EUROPEAN MEDICINES AGENCY
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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

RAVICTI

glycerol phenylbutyrate

Procedure no: EMEA/H/C/003822/P46/004

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 18th December 2017, the MAH submitted the final report and addendum of study HPN-100-011 for glycerol phenylbutyrate (Ravicti), according to Article 46 of Regulation (EC) No 1901/2006, as amended. This study is a post-authorisation measure.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Ravicti is indicated for use as a nitrogen-binding agent for chronic management of adult and paediatric patients ≥2 months of age (European Union/European Economic Area (EU/EEA)/United States of America (USA)) and adult and paediatric patients ≥2 years of age (Canada) with urea cycle disorders (UCDs) that cannot be managed by dietary protein restriction and/or amino acid supplementation alone. Ravicti (HPN-100) is a prodrug of phenylbutyric acid (PBA). PBA is converted via β-oxidation to its active metabolite phenylacetic acid (PAA), which is conjugated with glutamine to form phenylacetylglutamine (PAGN), which mediates waste nitrogen removal through urinary excretion.

Ravicti was first authorized in the USA in 2013, followed by the authorization in the EU/EEA in 2015 via centralized procedure under the name Ravicti 1.1 g/ml oral liquid. In 2016, marketing authorization for Ravicti was granted in Canada.

The HPN-100-011 protocol, "Long-Term Use of HPN-100 in Urea Cycle Disorders", allowed for continued use of Ravicti for subjects with a UCD who had completed 12 months of treatment in the safety extensions of HPN-100-005 (HPN-100-005SE), HPN-100-006 (HPN-100-007), and HPN-100- 012 (HPN-100-012SE); All base studies and the corresponding safety extension studies were included in the original marketing authorization application of Ravicti in the EU.

The purpose of the study was to provide study subjects completing Protocols HPN-100-005SE, HPN-100-007, or HPN-100-012SE continued access to Ravicti in the context of a protocol designed to collect long term safety information. The interim analysis of this study, presented as an abbreviated report dated 6 April 2014, was provided in the original marketing authorization application besides the above-mentioned study reports.

The MAH stated that HPN-100-011 is a stand-alone study.

An additional already finalized paediatric study is HPN-100-009, "An Open Label Study of the Safety, Efficacy and Pharmacokinetics of Glycerol Phenylbutyrate (GPB; RAVICTI®) in Pediatric Subjects Under Two Years of Age With Urea Cycle Disorders (UCDs)"(EudraCT number 2016- 003460-38) with last patient last visit on 17 July 2017 that is included in the paediatric investigation plan EMEA-000297-PIP02-12-M01; and the ongoing clinical study HPN-100-021, "A Randomised, Controlled, Open-Label Parallel Arm Study of the Safety, Pharmacokinetics and Ammonia Control of RAVICTI® (Glycerol Phenylbutyrate [GPB]) Oral Liquid and Sodium Phenylbutyrate

(NaPBA) in Phenylbutyrate Treatment Naïve Patients with Urea Cycle Disorders (UCDs)", EudraCT number 2015-000075-27 which is, together with HPN-100-011, part of the post marketing commitments for FDA.

In addition to the clinical trials, registries are underway in the US (HPN-100-014) and EU (HZNPRAV- 401).

2.2. Information on the pharmaceutical formulation used in the study

The same formulation was used by children and adults. This is an oral solution of 1.1 g/mL HPN-100 (providing 1.02 g/mL PBA) without any excipients. Ravicti is a colourless to pale yellow, nearly odourless and tasteless oral liquid and was supplied in 1-ounce teflon-screw-capped amber glass bottles containing 25 mL solution. Ravicti was administered undiluted orally or via gastrostomy tube. Ravicti was dispensed to the subject either through the investigator or designee at each site or by a centralized pharmacy per investigator order. The sponsor supplied food-grade flavourings provided for use by the Pharmacist, if requested by a subject. Disposable oral syringes and Adapta Caps™ for measuring and administering Ravicti were provided to the sites.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted final report for:

- **Study No. HPN-100-011** (data from the majority of subjects, enrolled at 17 US sites until the product was approved- data collected as of 29 October 2015)

And an **addendum** to this report containing further data collected in subjects (N=5) enrolled in Canada who continued to be monitored under the protocol of study HPN-100-011 until they discontinued or had access to Ravicti through the Health Canada Special Access Program or until Ravicti was commercially available in Canada- data collected as of 16 February 2017.

2.3.2. Clinical study

Study No. HPN-100-011: Long-Term Use of HPN-100 in Urea Cycle Disorders

Description

Non-randomized, open-label, safety extension study.

Methods

Objective(s)

Evaluate the long-term safety of HPN-100 (Ravicti) and its control of venous ammonia in the management of urea cycle disorders (UCDs). Hyperammonaemic crisis (HAC) events were to be characterized with respect to contributing factors such as intercurrent illness, diet and noncompliance with medication.

Study design

This was an open-label, long-term safety study of HPN-100 in subjects with UCD who completed the safety extensions of HPN-100-005 (HPN-100-005SE), HPN-100-006 (HPN-100-007, the safety extension of HPN-100-006), and HPN-100-012 (HPN-100-012SE). Of the 90 subjects who completed the previous trials, 88 subjects elected to enrol in this study.

The duration of treatment was open-ended. Subjects were to be seen at a minimum of every 6 months. At each clinic visit, subjects were queried about any adverse events (AEs) or HACs (defined as clinical symptoms associated with a venous ammonia concentration of ≥100 µmol/L) that occurred since the last visit, concomitant medication use, and current dietary protein and caloric intakes. (See section "outcomes/endpoints" for further assessments included in the study.)

All HACs were captured on the appropriate case report forms (CRFs), with, at minimum, the following information: precipitating factors, if due to noncompliance, reasons for noncompliance, ammonia level at hospital admission and signs and symptoms suggestive of hyperammonaemia.

Intercurrent episodes of hyperammonaemia may have been treated with rescue medication, with or without haemodialysis, at the investigator's discretion. Any hospitalization for hyperammonaemia was considered an SAE.

Presence of at least 2 of the following clinical criteria constituted evidence of chronic hyperammonaemia: recurrent vomiting, protein intolerance, episodic lethargy, psychosis (episodic), abnormal neurological examination, brain oedema (evidence on MRI or CT), chronic migraine headaches. New or worsening manifestations of chronic hyperammonaemia, as compared with baseline, may have been treated with a Ravicti dose adjustment or the use of rescue medications.

Study population /Sample size

Planned: Maximum of 90 subjects, Enrolled: 88, Completed: 77, Discontinued: 6, Ongoing: 5 subjects in Canada

Included in safety population: 88

Main criteria for inclusion: Male and non-pregnant, non-lactating females who completed the safety extensions of HPN-100-005 or HPN-100-012 or Study HPN-100-007 (the safety extension of HPN-100-006), and signed informed consent for this continued-access safety study were eligible for study participation.

Exclusion criteria included clinical or laboratory abnormality or medical condition that, at the discretion of the investigator, could have put the subject at increased risk during participation, known hypersensitivity to phenylacetate (PAA) or phenylbutyrate (PBA), and liver transplant (including hepatocellular transplant).

Treatments

Study medication: Ravicti (HPN-100; glyceryl tri-(4-phenylbutyrate)

Dose strength and form: 1.1 g/mL solution of HPN-100, providing 1.02 g/mL PBA

Study dosage: Individualized dose administered orally three times daily with meals. Maximum dose of 17.4 mL (20 g sodium phenylbutyrate [NaPBA]) per day.

The initial dose of Ravicti was the same dose they had been taking at the completion of the previous study. Dose adjustments (including frequency adjustments) were permitted as judged clinically appropriate by the investigator based on the subject's ammonia-scavenging needs (e.g., severity of the UCD defect, dietary protein intake, and urinary phenylacetylglutamine [PAGN] excretion).

Duration of treatment: open-ended, allowing subjects to remain in the study until Ravicti was commercially available or available through the Health Canada Special Access Program.

Concomitant medications: Medications used at the time of study initiation may have been continued with the permission of the investigator. All concomitant medications, including dose adjustments, and their indications were to be recorded on the CRF. Prohibited medications were not to be used during the study: drugs known to cause hyperammonaemia, such as valproate and drugs known to significantly affect renal clearance, such as probenecid. If any of these medications were needed for treatment of a study participant, the investigator, in conjunction with the medical monitor, was to discuss the feasibility of early termination.

Outcomes/endpoints

The exploratory efficacy parameters were plasma ammonia concentrations and number of HACs.

Routine study visits occurred every 6 months. Unscheduled visits may have occurred due to a hospitalization, a visit to the emergency room, or at the discretion of the investigator between routine study visits. The reason for the unscheduled visit was documented.

Safety assessments included monitoring of AEs (including HACs) and concomitant medications, amino acid panels, neuropsychological tests, physical examinations, vital signs, clinical safety laboratory evaluations (complete blood count, chemistry, and urinalysis), and pregnancy testing (if applicable).

Subjects underwent physical examinations (including height, weight, and vital sign monitoring) inclusive of neurological status, and blood samples were collected for the analysis of ammonia, amino acid panels, and routine clinical laboratory safety tests. If applicable, urine samples were collected for pregnancy testing. Blood samples were collected for the assessment of plasma ammonia concentrations at baseline, at least every 6 months, at all unscheduled visits, and at the end of study participation.

Neuropsychological tests included the Wechsler Abbreviated Scale of Intelligence (WASI) for adult subjects and paediatric subjects who were at least 6 years of age. In addition, the grooved pegboard test, the California Verbal Learning Test-Second Edition (CVLT-II), and digit span tests were performed for adult subjects; the Child Behavior Checklist (CBCL) and the Behavior Rating Inventory of Executive Function® (BRIEF®) were performed for paediatric subjects at least 5 years of age.

Neuropsychological tests were performed at baseline, every 12 months, and at the end of study participation.

Endpoints: The primary endpoint was the rate of AEs. Secondary endpoints included venous ammonia levels, the number and causes of HACs, and neuropsychological test results.

Statistical Methods

Only one analysis population was evaluated for this study, the safety population. All subjects who received any amount of study medication were included in the safety population. Descriptive summary statistics [number of subjects (n), mean, standard deviation [SD], median, minimum, and maximum] were presented for continuous variables, and frequencies and percentages were presented for categorical variables. Separate statistics were presented for adult (≥18 years), paediatric (<18 years), and the total number of subjects.

Results

Recruitment / Number analysed

A total of 88 subjects (45 paediatric and 43 adult) were enrolled; 77 subjects (42 paediatric and 35 adult) completed the study, 6 subjects withdrew from the study (3 subjects were lost-to-follow up, 1 subject withdrew from study participation, 1 subject relocated out of the country, and 1 subject underwent a liver transplantation procedure), and 5 subjects (1 paediatric and 4 adult) were ongoing at the Canadian site (at the time of this report). Among all subjects, the median duration of treatment during HPN-100-011 was 674.0 days (approximately 1.85 years), and the median total duration of treatment in all Ravicti studies (i.e., including feeder studies) was 1036.0 days (approximately 2.84 years).

6 subjects (2 paediatric and 4 adult) were enrolled in Canada from Site 07; 1 of the paediatric subjects completed the study, and the 5 remaining subjects (1 paediatric and 4 adult) are presented below as data from the addendum to the main report.

- Data from addendum to Study HPN-100-011

All 5 subjects (1 paediatric and 4 adult) who were ongoing at the time of the final CSR completed the study. Among these 5 subjects, the median duration of treatment during HPN-100-011 was 5.45 years, and the median total duration of treatment in all Ravicti studies (i.e., including feeder studies) was 6.51 years.

Baseline data

A total of 45 paediatric subjects between the ages of 1 and 17 years (median of 7.0 years) and 43 adult subjects between the ages of 19 and 61 years (median of 30.0 years) were enrolled. The majority of the subjects in each age group were female (≥60%), White (≥83%), and of non-Hispanic ethnicity (≥82%).

The study population included subjects diagnosed with UCD as neonates (24 subjects; 27.3%), as infants (18 subjects; 20.5%), and as children (>2 years) or adults (46 subjects; 52.3%). The majority of the subjects in both age groups (57.8% paediatric and 81.4% adult) had OTC deficiency. The most common method of diagnosis was deoxyribonucleic acid (DNA) mutational analysis (46.6%), followed by amino acid analysis (27.3%). Of the 88 enrolled subjects, 82 (93.2%) were receiving NaPBA at the time of entry in the initial Ravicti studies.

- Data from addendum to Study HPN-100-011

The 5 subjects comprised one 14-year-old paediatric subject who was female and 4 adult subjects (2 male, 2 female) between the ages of 21 and 33 years (median of 23.5 years). Two subjects were Asian (1 paediatric, 1 adult) and 3 adult subjects were white.

Exploratory Efficacy results

Continued ammonia control was observed with long-term dosing of Ravicti. Mean ammonia levels remained stable and below the adult upper limit of normal (ULN) (<35 µmol/L; Chernecky 2013) through 24 months of treatment in both the paediatric and adult groups; too few subjects were dosed beyond 24 months to draw meaningful conclusions. Of note, a single paediatric subject continued treatment past 30 months and remained below the paediatric ULN of 57 µmol/L (Chernecky 2013). The proportions of paediatric subjects with ammonia samples above the paediatric ULN at each scheduled time point up through 24 months of treatment (range: 8.7% to 17.4%) and at the End of Study assessment (17.9%) were comparable to baseline (13.6%).

Continued ammonia control with long-term Ravicti dosing was associated with fewer HACs. Overall, the number of subjects with HAC during this continued-access study was lower (22.7%; 43 crises) compared with the 12-month period prior to enrolment in Ravicti studies during treatment with NaPBA (30.7%; 49 crises). In particular, the decrease in the number of subjects with HAC was most evident among paediatric subjects who demonstrated a 42% decrease (42.2% [35 crises] pre-enrolment vs. 24.4% [22 crises] continued access). The annualized rate of HAC per paediatric subject decreased from 0.78 crises per year during the 12-month period prior to enrolment in Ravicti studies while receiving NaPBA, to 0.36 and 0.42 crises per year, respectively, in the 12-month safety extension studies and this continued-access study, demonstrating the durability of the response. Results for the adults showed an increase in the annualized rate of HAC per subject during this continued-access study (0.58 crises per year) compared with the 12-month safety extension studies (0.21

crises per year); however, this increase was attributable to a single subject who experienced 2 crises during 45 days of participation in the study resulting in an annualized rate of 15.9 crises per year for this subject.

The most commonly reported precipitating factors for HAC experienced during this continued-access study included intercurrent illness (23.3%; 6 paediatric and 4 adult subjects), infection (14%; 6 paediatric subjects), and noncompliance with study drug (14%; 2 paediatric and 4 adult subjects).

- Exploratory efficacy data from the addendum to Study HPN-100-011

Mean normalized ammonia levels remained below the ULN for the majority of time points through 66 months of treatment in the 4 adult subjects. The normalized ammonia level for the single paediatric subject was below the paediatric ULN at all time points. One adult subject experienced a HAC during this continued-access study; the precipitating factor was lack of adherence to diet.

CHMP comments

In this long term open label safety study, continued ammonia control for adults and children for a duration of almost 2 years was observed. Mean ammonia levels remained stable and below the adult ULN up through 24 months of treatment in both the paediatric and adult groups. In addition, a reduced number of subjects with HAC compared with the 12-month period prior to enrolment in Ravicti studies during treatment with NaPBA was documented. This reduction was more evident for paediatric patients. For paediatric patients the annualized rate of HAC also decreased.

The SmPC of Ravicti in section 5.1 describes paediatric data under two sub headings: “clinical studies in paediatric patients with UCDs” AND “open-label, uncontrolled, extension studies in paediatric patients”. In the latter section, long term, 12-month data are described as:

“Long-term (12-month), uncontrolled, open-label studies were conducted to assess monthly ammonia control and hyperammonaemic crisis over a 12-month period in three studies (Study 2, which also enrolled adults, and extensions of Studies 3 and 4). A total of 49 children ages 2 months to 17 years with deficiencies of OTC, ASS, ASL, and ARG were enrolled, and all but 1 had been converted from sodium phenylbutyrate to glycerol phenylbutyrate. Mean fasting venous ammonia values were within normal limits during long-term treatment with glycerol phenylbutyrate (range: 17-25 micromol/L). Of the 49 paediatric patients who participated in these extension studies, 12 patients (25 %) reported a total of 17 hyperammonaemic crises during treatment with glycerol phenylbutyrate as compared with 38 crises in 21 patients (43 %) in the preceding 12 months prior to study entry, while they were being treated with sodium phenylbutyrate.”

Study HPN-100-011 provides much longer data for the same patients who were also included in previous open label extension studies than those presented in the SmPC. The MAH concludes in the study report: “As compared to the 12 months preceding enrolment in Ravicti studies (while subjects were being treated with NaPBA), the decreased rate of HAC while receiving Ravicti was most pronounced in the paediatric subjects. This is particularly noteworthy as paediatric patients are the most vulnerable to crises and are at risk of sustaining permanent developmental damage as a result of high ammonia.” AND “Given the

serious consequences of high ammonia levels, these findings are clinically relevant in the UCD population". It is agreed that these data are clinically relevant as the main objective of treatment in UCD patients is maintaining normal ammonia levels and preventing HACs with an aim to reduce the incidence of serious acute complications such as encephalopathy, coma, and death, and chronic complications such as brain damage.

Based on the above, the MAH should update the paragraph in section 5.1 of the SmPC that presents data from "open-label, uncontrolled, extension studies in paediatric patients". This SmPC update should reflect the duration of the extension studies (with study HPN-100-011 currently being the longest completed study), the sustained ammonia control and effect on number of HACs.

Safety results

Long-term exposure to Ravicti was well tolerated in this continued-access study. Median duration of treatment among all subjects was 674.0 days (approximately 1.85 years).

Dose adjustments were common, especially for paediatric subjects (44.4% of paediatric vs. 25.6% of adult subjects had at least 1 dose adjustment). The most common reasons for dose adjustments were growth/increase in weight (13 paediatric and 2 adult subjects) and elevated glutamine level (5 paediatric and 5 adult subjects). Elevated glutamine levels in UCD patients have been associated with symptoms, and glutamine is used by some clinicians to assess ammonia control.

Treatment-emergent AEs (TEAEs) reported in ≥10% of adults were hyperammonaemia [25.6%], upper respiratory tract infection [18.6%], diarrhoea [16.3%], ammonia increased [14.0%], vomiting [11.6%], bronchitis [11.6%], and convulsion [11.6%]. TEAEs reported in ≥ 10% of paediatric subjects were hyperammonaemia [22.2%], upper respiratory tract infection [15.6%], vomiting [13.3%], and headache [13.3%]. These are consistent with the TEAEs reported in the 12-month safety extension studies and comparable to the adverse reactions occurring in ≥10% of paediatric patients (upper abdominal pain, rash, nausea, vomiting, diarrhoea, decreased appetite, hyperammonaemia, and headache) in the current Ravicti prescribing information. Among the TEAEs reported, diarrhoea (16.3% vs. 6.7%), bronchitis (11.6% and 2.2%), and convulsion (11.6% vs. 0%) occurred more frequently in adults than in paediatric subjects. No consistent increase in the overall incidence of TEAEs or for those events reported in ≥10% of adult or paediatric subjects was observed with prolonged Ravicti exposure.

Overall, the majority of the subjects reporting TEAEs had events that were considered by the investigator to be unrelated to study drug. TEAEs considered related to study drug were reported in 25.0% of all subjects, with comparable rates among adults (23.3%) and paediatric subjects (26.7%). TEAEs considered related to study drug reported in >1 paediatric subject were amino acid level decreased, blood alkaline phosphatase increased, and headache (2 paediatric subjects each; 4.4%). The only TEAE considered related to study drug reported in >1 adult subject was hypoesthesia (2 adult subjects; 4.7%).

Most of the subjects reporting TEAEs had events that were considered mild or moderate in severity. One life-threatening TEAE of localized infection of the left great toe was reported in an adult subject that was considered not related to study drug but likely due to an insect bite. TEAEs considered severe were reported in 26.1% of all subjects, and were more commonly observed in adults (32.6%) than in paediatric subjects (20.0%). The only severe TEAE reported in >1 paediatric subject was hyperammonaemia (6 paediatric subjects; 13.3%). Severe TEAEs reported in >1 adult subject were hyperammonaemia (7 adult subjects; 16.3%) and abdominal pain (3 adult subjects; 7.0%). None of the severe TEAEs reported in paediatric subjects were considered related to study drug. Two adult subjects experienced severe TEAEs considered possibly related to study drug (weight decreased and hypocapnia.

No subject died during the study. Treatment-emergent serious AEs (TESAEs) were more commonly observed in adults (41.9%) than in paediatric subjects (26.7%). TESAEs reported in >1 paediatric subject were hyperammonaemia (10 subjects; 22.2%) and dehydration (2 subjects; 4.4%). TESAEs reported in >1 adult subject were hyperammonaemia (11 subjects; 25.6%) and abdominal pain (3 subjects; 7.0%). Of all TESAEs reported during the study, only 2 were considered possibly related to study drug (hypocapnia in 1 adult subject and hyponatremia in 1 adult subject).

The overall incidence of TEAEs (93.0% vs. 75.6%) and TESAEs (41.9% vs. 26.7%) were more frequent in adult subjects than in paediatric subjects. 3 subjects had TEAEs with an action taken of drug withdrawn: pancreatitis in 1 adult subject, hypocapnia in 1 adult subject, and pancytopenia and hyperammonaemia in 1 paediatric subject.

- Safety data from the addendum to Study HPN-100-011

Long-term exposure to Ravicti was well tolerated by the 5 subjects. Median duration of treatment among all subjects was 5.45 years. No subject died, experienced a life-threatening treatment-emergent adverse event (TEAE), or prematurely discontinued study drug due to a TEAE.

The majority of the subjects reporting TEAEs had events that were considered by the investigator to be unrelated to study drug. TEAEs considered related to study drug reported for the paediatric subject were the non-serious events of alopecia and madarosis (reported previously in the final CSR), both mild in severity, and the non-serious event of blood potassium decreased, moderate in severity (reported previously in the final CSR). One adult subject reported a TEAE (arthritis, moderate in severity) considered related to study drug.

Hyperammonaemia, an expected adverse reaction, was the only TEAE reported in more than 1 of the 5 subjects (1 paediatric subject, 1 adult subject). The event was serious in both of these subjects, but considered by the investigator to be unrelated to study drug and due to noncompliance with diet. The only other treatment-emergent SAE was hypokalaemia in the paediatric subject; this event was considered by the investigator to be unrelated to study drug and due to noncompliance with medication.

CHMP comments:

The type and frequency of AEs documented for paediatric patients in this trial are consistent with the AEs mentioned in the product information. Treatment-emergent serious AEs were more commonly observed

in adults than in paediatric subjects.

Overall, treatment with the drug for an extended period was well tolerated by children and adults. A low number of subjects prematurely withdrew over the course of the study (6.8%). There were no deaths. No new safety concerns were identified.

Neuropsychological tests results

The MAH has not presented these results in their overview.

CHMP comments:

Currently the Ravicti SmPC only mentions the following regarding neurological impairment in patients with UCDs, in section 5.1: "Reversal of the pre-existing neurological impairment is unlikely following treatment and neurological deterioration may continue in some patients."

The duration of hyperammonaemia and the peak level of ammonia correlate with brain damage and neurodevelopmental outcomes. Theoretically, effective treatment may improve neurocognitive outcomes in children with UCDs or at least prevent further deterioration. It may be difficult to draw a conclusion about neurocognitive outcomes and any effect of Ravicti on those based on data from an uncontrolled study, in a small population with different UCDs and different disease onset, concomitant medications and other confounding factors. However, the MAH should provide a short overview and critical discussion of neuropsychologic findings in children enrolled in this study. Based on this discussion, the MAH should propose, if needed, SmPC amendments to include the results of neuropsychological tests in children.

2.3.3. Discussion on clinical aspects

In this long-term safety extension Study, Ravicti was effective in maintain ammonia control in adult and paediatric UCD subjects for up to 24 months and in some patients for much longer. In addition, as compared to the 12 months preceding enrolment in Ravicti studies (while subjects were being treated with NaPBA), a decreased rate of HAC while receiving Ravicti was observed which was most pronounced in paediatric subjects. Given the importance of sustaining ammonia control in UCD patients, the MAH should update the paragraph in section 5.1 of the SmPC that presents data from "open-label, uncontrolled, extension studies in paediatric patients". This SmPC update should reflect the duration of the extension studies (with study HPN-100-011 currently being the longest completed study), the sustained ammonia control and effect on number of HACs.

Long-term treatment with Ravicti was well tolerated. There were no deaths. The safety profile in both children and adults was consistent with the AEs mentioned in the product information. No new safety findings were revealed.

The MAH did not present an overview of findings from the neurophysiological tests conducted in children. The MAH should provide a short overview and critical discussion of neuropsychologic findings in children enrolled in

this study. Based on this discussion, the MAH should propose, if needed, SmPC amendments to include the results of neuropsychological tests in children.

3. CHMP preliminary conclusion and recommendation

The MAH concluded that "the information gained with the submitted paediatric study does not influence the benefit risk for Ravicti. There is no consequential regulatory action; no changes or amendments of the product information are proposed."

Based on the submitted study and the addendum to this study, the benefit:risk ratio of Ravicti in the paediatric population remains unchanged.

☒ **Not fulfilled:**

Based on the data submitted, the MAH should address the following questions as part of this procedure. (See section "Additional clarification requested")

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. The MAH should propose SmPC wording to update the paragraph in section 5.1 that presents data from "open-label, uncontrolled, extension studies in paediatric patients". This SmPC update should reflect the duration of the extension studies (with study HPN-100-011 currently being the longest completed study), the sustained ammonia control and effect on number of HACs.
2. The MAH should provide a short overview and critical discussion of neuropsychologic findings in children enrolled in this study. Based on this discussion, the MAH should propose, if needed, SmPC amendments to include the results of neuropsychological tests in children.

5. MAH responses to Request for supplementary information

1. The MAH should propose SmPC wording to update the paragraph in section 5.1 that presents data from "open-label, uncontrolled, extension studies in paediatric patients". This SmPC update should reflect the duration of the extension studies (with study HPN-100-011 currently being the longest completed study), the sustained ammonia control and effect on number of HACs.

Comment MAH:

As recommended, the following text has been proposed to be added to SmPC Section 5.1 (Study 5 is used to refer to Study HPN-100-011):

An open-label, long-term study (Study 5) was conducted to assess ammonia control in paediatric patients with UCD. The study enrolled a total of 45 paediatric patients between the ages of 1 and 17 years with UCD who had completed Study 2 and the safety extensions of Studies 3 and 4. The length of study participation ranged from 0.2 to 5.9 years. Venous ammonia levels were monitored at a minimum of every 6 months. Mean venous ammonia values in paediatric patients in Study 5 were within normal limits during long-term (24 months) treatment with glycerol phenylbutyrate (range: 15-25 micromol/L). Of the 45 paediatric patients participating in the open-label treatment with glycerol phenylbutyrate, 11 patients (24%) reported a total of 22 hyperammonemic crises.

CHMP comments:

The MAH has proposed wording for section 5.1 of the SmPC to include the results of this study. The text proposed is acceptable.

2.The MAH should provide a short overview and critical discussion of neuropsychologic findings in children enrolled in this study. Based on this discussion, the MAH should propose, if needed, SmPC amendments to include the results of neuropsychological tests in children.

Comment MAH:

Among urea cycle disorders (UCD), neonatal onset and prolonged hyperammonemic coma predict impairment of future neurocognitive performance. The duration and severity of hyperammonemia correlate with brain damage. Thus, prompt diagnosis and treatment of UCD is essential in order to optimise the outcome. Pre-existing neurological damage appears not to reverse and, in fact, even though liver transplantation is considered curative as far as enzyme deficiencies are concerned and allows termination of the low-protein diet and regular alternative pathway therapy, it does not reverse established neurological sequelae (Häberle J et al, 2012).

For study HPN-100-011: “Long-Term Use of HPN-100 in Urea Cycle Disorders”, neuropsychological tests were performed at baseline, every 12 months, and at the end of study participation and included the Wechsler Abbreviated Scale of Intelligence (WASI) for adult and paediatric subjects who were at least 6 years of age. In addition, the grooved pegboard test, the California Verbal Learning Test-Second Edition (CVLT-II), and digit span tests were performed for adult subjects; the Child Behavior Checklist (CBCL) and the Behavior Rating Inventory of Executive Function® (BRIEF®) were performed for paediatric subjects at least 5 years of age.

The results did not demonstrate any significant neuropsychological change from baseline to months 12, 24 or end of study. These data are consistent with information outlined in the RAVICTI SmPC illustrating that reversal of the pre-existing neurological impairment is unlikely to occur following treatment with RAVICTI.

Given these results, the MAH does not favour SmPC amendment.

CHMP comments:

As stated by the MAH, the duration and severity of hyperammonaemia correlate with brain damage. On the other hand, phenylacetic acid (PAA), the active metabolite of glycerol phenylbutyrate, is also associated with signs and symptoms of neurotoxicity, although this has not been documented in clinical trials with Ravicti. The MAH was asked to provide an overview and critical discussion of the neuropsychological results in children enrolled in this study. In response to this request, the MAH stated

that no significant neuropsychological changes were observed.

Section 5.1 of the SmPC contains the following text: “Reversal of the pre-existing neurological impairment is unlikely following treatment and neurological deterioration may continue in some patients.” Considering the limitations of this long-term, open label uncontrolled study and that no significant effects on neurocognition in either direction were found, it is considered that no useful information regarding neurocognitive impairment can be added to the SmPC further to the existing text.

The MAH’s proposal not to amend the SmPC with regards to neuropsychological findings from this study is acceptable.

6. CHMP overall conclusion and recommendation

The MAH submitted the final report and addendum of study HPN-100-011 for glycerol phenylbutyrate (Ravicti), according to Article 46 of Regulation (EC) No 1901/2006, as amended.

Based on the submitted study and the addendum to this study, the benefit:risk ratio of Ravicti in the paediatric population remains unchanged.

☒ **Fulfilled**

In addition, the SmPC of Ravicti should be amended in section 5.1 to include a summary of this open label, long-term safety study. The following is proposed:

Section 5.1

Paediatric population

….

An open-label, long-term study (Study 5) was conducted to assess ammonia control in paediatric patients with UCD. The study enrolled a total of 45 paediatric patients between the ages of 1 and 17 years with UCD who had completed Study 2 and the safety extensions of Studies 3 and 4. The length of study participation ranged from 0.2 to 5.9 years. Venous ammonia levels were monitored at a minimum of every 6 months. Mean venous ammonia values in paediatric patients in Study 5 were within normal limits during long-term (24 months) treatment with glycerol phenylbutyrate (range: 15-25 micromol/L). Of the 45 paediatric patients participating in the open-label treatment with glycerol phenylbutyrate, 11 patients (24%) reported a total of 22 hyperammonemic crises.

The MAH should submit a Type II variation to amend the product information within 60 days after adoption of the CHMP conclusion. If the MAH is unable to submit the variation within this timeframe, they must justify the delay and inform the EMA/Rapporteur and propose a new submission date.