AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

# AWMSG SECRETARIAT ASSESSMENT REPORT

## Glycerol phenylbutyrate (Ravicti®)
## 1.1 g/ml oral liquid

Reference number: 2127

## FULL SUBMISSION

PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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# AWMSG Secretariat Assessment Report
# Glycerol phenylbutyrate (Ravicti®▼) 1.1 g/ml oral liquid

## 1.0 KEY FACTS

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| **Assessment details** | Glycerol phenylbutyrate (Ravicti®▼) for use as an adjunctive therapy for chronic management of patients with urea cycle disorders including deficiencies of:<br>• carbamoyl phosphate synthetase I (CPS);<br>• ornithine carbamoyltransferase (OTC);<br>• argininosuccinate synthetase (ASS);<br>• argininosuccinate lyase (ASL);<br>• arginase I (ARG)<br>• and ornithine translocase deficiency hyperornithinaemia-hyperammonaemia homocitrullinuria syndrome (HHH)<br>who cannot be managed by dietary protein restriction and/or amino acid supplementation alone.<br><br>Ravicti® must be used with dietary protein restriction and, in some cases, dietary supplements (for example, essential amino acids, arginine, citrulline, protein-free calorie supplements).<br><br>▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.<br><br>Ravicti® is licensed for the full adult and paediatric population (≥ 0 months of age and older). Ravicti® is the first licensed oral liquid formulation of phenylbutyrate. |
| **Current clinical practice** | The treatment of urea cycle disorders is based on dietary protein restriction and dietary supplements. This is often complemented with the use of ammonia-scavenging medicines, such as sodium phenylbutyrate, that promote alternate pathways for nitrogen excretion. Sodium phenylbutyrate is available in various formulations and mainly used in Wales as an unlicensed liquid (1 g/5 ml). Clinical experts indicate there is an unmet need for the indication under consideration as current treatment options place a high treatment burden on the patient.<br><br>Ravicti® is the first licensed oral liquid of phenylbutyrate and shares the same mechanism of action and metabolic pathway as sodium phenylbutyrate. Ravicti® provides an alternative option and is in a formulation that may reduce the substantial treatment burden and unpleasant taste and odour associated with sodium phenylbutyrate. |

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|---|---|
| **Clinical effectiveness** | In a pivotal randomised phase III cross-over study, Ravicti® was non-inferior to sodium phenylbutyrate in controlling blood ammonia levels, although the pivotal study was limited to a four-week time frame. Pooled analyses from this study with three short-term (four-week), single-arm studies in adult and paediatric patients supported the efficacy of Ravicti®. The maintenance effects on blood ammonia were observed in three long-term (12-month), open-label extension studies. Although the medicine is considered well-tolerated, safety data are limited to 12 months and the company is required to collect further data over 10 years as a condition of marketing authorisation. |
| **Cost-effectiveness** | A cost-minimisation analysis compares Ravicti® with sodium phenylbutyrate (Ammonaps®) tablets.<br><br>The company base case suggests cost savings of [commercial in confidence figure removed] per patient per annum. AWTTC considers this to be a conservative estimate given the high usage of unlicensed liquid formulations in Wales.<br><br>Using cost-minimisation analysis is inappropriate, given the absence of well-designed equivalence trials and differences in medicine safety and formulation. |
| **Budget impact** | The company estimates that six patients in Wales are eligible to receive treatment with Ravicti® in Years 1 to 5. The company base case suggests cost savings of [commercial in confidence figure removed] per year in Years 1 to 5.<br><br>The budget impact analysis includes Ammonaps® tablets as the sole comparator and dosing of Ravicti® is not rounded. Therefore, the base case is unlikely to reflect the budget impact in the Welsh market with Ravicti®. |
| **Additional factors to consider** | AWTTC considers Ravicti® to be eligible to be appraised as an ultra-orphan medicine. |

This assessment report is based on evidence submitted by Swedish Orphan Biovitrum Ltd (SOBI) and an evidence search conducted by AWTTC on 14 August 2019[1].

## 2.0 BACKGROUND

### 2.1 Condition and clinical practice

Urea cycle disorders are a rare, serious and life threatening group of inherited deficiencies in an enzyme or transporter involved in converting ammonia to urea[2]. The absence or dysfunction of the enzyme or transporter results in toxic levels of ammonia accumulating in the blood and brain. Although genetically distinct, urea cycle disorders are typically considered as a group and the clinical manifestations are attributable to hyperammonaemia. Symptoms of hyperammonaemia include: seizures, cerebral oedema, hyperventilation, posturing, and coma, as well as milder symptoms such as loss of appetite, headache, cyclical vomiting and fatigue[2].

There are no consistent recommendations about medicines to treat urea cycle disorders[3]. Management of the individual urea cycle disorder subtypes is generally similar and involves decreasing ammonia production, by reducing the amount of protein in the diet and replacement of certain urea cycle intermediates[2]. If dietary measures are insufficient, medicines such as sodium phenylbutyrate and sodium benzoate that hydrolyse to nitrogen-scavenging compounds are used to remove excess ammonia from the blood[2].

### 2.2 Medicine

Glycerol phenylbutyrate (Ravicti®) is the first licensed oral liquid formulation of phenylbutyrate. It is a nitrogen-binding agent and prodrug of phenylbutyric acid, with the same mechanism of action as sodium phenylbutyrate[2]. In the gastrointestinal tract, pancreatic lipases hydrolyse glycerol phenylbutyrate to glycerol and phenylbutyric acid[2]. Phenylbutyric acid is oxidised to phenylacetic acid which combines with glutamine to form phenylacetylglutamine (PAGN) and provides removal of nitrogen through urinary excretion of PAGN[2].

Ravicti® was developed to offer an alternative to sodium phenylbutyrate, in a sugar-free and sodium-free liquid formulation[2]. It enters the circulation more slowly, with sustained-release characteristics to provide better nitrogen scavenging and ammonia control[2]. It must be used with dietary protein restriction and, in some cases, dietary supplements such as essential amino acids, arginine, citrulline, and protein-free calorie supplements[3].

The EMA approved Ravicti® in November 2015 to treat urea cycle disorders in patients aged 2 months and older[2]. In December 2018 the EMA extended the licence to include use in patients aged 0 to 2 months[4].

The recommended daily dose of Ravicti® is based on body surface area and ranges from 4.5 ml/$m^2$/day to 11.2 ml/$m^2$/day (5.3 g/$m^2$/day to 12.4 g/$m^2$/day)[3]. The total daily dose is divided into equal amounts and given with each meal or feeding, for example, three to six times daily either orally or by nasogastric or gastrostomy tube. Each of these doses should be rounded up to the nearest 0.1 ml for patients < 2 years of age and to the nearest 0.5 ml for patients ≥ 2 years of age. Different doses are recommended for patients who are taking a phenylbutyric acid prodrug for the first time, and patients who are switching to glycerol phenylbutyrate after taking sodium phenylbutyrate or sodium benzoate injection[3].

### 2.3 Comparators

The comparator included in the company's submission is sodium phenylbutyrate tablets (Ammonaps®)[1]. Ammonaps® is available in granules and tablets and is indicated in all patients with neonatal-onset presentation (complete enzyme deficiencies, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzyme deficiencies, presenting after the first month of life) who have a history of hyperammonaemic encephalopathy[5,6].

### 2.4 Guidance and related advice

- Suggested guidelines for the diagnosis and management of urea cycle disorders: first revision (2019)[7].

The All Wales Medicines Strategy Group (AWMSG) has previously recommended the use of sodium phenylbutyrate granules (Pheburane®) and sodium phenylbutyrate tablets and granules (Ammonaps®)[8,9].

### 2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, Ravicti® is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipates that Ravicti® may be supplied by a home healthcare provider[1].

## 3.0 CLINICAL EFFECTIVENESS

The company's submission includes results from eight clinical studies of Ravicti® in patients with urea cycle disorders[1]. Four short-term (≤ 4 weeks) studies assessed the efficacy of Ravicti® compared with sodium phenylbutyrate in a total of 85 patients: one was a pivotal phase III, randomised study (HPN-100-006) and is detailed below. Supportive evidence is included from the other short-term studies (UP 1204-003, HPN-100-012 and HPN-100-005). Pooled analyses of three long-term (12-month) open-label extension studies (HPN-100-012SE, HPN-100-005SE and HPN-100-007) assessing the efficacy and safety of Ravicti® in 100 patients, are also summarised[1].

The submission also includes an open-label study (HPN-100-009) of the safety and efficacy of Ravicti® in paediatric patients from birth to < 2 months of age, the results of which supported a licence extension of Ravicti® to treat patients aged 0 to 2 months[1,4].

### 3.1 Study HPN-100-006

This pivotal randomised phase III crossover study aimed to establish the non-inferiority of Ravicti® to sodium phenylbutyrate as assessed by blood ammonia levels[10,11]. The study enrolled 45 adults (14 men and 31 women; aged 18–75 years) with urea cycle disorders who had been on a stable dose of sodium phenylbutyrate for an average duration of about 10 years[11]. Forty patients (88.9%) had ornithine carbamoyltransferase deficiency, three (6.7%) had argininosuccinate synthetase deficiency and two (4.4%) had carbamoyl phosphate synthetase I deficiency. Most patients (n = 30; 67%) had been diagnosed with a urea cycle disorder before adulthood (i.e. at age < 18 years)[10,11].

Patients were randomly assigned in a 1:1 ratio to one of two treatment arms to receive:

- Arm A: two weeks of sodium phenylbutyrate tablets plus Ravicti® placebo, followed by two weeks of Ravicti® plus sodium phenylbutyrate placebo; or
- Arm B: two weeks of Ravicti® plus sodium phenylbutyrate placebo followed by two weeks of sodium phenylbutyrate tablets plus Ravicti® placebo[10,11].

Each patient received a specific dose of Ravicti®, determined at the screening visit and calculated to match their daily dose of sodium phenylbutyrate (phenylbutyric acid mole-equivalent) which was based on the severity of their enzyme deficiency, the content of their diet, and their intake of amino acids or supplements[11]. The maximum total daily dose of Ravicti® was 17.4 ml, equivalent to 20 g and corresponding to 40 tablets of sodium phenylbutyrate[11].

The study's primary endpoint was the 24-h area-under-the-curve ($AUC_{0-24}$) for blood ammonia on days 14 and 28[11]. Non-inferiority was met because the upper 95% confidence interval (CI) for the ratio of the least squares means between Ravicti® and sodium phenylbutyrate was ≤ the pre-specified margin of 1.25 (Table 1)[10].

Mean $AUC_{0-24}$ values for blood ammonia were not significantly lower after treatment with glycerol phenylbutyrate compared with treatment with sodium phenylbutyrate[10]. Secondary endpoints were supportive, with no significant differences between the two treatment groups for: maximum blood ammonia values; number and severity of symptomatic hyperammonaemic crises, and rates of adverse events.

### 3.2 Pooled results from short-term studies and long-term extension studies

Three short-term, single-arm, switch-over studies were conducted in adult and paediatric patients who were receiving treatment with sodium phenylbutyrate for urea cycle disorders. Patients were given individualised doses of Ravicti® as a replacement for sodium phenylbutyrate. After completing the short-term study patients could then enter into one of three open-label extension studies of 12-month treatment with Ravicti® (Table 1). The similar design of the four short-term studies (HPN-100-006 [patients aged ≥ 18 years], UP 1204-003 [patients aged ≥ 18 years], HPN-100-012 [patients aged 29 days to 5 years] and HPN-100-005 [patients aged 6–17 years]) and three long-term studies allowed for the results to be pooled for comparative analyses (Table 1)[2].

**Table 1. Results of the pivotal study and pooled clinical studies of Ravicti® in patients with urea cycle disorders[2].**

| | Pivotal study | Pooled short-term studies | Pooled long-term studies |
|---|---|---|---|
| **Study names** | HPN-100-006 | HPN-100-006<br>UP 1204-003<br>HPN-100-012<br>HPN-100-005 | HPN-100-012SE<br>HPN-100-005SE<br>HPN100-007 |
| **Numbers of patients (intent-to-treat population; n)** | 44 | 78 | 100 |
| **Duration of Ravicti® treatment** | 4 weeks | 1–4 weeks | 12 months |
| **Blood ammonia $AUC_{0-24}$: ratio of geometric means: Ravicti® / sodium phenylbutyrate** | | | |
| Ratio | 0.91 | 0.84 | n/a |
| 95% Confidence interval | 0.799 to 1.034 | 0.740 to 0.949 | n/a |
| P value | 0.315 | 0.002 | n/a |
| **Hyperammonaemic crises (events per patient per year)** | | | |
| In 12 months before enrolling in study | n/a | n/a | 0.53 |
| On Ravicti® treatment | n/a | n/a | 0.27 |

n/a: not applicable
$AUC_{0-24}$ : area under the curve during 24 hours

Results from the pooled analyses showed a clinically meaningful and statistically robust difference in favour of Ravicti® over sodium phenylbutyrate in control of blood ammonia levels, as measured by $AUC_{0-24}$[2]. The 24-h blood ammonia pattern with Ravicti® was consistent with the individual studies and showed post-prandial increases in mean blood ammonia were higher early in the day (from 4 to 5 h after dosing) and lower in the afternoon and night (from 6 to 12 h after dosing) compared with sodium phenylbutyrate. Mean 24-h blood ammonia levels were lower on Ravicti® than sodium phenylbutyrate at most time points; differences in the blood ammonia profile were attributed to the difference in pharmacokinetics of the two medicines. Average daily ammonia levels were significantly lower with Ravicti® than sodium phenylbutyrate ($p = 0.008$, paired t-test)[2].

Pooled data from the long-term studies showed that 12 months of Ravicti® results in around 50% fewer total hyperammonaemic crises, compared with the previous 12 months of sodium phenylbutyrate treatment (Table 1)[2]. Across the long-term studies the rates of hyperammonaemic crises were highest among patients aged 2–5 years, who are more susceptible to the toxic effects of ammonia, both in the 12 months preceding the studies (1.44/patient vs 0.53/patient overall) and during long-term treatment with Ravicti® (0.63/patient vs 0.27/patient overall)[2].

In study HPN-100-007, after three months of treatment patients were asked to indicate their preference for Ravicti® or sodium phenylbutyrate[12]. Results from 50 adult patients showed that 45 (90%) preferred Ravicti®; two preferred sodium phenylbutyrate and three had no preference[12].

### 3.3 Study HPN-100-009

The open-label study HPN-100-009 assessed the safety, efficacy and pharmacokinetics of transition to Ravicti® treatment in 16 paediatric patients with urea cycle disorders, aged from birth to < 2 months[4]. Efficacy was assessed by successful transition to Ravicti® with controlled blood ammonia (no symptoms of hyperammonaemia and ammonia < 100 micromol/l); transition within three days was successful in all 16 patients[4].

### 3.4 Comparative safety

The safety profile in the pooled analysis of the short-term controlled studies is similar in type and frequency to the pivotal study. Most events were generally mild, none were life-threatening and no patients died. The nature and severity of adverse events tended to decrease with continued exposure. Overall, the most frequently reported adverse reactions were gastrointestinal related: diarrhoea, flatulence and headache (8.8%); decreased appetite (7%); vomiting (6.1%); fatigue, nausea and abnormal skin odour (5.3%)[2]. No patients discontinued Ravicti® treatment because of a treatment-emergent adverse event in any of the four short-term studies; two patients discontinued sodium phenylbutyrate treatment because of high ammonia levels[2]. The incidence of hyperammonaemia was higher in the under two month's age group although this was not unexpected as the neonatal population are known to have more severe disease[4].

In the long-term, open-label extension studies the majority of adverse effects were mild or moderate in severity and the Committee for Medicinal Products for Human Use (CHMP) concluded that Ravicti® is well tolerated. However, due to the lack of long-term data (limited to 12 months), the company is required to collect safety data over 10 years from a multicentre, prospective, non-interventional registry in patients with urea cycle disorders treated with Ravicti®, as a condition of marketing authorisation. A final study report is expected in July 2030.

### 3.5 Ongoing studies

- A randomised, controlled, open-label, parallel-arm, phase III study to assess safety, tolerability, pharmacokinetics and blood ammonia control of Ravicti® compared with sodium phenylbutyrate in patients with urea cycle disorders who have not previously received phenylbutyrate. Expected to complete in 2020.
- A 10-year observational study to collect information on patients with urea cycle disorders, including medications used to manage the disorder. Expected to complete in 2026.

### 3.6 AWTTC critique

- The pivotal study and pooled analysis from the short-term studies showed Ravicti® was not inferior to sodium phenylbutyrate tablets in managing blood

ammonia levels. The pivotal study however was limited to a four-week time frame. Analysis of the pooled long term studies showed Ravicti® reduced the frequency of hyperammonaemic events[9].

- The AWMSG previously recommended Ammonaps® and Pheburane® as an option for use within NHS Wales. These medicines are indicated as adjunctive therapy in the chronic management of urea-cycle disorders, involving deficiencies of CPS, OTC and ASS. Ravicti® has a broader indication and includes other enzyme deficiencies such as ASL, ARG and HHH.
- The company did not provide a comparison with sodium phenylbutyrate granules Ammonaps® (940 mg/g granules), Pheburane® (480 mg/g granules), and unlicensed 1 g/5 ml sodium phenylbutyrate liquid, although these are anticipated to be displaced by Ravicti®. Welsh clinical experts have stated the main formulation of sodium phenylbutyrate used is the unlicensed 1 g/5 ml liquid.
- Clinical experts sought by AWTTC indicate there is an unmet need for Ravicti® as current treatment options place a high treatment burden on the patient. Ravicti® is the first licensed oral liquid phenylbutyrate and experts consider that it would provide an alternative to all existing formulations of sodium phenylbutyrate and have the potential to improve adherence. Ravicti® is in a formulation that may reduce treatment burden and may also be more palatable (particularly to children) as it masks the unpleasant taste and odour associated with sodium phenylbutyrate formulations[2].
- The control of blood ammonia is a surrogate marker. However, CHMP acknowledged that control of blood ammonia is a primary objective of clinical management, which correlates with clinical outcome[2].
- The slower gastrointestinal absorption of Ravicti® compared with sodium phenylbutyrate is associated with sustained-release characteristics allowing more even distribution of urinary PAGN excretion, providing a better control of blood ammonia during the day[2].
- Seven of the eight clinical studies included all six subtypes of urea cycle disorders covered by the marketing authorisation for Ravicti®. Only three urea cycle disorder subtypes are represented in the 0 to < 2 months cohort. However, as all subtypes have the same clinical sequelae this difference was not considered important[4].
- The only long-term data are from 12-month, open-label, non-controlled studies. This is a limitation considering that urea cycle disorders are chronic conditions which require long-term treatment. To address the uncertainty about long-term safety, the marketing authorisation holder is required to collect further data during the post-approval setting to further characterise long-term use.
- The Summary of Product Characteristics (SPC) for Ravicti® recommends that phenylbutyrate-naïve patients have a different dosing regimen to patients switching from sodium phenylbutyrate or sodium benzoate injection[3]. However, there is a lack of evidence for the use of Ravicti® in treatment-naïve patients and in patients switching from sodium benzoate injection, with the exception of HPN-100-009, in which 2 of 16 patients (13%) were treatment naïve. All clinical studies other than HPN-100-009 enrolled patients with urea cycle disorders well controlled on a stable dose of sodium phenylbutyrate.
- Ravicti® is sodium-free, which may be more suitable for patients who have sodium retention with oedema.
- Ravicti® can be easily administered either through a nasogastric tube or gastrostomy tube compared with the current approved sodium phenylbutyrate formulations[2].

## 4.0 COST-EFFECTIVENESS

### 4.1 Context

The company's submission includes a cost-minimisation analysis (CMA) comparing Ravicti® (glycerol phenylbutyrate 1.1 g/ml oral liquid) with Ammonaps® (sodium phenylbutyrate 500 mg tablets) for the full licensed indication for Ravicti®[1].

A simple Excel-based cost comparison model estimates the difference in medicine acquisition costs between Ravicti® and Ammonaps®. The analysis adopts a one-year time horizon and an NHS Wales perspective. Acquisition costs are calculated based on the assumption of a 70 kg patient with a body surface area of approximately 1.6 $m^2$ and an assumed daily dose of 9.9 $g/m^2$ for Ammonaps®. The required daily dose of Ammonaps® is divided into 3 equal doses (to be taken at meal times) and then rounded to the nearest 500 mg tablet. The SPC dose conversion factor (1 g tablets = 0.86 ml Ravicti®)[3] is applied to the rounded total daily dose of Ammonaps® to calculate a therapeutically equivalent daily dose for Ravicti®. Ravicti® dosing is also divided into three daily doses and then rounded to the nearest 0.5 ml for each dose (or to the nearest 0.1 ml in the 10 kg paediatric scenario). The daily costs have been multiplied by 365 days to calculate annual costs. The submission incorporates a Wales Patient Access Scheme discount for Ravicti®. The acquisition cost for Ammonaps® is sourced from Monthly Index of Medical Specialities[13]. No discounting is applied given the short time horizon of the model. No other costs have been included in the analysis.

The company conducted sensitivity and scenario analyses to explore the impact of:

- varying weight and body surface area;
- alternative dosing regimen; and
- using Ammonaps® granules as an alternative comparator.

### 4.2 Results

The results of the base case analysis and scenario and sensitivity analyses are detailed in Table 2. When compared with Ammonaps®, Ravicti® is less costly in the base case. Sensitivity analyses exploring alternative weight/BSA and dosing regimens generate results ranging from savings of [commercial in confidence figure removed]. per patient per year to additional costs of [commercial in confidence figure removed] per patient per annum. When granules are substituted as the comparator in the base case this results in estimates of additional costs of [commercial in confidence figure removed] per person per year.

**Table 2. Results of the base case analysis and scenario and sensitivity analyses**

| Scenario | Costs | Ravicti® | Comparator | Difference | Plausibility |
|---|---|---|---|---|---|
| **Base case:** assumes 70 kg patient with body surface area of 1.6 $m^2$ | | | | | |
| Ravicti® versus Ammonaps®<br><br>Dosing 9.9 g Ammonaps® tablets/$m^2$/day | Medicine acquisition costs | ¶¶ | £23,728.65 | ¶¶ | Whilst there is usage of Ammonaps® tablets in Wales, AWTTC sought clinical expert opinion and Welsh prescribing data identify unlicensed 1 g/5 ml sodium phenylbutyrate liquid as the primary comparator.<br><br>The exclusion of the unlicensed liquid from the |

| Scenario | Costs | Ravicti® | Comparator | Difference | Plausibility |
|---|---|---|---|---|---|
| | | | | | base case underestimates the potential cost savings associated with the use of Ravicti® in Wales.<br><br>The average body weight of patients and dosing used in Wales are unknown. |
| **Sensitivity and scenario analyses** | | | | | |
| **Base case with variable dose:** assumes 70 kg patient with body surface area of 1.6 $m^2$ | | | | | |
| 13 g Ammonaps® tablets/$m^2$/day | Medicine acquisition costs | ¶¶ | £30,200.10 | ¶¶ | Current dosing practices in Wales are unknown.<br><br>This may offer a plausible alternative to the base case for patients currently receiving Ammonaps® tablets. However, this scenario does not include the primary comparator and consequently underestimates potential cost savings for the population as a whole. |
| Treatment-naïve dosing<br><br>Median dose of Ammonaps® tablets 11.45 g/$m^2$/day<br><br>Median dose of Ravicti® 7.85 ml/$m^2$/day | Medicine acquisition costs | ¶¶ | £25,885.80 | ¶¶ | This scenario does not attempt to apply therapeutically equivalent/similar dosing. This is not a plausible scenario for treatment naive patients given that most patients in Wales are currently initiated on unlicensed liquid. |
| Paediatric patient 10kg<br><br>500mg Ammonaps® tablets kg/day | Medicine acquisition costs | ¶¶ | £6,471.45 | ¶¶ | This scenario explores an alternative dosing regimen. However, Welsh clinical experts advise that paediatric patients are most commonly prescribed unlicensed liquid. This is not a plausible scenario. |
| **Base case dosing with alternative weight/body surface area (BSA)** | | | | | |
| 60kg patient with BSA 1.48$m^2$ | Medicine acquisition costs | ¶¶ | £22,504.88 | ¶¶ | This scenario offers a useful exploration of cost for patients of this weight/BSA. However, this scenario excludes the primary comparator and therefore underestimates comparator costs. |
| ¶¶: commercial in confidence figure removed | | | | | |

The results of the sensitivity and scenario analyses show that the outcome of the cost comparison (that is, whether the introduction of Ravicti® is cost saving or costs more) is sensitive to weight/BSA and alternative dosing regimens, but is most sensitive to the inclusion of Ammonaps® granules as a comparator.

### 4.3 AWTTC critique

The reliability of the CMA depends on the extent to which Ravicti® is considered to be therapeutically equivalent to Ammonaps®. The company justified using a CMA, as opposed to a cost-utility analysis (CUA), on the basis that the supporting pivotal study reported non-inferiority for Ravicti® versus sodium phenylbutyrate in terms of ammonia control[10,11]. The results of the CMA base case show that Ravicti® is cost-saving when compared with Ammonaps® tablets.

In the absence of well-designed equivalence trials and evidence of close comparability of other effects (impact on health-related quality of life (HRQoL), adverse events, patient preference, adherence and survival), AWTTC considers a CMA to be an inappropriate approach in this instance.

The submission is characterised by strengths and limitations:

Strengths:

- The submission gives a transparent account of the methods and data sources used in the cost calculation.

Limitations:

- The company's justification for using a CMA is not convincing, given that the pivotal study concluded non-inferiority, which does not infer equivalence. Also, the profiles of Ravicti® and Ammonaps® are different in terms of the reported frequency of adverse events. In the pivotal short-term clinical study, the adverse event profile favoured the comparator, whereas the pooled analysis of the long-term studies showed Ravicti® was associated with fewer hyperammonaemia crises. These differences highlight that a CUA would have provided a more appropriate comparison and that there is potential for bias in adopting a CMA approach to evaluation. The company's submission indicates a collection of preference-based HRQoL and patient preference data, but these are not reported.
- Rounding at the split dose level results in loss of therapeutic equivalence in daily dosing, which further supports use of a CUA approach for evaluation purposes.
- The choice of comparators is limited to Ammonaps® tablets. Clinical expert opinion sought by AWTTC suggests that this patient group is treated with sodium phenylbutyrate in tablet or (unlicensed) liquid form, in addition to sodium benzoate in an acute care setting and granule formulations in a minority of patients. Exclusion of comparators used in Wales introduces bias. The submission included a separate analysis on the use of Ammonaps® granules as a comparator; AWTTC do not consider this a plausible alternative base case. The scenario analyses are limited in their exploration of alternative treatment options.
- Welsh prescribing data supports clinical expert opinion that sodium phenylbutyrate is mainly used in Wales as an unlicensed liquid (1 g/5 ml). The liquid is associated with a higher acquisition cost than Ravicti®; therefore, its exclusion has the potential to underestimate cost savings.

- The base case has been conducted assuming a patient demographic of 70 kg body weight with a body surface area of 1.6 $m^2$, combined with dosing guided by the lowest recommended daily dose for Ammonaps® (9.9 $g/m^2$/day). This is unlikely to capture the distribution of patient demographics in Wales and fails to take account of the varying dosing regimens for patients who switch and those who are naive to treatment. However, additional company analyses have explored these to some degree.
- The CMA is limited to consideration of medicine acquisition costs only. This does not facilitate consideration of wider NHS resource implications (e.g. costs associated with adverse events, monitoring, and administration), thereby limiting the scope of the analysis. The SPC states that in some cases Ravicti® must be used with dietary supplements. Likewise, the Ammonaps® SPC states that in some patients it should be combined with essential amino acid and carnitine supplementation[5]. It would have been beneficial to explore administration, monitoring and supplementary nutrition costs.

### 4.4 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC did not identify any studies relevant to the cost-effectiveness of Ravicti® versus Ammonaps® in the treatment of patients in the population of interest.

## 5.0 BUDGET IMPACT

### 5.1 Context and methods

The company has estimated that there will be six people with the targeted indication in Wales in Years 1 to 5. This is based on prevalence figures generated by an incidence-survival model, which was designed to estimate the prevalence of urea cycle disorders in the 0–17 year-old population in five European markets (France, Germany, Italy, Spain and the UK)[14]. To calculate the number of people who need treatment in Wales, the company has combined these prevalence estimates with incidence estimates of urea cycle disorders (also taken from the literature)[15] and a 2% mortality rate. The mortality rate is informed by ONS data for Wales[16]. Clinical expert interviews were also undertaken to identify the percentage of people with urea cycle disorders treatable under the license. An assumed market share of 100% in each year is further applied to estimate the number of people likely to be prescribed Ravicti® in Wales for the indication covered. No sensitivity analyses have been performed to explore the effects of varying market shares, dosing, rounding or alternative comparators.

### 5.2 Results

The budget impact is presented in Table 3. The company estimates that introducing Ravicti® would lead to an overall cost saving of [commercial in confidence figure removed] in Years 1 to 5. This estimate incorporates cost differences resulting from the displacement of Ammonaps® tablets only. No monitoring or adverse event costs are included in the analysis. No additional sensitivity analyses have been conducted.

**Table 3. Company-reported costs associated with use of Ravicti® for the treatment of urea cycle disorders**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Sub-population of eligible patients (indication under consideration)** | 6 | 6 | 6 | 6 | 6 |
| **Uptake of new medicine (%)** | ¶¶ | ¶¶ | ¶¶ | ¶¶ | ¶¶ |
| **Number of patients receiving new medicine allowing for discontinuations** | 6 | 6 | 6 | 6 | 6 |
| **Medicine acquisition costs in a market without new medicine** | £135,618 | £135,618 | £135,618 | £135,618 | £135,618 |
| **Medicine acquisition costs in a market with new medicine** | ¶¶ | ¶¶ | ¶¶ | ¶¶ | ¶¶ |
| **Net medicine acquisition costs (savings/costs) - including supportive medicines where applicable** | ¶¶ | ¶¶ | ¶¶ | ¶¶ | ¶¶ |
| ¶¶: commercial in confidence figure removed. | | | | | |

### 5.3 AWTTC critique

- The submission gives a transparent account of the methods and data sources used to estimate budget impact. The company has also factored mortality into the calculations.
- The analysis does not explore the impact of rounding, and is limited to the same comparator as the primary CMA (that is, it only includes Ammonaps® tablets). This limits the potential value of the analyses in facilitating informed decisions. Applying rounding to reflect the primary CMA results in higher annual cost savings of [commercial in confidence figure removed]. Given that unlicensed liquid formulations are in high use in Wales, higher cost savings could be actualised than those modelled.
- The prevalence figure of 1.71 per 100,000 used in the model was generated by an incidence-survival model, which was designed to estimate the prevalence of urea cycle disorders in the 0–17 year-old population in five European markets (France, Germany, Italy, Spain and the UK)[14]. The EMA reports a higher prevalence of 1.77 per 10,000 people[18].
- The budget impact considerations are limited to acquisition costs only; other resource use is not included (such as administration and monitoring costs, and costs associated with adverse events). This limits any exploration of wider costs and a more informative assessment of resource implications for the NHS.
- The prediction that all patients in Wales will be switched to Ravicti® has not been rationalised. Furthermore, the medicines used to calculate the effects of market share displacement are limited to Ammonaps® tablets. Therefore, these projections are possibly limited in scope. Further sensitivity analyses would have been beneficial to explore the impact of displacing other comparators used in Wales.

## 6.0 ADDITIONAL FACTORS TO CONSIDER

### 6.1 Medicines developed to treat rare diseases

The applicant company suggests Ravicti® should be considered as an orphan medicine. AWTTC considers Ravicti® eligible to be appraised as an ultra-orphan medicine. The medicine has European Medicines Agency designated orphan status due to the prevalence of the six urea cycle disorders being below the ceiling for orphan designation, 5 people in 10,000[17]. Welsh clinical expert opinion indicates that the full population of the licensed indication in Wales is below the ceiling for ultra-orphan status; 1 person in 50,000.

New Medicines Group (NMG) and AWMSG will consider additional criteria (see Table 4) if they consider new medicine is a medicine developed to treat a rare disease.

**Table 4. Evidence considered by NMG/AWMSG**

| NMG/AWMSG considerations | AWTTC comments |
|---|---|
| Severity of the disease | For patients with urea cycle disorders, early treatment and consistent ammonia control are important for maintaining intellectual function and preventing further neurologic damage. |
| Unmet need | The company suggests that Ravicti® will facilitate access to a taste-masked formulation with a reduced medicine volume; which could facilitate better dosing, compliance and outcomes. |
| Innovative nature of the medicine | Ravicti® is associated with reduced frequency of hyperammonaemic crises when compared with sodium phenylbutyrate. The liquid formulation has the potential to improve adherence to treatment, especially for children. |
| Societal impact on non-health benefits that may not adequately be captured in the QALY | This criterion is not applicable as the company has submitted a cost-minimisation analysis not a cost-utility analysis.<br><br>However, the company has identified the following potential benefits, which are not included in its analysis: reduced treatment burden, ease of administration, improved palatability and the potential for improved ammonia control. |
| Does the medicine cure or reverse rather than stabilise the condition? | The medicine stabilises but does not cure or reverse the condition. |
| AWMSG: All Wales Medicines Strategy Group; AWTTC: All Wales Therapeutics and Toxicology Centre; NMG: New Medicines Group; QALY: quality-adjusted life year | |

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