PASS information

Title	European Post-Authorisation Registry for RAVICTI® (Glycerol Phenylbutyrate) Oral Liquid in Partnership with the European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD) Study no: HZNP-RAV-401
Version identifier of the final study report	1.0
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EU PAS register number	17267
Active substance	Glycerol phenylbutyrate ATC code: A16AX09
Medicinal product	RAVICTI
Product reference	HC003822
Procedure number	EMEA/H/C/003822
Marketing authorisation holder	Immedica Pharma AB
Joint PASS	No
Research question and objectives	This post-authorisation safety study was set up to further evaluate and characterise the safety profile of RAVICTI and track long-term outcomes in patients with urea cycle disorders treated with RAVICTI. In addition, the study included a comparator group treated with alternative nitrogen scavenging medication, allowing to compare long-term safety of RAVICTI with that of other nitrogen scavenging medication.
Countries of study	Study sites in Austria, Denmark, France, Germany, and Poland were initiated. The study sites in France and Poland did not enrol any patients.
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Marketing authorisation holder

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1 Abstract

Title:

European Post-Authorisation Registry for RAVICTI® (glycerol phenylbutyrate) Oral Liquid in Partnership with the European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD)

Date of abstract: 31 October 2022

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Keywords:

Glycerol phenylbutyrate, long-term safety, nitrogen scavenging medication, post-authorisation safety study, urea cycle disorder

Rationale and background:

Urea cycle disorders (UCDs) are rare, inborn defects in the metabolism of waste nitrogen resulting in accumulation of toxic levels of ammonia in the blood (hyperammonaemia). Severe deficiencies may lead to death or to severe neurological injury. The main goal of medical management of patients with UCD is to prevent chronic or acute hyperammonaemic states leading to central nervous system damage. This requires restriction in dietary protein intake, amino acid supplementation and the use of nitrogen scavenging agents if diet alone does not adequately control patients. Liver transplantation in selected patients may cure the enzyme defect but does not reverse neurological damage.

RAVICTI® (glycerol phenylbutyrate) is a nitrogen binding drug which was approved in the EU in November 2015. It is currently indicated for use as adjunctive therapy for chronic management of adult and paediatric patients with UCDs who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.

Clinical trials in the clinical development programme of RAVICTI did not include pregnant or lactating females and patients with renal impairment. Furthermore, only a limited number of patients were exposed to RAVICTI for a long-term period. Therefore, the present post-authorisation safety study (PASS) was performed following a post approval commitment agreed with the EMA to investigate important potential risks and missing information in the EU risk management plan (RMP) for RAVICTI. The main objective of the study was to collect data on the long-term safety profile of RAVICTI or alternative nitrogen scavenging medication other than RAVICTI in patients with UCD, including the aspect of potential phenylacetic acid (PAA) toxicity and malignancies, and to evaluate pregnancy outcomes in children born to female patients exposed to RAVICTI during pregnancy or children exposed during lactation.

Research question and objective:

This study was set up to further evaluate and characterise the safety profile of RAVICTI and track long-term outcomes in patients with UCD treated with RAVICTI.

Thus, the study was set up to:

- Collect relevant long-term safety data in patients with UCDs treated with RAVICTI.
- Collect information on incidence rate and type of cancer in patients with UCDs treated with RAVICTI.
- Collect information on potential PAA toxicity in patients with UCDs treated with RAVICTI.

- Collect safety information in patients with UCDs and concurrent renal impairment treated with RAVICTI.
- Evaluate pregnancy outcomes in children born to female patients exposed to RAVICTI during pregnancy or children exposed during lactation.

In addition, the study included a comparator group, treated with alternative nitrogen scavenging medication other than RAVICTI. Thus, the data specified above were also collected in the comparator group thereby allowing to compare the long-term safety in patients with UCDs treated with RAVICTI with that in patients treated with alternative nitrogen scavenging medication other than RAVICTI, specifically to:

- Compare incidence rate of adverse events in patients treated with RAVICTI and patients in the comparator group.
- Compare incidence rate of cancer in patients treated with RAVICTI and patients in the comparator group.
- Compare safety information collected in patients with renal impairment treated with RAVICTI to patients with renal impairment treated with comparator medication.
- Compare pregnancy outcomes in children born to female patients exposed to RAVICTI to outcomes in children born to female patients exposed to comparator drugs during pregnancy or children exposed during lactation.

Study design:

This was a multi-centre, prospective, non-interventional PASS conducted in partnership with the E-IMD designed to collect data on safety and outcomes in patients with UCDs on treatment with RAVICTI. The same data were collected in a comparator group, receiving alternative nitrogen scavenging medication other than RAVICTI.

Setting:

The study used observational methods to prospectively collect data on specified outcomes in patients with UCDs to monitor the long-term safety of RAVICTI.

In the E-IMD registry, children and adults with UCD are followed using a standardised assessment schedule including demographic data, family history, age at diagnosis, first symptoms, characterisation of UCD subtype, frequency and duration of hospitalisation, medical and developmental history, physical and neurological examination, and neuropsychological tests.

The present study extended the E-IMD registry regarding safety data. Thus, the already existing data collection was augmented by collection of additional data with the aim of gathering information from patients with characteristics not previously studied or underrepresented in the clinical program for RAVICTI and characterising the demographics and long-term clinical course of the patient population diagnosed with UCD and being treated with RAVICTI.

Patients and study size, including dropouts:

It was planned to include about 100 patients receiving RAVICTI and 100 patients receiving an alternative nitrogen scavenging medication. However, the study was terminated prematurely when a total of 35 patients had been included. Three patients discontinued the study.

Variables and data sources:

Study endpoints included:

- Long-term safety data:
  - Incidence rate and type of adverse events (AEs), serious adverse events (SAEs) and AEs leading to withdrawal.
  - Hospitalisation due to hyperammonaemic crisis.
  - Physical examination (movement disorders, hypotonia).
  - Laboratory tests (kidney function, liver function).
  - Neuropsychological tests.
- Incidence rate and type of cancer.
- Potential PAA toxicity.
- Safety information for patients with UCDs and concurrent renal impairment.
- Outcomes in children exposed during pregnancy or children exposed during lactation.

These endpoints were assessed for patients with UCDs treated with RAVICTI (the RAVICTI group) and compared with patients treated with alternative nitrogen scavenging medication other than RAVICTI (the comparator group).

The study used available data documented at the participating site for the enrolled patient during each patient contact. Participating investigators selected data during the visits from the patient's medical record including physician's or nurse's notes, consultancy reports, discharge summaries, laboratory sheets, etc. Those data were entered during the patient visits in the electronic registry record forms provided by the E-IMD.

The E-IMD routinely collected data for all enrolled patients at least annually and at time points in between if the patient was seen as standard of care or the patient experienced a hyperammonaemic crisis and was seen as an emergency patient.

Health-related information was collected as available during the patient's participation in the study. Results of age-appropriate neuropsychological testing were recorded according to the E-IMD registry protocol. For additional safety data, which were collected for the present study, participating investigators were asked to complete the respective information including reason for the visit, information on RAVICTI or comparator treatment, and respective safety data (AE, pregnancy, lactation) during each regular and any additional unscheduled or emergency patient visit. Safety-related data were collected in the comparator group for alternative ammonia scavenging medication other than RAVICTI using the same approach and tools.

Results:

In total, 36 patients were screened, 35 patients entered the study, and 3 patients discontinued the study:

Variable	RAVICTI group			Comparator group	Total
	Patients treated with RAVICTI during the whole study	Patients switched to RAVICTI during the study	Total		
Screened patients	16	4	20	16	36
Patients who entered the study	16	4	20	15	35
Completed patients	0	0	0	0	0
Discontinued patients	2	0	2	1	3
- Withdrawal of consent	0	0	0	1	1

- Liver transplant	2	0	2	0	2

In total, 17 men and 18 women, all White, were included. The mean (SD) age was 13.6 (10.9) years. The patients in the comparator group were in general older than the patients in the RAVICTI group. More patients in the RAVICTI group had an early onset of disease while in the comparator group, more patients had a late onset. About 2/3 of patients in both groups had a peak plasma ammonia level >500 µmol/L at disease onset. Renal disease was very rare.

The maximum follow-up period was 4.4 years. Both the mean and median follow-up times in the study were longer for the comparator group compared with the RAVICTI group.

Data from the study did not indicate any new relevant safety findings for RAVICTI in the treatment of patients with UCDs:

- Proportionally more patients in the comparator group reported non-serious AEs compared with the RAVICTI group (93.3% versus 60.0%).
- Proportionally more patients in the comparator group reported SAEs compared with the RAVICTI group (53.3% versus 45.0%).
- The difference in the occurrence of AEs and SAEs between the treatment groups was not statistically significant (p=0.2641).
- No AEs led to death or discontinuation.
- Serious hyperammonaemia was reported in 7 (35.0%) patients in the RAVICTI group and 6 (40.0%) patients in the comparator group, of which 2 patients in the RAVICTI group also reported serious ammonia increased.
- There were no differences between the treatment groups in the variables included in the physical examination.
- There were no differences between the treatment groups in renal or liver function.

Only a few patients completed the neuropsychological tests, and no meaningful analyses or comparisons could therefore be done.

No events of malignancy were reported during the study.

No patients reported AEs or SAEs with reported elevated PAA levels in plasma.

One patient in each treatment group had mildly decreased renal function (GFR 60-89 mL/min) at the baseline visit (BV). The patient in the RAVICTI group did not report any AEs and discontinued from the study 3 months after the BV due to liver transplantation and the patient in the comparator group reported 2 mild AEs.

There were no pregnancies during the study nor any reports of breastfeeding.

Discussion:

This study was performed following a post approval commitment agreed with the EMA to investigate important potential risks and missing information in the EU RMP for RAVICTI. The main objective of the study was to collect data on the long-term safety profile of RAVICTI or alternative nitrogen scavenging medication other than RAVICTI in patients with UCD, including the aspect of potential PAA toxicity and malignancies, the safety in UCD patients with concurrent renal impairment and to evaluate pregnancy outcomes in children born to female patients exposed to RAVICTI during pregnancy or children exposed during lactation.

Following a review of available data, it was agreed with EMA to remove the important potential risk of carcinogenicity from the EU RMP and alternate methods to address the important potential risk of PAA toxicity were implemented. In addition, the remaining study objectives (which are included as missing information in the EU RMP) will be followed through routine pharmacovigilance. Accordingly, there was no longer a requirement to address the study objectives and it was agreed with EMA and Medicines and Healthcare products Regulatory Agency (MHRA) to terminate the study prematurely. At termination, a total of 35 patients had been enrolled.

There are several limitations to make any firm conclusions based on data collected in the study, including a lower number of subjects than planned, shorter study durations as well as shortcomings usually present in a non-interventional setting. However, based on the data collected, the results did not indicate any new relevant safety findings for RAVICTI in the treatment of patients with UCDs. There were overall no major differences in the assessed safety parameters between patients treated with RAVICTI compared with the comparator group although proportionally more patients in the comparator group reported non-serious AEs compared with the RAVICTI group (93.3% versus 60.0; p=0.2641).

Serious events of hyperammonaemia were reported in 7 (35.0%) patients in the RAVICTI group and 6 (40.0%) patients in the comparator group. Two of the patients in the RAVICTI group who reported serious hyperammonaemia also reported serious events of ammonia increased. This is in accordance with previously published studies.

No events of malignancy were reported during the study in either of the treatment groups, recognizing that the possibilities to evaluate such events would be limited due to the number of subjects and study duration.

No events of PAA toxicity and no data on PAA levels were reported in the study. To further evaluate potential PAA toxicity, events which may occur in the event of PAA toxicity were analysed, including vomiting, headache and nausea. These events are common in the UCD patient population and are typical symptoms of hyperammonaemia and can therefore not be interpreted as signs of PAA toxicity in the absence of additional information. Due to the lack of analysis of PAA levels in the present study, it was not possible to assess the relationship between the reported events and a potential PAA toxicity. There were no apparent differences in vomiting, headache or nausea between the treatment groups. Thus, there is no reason to suspect any difference between patients treated with RAVICTI with regards to PAA toxicity compared to patients treated with other nitrogen scavenging medication.

One patient in each treatment group had mildly decreased renal function at BV based on the GFR assessments. The patient in the RAVICTI group did not report any AEs and the patient in the comparator group reported 2 unrelated, mild AEs (vomiting and renal impairment) during the study. Thus, the study treatments did not identify any deteriorations of the renal function or increased risk of AEs in these patients.

The mean daily dose of RAVICTI was 219.1 mg/kg at the BV and 190.9 mg/kg at the end of the study for the patients treated with RAVICTI during the whole study. If the 4 patients who switched treatment to RAVICTI during the study are included, the mean daily dose for all RAVICTI patients was 174.8 mg/kg at the end of the study. These doses are slightly lower mean doses than seen in previous studies. However, the latter studies only included monotherapy, whereas the current also allowed combination therapy.

Four patients in the comparator group switched treatment to RAVICTI during the study. The outcomes in these 4 patients did not differ as compared to the other groups, i.e., the switches seemed to be uneventful which is in line with previously published real-world studies.

Since there were no pregnancies nor any reports of breastfeeding reported during the study, the outcomes in children exposed to RAVICTI or other nitrogen scavenging medications during pregnancy or children exposed during lactation could not be evaluated. In conclusion, data obtained in the current, prospective, non-interventional PASS did not indicate any new relevant safety findings for RAVICTI. Furthermore, there were overall no major differences in the assessed safety parameters between patients treated with RAVICTI compared with the comparator group although proportionally fewer patients in the RAVICTI group reported AEs and SAEs as compared with the patients in the comparator group. No new safety findings were identified in the few patients who switched from other nitrogen scavenging medication to RAVICTI. Based on these results, there is no new significant safety information indicating a change in the risk-benefit profile of RAVICTI.
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