# Review of Request (Amended) for Orphan-Drug Designation

FILE COPY

**Application number:** 05-2035

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| Date received: | March 22, 2005 |
| Date 1st review completed: | May 2, 2005 (reviewer T. Nguyen) |
| Date 1st amendment received: | May 11, 2006 |
| Date 2nd review completed: | July 5, 2006 (reviewer T. Nguyen) |
| Date 2nd amendment received: | December 22, 2008 |
| Date 3rd review completed: | April 6, 2009 |

**Generic name:** Glyceryl tri(4phenylbutyrate)

**Trade name:** Not established

**Company name:** HPN-100

**Sponsor name and address:** Hyperion Therapeutics, Inc.
601 Gateway Blvd., Suite 200
South San Francisco, CA 94080

**Contact name and address:** Crystal P. Browning
Senior Manager of Regulatory Affairs
Hyperion Therapeutics
Telephone: 650-745-7824
Email: crystal.browning@hyperiontx.com

**Proposed orphan indication:** Maintenance treatment of patients with deficiencies in enzymes of the urea cycle

**Regulatory status:** Hyperion is the sponsor of IND 73,840 for HPN-100.

## 1.0 BACKGROUND

The following is from the July 5, 2006 review of the May 11, 2006 amendment:

> On March 18, 2005, the sponsor submitted a request for orphan-drug designation of glyceryl tri(4-phenylbutyrate) (hereinafter, "GT4P") for "maintenance treatment of patients with deficiencies in enzymes of the urea cycle." After reviewing the request, the Office of Orphan Products Development (OOPD) did not grant the sponsor's request since GT4P, being an esterified prodrug of phenylbutyrate, is considered the same drug under 21 C.F.R. 316.3(b)(13)(i) as Buphenyl® (sodium phenylbutyrate), which was previously approved with orphan-drug exclusive approval for the same use. In order for GT4P to gain orphan-drug designation, the sponsor would need to present a plausible hypothesis that it is clinically superior to Buphenyl (see § 316.20(a)). That is, GT4P may provide a significant therapeutic advantage over and above that provided by Buphenyl by conferring greater effectiveness on a clinically

meaningful endpoint, or greater safety in a substantial portion of the target population, or, where neither of these has been shown, it otherwise makes a major contribution to patient care (see § 316.3(b)(3)).

Based on information submitted in the original request, OOPD found no reason to believe that GT4P would confer greater safety or greater effectiveness than Buphenyl in the treatment of urea cycle disorders (UCD). Moreover, there was a lack of objective evidence to believe that GT4P, at the proposed dosages, would have comparable safety and effectiveness profiles as those of Buphenyl. Finally, OOPD does not believe the taste advantage offered by GT4P meets the high bar of major contribution to patient care. Please see the original designation review for more details.

These issues were communicated to the sponsor in a letter dated October 10, 2006.

## 2.0 REVIEW OF CURRENT AMENDMENT

On December 22, 2008, the sponsor submitted an amendment to their orphan-drug application (see Appendix A for summary of amendment).

**Reviewer's comments:** *The sponsor claims that HPN-100 is different than the approved product because it is more efficacious, safer, and a major contribution to patient care. However, the only salient aspect of the amendment that is relevant to the potential designation of HPN-100 for the maintenance treatment of patients with deficiencies in enzymes of the urea cycle is the difference in the sodium content of the approved product, Buphenyl, compared to HPN-100. The approved labeling for Buphenyl states that each tablet contains 62 mg of sodium (corresponding to 124 mg of sodium per gram of sodium phenylbutyrate) and that Buphenyl powder contains 11.7 gm of sodium, corresponding to 125 mg of sodium per gram of sodium phenylbutyrate. The recommended total daily dose of Buphenyl is 9.9 to 13.0 g/M$^2$/d in patients weighing more than 20 kg. For an average size adult (1.7M$^2$), this means that a person would need to take as many as 44 tablets per day which would contain 2.728 g of sodium. This is a significant sodium load and in the Warnings section of the labeling for Buphenyl, it states that "Buphenyl should be used with great care, if at all, in patients with congestive heart failure or severe renal insufficiency, and in clinical states in which there is sodium retention with edema." In contrast, HPN-100 contains no sodium. The current recommended daily allowance of sodium is less than 2.4 g per day. When dietary intake of sodium is added to the sodium intake from Buphenyl, a person could be taking over 5 gm of sodium every day.*

*As noted by the sponsor, there are no reports of the clinical effects of the high sodium content of Buphenyl in patients with urea cycle disorders. However, Buphenyl has been used to treat other diseases in which the sodium content of the drug adversely impacted patient health. The application contained the following summary of the use of Buphenyl in treating other diseases:*

In a study of oral sodium PBA in 23 adults with refractory solid tumors, six subjects (26%) had edema, including one with significant worsening in edema that resolved 3

weeks after discontinuing sodium PBA. Among 6 subjects with sickle-cell anemia treated in a pilot study with oral sodium PBA at 13 g/m$^2$/day, 4 subjects (67%) gained weight during sodium PBA treatment, including 1 subject who had ankle edema concomitant with a 4 - 5-kg gain in weight from baseline after 2 weeks of therapy (Dover 1994). Among 12 subjects with 13-thalassemia treated with 20 g/day oral sodium PBA, 3 (25%) developed significant edema during treatment (attributed by the authors to the sodium content of sodium PBA), and 7 (58%) had epigastric discomfort associated with drug intake (and thus likely an effect of the formulation) (Collins 1995).

*Although these reports are not in patients with urea cycle disorders, the clinical effects attributed to the sodium content in Buphenyl highlight the risk associated with the drug. The risk of high sodium intake leading to hypertension and eventual heart disease is well recognized in the medical community. Therefore, HPN-100, with no sodium in the formulation, is safer than Buphenyl and should be considered a different drug for purposes of orphan designation.*

## 3.0 REVIEWER'S EVALUATION AND RECOMMENDATION

In this application, Hyperion Therapeutics is requesting orphan-drug designation of HPN-100 for the maintenance treatment of patients with deficiencies in enzymes of the urea cycle. Based on the lack of sodium in the formulation of HPN-100 and the high sodium content in the approved product, HPN-100 is a different drug and is eligible for orphan designation. The prevalence from the initial review was 10,000.

Therefore, it is recommended that the sponsor's request for orphan designation of HPN-100 for maintenance treatment of patients with deficiencies in enzymes of the urea cycle be granted. The following paragraph should be included in the designation letter:

Please note that HPN-100 was granted orphan-product designation on the basis that it is clinically superior pursuant to 21 CFR 316.3(a)(3)(i). In order to obtain market exclusivity for your product when a New Drug Application (NDA) for HPN-100 is approved, clinical studies submitted with the NDA need to provide evidence that HPN-100 is safer than and comparable in efficacy to the approved formulation of sodium phenylbutyrate.

Peter L. Vaccari, R.Ph., RAC
Reviewing Pharmacist
OOPD/OC/FDA

4/10/09

Concurrence:

Date: 20 APR 09

Timothy R. Coté, M.D., M.P.H.
Director, Office of Orphan Products Development

cc:

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## Appendix A
## Summary of Information in Current Amendment

HPN-100 shares the same active moiety, phenylacetate (PAA), and the same vehicle for waste nitrogen excretion (phenylacetylgiutamine [PAGN]) as BUPHENYL® (sodium phenylbutyrate). BUPHENYL is an orphan-designated drug approved by the FDA in 1996 for the chronic management of patients with UCDs. HPN-100 is a triglyceride (three 4-PBA molecules attached to a glycerol backbone via an ester linkage), from which PBA is released through the action of gastrointestinal lipases. PBA is then converted by B-oxidation to PAA, which conjugates with glutamine via acetylation to form PAGN. PAGN is excreted by the kidneys, resulting in removal of waste nitrogen with efficiency comparable to urea (both urea and PAGN contain two molecules of nitrogen).

Hyperion has reviewed the prior communications regarding Orphan-Drug Designation Request 05-2035 and generated a substantial amount of new information [e.g. new clinical trial results, physician and patient/caregiver surveys, additional analyses of the dataset resulting in the approval of AMMONUL® (sodium phenylacetate and sodium benzoate) 10%/10% Injection, analysis from the UCD Consortium-Sponsored Longitudinal Study (Tuchman 2008), discussions with physicians and the National Urea Cycle Disorders Foundation (NUCDF), and UCD patient/caregiver testimonials] pertaining to the use of BUPHENYL® (sodium phenylbutyrate) and the safety and effectiveness of HPN-100 and agrees with many, although not all, of Ucyclyd' s arguments.

Based on the analysis of these additional clinical data, Hyperion agrees with the Agency's comments regarding BUPHENYL's production of too high a level of PAA in UCD patients. PK/PD analysis and modeling of all available data, including recent data from 10 UCD subjects (study UP 1204-003) described in detail in this application, indicates that PAA levels are similar in UCD patients following three times daily dosing of BUPHENYL and HPN-100. However, the modeling also indicates that overall bioavailability of HPN-100 in all patient populations (52%) and BUPHENYL (60%) are similar and further demonstrates that UCD subjects have higher bioavailability of HPN-100 (approximately 60%) compared to healthy individuals; BUPHENYL bioavailability does not show such a difference between healthy and UCD subjects as previously suggested by the Agency (Pharsight Modeling Report 2008).

Hyperion also believes that the data presented throughout this orphan designation request strongly support the view that HPN-100 does offer a major advance in the management of patients with UCDs as defined in the orphan drug regulations, and offers the potential for superior safety and ammonia control. HPN-100 provides a more palatable product that delivers a comparably effective dose in a smaller drug volume than BUPHENYL. As compared with BUPHENYL, with which patients struggle to comply, HPN-100 will improve the ease and comfort of administration and the overall quality of life, which will lead to better compliance with medication. Moreover, physicians indicate that about 33% of adult patients and 25% of pediatric patients are prescribed a lower than ideal dose of BUPHENYL, often because it is difficult for the patient to tolerate, and a substantial

fraction of patients discontinue BUPHENYL because of tolerability problems. Improved compliance with medication and optimized dosing will reduce the number of acute hyperammonemic events that are associated with non compliance with medication thereby reducing overall morbidity (neurological damage, hospitalization costs associated with acute hyperammonia, and deaths). Objective scientific evidence has been generated to support the argument that BUPHENYL presents a major compliance challenge for UCD patients due to its significant bad taste, odor and large drug volume and regimen. Further, noncompliance with BUPHENYL does result in severe hyperammonemic crises that contribute to disease morbidity. In addition, the palpability issues and side effects of BUPHENYL also contribute to disease morbidity [e.g. G-Tubes to manage administration, symptoms consistent with oral mucositis and upper gastrointestinal (GI) mucosal irritation, unnecessary sodium burden, and emotional/psychological trauma] in this already fragile population.

The following summarizes the new information included in this orphan designation request, which provides objective scientific evidence to support the granting of orphan designation to HPN-100 on both the basis of major contribution to patient care and superiority on the basis of safety and efficacy:

1. UP 1204-003: A phase 2 study in adult UCD patients
2. Re-analysis of the AMMONUL® NDA dataset:
   It is acknowledged that the noncompliance rate Ucyclyd attributed to BUPHENYL (sodium phenylbutyrate) was obtained from the clinical study evaluating the effects of AMMONUL in treating acute hyperammonemic crisis, and that this study was not a study of the use of BUPHENYL. The AMMONUL study (conducted between 1982 and 2003) was an uncontrolled, open-label study of AMMONUL in which 316 UCD patients were hospitalized and treated for 1045 episodes of acute hyperammonemia. As part of this study, the treating physician was asked to identify what treatment the patient was receiving prior to the hospitalization (e.g. sodium phenylbutyrate), and the precipitating cause for the hyperammonemic event(s) (e.g. noncompliance with medication). This study resulted in two publications; Enns et al (2007) published data on survival of the acute crisis with treatment of AMMONUL, and Summar et al (2008) published data of diagnosis, symptoms, frequency and mortality of the patient population. As stated by Summar et al (2008), this dataset represents "the most comprehensive dataset in existence on these patients" and provides "evidence-based" insights on this patient population.

   This data set represents a unique resource with respect to precipitating causes for hyperammonemia. Hyperion does not understand the Agency's determination that use of such data to support non compliance rates with BUPHENYL is "misleading" and requests that the Agency reconsider the use of this data as supportive, objective evidence that noncompliance with BUPHENYL occurs at a higher rate than that presented in the BUPHENYL NDA. Hyperion summarizes the Summar et al 2008 publication on this dataset and present new analysis on causes leading to hyperammonemic crisis in this study.
3. NIH-funded Urea Cycle Disorder Consortium Longitudinal Study
4. Harris Interactive Physician and Patient/Caregiver Survey

Hyperion funded a survey, conducted by an independent third party (Harris Interactive®), who worked in collaboration with the NUCDF, to objectively confirm or refute the noncompliance and quality of life issues related to BUPHENYL that have been communicated either verbally or in writing to Hyperion (as discussed throughout this document). The following lists the primary objectives of the survey and a copy of the final report of the survey results is provided:

- Understanding how physicians currently manage their UCD patient population with BUPHENYL
- Understanding patient experience with UCD Treatments (e.g. efficacy, route of administration, dosing, safety)
- Measuring the frequency of side-effects associated with BUPHENYL
- Identifying unmet needs of physicians when treating with BUPHENYL
- Quantifying the extent of BUPHENYL patient compliance from the patient and physician perspective
- Measuring compliance and overall experience of patients currently taking BUPHENYL

The quantitative research consisted of three surveys— one for physicians, one for patients over the age of 18 and one for caregivers — administered both online and in paper-pencil form. Caregivers were included primarily to capture the experience of pediatric patients.

5. Physician and Patient/Caregiver Perspective as reflected in testimonial letters

**Basis for Orphan-Drug Designation**

BUPHENYL (sodium phenylbutyrate) is a life-saving drug that has changed the natural history of UCDs; however, new data and analyses included with this application document that noncompliance with BUPHENYL is common and has severe consequences. In addition, palatability issues and side effects increase morbidity (e.g. G-Tubes, symptoms consistent with mucositis, and/or emotional/psychological trauma) in an already fragile patient population.

Hyperion requests orphan designation for HPN-100 as therapy for the chronic management of UCDs based on the following:

1. Major Contribution to Patient Care — Improved Compliance with Medication Resulting in Decreased Risk of Hyperammonemia.

a. BUPHENYL is a difficult drug to take and compliance is suboptimal

i. Approximately 84% of physicians who prescribe BUPHENYL and 47% of patients who currently take it indicate that BUPHENYL is very or somewhat difficult to take. One-in-four (28%) current BUPHENYL patients and 15% of caregivers who currently take care of a BUPHENYL user indicate they sometimes or often miss a dose of BUPHENYL for this reason. Furthermore, there are patients who discontinue BUPHENYL therapy due to its poor palatability and tolerability, and a substantial fraction (see point 2b below) of patients and caregivers opt to use G-Tubes or NG-Tubes to ease the administration. HPN-100 will significantly advance the ease and comfort of drug administration: it's a

nearly tasteless and odorless liquid (oil) product, which offers superior palatability and ease in administration, which will improve patient compliance.

ii. HPN-100 reduces the total daily drug volume and regimen: HPN-100 requires less frequent dosing [three times a day (TID) vs. 4 or more times a day as recommended by the 2001 Consensus Guidelines], and lower drug volume (approximately 17 mL vs. 40 tablets or 40 mL powder dissolved in liquid). A simplified dosing regimen and reduced drug volume will improve compliance with medication.

iii. There is documented evidence that approximately 9% of hyperammonemic crises are the result of noncompliance with medication and that as many as 18% of patients taking BUPHENYL experience hyperammonemia due to noncompliance, Improvements in compliance have the potential to reduce the risk of these crises and their associated morbidity/mortality.

2. HPN-100 offers safety advantages over BUPHENYL.

a. HPN-100 has no sodium while the adult dose of BUPHENYL (20g) has approximately 23g of sodium, equal to the total recommended daily allowance. High sodium intake and increased risk of hypertension is well established in the general population. In the recently completed UCD clinical trial 4 of the 14 subjects screened had a medical history of hypertension, and the UCD patients with argininosuccinate lyase (ASL) deficiency are reportedly prone to hypertension. Furthermore, the Harris Interactive® Survey indicates that on average each physician has 1.5 out of 8 patients who experience problems attributed to the sodium load of BUPHENYL, and 1.5 out of 8 patients whose diets are altered as a result of their high intake of sodium from BUPHENYL.

b. Based on the Harris Interactive® Survey of UCD patients and caregivers, 39% indicate use of a G-Tube or NG-Tube. Only 6% of patients/caregivers indicate that dietary management was the sole reason for the placement of the GTube/NG-Tube vs. 15% who indicate the sole reason was for the ease of BUPHENYL administration. This is corroborated by the 21% (22/103) of patients in the NIH-Funded UCD Consortium-Sponsored Longitudinal Study who require the use of a G-Tube. Given that HPN-100 is a liquid, odorless and nearly tasteless product that has a reduced drug volume the requirement for G-tube placement to manage medication should be reduced.

c. BUPHENYL-associated symptoms consistent with irritation of the oral (e.g. burning in the mouth and throat) and/or upper gastrointestinal (e.g. nausea, vomiting, heartburn, stomach ache) mucosa are frequently reported by patients and physicians, according to the Harris Interactive® Survey. When administered at BUPHENYL-equivalent clinical doses in clinical study UP 1204- 003, the overall safety profile of HPN-100 was comparable, with overall fewer upper GI side effects. Furthermore, two serious adverse events (SAEs) of hyperammonemia occurred during BUPHENYL treatment (attributed to noncompliance) while no SAEs occurred while on HPN-100.

3. HPN-100 provides an advantageous pharmacokinetic (PK) profile, offering sustained and potentially superior ammonia control.

    a. As compared with BUPHENYL, HPN-100 exhibits slow release characteristics and was associated with a reduction in ammonia values in UCD patients of approximately 30% (non-statistically significant), primarily due to better nocturnal control (Section 5).

In closing, Hyperion is conducting an extensive development program on HPN-100 (GT4P), which includes a full ICH toxicology program [Absorption, Distribution, Metabolism and Excretion (ADME) studies, cardiovascular effect studies, 12-month chronic primate study, juvenile animal studies in rodents and primates, full reproductive toxicology and carcinogenicity studies], detailed PKIPD studies in UCD patients (adults and pediatrics), and randomized, controlled efficacy and safety studies. None of these development studies were performed for BUPHENYL. Hyperion's investment will not only contribute to the understanding of HPN-100, but will also provide the UCD community with greater scientific understanding of nitrogen scavenging effects of PAA.

## References

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