams of doses and dosing site orientation reproduced below). Dose selection of 8-MOP and UV irradiation was based upon results from a previous non-GLP pilot study (PROT-55-NP101-008A/S08715). Animals were anesthetized (isoflurane inhalation) during UV irradiation, which commenced after the 4-hour NP101 patch application was completed and the patch site was cleaned in Group 1 or approximately 30 minutes after 8-MOP application in Group 2 animals. Blood samples collected from NP101-treated animals at approximately 20 minutes after completion of UV irradiation confirmed systemic sumatriptan exposure (range, 15.8-23.7 ng/mL). Animals were monitored following exposures until scheduled necropsy on Day 8. Skin samples collected from the center of each dose and control application site for each animal were preserved in 10% buffered formalin and submitted for microscopic histopathology examination.

Patch	Attaching Components (b) (4)
NP101 Patch	Anode*
	Cathode

*The theoretical dose delivered over 4 hours of iontophoresis is approximately (b) (4) mg sumatriptan.

Figure 1 Orientation of Group 1 Test Sites and Exposures

Group 1*

Right Side

Head	Site 1 NP101 UV exposed	Site 2 No treatment UV exposed
	Site 3 NP101 No UV exposure	Site 4 No treatment No UV exposure

Tail

Left Side

Figure 2 Orientation of Group 2 Test Sites and Exposures

Group 2

Right Side

Head	Site 1 0.01% 8-MOP UV exposed	Site 2 0.1% 8-MOP UV exposed	Site 3 No treatment UV exposed
	Site 4 0.01% 8-MOP No UV exposure	Site 5 0.1% 8-MOP No UV exposure	Site 6 No treatment No UV exposure

Tail

Left Side

Modified Draize Scoring Scale

Score	Definition
0	No erythema
1	Minimal erythema
2	Moderate erythema with sharply defined borders
3	Intense erythema with or without edema
4	Intense erythema with edema and blistering/erosion

All animals survived to scheduled necropsy. Results of modified Draize scoring and histopathology examination are summarized in the sponsor's tables reproduced below. Findings indicate that NP101 patch application induced mild skin irritation throughout the first 24 hours following application, with or without UV irradiation. There was positive evidence of a phototoxic reaction in 8-MOP-treated skin exposed to UV, but no comparable evidence in skin sites treated with NP101 in combination with UV. The

conclusion of the report is that treatment with the NP101 sumatriptan iontophoretic transdermal patch did not result in evidence of phototoxicity under the conditions of this study. The design and conduct of the study appears to have been reasonably adequate relative to OECD guidance, although experience with miniature swine as a test system appears to be limited.

Table 4 Group Means of Test Site Modified Draize Scores

Group I.D.	Test site	UVR received	Pre-Dose	Patch Removal	Post UVR	1 hr post	4 hr post	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
1	NP101 Patch	35 min	0.0	0.7	0.0	0.3	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	No treatment	35 min	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	NP101 Patch	none	0.0	0.3	0.7	1.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	No treatment	none	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	0.01% 8-MOP	35 min	0.0	0.0	0.0	0.0	0.0	0.0	1.0	1.0	1.3	1.3	1.0	0.7
	0.1% 8-MOP	35 min	0.0	0.0	0.0	0.0	0.0	0.7	1.7	2.3	2.3	2.3	2.3	2.0
	0% 8-MOP	35 min	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	0.01% 8-MOP	none	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	0.1% 8-MOP	none	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	0% 8-MOP	none	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Animal	1M1: 5766				1M2: 5776				1M3: 5763			
Sex	Male				Male				Male			
Group	1				1				1			
Day	8				8				8			
Treatment	Patch-Anode	Control	Patch-Anode	Control	Patch-Anode	Control	Patch-Anode	Control	Patch-Anode	Control	Patch-Anode	Control
Block	1	2	3	4	1	2	3	4	1	2	3	4
Site	1	3	4	6	1	3	4	6	1	3	4	6
UV Exposure	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	No	No
SKIN / Finding	+	-	-	-	-	+	+	-	+	+	+	-
Parakeratosis	**1**	0	0	**1**	0	0	0	0	0	0	0	0
Vacuolization, epidermis, focal	**1**	0	0	0	0	**1**	**1**	0	**1**	0	**1**	0
Mononuclear cell infiltrates, focal, dermis	0	0	0	0	0	**1**	0	0	0	0	0	0
Mononuclear cell infiltrates, focal, epidermis	0	0	0	0	0	0	0	0	**1**	0	**1**	0
Mononuclear cell infiltrates, focal, follicular	0	0	0	0	0	0	0	0	**1**	**1**	0	0
Mononuclear cell infiltrates, multifocal, perivascular	0	0	0	0	0	0	0	0	**1**	0	0	0
Crust, serocellular	0	0	0	0	0	0	0	0	0	0	0	0
Acanthosis	0	0	0	0	0	0	0	0	0	0	0	0
Degeneration, keratinocyte/epidermis	0	0	0	0	0	0	0	0	0	0	0	0
Mixed cell infiltrates, papillary dermis, diffuse	0	0	0	0	0	0	0	0	0	0	0	0
Edema, papillary dermis	0	0	0	0	0	0	0	0	0	0	0	0
Hemorrhage, papillary dermis	0	0	0	0	0	0	0	0	0	0	0	0
Ulceration, epidermis	0	0	0	0	0	0	0	0	0	0	0	0

Patch = ND101 Sumatriptan Iontopheretic Transdermal Patch
8-MOP = 8-Methoxypsoralen in Methanol;
+=Finding Present; -=Finding Not Present;
0=Not Present; 1=Minimal; 2=Mild; 3=Moderate

Animal	2M1: 5782						2M2: 5769						2M3: 5732					
Sex	Male						Male						Male					
Group	2						2						2					
Day	8						8						8					
Treatment	0.01% 8-MOP	0.1% 8-MOP	Control	0.01% 8-MOP	0.1% 8-MOP	Control	0.01% 8-MOP	0.1% 8-MOP	Control	0.01% 8-MOP	0.1% 8-MOP	Control	0.01% 8-MOP	0.1% 8-MOP	Control	0.01% 8-MOP	0.1% 8-MOP	Control
Block	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
Site	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
UV Exposure	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	No	No
SKIN / Finding	+	+	-	-	-	-	+	+	-	-	+	-	+	+	-	-	-	+
Parakeratosis	0	0	0	0	0	**1**	0	**2**	0	0	**1**	0	0	**1**	0	0	0	0
Vacuolization, epidermis, focal	0	0	0	0	0	0	0	0	0	0	0	0	0	**1**	0	0	0	0
Mononuclear cell infiltrates, focal, dermis	**1**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mononuclear cell infiltrates, focal, epidermis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mononuclear cell infiltrates, focal, follicular	0	0	0	0	0	0	0	0	0	0	0	0	**1**	0	0	0	0	0
Mononuclear cell infiltrates, multifocal, perivascular	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**1**
Crust, serocellular	**3**	**3**	0	0	0	0	**1**	**1**	0	0	0	0	0	**1**	0	0	0	0
Acanthosis	**2**	**2**	0	0	0	0	**1**	**2**	0	0	0	0	0	**1**	0	0	0	0
Degeneration, keratinocyte/epidermis	**1**	**2**	0	0	0	0	**1**	**1**	0	0	0	0	0	**1**	0	0	0	0
Mixed cell infiltrates, papillary dermis, diffuse	**1**	**1**	0	0	0	0	**1**	**1**	0	0	0	0	0	0	0	0	0	0
Edema, papillary dermis	**1**	**1**	0	0	0	0	**1**	**1**	0	0	0	0	0	**1**	0	0	0	0
Hemorrhage, papillary dermis	**1**	**2**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ulceration, epidermis	0	**2**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Study title: A Sensitization Study of Sumatriptan Administered by the Dermal Route to Guinea Pigs-Maximization Design

Study no.:	PROT-55-NP101-007/UKA00004
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	17 September 2008
GLP compliance:	Yes, except for test article characterization and stability analysis
QA statement:	Yes
Drug, lot #, and % purity:	Sumatriptan Succinate, lot #7779297, Purity 100.4%; Sumatriptan gel solution (b) (4)), lot #8/21057/08; Sumatriptan gel solution ((b) (4)), lot #8/21054/08; Sumatriptan gel solution (b) (4)), lot #8/21055/08; Sumatriptan gel solution (b) (4)), lot #8/21056/08

Summary Description and Conclusions

NB: At sponsor's discretion, study PROT-55-NP101-007/UKA00004 was deemed invalid and subsequently repeated under study number PROT-55-NP101-009/UKA00005 (reviewed below).

Reproduced below are selected portions of the sponsor's summary and conclusions for study PROT-55-NP101-007/UKA00004, including a rationale for their determination that the study was invalid. Following that are selected summaries of study design and results from the dose range-finding phase of the study that was considered to have been valid, as study PROT-55-NP101-009/UKA00005 (reviewed below) relies upon these data.

> "The dermal sensitization potential of sumatriptan (Test Article 1), the active drug substance in the iontophoretic transdermal delivery device (NP101), and the sumatriptan polyamine gel solution employed in the device (Test Article 2) were evaluated in Hartley-derived albino guinea pigs….Based on the results of the range-finding studies, appropriate test article concentrations were determined for use in the main phase. However, the results of the main phase of the sensitization study with sumatriptan solution (b) (4) % in sterile water) and sumatriptan gel solution are considered invalid due to a dosing error during the topical induction. The results of the DNCB positive control study demonstrated that a valid test was performed and indicated that the test design would detect potential contact sensitizers. The main study phase was repeated under Study Number UKA00005."

Experimental Design for the Topical Range-Finding Phase

Group	Site	No. of Range-Finding Animals		Dose Material	Dose Level
		Males	Females		
1	1	5	5	Test Article 1	100%[a]
	2			Test Article 1	75%[b]
	3			Test Article 1	50%[b]
	4			Test Article 1	25%[b]
	5			Control Article 2	100[a]
2	1	5	5	Test Article 2	100%
	2			Test Article 3	100%
	3			Test Article 4	100%
	4			Test Article 5	100%

[a]A 4% concentration in sterile water preparation was prepared and considered the 100% concentration.
[b]The vehicle used was sterile water.

Experimental Design for the Intradermal Range-Finding Phase

Group	Site	No. of Range-Finding Animals		Dose Material	Dose Level[a]
		Males	Females		
3	1	5	5	Test Article 1	5.0%
	2			Test Article 1	3.0%
	3			Test Article 1	1.0%
	4			Test Article 1	0.1%

[a]A 4% concentration in sterile water preparation was prepared and considered the 100% concentration. This concentration was then diluted to 5.0%, 3.0%, 1.0%, and 0.1% with sterile water.

TOPICAL RANGE-FINDING DATA
[TEST ARTICLE 1 AND CONTROL ARTICLE 2]

		RANGE-FINDING DERMAL SCORES									
		TEST ARTICLE 1								CONTROL ARTICLE 2	
	ANIMAL NO./SEX	100%[a]		75%[b]		50%[b]		25%[b]		100%[c]	
GROUP	BODY WEIGHT (G)	24 HOURS	48 HOURS	24 HOURS	48 HOURS	24 HOURS	48 HOURS	24 HOURS	48 HOURS	24 HOURS	48 HOURS
TOPICAL RANGE-FINDING	G3072/M 324	0	0	0	0	0	0	0	0	0	0
	G3073/M 312	0	0	0	0	±	0	±	0	0	0
	G3074/M 349	0	0	0	0	0	0	0	0	0[IT]	0
	G3075/F 320	0	0	0	0	0	0	0	0	0[IT]	0[IT]
	G3076/M 319	0	0	0	0	0	0	0	0	0	0
	G3082/F 330	0	0	0	0	0	0	0	0	0	0
	G3083/F 352	0	0	0	0	0	0	0[IT]	0	0	0
	G3084/F 318	0	0	0	0	0	0	±	0	0	0
	G3085/F 336	0	0	0	0	0	0	0	0	0	0
	G3086/F 326	0	0	0	0	0	0	0	0	0	0

NOTE: SEE PROTOCOL ATTACHMENT 1 FOR DEFINITION OF CODES.
[a]A 4% CONCENTRATION IN STERILE WATER WAS PREPARED AND CONSIDERD THE 100% CONCENTRATION.
[b]THE VEHICLE USED WAS STERILE WATER.
[c]AS RECEIVED.

GROUP	ANIMAL NO./SEX BODY WEIGHT (G)	RANGE-FINDING DERMAL SCORES TEST ARTICLE 2 100%[a] 24 HOURS	48 HOURS	TEST ARTICLE 3 100%[a] 24 HOURS	48 HOURS	TEST ARTICLE 4 100%[a] 24 HOURS	48 HOURS	TEST ARTICLE 5 100%[a] 24 HOURS	48 HOURS
TOPICAL RANGE-FINDING	G3077/M 323	0	0	±	0	0	0	±	±
	G3078/M 326	±	±	1	±	0	0	1	±
	G3079/M 328	±	±	±	0	0	0	0	0
	G3017/M 413	0[IT]	0[IT]	±	0	±	0	±	±
	G3018/M 404	±[IT]	±	±[IT]	±	±[IT]	±	±[IT]	±
	G3087/F 337	0	0	0	0	±[IT]	0	±[IT]	0
	G3088/F 328	±	±	±	0	0	0	±	0
	G3089/F 319	0	0	±	0	0	0	0	0
	G3090/F 326	±	±	±	±	0	0	0	0
	G3091/F 340	±	±	±	0	±	0	1	±

NOTE: SEE PROTOCOL ATTACHMENT 1 FOR DEFINITION OF CODES.
[a]AS RECEIVED.

GROUP	ANIMAL NO./SEX BODY WEIGHT (G)	RANGE-FINDING DERMAL SCORES TEST ARTICLE 1 5.0%[a] 24 HOURS	48 HOURS	3.0%[a] 24 HOURS	48 HOURS	1.0%[a] 24 HOURS	48 HOURS	0.1%[a] 24 HOURS	48 HOURS
INTRADERMAL RANGE-FINDING	G2982/M 418	1	1	1	1	1	1	1	1
	G2984/M 409	1	1	1	1	1[ED-1]	1	1[ED-1]	1
	G2988/M 405	1	1	1	1	2	1	2	1
	G2995/M 413	2[ED-1]	1	2[ED-1]	1	2[ED-1]	1	2[ED-1]	1
	G2996/M 426	1	1	2	1	2	1	2	1
	G3020/F 378	1	1	1	1	1	1	2[ED-1]	1
	G3026/F 383	1	1	1[ED-1]	1	1	1	1[ED-1]	1
	G3029/F 380	1	1	1	1	1	1	1	1
	G3031/F 374	1	1	1	1	1	1	1	1
	G3032/F 405	1	1	1	1	2	1	1	1

NOTE: SEE PROTOCOL ATTACHMENT 1 FOR DEFINITION OF CODES.
[a]A 4% CONCENTRATION IN STERILE WATER WAS PREPARED AND CONSIDERED THE 100% CONCENTRATION. THIS CONCENTRATION WAS THEN DILUTED TO 5.0%, 3.0%, 1.0%, AND 0.1% WITH STERILE WATER.

Macroscopic Dermal Grading System

ERYTHEMA AND EDEMA OBSERVATIONS		
OBSERVATION	DEFINITION	CODE
Erythema - Grade 0	No reaction	0
Erythema - Grade ±	Slight patchy erythema	±
Erythema - Grade 1	Slight, but confluent or moderate patchy erythema	1
Erythema - Grade 2	Moderate, confluent erythema	2
Erythema - Grade 3	Severe erythema with or without edema	3
Maximized Grade 3	Notable dermal lesions	M-3 (see below)
Edema - Grade 1	Very slight edema (barely perceptible)	ED-1
Edema - Grade 2	Slight edema (edges of area well defined by definite raising)	ED-2
Edema - Grade 3	Moderate edema (raised approximately 1 millimeter)	ED-3
Edema - Grade 4	Severe edema (raised more than 1 millimeter and extends beyond the area of exposure)	ED-4
An erythema code will be assigned to each test site. An edema code will be assigned only if edema is present at the test site. If notable dermal lesion(s) (> grade 1) are present, then the "Maximized Grade 3" is assigned to the test site in place of the erythema score and the type of the notable dermal lesion(s) will be noted (e.g., M-3 [ES-2]).		

NOTABLE DERMAL LESIONS		
OBSERVATION	DEFINITION/EXPLANATION	CODE
Eschar	A crust-like formation within or on the test area. Characterized as scab-like (dried blood or lymph) or dead layers of tissue/crust. The area is hardened to the touch and not very pliable. Note: Since erythema cannot be observed through eschar and eschar is considered to be a notable dermal lesion, the erythema score will be maximized when eschar is present greater than ES-1. The test site may be observed for reversibility in order to determine if the eschar is an in-depth injury. To be coded using an area designation (see below).	--
Eschar - Grade 1	Focal and/or pinpoint areas up to 10% of test site	ES-1
Eschar - Grade 2	> 10% < 25% of test site	ES-2
Eschar - Grade 3	> 25% < 50% of test site	ES-3
Eschar - Grade 4	> 50% of test site	ES-4
Blanching	Characterized by areas of white to yellow or tannish discoloration in the test site due to a decreased blood flow to the skin. Note: An erythema score cannot be determined and blanching is considered a notable dermal lesion; therefore, the erythema score will be maximized when blanching is present greater than BLA-1. The test site may be observed for reversibility in order to determine if the blanching is an in-depth injury. To be coded using an area designation (see below).	--
Blanching - Grade 1	Focal and/or pinpoint areas up to 10% of the test site	BLA-1
Blanching - Grade 2	> 10% < 25% of test site	BLA-2
Blanching - Grade 3	> 25% < 50% of test site	BLA-3
Blanching - Grade 4	> 50% of test site	BLA-4
Ulceration	An open lesion in the skin possibly due to the exfoliation of necrotic tissue or eschar formation. Characterized by a crater-like area which is generally inflamed and has a moist exudate. The erythema score will be maximized when ulceration is present greater than U-1. Ulceration is considered an in-depth injury. To be coded using an area designation (see below).	--
Ulceration - Grade 1	Focal and/or pinpoint areas up to 10% of the test site	U-1
Ulceration - Grade 2	> 10% < 25% of test site	U-2
Ulceration - Grade 3	> 25% < 50% of test site	U-3
Ulceration - Grade 4	> 50% of test site	U-4
Necrosis	The apparent death of a portion of tissue which may result in irreversible damage depending on the severity of injury based on the color, area and	--

ADDITIONAL FINDINGS		
OBSERVATION	DEFINITION/EXPLANATION	CODE
Dermal Irritation - Outside of the Test Site in Tape/Binder Area	Noticeable irritation outside of test site probably due to the binding tape material. This notation will only be made for reactions greater than what are normally observed from tape removal which don't interfere with the scoring of the test site. The study director or study director designee should be contacted for irritation outside the test site which may affect the scoring of the test site. Since this finding can only occur on a dermal study it will not be conducted daily as a clinical observation but recorded at the dermal scoring intervals.	IT

NOTABLE DERMAL LESIONS		
OBSERVATION	DEFINITION/EXPLANATION	CODE
	texture. It is characterized by a dark (ranging from gray to black) and often in-depth discoloration of the tissue. Affected areas can be focal or well-defined. Since this term is considered to be diagnostic, this observation is only to be made with the approval of the study director or study director designee and will be accompanied by a full description (the color should be noted). The erythema score will be maximized when necrosis is present greater than NEC-1. Necrosis is considered a notable dermal lesion and an in-depth injury. To be coded using an area designation (see below).	
Necrosis - Grade 1	Focal and/or pinpoint areas up to 10% of the test site	NEC-1 (*color*)
Necrosis - Grade 2	> 10% < 25% of test site	NEC-2 (*color*)
Necrosis - Grade 3	> 25% < 50% of test site	NEC-3 (*color*)
Necrosis - Grade 4	> 50% of test site	NEC-4 (*color*)

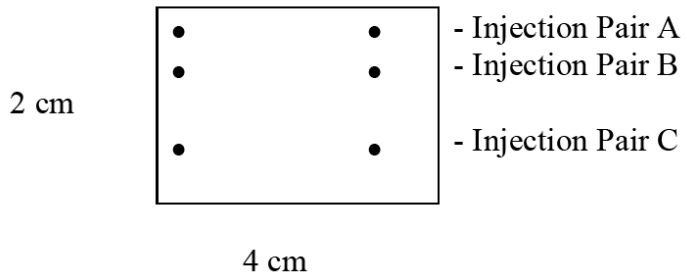
ADDITIONAL DERMAL OBSERVATIONS		
OBSERVATION	DEFINITION/EXPLANATION	CODE
Desquamation	Characterized by scaling or flaking of dermal tissue with or without denuded areas. Desquamation may consist of a range from dry flaking of the skin to more pronounced flaking with denuded areas (in these cases the desquamation may have a slight harder "feel" to it as compared to normal tissue; however, this should not be confused with a notable dermal lesion such as eschar). Areas of eschar are not scored for desquamation. This finding is generally not considered significant if the test site is otherwise clear for erythema, edema, etc.	DES
Fissuring	Characterized by cracking of the skin or eschar formation (slough and/or scab) that is associated with moist exudate. Fissuring should be check prior to removing the animal from the cage and manipulating the test site.	FIS
Eschar Exfoliation	The process by which areas of eschar flake off the test site. This observation should be noted only with an ES observation.	EXF
Test Site Staining	Skin located at the test site appears to be stained/discolored possibly due to test article (note color of staining).	TSS (*color*)
Erythema Extends Beyond the Test Site	The erythema extends beyond the test site. Note: A study director should be contacted for erythema extending beyond the test site.	ERB
Superficial Lightening	Characterized by pale area(s) (almost a burn-like appearance) in the test site. However, erythema may still be observed through the pale area. Note: This observation may affect the overall erythema score of the test site. This observation may progress to other observations resulting in notable dermal lesions, but SL itself will not be considered a notable dermal lesion that will result in a dermal score to be maximized. To be coded using an area designation (see below).	--
Superficial Lightening - Grade 1	Focal and/or pinpoint areas up to 10% of the test site	SL-1
Superficial Lightening - Grade 2	> 10% < 25% of test site	SL-2
Superficial Lightening - Grade 3	> 25% < 50% of test site	SL-3
Superficial Lightening - Grade 4	> 50% of test site	SL-4

Study title: A Sensitization Study of Sumatriptan Administered by the Dermal Route to Guinea Pigs-Maximization Design

Study no.:	PROT-55-NP101-009/UKA00005
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	12 November 2008
GLP compliance:	Yes, except for test article characterization and stability analysis
QA statement:	Yes
Drug, lot #, and % purity:	Sumatriptan Succinate, lot #7779297, Purity 100.4%; NP101 Reservoir Card (containing (b) (4) polyamine and (b) (4) sumatriptan succinate), lot #7037628

Summary Description and Conclusions

The dermal sensitization potential of sumatriptan, alone and as delivered via the sponsor's NP101 iontophoretic patch system, was assessed in Hartley-derived albino guinea pigs using a modified Maximization test methodology that incorporated both intradermal injections and topical applications during the induction phase. This two-route induction phase was judged to optimally compensate for the inability to utilize iontophoresis to deliver test article. Hair was removed from the application sites (scapular area on either side of the spinal cord) by clipper prior to treatments, which are summarized in the sponsor's figures/tables reproduced below. The dose concentrations for intradermal and topical induction were based on results from those aspects of study PROT-55-NP101-007/UKA00004 (reviewed above) that were deemed valid. Study results are summarized in the sponsor's tables reproduced below; the dermal grading scale and codes employed are summarized in the sponsor's tables reproduced in the review of study PROT-55-NP101-007/UKA00004 above. Under the conditions of this test, (b) (4) sumatriptan solution (Test Article 1) and sumatriptan gel solution ((b) (4) % polyamine and (b) (4) sumatriptan) (Test Article 2) were judged unlikely to induce contact sensitization.



Experimental Design[a]

Group	No. of Animals Males/Females	Phase/Treatment			
		Intradermal Induction	Topical Induction	Challenge	Rechallenge[b]
Test 1	5/5	FCA emulsion Test Article 1 ((b) (4) sumatriptan in water) Test Article 1 preparatoin/FCAemulsion	Test Article 1 ((b) (4) sumatriptan in water)	Test Article 1 ((b) (4) sumatriptan in water)	Test Article 1 ((b) (4) sumatriptan in water
Test 2	5/5	FCA emulsion Test Article 1 ((b) (4) sumatriptan in water) Test Article 1 preparation/ FCA emulsion	Test Article 2	Test Article 2	Test Article 2
Common Challenge Control	5/5	FCA emulsion Control Article (sterile water) Control Article 1/FCA emulsion	Control Article (sterile water)	Test Article 1 ((b) (4) sumatriptan in water) Test Article 2	--
Common Rechallenge Control	5/5	FCA emulsion Control Article (sterile water) Control Article 1/FCA emulsion	Control Article (sterile water)	--	Test Article 1 ((b) (4) sumatriptan in water) Test Article 2
DNCB Test	5/5	FCA emulsion 0.1% DNCB preparation 0.1% DNCB/FCA emulsion	0.1% DNCB	0.1% and 0.05% DNCB	--
DNCB Control	5/5	FCA emulsion 0.5% Acetone/propylene glycol 0.1% Acetone/propylene glycol/FCA emulsion	0.5% Acetone/propylene glycol	0.1% and 0.05% DNCB	--

[a]Based on OECD 406 guideline for study design.
[b]A rechallenge phase was not conducted since the challenge results were definitive.

GROUP	ANIMAL NO./ SEX	DERMAL SCORES 100%[a] 24 HOURS	48 HOURS
TEST 1	G3255/M	0	0
	G3256/M	0	0
	G3257/M	0	0
	G3258/M	0	0
	G3259/M	0[IT]	0
	G3285/F	0	0
	G3286/F	0[IT]	0
	G3287/F	0	0
	G3288/F	0	0
	G3289/F	0	0
	MEAN	0.0	0.0

NOTES: SEE PROTOCOL ATTACHMENT 1 FOR DEFINITION OF CODES. IT = IRRITATION OUTSIDE TEST SITE.
[a]A (b) (4) CONCENTRATION IN STERILE WATER WAS PREPARED AND CONSIDERED THE 100% CONCENTRATION.

GROUP	ANIMAL NO./ SEX	DERMAL SCORES 100%[a] 24 HOURS	48 HOURS
TEST 2	G3260/M	0	0
	G3263/M	0	0
	G3265/M	±	0
	G3267/M	±	±
	G3268/M	0	0
	G3290/F	0	0
	G3291/F	0	0
	G3292/F	0	0
	G3293/F	0	0
	G3294/F	0	0
	MEAN	0.1	0.1

NOTE: SEE PROTOCOL ATTACHMENT 1 FOR DEFINITION OF CODES. FOR PURPOSE OF CALCULATION, ± = 0.5.
[a]AS RECEIVED.

GROUP	ANIMAL NO./ SEX	DERMAL SCORES 100%[a] TEST ARTICLE 1 24 HOURS	48 HOURS	100%[b] TEST ARTICLE 2 24 HOURS	48 HOURS
CHALLENGE CONTROL	G3269/M	0	0	0	0
	G3270/M	0	0	0	0
	G3271/M	0	0	0	0
	G3272/M	0	0	0[IT]	0
	G3274/M	0	0	0	0
	G3295/F	0	0	0	0
	G3296/F	0	0	0	0
	G3038/F	0	0	0	0
	G3039/F	0	0	0	0
	G3035/F	0	0	0	0
	MEAN	0.0	0.0	0.0	0.0

NOTES: SEE PROTOCOL ATTACHMENT 1 FOR DEFINITION OF CODES. IT = IRRITATION OUTSIDE THE TEST SITE.
[a]A (b) CONCENTRATION INSTERILE WATER WAS PREPARED AND CONSIDERED THE 100% CONCENTRATION.
[b]AS RECEIVED.

GROUP	ANIMAL NO./ SEX	DERMAL SCORES 0.1%[a] 24 HOURS	48 HOURS	0.05%[a] 24 HOURS	48 HOURS
DNCB TEST	G3279/M	2[TSSY, TAS, BLA-1 ED-2]	M-3[TSSY, TAS, ED-2, BLA-3]	1[TSSY, TAS, ED-1]	1[TSSY, TAS, ED-1]
	G3280/M	M-3[TSSY, TAS,ED-2, BLA-2]	M-3[TSSY, TAS, ED-2, BLA-3]	1[TSSY, TAS, ED-1]	1[TSSY, TAS, ED-1]
	G3281/M	2[TSSY, TAS, SL-1, BLA-1, ED-2]	M-3[TSSY, TAS, BLA-2, ED-2]	2[TSSY, TAS, ED-1, SL-1]	1[TSSY, TAS, ED-1]
	G3282/M	2[TSSY, TAS, ED-2]	2[TSSY, TAS, BLA-1, ED-1]	1[TSSY, TAS, ED-1]	1[TSSY, TAS]
	G3283/M	2[TSSY, TAS, SL-2, ED-2]	2[TSSY, TAS, ED-2, BLA-1]	1[TSSY, TAS, ED-1]	1[TSSY, TAS, ED-1]
	G3301/F	1[TSSY, TAS, ED-1]	1[TSSY, TAS, BLA-1, ED-1]	1[TSSY, TAS, ED-1]	1[TSSY, TAS, ED-1]
	G3302/F	1[TSSY, TAS, ED-1]	1[TSSY, TAS, ED-1]	1[TSSY, TAS, ED-1]	1[TSSY, TAS, ED-1]
	G3303/F	M-3[TSSY, TAS, ED-2, BLA-3]	M-3[TSSY, TAS, BLA-4, ED-2]	1[TSSY, TAS, ED-1]	1[TSSY, TAS, ED-1]
	G3304/F	M-3[TSSY, TAS, ED-2, BLA-2]	M-3[TSSY, TAS, ED-2, BLA-2]	2[TSSY, TAS, ED-1]	1[TSSY, TAS, ED-1]
	G3305/F	M-3[TSSY, TAS, BLA-2, ED-2]	M-3[TSSY, TAS, BLA-4, ED-2]	1[TSSY, TAS, ED-1]	1[TSSY, TAS, ED-1]
	MEAN	2.2	2.4	1.2	1.0

NOTES: SEE PROTOCOL ATTACHMENT 1 FOR DEFINITION OF CODES. TSSY = TEST SITE STAINING YELLOW. TAS = TEST SITE STAINING DID NOT INTERFERE WITH SCORING.
[a]THE VEHICLE USED WAS ACETONE/PROPYLENE GLYCOL.

GROUP	ANIMAL NO./ SEX	DERMAL SCORES 0.1%[a] 24 HOURS	48 HOURS	0.05%[a] 24 HOURS	48 HOURS
DNCB CONTROL	G3284/M	±[TSSY, TAS]	0[TSSY, TAS]	0[TSSY, TAS]	0[TSSY TAS]
	G3273/M	0[TSSY, TAS]	0[TSSY, TAS]	0[TSSY, TAS]	0[TSSY, TAS]
	G3264/M	0[TSSY, TAS]	0[TSSY, TAS]	±[TSSY, TAS]	0[TSSY, TAS]
	G3277/M	0[TSSY, TAS]	0[TSSY, TAS]	0[TSSY, TAS]	0[TSSY, TAS]
	G3278/M	0[TSSY, TAS]	0[TSSY, TAS]	0[TSSY, TAS]	0[TSSY, TAS]
	G3311/F	±[TSSY, TAS]	0[TSSY, TAS]	0[TSSY, TAS]	0[TSSY, TAS]
	G3312/F	0[TSSY, TAS, IT]	0[TSSY, TAS]	0[TSSY, TAS]	0[TSSY, TAS]
	G3313/F	0[TSSY, TAS]	0[TSSY, TAS]	0[TSSY, TAS]	0[TSSY, TAS]
	G3314/F	0[TSSY, TAS]	0[TSSY, TAS]	0[TSSY, TAS]	0[TSSY, TAS]
	G3300/F	0[TSSY, TAS]	0[TSSY, TAS]	0[TSSY, TAS]	0[TSSY, TAS]
	MEAN	0.1	0.0	0.1	0.0

NOTES: SEE PROTOCOL ATTACHMENT 1 FOR DEFINITION OF CODES. FOR PURPOSE OF CALCULATION ± = 0.5. TSSY = TEST SITE STAINING YELLOW. TAS = TEST SITE STAINING DID NOT INTERFERE WITH SCORING. IT = IRRITATION OUTSIDE TEST SITE.
[a]THE VEHICLE USED WAS ACETONE/PROPYLENE GLYCOL

Study title: ISO Agarose Overlay Using L-929 Mouse Fibroblast Cells

Study no.:	PROT-55-NP101-012/118148
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E-Patch (with (b) (4) removed); Testing (b) (4) ((b) (4)); Pad transfer ring ((b) (4) Ring); Overtape with adhesive ((b) (4) Foam Barrier with adhesive, Lot # 8/21046/08

Summary Description and Conclusions

The cytotoxicity of certain components of the NP101 transdermal patch was assessed *in vitro* using cultured L-929 mouse fibroblast cells under an ISO 10993-5-compliant protocol designed to assess biocompatibility of medical devices (ISO 10993-5: 1999 "Biological Evaluation of Medical Devices, Part 5: Tests for In Vitro Cytotoxicity. "). The study was designed to assess the potential for extracts from solid device components that were laid atop an agarose barrier to leach out and diffuse through the barrier and induce signs of toxicity in the cultured cells below. Triplicate test and control cultures (see sponsor's summary table reproduced below) were incubated at 37°C for 24-25 hours and then stained with neutral red, followed by macroscopic/microscopic scoring (see sponsor's Table 2 below). Results are summarized in the sponsor's Table 3 below. They indicate that the criteria for a valid assay were met (positive and negative controls scored 3-4 and 0, respectively) and that the test article was non-toxic (scored ≤2) under the conditions of the test.

TABLE 1: CONTROL / CELL LINE RECORD

CONTROL IDENTIFICATION:	CLASS	LOT #	SUPPLIED BY:	EXPIRATION
Penrose Tubing	Positive control		(b) (4)	07/15/09
HDPE Tubing	Negative control			N/A
L-929	Cell line			N/A
2X E-MEM + 10% FBS	Medium			04/10/09
2% Agarose	Agarose			07/06/09

TABLE 2: TEST SCORING

GRADE	CONDITIONS OF ALL CULTURES
0	No detectable zone under or around specimen.
1	Some malformed or degenerated cells under sample.
2	Zone limited to area under specimen.
3	Zone extends 0.5 - 1.0 cm beyond specimen.
4	Zone extends greater than 1.0 cm beyond specimen.

TABLE 3: TEST RESULTS

TEST ARTICLE	CYTOTOXIC SCORE		
	PLATE 1	PLATE 2	PLATE 3
Test Article	0	0	0
Positive Control	4	4	4
Negative Control	0	0	0
Cell Control	0		

Study title: Repeated Patch Dermal Sensitization Test (Buehler Method Modified for Medical Devices)

Study no.: PROT-55-NP101-013/118149
Study report location: EDR
Conducting laboratory and location: (b) (4)
Date of study initiation: 17 March 2009
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: E-Patch (with (b) (4) removed); Testing (b) (4) ((b) (4)); Pad transfer ring (b) (4) Ring); Overtape with adhesive ((b) (4) Foam Barrier with adhesive, Lot # 8/21046/08

Summary Description and Conclusions

The dermal sensitization potential of certain components of the NP101 transdermal patch was assessed in male Hartley albino guinea pigs under an ISO 10993-10-compliant protocol designed to assess biocompatibility of medical devices (ISO 10993-10: 2002 Standard, "Biological Evaluation of Medical Devices", Part 10-Tests for Irritation and Delayed-Type Hypersensitivity"). The repeated patch method of Buehler was used but modified to include a longer induction exposure period for solid test articles. Animals (10 test and 5 control) were patched 6 hr/day, 3 day/week for 3 weeks (a total of 9 patches) during induction. Following a 2-week rest period, animals were challenged with a 6-hr patching on the opposite flank with the appropriate test or control

article, and then scored for erythema and edema at 24 and 48 hours post patch removal (see sponsor's Table 4 reproduced below). Under the conditions of the study, there was no evidence of a sensitization response to the test article (see sponsor's results summary table reproduced below). Results of a positive control assay (dinitrochlorobenzene, DNCB) conducted within 6 months of the test assay (per ISO guidelines) were available and confirmed sensitivity of the test system.

TABLE 4: DERMAL OBSERVATION SCORING

PATCH TEST REACTION	GRADING SCALE
No visible change	0
Discrete or patchy erythema	1
Moderate and confluent erythema	2
Intense erythema and swelling	3

Note: Erythema is defined as redness and edema is defined as a swelling at the challenge site. Any other adverse changes at the skin sites were recorded and reported.

TABLE 6: CHALLENGE DERMAL OBSERVATIONS

ANIMAL #	24 HOURS SCORE	48 HOURS SCORE
TEST GROUP		
1	0	0
2	0	0
3	0	0
4	0	0
5	0	0
6	0	0
7	0	0
8	0	0
9	0	0
10	0	0
Total of Scores	0	0
Severity (Total/10)	0/10	0/10
Incidence %	0%	0%
NEGATIVE CONTROL GROUP		
11	0	0
12	0	0
13	0	0
14	0	0
68911	0	0
Total of Scores	0	0
Severity (Total/5)	0/5	0/5
Incidence %	0%	0%

Study title: Primary Skin Irritation

Study no.:	PROT-55-NP101-014/118150
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	19 March 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	E-Patch (with (b) (4) removed); Testing (b) (4) ((b) (4); Pad transfer ring ((b) (4) Ring); Overtape with adhesive ((b) (4) Foam Barrier with adhesive, Lot # 8/21046/08

Summary Description and Conclusions

The dermal irritation potential of certain components of the NP101 transdermal patch was assessed in male albino New Zealand White rabbits under an ISO 10993-10-compliant protocol designed to assess biocompatibility of medical devices (ISO 10993-10: 2002 Standard, "Biological Evaluation of Medical Devices", Part 10-Tests for Irritation and Delayed-Type Hypersensitivity"). Three animals were clipped on both sides of the dorsal trunk and then were patched with test and control articles (wetted with tap water) on opposite sides. The patches were held in place for 4 hours with elastic wrap and hypoallergenic tape. Dermal scoring (see sponsor's summary tables reproduced below) was performed at 1, 24, 48, and 72 hours post unwrapping. Results are summarized in the sponsor's Tables 4 and 5 reproduced below. Under the conditions of this study, the test article was considered to be non-irritating.

TABLE 2: DERMAL OBSERVATION SCORING

ERYTHEMA	EDEMA
0 = No erythema	0 = No edema
1 = Very slight erythema (barely perceptible)	1 = Very slight edema (barely perceptible)
2 = Well defined erythema	2 = Slight edema (raised edges)
3 = Moderate to severe erythema	3 = Moderate edema (raised ~ 1 mm)
4 = Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4 = Severe edema (raised > 1 mm and extending beyond area)

TABLE 3: PRIMARY IRRITATION RESPONSE CATEGORIES IN THE RABBIT

RESPONSE CATEGORY	COMPARATIVE MEAN SCORE (PII)
Negligible	0 to 0.4
Slight	0.5 to 1.9
Moderate	2 to 4.9
Severe	5 to 8

Note- The Primary Irritation Index (PII) was determined by subtracting the Total Primary Irritation Score of the control sites from the Total Primary Irritation Score of the test sites and dividing that value by the total number of animals used in the study.

TABLE 4: TEST AND CONTROL TOTALS AND CALCULATION OF THE PRIMARY IRRITATION SCORE

RABBIT # 10233	60 MINUTES		24 HOUR		48 HOUR		72 HOUR		TOTAL SCORE	PRIMARY IRRITATION SCORE
	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT		
Total TEST Scores	0	0	0	1	0	0	0	0	1	0.2
Total CONTROL Scores	0	0	0	0	0	0	0	0	0	0
RABBIT # 10231	**60 MINUTES**		**24 HOUR**		**48 HOUR**		**72 HOUR**		**TOTAL SCORE**	**PRIMARY IRRITATION SCORE**
	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT		
Total TEST Scores	0	0	0	0	0	0	0	0	0	0
Total CONTROL Scores	0	0	0	0	0	0	0	0	0	0
RABBIT # 10232	**60 MINUTES**		**24 HOUR**		**48 HOUR**		**72 HOUR**		**TOTAL SCORE**	**PRIMARY IRRITATION SCORE**
	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT		
Total TEST Scores	0	0	0	0	0	0	0	0	0	0
Total CONTROL Scores	0	0	0	0	0	0	0	0	0	0

TABLE 5: CALCULATION OF THE PRIMARY IRRITATION INDEX AND FINAL RESULT

Rabbit #	Primary Irritation Scores		Irritation Response Category
	Test	Control	
10233	0.2	0	0 to 0.4 -------- **Negligible**
10231	0	0	
10232	0	0	
Total	0.2	0	
Primary Irritation Index (PII) Total Test – Total Control / 3	0.1		

11 Integrated Summary and Safety Evaluation

NDA 202,278 is an original 505(b)(2) application (Nupathe, Inc.) for a drug/device combination product incorporating iontophoretic technology to deliver sumatriptan transdermally for the treatment of acute migraine with and without aura. Developmental work for the application was conducted under IND 74,877. The sponsor identifies Imitrex® (GlaxoSmithKline, all three formulations) as RLDs for the application. CDER/DNP has been assigned lead responsibility for this drug/device combination; CDRH has been consulted.

Agency guidance (Guidance for Industry and Review Staff: Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route, CDER, 2008) does not specifically address the type/quantity of nonclinical data needed to support iontophoretic drug delivery of a previously approved

drug substance. Recommendations are provided for dermal formulations or patches generally, including that "…acute and repeat dose local toxicity studies with histological evaluation" of the skin should be conducted in one species and that "nonclinical dermal studies generally should be conducted with untreated control, vehicle control, and complete formulation groups." Also recommended for consideration to support dermal patches are assessments of the potential to induce delayed hypersensitivity and photoirritation (if the patch is permeable to light and applied to sun-exposed skin). Finally, the guidance recommends that a 9-month repeated-dose toxicity study be conducted in a non-rodent species when the API has not previously been administered by the dermal route. The guidance states that the need for a dermal carcinogenicity study may be considered.

The Division met with the sponsor (24 November 2009) to discuss a potential NP101 NDA filing. A single question from the sponsor requested Division feedback on the adequacy of the sponsor's proposed nonclinical data package. Taking into consideration the above-noted Guidance recommendations, the Division communicated the following to the sponsor (see Pre-NDA Meeting Minutes, L. Chen, 5 March 2010): "In order for us to waive a dermal carcinogenicity study, you will need to demonstrate that a meaningful study in rodent cannot be conducted. The adequacy of the 9-month dermal study in minipig will be a matter of review."

The nonclinical data package in the sponsor's NDA submission includes reports of GLP acute and chronic (9-month) toxicity/local tolerance studies with the patch in miniature swine; dermal sensitization studies in guinea pigs; and phototoxicity studies in miniature swine. They have also submitted pilot studies for the above, plus assessments of the *in vitro* cytotoxicity, dermal sensitization, and primary skin irritation of the patch components (i.e., 'device biocompatibility' studies). Importantly, the sponsor has provided no nonclinical data to address the comparability of metabolism of sumatriptan following administration via approved routes as compared to transdermal iontophoretic administration. Rather, in their Nonclinical Overview, the sponsor states the following:

> "At the request of the FDA, a study was conducted to confirm that the metabolism of sumatriptan when administered by NP101 was comparable to that reported via the oral route of administration. While this request was provided by the pharmacologist and a nonclinical study was initially planned, NuPathe felt that performance of this study in humans was more appropriate, especially in light of the existence of an ester glucuronide metabolite (M3) that is apparently absent in the various animal models studied to date."

Finally, the sponsor's submission includes a rationale for why the requirement for a dermal carcinogenicity assessment of the product should be waived. This rationale is reproduced below directly from the sponsor's submission.

> "After considerable consultation with experts in the biomechanical engineering it was determined that the miniaturization of NP101 for the assessment in rodents of dermal carcinogenic potential was not feasible. Moreover, dermal carcinogenicity studies are not warranted for the following reasons: (1) NP101 is intended for acute use, not for chronic use, which precludes continuous insult to the skin and dermis that could promote carcinogenic transformation; (2) sumatriptan was shown not to be carcinogenic in rats dosed orally for 104 weeks with exposures of approximately 15-times the total systemic

> exposure (AUC) provided by the maximum recommended human oral dose (MRHD) and in mice treated orally for 78 weeks at 40-times the exposure provided by the MRHD; (3) sumatriptan was not mutagenic in two microbial reverse mutation assays with Salmonella typhimurium and in another assay with Escherichia coli or in the gene mutation assay conducted in Chinese hamster V79 cells and was not clastogenic in an in vitro human lymphocyte chromosomal aberration assay or in an in vivo rat micronucleus assay, with and without metabolic activation; (4) NP101 treatment for nine consecutive months at weekly intervals provided no evidence for epidermal or dermal toxicity, much less evidence of proliferative or pre-neoplastic changes that might precede malignant transformation; (5) NP101 is not phototoxic, reducing any risk for photocarcinogenicity, (6) post-marketing surveillance data with sumatriptan has not indicated a risk for carcinogenicity despite many years of patient use, (7) neither the NP101 patch components or sumatriptan were cytotoxic or sensitizing on the skin in animal studies, (8) transdermal delivery of sumatriptan did not appear to alter the catabolism of this drug substance formerly characterized after oral administration; thus, there is no evidence for unique metabolites being produced by this route of administration and (9) finally, it is impossible to test the NP101 patch on a small rodent, owing to the large size of the patch (8 inches by 4 inches). Topical application of sumatriptan succinate on the skin without iontophoresis has been shown to result in no systemic exposure, precluding the value of traditional dermal carcinogenicity studies. Therefore, no additional studies were required or have been sponsored by NuPathe and NuPathe requests a waiver for the conduct of such a study with NP101."

In the opinion of this reviewer, the sponsor has adequately addressed the issues of potential dermal sensitization and phototoxicity of the existing NP101 product. However, from a nonclinical perspective, the overall application is inadequate for multiple reasons, key among which are the following:

- CDER/ONDQA has communicated to the sponsor (Information Request, T.W. Ocheltree, 16 May 2011) a list of 37 CMC issues with the product, which may be summarized succinctly by the opening sentence of the itemization: "The fundamental design of NP101 is not acceptable." It remains unclear at present to what extent, if any, the sponsor will attempt to address the identified CMC deficiencies by the end of the current review cycle and, importantly, to what extent any such attempt to address some or all of these deficiencies will invalidate the relevance of the existing nonclinical data for assessing the safety of the proposed clinical drug product/device combination.
- Due to fundamental inadequacies as outlined above in both the design and conduct of their 9-month repeated-dose toxicity study in miniature swine (PROT-55-NP101-006/S08719), the sponsor has failed to address the potential for the NP101 drug formulation—not only the sumatriptan API, but each of the excipients as well—to induce either local or systemic toxicity following repeated transdermal iontophoretic administration.
- The sponsor has provided no nonclinical data to address whether sumatriptan administered via transdermal iontophoresis results in a metabolite profile comparable to that of currently approved sumatriptan drug product formulations and routes of administration. It will be a clinical review team decision as to whether any human clinical data provided by the sponsor are sufficient and adequate to address this issue.

- The sponsor has provided evidence—without sufficiently addressing it—of a potential human clinical risk based on findings that a single 4-hour patch administration with a prototype patch (NP101-PC003/SRCS07562) resulted in observations of “slight epidermal necrosis” and “severe erythema or injuries in depth” in miniature swine. In fact, the sponsor has submitted human clinical data that indicate similar effects have been observed in some humans.
- The sponsor has not provided adequate justification for waiving the requirement for conducting a dermal carcinogenicity study with the proposed clinical drug product formulation. The Division does not dispute the sponsor’s assertion that the NP101 patch cannot be reduced to a size appropriate to assess iontophoretic delivery in existing rat or mouse carcinogenesis models. However, they have failed to address the questions of whether a dermal painting study with the clinical drug product formulation is, one, feasible and, two, relevant to an assessment of potential human risk.

In conclusion, based on the issues outlined above, this reviewer finds the current application to be inadequate from a nonclinical perspective and, therefore, recommends that the application be considered not approvable.

Nonclinical data needed to address the current deficiencies will depend, in large measure, on what changes (to clinical drug formulation and/or device) are implemented by the sponsor to address the deficiencies outlined by ONDQA. Given the extensive nature of the list, it is highly probable that all nonclinical studies would need to be repeated with the product of any sufficiently responsive redesign of the clinical drug product/device combination. One possible exception to this likely outcome could arise in the case of a determination by the clinical review team that existing human clinical data and labeling are sufficient and adequate to mitigate a known or suspected human risk (e.g., dermal sensitization risk).

However, assuming for the moment that the currently proposed clinical drug product/device combination will not be modified to any significant extent, then it is recommended that the sponsor be advised the following nonclinical data will be needed to address existing deficiencies.

- The acute dermal toxicity study in miniature swine (or other appropriate species) should be repeated with the actual to-be-marketed clinical drug product/device combination. The study design should include appropriate controls (vehicle/untreated), adequate numbers of animals for meaningful interpretation at each sacrifice (minimally, 4/sex/dose group), and should include multiple dose levels to allow assessment of the dose responsiveness of any toxicity observed.
- The chronic (9-month) toxicity study in non-rodent (miniature swine or other appropriate species, all of a single strain) should be repeated utilizing a study design that is consistent with relevant Agency guidance (i.e., Guidance for Industry and Review Staff: Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route, CDER, 2008). Specifically, the study design should incorporate adequate numbers of

animals for meaningful interpretation at each sacrifice (minimally, 4/sex/dose group) and should include appropriate control groups (vehicle/untreated). Multiple dose levels should be included to allow assessment of the dose responsiveness of any toxicity observed, up to a dose documented to be either a maximum tolerated or maximum feasible dose (MTD/MFD). The dosing regimen should consist minimally of 3 patch applications per week per animal on the same application site. Inclusion of at most one interim sacrifice into the study design may be appropriate. Toxicokinetic analyses should be included in the study design.

- If a determination is made by the clinical review team that in humans the metabolite profile of sumatriptan administered via transdermal iontophoresis is different from that of the RLDs, then the sponsor will need to provide appropriate nonclinical data to confirm that any unique (or quantitatively greater) metabolites have been adequately tested in animal(s).
- Finally, unless a repeated and sufficiently robust chronic dermal toxicity study in non-rodent (see second bullet above) results in absolutely no evidence of any neoplastic and/or pre-neoplastic responses, the sponsor will need to provide appropriate justification for why a dermal painting carcinogenicity study is not relevant and not feasible.

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/s/

DONALD C THOMPSON
06/28/2011

LOIS M FREED
06/29/2011