CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202278Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Deferral of Risk Evaluation and Mitigation Strategies (REMS) Review

Date:	June 15, 2011; *Revised July 6, 2011*
Reviewer(s):	Carolyn L. Yancey, M. D., Senior Medical Officer, Risk Management Reviewer, Division of Risk Management (DRISK)
Team Leader:	Kendra Worthy, Pharm. D., DRISK
Division Director:	Claudia Karwoski, Pharm. D., DRISK
Drug Name(s):	Zelrix™ (sumatriptan) Iontophoretic Transdermal System
Therapeutic Class:	Selective 5-Hydroxytryptamine Receptor Agonist
Dosage and Route:	Sumatriptan 6.5 mg delivered over 4 hours by a controlled iontophoretic transdermal system.
Application Type/Number:	NDA 202-278; Serial Number 000
Applicant:	Nupathe Inc.
OSE RCM #:	2011-48
TSI #:	Not Applicable

This Office of Surveillance and Epidemiology (OSE), Division of Risk Managment (DRISK) review is to defer comment on the proposed risk evalution and mitigation strategy (REMS) for Zelrix (sumatriptan) Iontophoretic Transdermal System voluntarily submitted by the applicant under NDA 202-278 (dated October 29, 2010). The applicant's proposed REMS for Zelrix includes a Medication Guide (b) (4). In addition to these proposed REMS elements, the applicant submitted (b) (4)

(b) (4)

On January 10, 2011, the Office of New Drugs (OND), Division of Neurology Products (DNP) requested that the DRISK review the proposed REMS for Zelrix including the Medication Guide (b) (4) cited above. The formulation, NP101 for Zelrix (sumatriptan) iontophoretic transdermal system, is a disposable, single-use, co-packaged drug/device combination product that utilizes iontophoretic technology to deliver sumatriptan transdermally for the treatment of acute migraine attacks, with or without aura, in adults. The NP101 formulation/device is not currently marketed.

The DNP concluded (April 13, 2011) that Zelrix (sumatriptan) Iontophoretic Transdermal System (Control # 2011-48) does not require a REMS to mitigate the well known risks associated with sumatriptan that are to be included in proposed labeling. Application of the Zelrix patch device was demonstrated to be problematic and may require patient instruction, if the NDA is resubmitted, reviewed and approved. As of this review, sumatriptan-containing approved products do not have a requried REMS.

Background

Sumatriptan is approved by the Agency for oral, subcutaneous, and intransal teatment of migraine headache, with or without aura, in adults. Generic sumatriptan oral tablets, nasal spray and injection are available. The safety and efficacy of sumatriptan has been studied extensively. The applicant's rationale for the proposed iontophoretic transdermal system is to address the concern about triptan adverse events, mainly the increased cardiovascular risk of heart attack, stroke or death, associated with high plasma concentrations of sumatriptan by using a controlled, transdermal delivery of efficacious concentrations of sumatriptan without reaching peak plasma concentrations that may lead to these triptan adverse events.

According to the preliminary clinical review of the pivotal Phase 3, Study NP101-007, statistically significant superiority of the NP101 iontophoretic patch compared to a placebo (PBO) was demonstrated across a range of migraine headache sypmtoms. Significantly more patients were headache pain free two hours after treatment with the NP101 patch compared with the PBO patch (18% verus 9%, respectively; p=0.0092).

Accordng to the preliminary review of safety, the most common reported adverse event was application site conditions. The incidence of triptan adverse events and adverse drug reactions was 0.8% (5 of 606 patients). The triptan sensation events were shown to be higher following subcutaneous injection or oral administration of sumatriptan compared to that observed with NP101 iontophoretic patch and proper placement. The preliminary safety analysis demonstrated that NP101 appears to be safe and well tolerated.

Rationale for Complete Response Other Than The Proposed REMS for Zelrix

Due to outstanding deficiencies in Chemistry and Manufacturing Controls (CMC), Product Quality Microbiology, and Pharmacology Toxicology in NDA 202-278 Zelrix (sumatriptan) Iontophoretic Transdermal System, the DNP plans to issue a Complete Response (CR) letter to the applicant prior to the Prescription Drug User Fee Act (PDUFA) deadline of August 29, 2011. The 74-Day Filing Communication to the applicant included 13 requests for additional information and or clarification.

DRISK defers comment on the applicant's proposed REMS for Zelrix and patient labeling at this time.

Comments

A final discussion on the appropriate risk management strategy will be undertaken after the applicant submits a satisfactory response to the Complete Response letter.

Please send DRISK a new consult request at such time. This memo serves to close the existing consult request for Zelrix (sumatriptan) Iontophoretic Transdermal System under NDA 202-278/ Serial Number 000.

Please notify DRISK if you have any questions.

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

/s/

CAROLYN L YANCEY
07/06/2011
Deferral of REMS Review for Zelrix (sumatriptan iontophoretic transdermal system)

CLAUDIA B KARWOSKI
07/06/2011
concur