CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203284Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA	203-284	*Submission Date(s)*	December 23, 2011, February 22, March 13, March 27, April 20, June 29, July 03, July 05, August 23, 2012
Brand Name	Ravicti®		
Generic Name	Glycerol phenylbutyrate		
Reviewer	Insook Kim, Ph.D.		
Team Leader	Sue-Chih Lee, Ph.D.		
Division Director	Capt. Edward D. Bashaw, Pharm.D.		
OCP Division	Division of Clinical Pharmacology 3		
OND Division	Division of Gastroenterology and Inborn Errors Products		
Sponsor	Hyperion		
Submission Type;	Original		

Executive Summary

This is an addendum to the original clinical pharmacology review of NDA 203-284 dated 1/2/13 to discuss two post-marketing studies. We require a pharmacokinetic study in pediatric patients < 2 years old and recommend an in vivo drug interaction study with a sensitive CYP3A4 substrate as a post-marketing commitment as below.

Post-Marketing Requirement

Pharmacokinetic studies in pediatric patients from birth to less than 2 years of age with Urea Cycle Disorders. PK of glycerol phenylbutyrate and its metabolites (PBA, PAA and PAGN) must be characterized and the exposure-response relationship should be evaluated for safety and efficacy.

Rationale

In the NDA, Ravicti was not studied in patients younger than 2 month old and very few data on patients in the age category of 2 months to 2 years were included. Because of no or insufficient data in patients younger than 2 years old, additional clinical studies will be required in these two age groups i.e. < 2 months old and 2 months to 2 years old.

In the age category of 2 months to 2 years, two of the four patients had PAA levels ~ 500 µg/mL when on buphenyl or HPN-100. Therefore we recommend PK blood samples be collected to characterize PK of Ravicti and its metabolites, PBA, PAA and PAGN.

PAA toxicity with neurological and gastrointestinal manifestations has been demonstrated with IV administration of PAA. In cancer patients, the symptoms at PAA levels of ~500 µg/mL were somnolence, emesis and lethargy in patients with cancer who received IV PAA. More severe toxicity (confusion and psychomotor depression)

occurred in patients with mean peak PAA level of 682 µg/mL[1]. In patients with acute hyperammonemia, overdose of IV PAA in children has been reported to cause death and coma.[2] Levels of PAA in these children were > 1000 µg/mL.

Post-Marketing Commitment

In vivo drug interaction study to evaluate the effect of Ravicti on a concomitant drug that is metabolized by CYP3A4.

The highest proposed dose of Ravicti should be used to maximize the potential of in vivo drug interaction while the dose for individual patients may vary.

Rationale: Based on the in vitro studies suggested drug interaction potential with substrates of three CYP enzymes, we are requesting one in vivo study with CYP3A.

The [I]/Ki of PBA was the highest for CYP2C9 i.e. 0.451 and it was 0.393 for CYP2D6 and [I]/IC_{50} for CYP3A4 was 0.325. Although the [I]/Ki was higher for CYP2C9 than for CYP3A4, we recommend that in vivo drug interaction study with a sensitive substrate of CYP3A4/5 based on following:

1) The wider range of drugs that are metabolized by CYP3A4
2) The significant contribution of CYP3A4 to the metabolism in the intestine because phenylbutyrate, a metabolite of glycerol phenylbutyrate is presumably generated in the intestine.
3) Phenylacetate (PAA), which is converted from phenylbutyrate, showed an inhibitory effect on CYP3A4 and CYP2C9 at a concentration higher than the observed plasma concentrations. While the possibility of in vivo drug interaction with CYP2C9 substrate is unlikely based on the [I]/Ki of PAA for CYP2C9 determined in an additional study, the [I]/Ki of PAA for CYP3A4 was not determined. Therefore, potential effects PAA on CYP3A4 can not be ruled out.

[1] Thibault A et al, Phase I study of phenylacetate administered twice daily to patients with cancer. Cancer 1995;75:2932-8.
[2] Parphanphoj et al (2000), Three cases of intravenous sodium benzoate and sodium phenylacetate toxicity occurring the treatment of acute hyperammonemia, J. Inherit. Metab. Dis 23: 129-36.

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/s/

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01/18/2013

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01/23/2013

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01/23/2013

CLINICAL PHARMACOLOGY REVIEW

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Generic Name	Glycerol phenylbutyrate		
Reviewer	Insook Kim, Ph.D.		
Team Leader	Sue-Chih Lee, Ph.D.		
PM Reviewer	Kevin Krudys, Ph.D.		
PM Team Leader	Nitin Mehrotra, Ph.D.		
OCP Division	Division of Clinical Pharmacology 3		
OND Division	Division of Gastroenterology and Inborn Errors Products		
Sponsor	Hyperion		
Submission Type;	Original	505(b)(1)	
Formulation; Strengths; Regimen	Liquid for oral administration 1.1 g of glycerol phenylbutyrate (GPB) in 1 ml of Ravicti® (equivalent to 1.02 g phenylbutyric acid) • Recommended starting total daily dose is as below (b) (4) • Dose range: 4.5-11.2 ml/m^2 (5-12.4 g/m^2) • Not to exceed 17.5 ml (19 g) total • Total daily dose should be administered in three divided doses with meals		
Indication	Adjunctive therapy for chronic management of adult and pediatric patients with urea cycle disorders involving deficiencies of the following enzymes: Carbamyl phsphate synthetase (CPS), Ornithine transcarbamylase (OTC), Argininosuccinate synthetase (ASS), Argininosuccinate lyase (ASL), Arginase (ARG), Mitochondrial transporter ornithine translocase (HHH deficiency)		

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