SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
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NHS SCOTLAND
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glycerol phenylbutyrate 1.1g/mL oral liquid (Ravicti®) SMC No 1342/18
Swedish Orphan Biovitrum Ltd

6 July 2018

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

glycerol phenylbutyrate (Ravicti®) is accepted for use within NHS Scotland.

Indication under review: For use as adjunctive therapy for chronic management of adult and paediatric patients ≥2 months of age with urea cycle disorders (UCDs) including deficiencies of carbamoyl phosphate synthase I (CPS), ornithine carbamoyltransferase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase I (ARG) and ornithine translocase deficiency hyperornithinaemia-hyperammonaemia homocitrullinuria syndrome (HHH) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. Glycerol phenylbutyrate must be used with dietary protein restriction and, in some cases, dietary supplements (e.g. essential amino acids, arginine, citrulline, protein-free calorie supplements).

Glycerol phenylbutyrate is non-inferior to sodium phenylbutyrate for control of blood ammonia levels in patients with UCDs.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of glycerol phenylbutyrate. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Published 13 August 2018

Indication

For use as adjunctive therapy for chronic management of adult and paediatric patients ≥2 months of age with urea cycle disorders (UCDs) including deficiencies of carbamoyl phosphate synthase I (CPS), ornithine carbamoyltransferase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), arginase I (ARG) and ornithine translocase deficiency hyperornithinaemia-hyperammonaemia homocitrullinuria syndrome (HHH) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. Glycerol phenylbutyrate must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements).[1]

Dosing Information

In phenylbutyrate-naïve patients the recommended starting dose of glycerol phenylbutyrate is 8.5 mL/m^2/day (9.4g/m^2/day) for patients with a body surface area (BSA) < 1.3m^2 and 7 mL/m^2/day (8 g/m^2/day) for patients with a BSA ≥ 1.3m^2
In patients switching from sodium phenylbutyrate the starting dose of glycerol phenylbutyrate should contain the same amount of phenylbutyric acid based on the conversions:
• Total daily dosage of glycerol phenylbutyrate (mL) = total daily dosage of sodium phenylbutyrate tablets (g) x 0.86
• Total daily dosage of glycerol phenylbutyrate (mL) = total daily dosage of sodium phenylbutyrate powder (g) x 0.81

The total daily dose of glycerol phenylbutyrate should be divided into equal amounts and given with each meal or feeding (e.g. three times to six times per day) either orally or by nasogastric or gastrostomy tube. Each dose should be rounded up to the nearest 0.5 mL.

The daily dose of glycerol phenylbutyrate should be individually adjusted according to the patient's estimated urea synthetic capacity, if any, protein tolerance and the daily dietary protein intake needed to promote growth and development. This is described in detail in the summary of product characteristics. The recommended total daily dose range of glycerol phenylbutyrate is 4.5 to 11.2 mL/m^2/day (5.3 to 12.4 g/m^2/day). Glycerol phenylbutyrate therapy may be required life-long unless orthotopic liver transplantation is elected.

Glycerol phenylbutyrate must be used with dietary protein restriction and sometimes dietary supplements (e.g. essential amino acids, arginine, citrulline, protein-free calorie supplements) depending on the daily dietary protein intake needed to promote growth and development.

Glycerol phenylbutyrate should be prescribed by a physician experienced in the management of UCDs.[1]

Product availability date

March 2018. Glycerol phenylbutyrate meets SMC orphan criteria.

Summary of evidence on comparative efficacy

Urea cycle disorders (UCD) are inherited deficiencies of enzymes or transporters necessary for the synthesis of urea from ammonia. They can be associated with accumulation of toxic ammonia levels. Glycerol phenylbutyrate is a prodrug hydrolysed by pancreatic lipases in the gastro-intestinal tract to phenylbutyric acid. Phenylbutyric acid is oxidised to phenylacetic acid, which binds to glutamine to form phenylacetylglutamine (PAGN). This provides an alternative pathway for removal of nitrogen through urinary excretion of PAGN.[2]

A double-blind phase III study (HPN-100-006) recruited adults aged at least 18 years with UCD including carbamoyl synthetase (CPS), ornithine transcarbamylase (OTC) and argininosuccinate synthetase (ASS) who had controlled ammonia levels (<100 micromol/L without signs and symptoms of hyperammonaemia) on a stable maintenance dose of sodium phenylbutyrate. They were randomised equally to sodium phenylbutyrate for 14 days followed by crossover to glycerol phenylbutyrate for 14 days or vice versa. Treatment was blinded by use of relevant placebos. The dose of glycerol phenylbutyrate was calculated to deliver the same dose of phenylbutyric acid as the patient's baseline sodium phenylbutyrate dose. The primary outcome was the 24-hour area-under-curve (AUC) for serum ammonia assessed in the intention-to-treat (ITT) population, defined as all randomised patients who received at least one dose of either study drug. The primary analysis assessed non-inferiority of glycerol phenylbutyrate compared with sodium phenylbutyrate using ratio of geometric means. If the upper limit of 95% confidence interval (CI) around this did not exceed 1.25 then non-inferiority was considered demonstrated.[2-5]

In the primary analysis the ratio (glycerol phenylbutyrate / sodium phenylbutyrate) of geometric means for 24-hour ammonia AUC was 0.91 (95% CI: 0.799 to 1.034). As the upper limit of the 95% CI did not exceed 1.25, non-inferiority of glycerol phenylbutyrate compared with sodium phenylbutyrate was considered demonstrated. Similar results, with no significant differences, were observed between the respective treatment groups for the secondary outcomes, mean blood ammonia maximum concentration (Cmax): 60.9 and 70.8 micromol/L; percentage of ammonia samples above the upper limit of normal (ULN): 36% and 36%; mean blood glutamine (which correlates with blood ammonia): 761.2 and 805.5 micromol/L; and mean 24-hour urinary excretion of PAGN (i.e. amount of nitrogen removed): 13.5g and 13.6g.[3-5]

Supportive evidence is from three open-label phase II studies, which recruited patients with UCD aged at least 18 years (in UP 1204-003),[6] at least six years but less than 18 years (in HPN-100-005)[7] and at least 29 days but less than six years (in HPN-100-012)[4]. Patients had controlled ammonia levels on stable doses of sodium phenylbutyrate and continued these after enrolment for one week within the studies of adult and children (aged at least six years) and for one day in the study of infants (aged less than six years). Then in all studies blood ammonium levels and pharmacokinetic parameters were assessed before patients crossed over to receive glycerol phenylbutyrate that would provide an equivalent dose of phenylbutyrate. Ammonia levels and pharmacokinetic parameters were re-assessed within the studies of adult and children (aged at least six years) after one week and in the study of infants (aged less than six years) after four to ten days. The studies were designed to characterise safety, ammonia control and pharmacokinetics. Data from these studies have been pooled with results from HPN-100-006 as shown in table 1.

In the pooled analysis, 24-hour blood ammonia pattern with glycerol phenylbutyrate compared with sodium phenylbutyrate was consistent with the individual studies. Post-prandial increases in mean blood ammonia levels were higher early in the day with glycerol phenylbutyrate (from 4 to 5 hours after dosing) and lower in the afternoon and overnight (from 6 to 12 hours after dosing) compared with sodium

phenylbutyrate treatment. The differences may be explained by differences in the pharmacokinetics of the two study treatments.[2]

Table 1: Results of phase II and III studies and pooled analyses.[2-7]

	HPN-100-006	UP-1204-003	HPN-100-005	HPN-100-012	Pooled
N	45	14	11	15	85
Ammonia 24-hour AUC ratio (glycerol PB/sodium PB) of geometric mean					
Ratio	0.91	0.63	0.78	0.79	0.84
95% CI	0.799, 1.034	0.361, 1.116	0.556, 1.095	0.593, 1.055	0.740, 0.949
p-value	0.315	0.084	0.054	0.033	0.002
PAGN mean 24-hour urinary excretion (g)					
Glycerol PB	13.5	10.8	12.5	-	13.3
Sodium PB	13.6	12.2	12.5	-	13.5
Ammonia mean percentage of samples greater than upper limit of normal (ULN)					
Glycerol PB	36	27	18	13	28
Sodium PB	36	43	31	38	37

N = number of patients; CI = confidence interval; glycerol PB = glycerol phenylbutyrate; sodium PB = sodium phenylbutyrate; PAGN = phenylacetylglutamine; AUC = area-under-curve; ULN = upper limit of normal, 35 micromol/L.

In one-year open-label extension studies (HPN-100-007, HPN-100-005E and HPN-100-012E) 51 adults and 49 children (26 children aged 6 to 17 years and 23 children aged less than six years) received glycerol phenylbutyrate. Effects on mean blood ammonia levels were maintained and these were within the therapeutic range at monthly visits. The rate of hyperammonaemic crises with glycerol phenylbutyrate prospectively reported within the controlled conditions of these clinical studies, 0.27 per patient year, was noted to be lower than that reported retrospectively during routine clinical practice in the preceding year when patients received sodium phenylbutyrate, 0.53 per patient year.[2]

Summary of evidence on comparative safety

The most robust comparative data were from the double-blind pivotal phase III study (HPN-100-006) where patients were randomised to receive glycerol phenylbutyrate and sodium phenylbutyrate over identical time periods of two weeks. There was also a pooled analysis of data from this study and the other short-term cross-over studies (UP-1204-003, HPN-100-005 and HPN-100-012), which were open-label. In two of these studies (UP-1204-003, HPN-100-005, which recruited adults and children aged at least six years) treatment durations of glycerol phenylbutyrate and sodium phenylbutyrate were identical (i.e. one week). However, in the study in young children aged less than six years (HPN-100-012) there was a difference in treatment duration of glycerol phenylbutyrate (nine days) versus sodium phenylbutyrate (one day). In the respective glycerol phenylbutyrate and sodium phenylbutyrate groups, adverse events were reported by 61% (27/44) and 51% (23/45) in the phase III study and by 54% (43/80) and 39% (33/85) in the pooled analysis. Across the pooled analyses there were no discontinuations from glycerol phenylbutyrate due to adverse events and two patients withdrew from sodium phenylbutyrate (one due to hyperammonaemic crisis related to noncompliance with diet and one patient due to high ammonia levels and headache on day one). Serious adverse events comprised these two patients in the sodium phenylbutyrate group plus one patient in the glycerol phenylbutyrate group who had acute gastroenteritis attributed to food poisoning.[2,4]

In the double-blind pivotal phase III study the most common adverse events were gastro-intestinal and within the respective glycerol phenylbutyrate and sodium phenylbutyrate groups were reported by 36% versus 29%. These included diarrhoea, 16% versus 6.7%; flatulence, 14% versus 2.2%; nausea, 2.3% versus 6.7%; vomiting, 6.8% versus 4.4%; abdominal discomfort, 0 versus 6.7%; abdominal pain, 6.8%

versus 4.4%; dyspepsia, 4.5% versus 6.7%; and oral discomfort, 0 versus 4.4%. Other common adverse events included headache, 14% versus 8.9% and decreased appetite, 6.8% versus 4.4%. In the pooled analyses of short-term cross-over studies gastrointestinal adverse events were also the most common in the respective glycerol phenylbutyrate and sodium phenylbutyrate groups: 30% versus 21%. These included diarrhoea, 8.8% versus 4.7%, flatulence, 8.8% versus 4.7%, nausea, 1.3% versus 8.2% and vomiting, 7.5% versus 3.5%. Other common adverse events included headache, 8.8% versus 4.7%.[2,4]

Summary of clinical effectiveness issues

Glycerol phenylbutyrate is the second medicine (after sodium phenylbutyrate) that is prodrug of phenylbutyric acid, which is used in the treatment of UCDs. Glycerol phenylbutyrate has been designated as an orphan medicinal product and meets SMC orphan criteria.[1,2]

UCDs are rare inherited deficiencies of enzymes or transporters necessary for the synthesis of urea from ammonia. They can be associated with accumulation of toxic ammonia levels. Although genetically distinct, UCDs share important clinical manifestations attributable to hyperammonaemia. Symptoms of hyperammonaemia can include seizures, cerebral oedema, hyperventilation, posturing and coma, loss of appetite, headache, cyclical vomiting, somnolence, lethargy, fatigue, disorientation, behavioural abnormalities, sleep disorders, delusions, hallucinations, psychosis, nausea. Management of the individual UCD subtypes is generally similar and involves decreasing ammonia production through reduction of protein in the diet, removal of excess ammonia via waste nitrogen scavenging drugs (e.g. sodium phenylbutyrate) and replacement of certain urea cycle intermediates.[2]

In the pivotal phase III study, which recruited adults, glycerol phenylbutyrate was non-inferior to sodium phenylbutyrate for control of blood ammonia levels as measured by 24-hour AUC. It was also associated with similar rates of blood ammonia greater than the ULN and comparable amounts of urinary nitrogen excretion assessed by 24-hour urinary PAGN. These data were supported by similar results in open-label phase II studies, which also included children, and in pooled analyses of these short-term studies. Maintenance of effects on blood ammonia levels was observed in one-year extension studies.[2]

The primary outcome of the pivotal phase III study may be regarded as a surrogate marker. However, control of blood ammonia levels is one of the main objectives of clinical management and has been shown to correlate to clinical outcome.[2]

The key limitation of the evidence base is lack of an active comparator in the long-term studies. In the absence of this the rate of hyperammonaemic crises reported prospectively with glycerol phenylbutyrate in the one-year extension studies was compared with the rate with sodium phenylbutyrate in clinical practice in the preceding year collected retrospectively. This has inherent limitations and does not provide robust evidence of comparative efficacy over the long-term.

The open-label design of the phase II crossover studies and difference in duration of treatment across the groups in one of the studies may limit the comparative safety data in the pooled analyses of short-term studies.

The majority of patients recruited to the short-term studies had the OTC subtype of UCD.[6,7] Subgroup analysis suggest a consistent effect on blood ammonia levels irrespective of UCD subtype (i.e. OTC versus non-OTC), although the small sample sizes should be noted.[4] The studies did not include patients who were naïve to sodium phenylbutyrate or patients with ammonia levels uncontrolled by their current dose of sodium phenylbutyrate and this may limit application of the results to these groups.

Clinical experts consulted by SMC consider that glycerol phenylbutyrate would provide an alternative to sodium phenylbutyrate, with some suggesting that it may be more palatable than existing formulations of sodium phenylbutyrate and has the potential to reduce pill burden and improve adherence. They note that it is unlikely to be associated with any service implications.

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis which compared glycerol phenylbutyrate against sodium phenylbutyrate tablets in patients with UCDs in the licensed indication.

The economic analysis used a simple model structure which focussed on calculating the cost per year of glycerol phenylbutyrate and sodium phenylbutyrate. Specifically the economic model estimated a dose per day for sodium phenylbutyrate tablets by assuming a patient weight of 70kg and a body surface area (BSA) of 1.6m^2, and then applied the dose conversion for glycerol phenylbutyrate (i.e. multiply the daily dose of sodium phenylbutyrate tablets by 0.86) to obtain a daily dose for glycerol phenylbutyrate. The dose per day for both medicines was subsequently multiplied by 365 to obtain the dose per year, and then the dose per year was multiplied by the relevant cost per mg or mL to obtain the yearly cost for glycerol phenylbutyrate and sodium phenylbutyrate tablets. It is also worth noting that the conversion factor used in the model (i.e. multiply the daily dose of sodium phenylbutyrate tablets by 0.86) reflects the rate used for patients switching from sodium phenylbutyrate, as opposed to naïve to sodium phenylbutyrate.

The clinical data used to support the comparative efficacy of glycerol phenylbutyrate and the comparator were based on pooled evidence from four short term (≤4 weeks) studies: UP-1204-003, HPN-100-005, HPN-100-006 and HPN-100-012.

Only medicine costs for glycerol phenylbutyrate and sodium phenylbutyrate were included in the economic model.

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland.

The base case results and selected sensitivity analyses are presented in tables 2 and 3 below:

Table 2: Base case cost-minimisation analysis results using the list price for glycerol phenylbutyrate

Comparator	Total cost	Incremental cost (glycerol phenylbutyrate vs. sodium phenylbutyrate)
Sodium phenylbutyrate Tablets	£22,779.50	-
Glycerol phenylbutyrate	£32,020.81	£9,241.31

Table 3: Selected sensitivity analysis using the list price for glycerol phenylbutyrate

Analysis	Incremental cost (glycerol phenylbutyrate vs. sodium phenylbutyrate)
Adult patients 60kg BSA approx. 1.48m^2	£8,547.04
Adult patients 90kg BSA approx. 1.82m^2	£10,513.16
Paediatric patients 30kg BSA approx. 1.05m^2	£6,067.53
Paediatric patients 10kg	£2,917.08
Comparison versus sodium phenylbutyrate granules	£13,328.42
Dose of sodium phenylbutyrate/m^2/day 11g (9.9g in base case)	£10,268.12
Dose of sodium phenylbutyrate/m^2/day 13g (9.9g in base case)	£12,135.05
Patients naïve to sodium phenylbutyrate	£3,177.54
Rounded dosing	£12,249.40

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision but as the PAS is commercial in confidence only the without-PAS figures can be presented. With the PAS, glycerol phenylbutyrate became a cost-effective treatment option.

The main weaknesses were

- The company did not present any subgroup analyses in the initial submission for adults or paediatric patients, or for patients naïve to sodium phenylbutyrate (which may require different dosing to those who switch from sodium phenylbutyrate). However the company subsequently provided additional sensitivity analyses upon request and the results are available in table 3 above.
- The economic model also used the tablet formulation of sodium phenylbutyrate (and not granules which has a separate conversion rate), and the dose of sodium phenylbutyrate reflected those who weigh more than 20kg and not less than 20kg. In addition, the BSA estimate and dose of sodium phenylbutyrate were not subject to sensitivity analysis in the initial submission presented by the company. However the submitting company presented further sensitivity analysis to address these issues and the results are also available in table 3.
- The daily dose of glycerol phenylbutyrate may be administered at meal times with each dose rounded to the nearest 0.5mL. However, the dose and costs used in the economics appeared to simply convert a dose of sodium phenylbutyrate into a dose of glycerol phenylbutyrate, without applying rounding to the dosing estimates. The company has provided a sensitivity analysis which included rounded dosing in the economic model and the results are presented in table 3 above. Following discussions at the SMC the company's dosing estimates which did not include rounding were preferred, as the rounded estimates may imply different strengths of the comparator medicines were being compared in the cost-minimisation analysis.

The Committee also considered the benefits of glycerol phenylbutyrate in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as glycerol phenylbutyrate is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and after application of the appropriate SMC modifiers, the Committee accepted glycerol phenylbutyrate for use in NHS Scotland.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Metabolic Support UK, which is a registered charity.
- Metabolic Support UK has received 2.6% pharmaceutical funding in the past two years, including from the submitting company.
- UCDs are complex inherited metabolic disorders with a wide spectrum of severity. Severely affected patients (with little to no enzyme function) need to be seen very regularly by a range of specialist teams including metabolic consultants, paediatricians, dieticians, speech and physiotherapists, social care etc. These patients are more likely to have learning difficulties. There are many common challenges to everyday life for people with UCDs and their carers. These range from difficulty in administering treatment, to physically attending lots of appointments, hospital admissions and worries about the future.
- Patients are managed on sodium phenylbutyrate along with dietary management. The patient group highlighted that sodium phenylbutyrate is reported by patients and carers to be extremely difficult to take/administer and involves taking unpalatable powder/large number of pills every day. Young children particularly suffer from sickness due to the taste and frequency of dose, as well as other effects such as a reduced appetite which leads to a struggle to ensure sufficient calories are taken.
- Ravicti® is a liquid medicine with little to no taste, which is taken orally three times per day. The patient group emphasised that the benefits of a palatable treatment, administered less often and in an easier format would be expected to have a very positive impact on UCD patients, their families and carers. They reported that some described the potential benefits as 'life changing'.

Additional information: guidelines and protocols

There were no relevant guidelines.

Additional information: comparators

Sodium phenylbutyrate, which is also a prodrug of phenylbutyric acid, is available as Ammonaps® tablets and granules[8,9] and Pheburane® granules[10].

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Glycerol phenylbutyrate (oral liquid) Ravicti®	**3mL to 5.5mL three times daily (i.e. 9.9 to 18.15g daily)**	**21,091 to 38,640**
Sodium phenylbutyrate (tablets) Ammonaps®	21 to 38 (500mg) tablets daily (i.e. 10.5 to 19g daily)	15,074 to 27,277
Sodium phenylbutyrate (granules) Ammonaps®	11 to 20g of granules daily (i.e. 10.34 to 18.8g daily)	12,945 to 23,537
Sodium phenylbutyrate (granules) Pheburane®	21.5 to 40g of granules daily (i.e. 10.4 to 19.3g daily)	14,887 to 27,679

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 3 March 2018 and MIMS. Costs do not take any patient access schemes into consideration. The dose ranges provide approximate molar equivalents of phenylbutyric acid. A molar equivalent conversion factor for 0.95 was used to convert sodium phenylbutyrate (grams) to glycerol phenylbutyrate (grams). A sample dose range of glycerol phenylbutyrate was used, with the lower end corresponding approximately to the dose for a patient with a body surface area of 1.8m^2 given a dose at the lower end of the recommended range (i.e. 4mL or 5.3g/m^2/day) and the upper end corresponding approximately to the phenylbutyric acid molar equivalent of the maximum recommended daily dose of sodium phenylbutyrate (i.e. 20g). Each gram of Ammonaps® granules contains 940mg of sodium phenylbutyrate. Each gram of Pheburane® granules contains 483mg of sodium phenylbutyrate. Each mL of Ravicti® oral liquid contains 1.1mg of glycerol phenylbutyrate.

Additional information: budget impact

The company estimated there would be 12 patients eligible for treatment in year 1 rising to 17 in year 5. The uptake rates were 50% (5 patients) in year 1 rising to 75% (12 patients) in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to allow estimation of the predicted budget with the PAS.

*Other data were also assessed but remain commercially confidential.**

References

1. Swedish Orphan Biovitrum Ltd. Summary of product characteristics for glycerol phenylbutyrate (Ravicti®), last updated 13 March 2018.

2. European Medicines Agency. European public assessment report for glycerol phenylbutyrate (Ravicti®), Committee for Medicinal Products for Human Use (CHMP) assessment report, EMA/676925/2015, 24 September 2015.

3. Diaz GA, Krvitzky LS, Mokhtarani M, et al. Ammonia control and neurocognitive outcome among urea cycle disorder patients treated with glycerol phenylbutyrate. Hepatol 2013; 57: 2171-2179.

4. US Food and Drug Administration. Medical review of glycerol phenylbutyrate (Ravicti®)

5. US Food and Drug Administration. Statistical review of glycerol phenylbutyrate (Ravicti®)

6. Lee B, Rhead W, Diaz GA, et al. Phase 2 comparison of a novel ammonia scavenging agent with sodium phenylbutyrate in patients with urea cycle disorders: safety, pharmacokinetics and ammonia control. Mol Gen Metabol 2010; 100; 221-8.

7. Lichter-U, Diaz GA, Merritt JL, et al. Ammonia control in children with urea cycle disorders (UCDs): phase 2 comparison of sodium phenylbutyrate and glycerol phenylbutyrate. Mol Gen Metabol 2011; 103: 323-9.

8. Swedish Orphan Biovitrum Ltd. Summary of product characteristics for sodium phenylbutyrate tablets (Ammonaps®), last updated 19 December 2016.

9. Swedish Orphan Biovitrum Ltd. Summary of product characteristics for sodium phenylbutyrate granules (Ammonaps®), last updated 19 December 2016.

10. Lucane Pharma Ltd. Summary of product characteristics for sodium phenylbutyrate granules (Pheburane®).

This assessment is based on data submitted by the applicant company up to and including 10 May 2018.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts

a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.