CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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
Office of Medication Error Prevention and Risk Management

Risk Management Review

Date:	December 13, 2012
Reviewer(s):	Yasmin Choudhry, M.D., Medical Officer, Division of Risk Management (DRISK) Kendra Worthy, Pharm. D., Team Leader, DRISK
Division Director:	Claudia Manzo, Pharm. D., DRISK
Drug Name(s):	Ravicti (glycerol phenylbutyrate)
Indication(s):	As adjunctive therapy for chronic management of adult and pediatric patients ≥ (b) (4) of age with Urea Cycle Disorders
Formulation and Route:	Liquid for oral administration
Application Type/Number:	NDA 203284
Applicant/sponsor:	Hyperion Therapeutics
OSE RCM #:	2012-72

1 INTRODUCTION

This is a review of Hyperion Therapeutics' proposed Risk Evaluation and Mitigation Strategy (REMS) submitted with NDA 203284 to the Division of Gastroenterology and Inborn Errors (DGIEP) for Ravicti (glycerol phenylbutyrate) on December 23, 2011.

2 BACKGROUND

Ravicti (glycerol phenylbutyrate) is a triglyceride containing three molecules of phenylbutyrate (PBA) joined via ester linkage to a glycerol backbone. It is a prodrug of PBA and a pre-prodrug of phenyl acetic acid (PAA), the active moiety of the compound. The proposed indication is adjunctive therapy for chronic management of Urea Cycle Disorders (UCD) in adult and pediatric patients of ≥ (b) (4) of age.

The Ravicti NDA 203284 was submitted as 505b(1) with reference listed drug Buphenyl (sodium phenylbutyrate). Buphenyl oral tablet and powder formulation was approved in 1996 as adjunctive therapy in the chronic management of UCD in adult and pediatric patients of all ages and is the only approved nitrogen scavenging drug for chronic management of UCD.

At the time of NDA submission, data on pediatric patients less than 6 years of age were not available. In order to limit access to Ravicti only to patients 6 years of age and older, DGIEP requested the Applicant submit a proposed REMS (Information Request letter dated September 13, 2011). The pediatric data were subsequently submitted in April 2012 (with 120-day safety and efficacy update).

2.1 Materials Reviewed

- Proposed REMS for Ravicti NDA 203284 submitted on December 23, 2011
- Buphenyl label
- Clinical review Ravicti NDA 203284 by Nancy F. Snow MD dated November 27, 2012

2.2 Overview of Clinical Program

Ravicti was studied in a total of 180 patients in short-term and open-label safety extension studies. The key studies that demonstrated non-inferiority to Buphenyl are:

- Study HPN-100-006, a Phase 3, randomized, double-blind, cross-over active-controlled study in adult patients (n=44) with UCD.

- Study HPN-100-012, a Phase 2, switch-over, open-label study was completed in April 2012. A total of 15 pediatric patients (with UCD) ≥ 29 days were studied. This study provided efficacy and safety data in pediatric patients for Ravicti that had previously been missing.

See Dr. Nancy Snow's clinical review for details of the clinical development for Ravicti.

Common adverse events seen in the Ravicti clinical trials included gastrointestinal disorders, dizziness and headache. Serious adverse events included acute gastroenteritis, hyperammonemia, aggression, abdominal pain, dizziness, lobar pneumonia, lung infiltration, peripheral neuropathy, psychotic disorder, and pelvic pain. No serious adverse events were noted in the pediatric study HPN-100-012. These adverse events can be addressed by the label.

No deaths were reported in UCD patients during the Ravicti clinical trials. The safety issues raised by the clinical reviewer for Ravicti include the following:

- A 2-year carcinogenicity study in rats showed an increased incidence of tumors of the pancreas, thyroid, adrenal cortex, uterus, Zymbal's glands, and cervix. Because Buphenyl and Ravicti share the same active moiety these findings would pertain to Buphenyl as well. No carcinogenicity studies were submitted in support of the Buphenyl application and a search by the Division of Pharmacovigilance for reports in the adverse events reporting system, or literature reports of neoplasms in UCD patients taking Buphenyl did not yield any cases. The postmarketing requirements and commitments are still under review by DGIEP.
- A potential risk for Ravicti is toxicity of the active metabolite PAA. According to the clinical reviewer, this is based on toxicity seen in non-UCD population at the range of 499-1285 mcg/mL. PAA toxicity may present as nausea, headache, emesis, fatigue, weakness, lethargy, somnolence, dizziness, slurred speech, memory loss, confusion, and disorientation. Adverse events suggestive of PAA toxicity were not seen in clinical trials with Ravicti. In adult UCD patients PAA levels were lower with Ravicti than Buphenyl however, in pediatric patients PAA levels were higher compared to adults.

The clinical reviewer stated that based on the data available there was no correlation between PAA levels and adverse events in UCD patients and recommended that the PAA levels should be measured in UCD patients, particularly in the context of neurological adverse effects at >476 mcg/ml PAA levels. These concerns will be addressed in the postmarketing requirement/commitment (under review).

2.3 Risk Management Proposed by Applicant

The proposed REMS for Ravicti submitted with the original application in response to the September 13, 2011 IR consisted of:

(b) (4)

The proposed goal was to support informed dosing and treatment decisions, including key PK differences between adults and children and limit access to patients ≤ 6 years of age.

The additional pediatric data (Study HPN-100-012) submitted as 120-day Safety in April 2012 was considered adequate by DGIEP for approval of Ravicti as adjunctive therapy for chronic management of UCD in pediatric patients ≥ (b) (4). A decision was made by DRISK in conjunction with DGIEP and the REMS Oversight Committee (ROC) (email communication dated September 26, 2012) that a REMS for Ravicti is not necessary at this time.

3 DISCUSSION

Urea Cycle Disorders are rare disorders comprising a group of inherited deficiencies of one of the enzymes or transporters involved in the urea cycle, which converts ammonia to urea. Clinical manifestations of UCD are due to hyperammonemia and management is largely aimed at controlling ammonia levels and preventing seizures, cerebral edema, hyperventilation, posturing and coma[1].

Ravicti (glycerol phenylbutyrate) liquid formulation was found non-inferior to Buphenyl (sodium phenylbutyrate). The number of pediatric patients studied, even though small, was acceptable for this rare disease that has a prevalence of < 2000 patients in US. Compared to Buphenyl, Ravicti liquid formulation has an advantage of being neutral in taste/odor, the pill burden and volume of liquid with drug administration is less, and is sodium free (high sodium load of Buphenyl is undesirable in a subtype of UCD patients who are prone to hypertension).

DGIEP requested the Applicant submit a proposed REMS to limit use of the drug to only patients greater than 6 years of age because data below this age was not available at the time of submission. The Applicant has subsequently submitted data in pediatric patients down to 29 days. The overall adverse event profile of Ravicti is similar to that of Buphenyl, and the clinical trials showed that the adverse events tended to diminish over time. Since Ravicti is broken down into the active metabolite PAA and PAA toxicity can occur at high levels, the clinical reviewer believes that pediatric patients who develop neurological symptoms be monitored for PAA levels (even though no specific adverse events have been identified with PAA. As noted above, the PAA toxicity and the signal

[1] Clinical review Ravicti NDA 203284 by Nancy F. Snow MD dated November 27, 2012

for carcinogenicity will be closely followed in the postmarketing period (the postmarketing requirements and/or commitments are still under review).

DRISK concurs with DGIEP that the risks associated with treatment of Ravicti can be managed at this time through labeling and routine pharmacovigilance and that a REMS for Ravicti is not necessary to ensure the benefits outweigh the risks.

4 CONCLUSION

DGIEP and DRISK are in agreement[2] that the Study HPN-100-012 provides the pediatric efficacy and safety data for Ravicti NDA 203284 that had previously been missing, and obviates the need for a REMS. DRISK believes that labeling and routine pharmacovigilance measures are sufficient to manage the risks associated with Ravicti at this time. DGIEP should consult DRISK if additional safety information is identified that warrants risk mitigation measures.

[2] Additional concurrence was obtained from the REMS Oversight Committee (ROC) via email on September 26, 2012.

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/s/

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12/13/2012

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