21 April 2017  
EMA/CHMP/404487/2017  
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

**Ucedane**

International non-proprietary name: carglumic acid

Procedure No. EMEA/H/C/004019/0000

**Note**

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>Acq.</td>
<td>acquisition</td>
</tr>
<tr>
<td>AMS</td>
<td>analytical method summary</td>
</tr>
<tr>
<td>ASMF</td>
<td>Active Substance Master File = Drug Master File</td>
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<tr>
<td>Base.</td>
<td>baseline</td>
</tr>
<tr>
<td>BLQ</td>
<td>below the limit of quantitation</td>
</tr>
<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human use</td>
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<tr>
<td>Conc.</td>
<td>concentration</td>
</tr>
<tr>
<td>cps</td>
<td>counts per second</td>
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<tr>
<td>CV</td>
<td>coefficient of variation (%)</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
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<tr>
<td>%Dev</td>
<td>percent deviation</td>
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<tr>
<td>Da</td>
<td>dalton</td>
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<tr>
<td>EC</td>
<td>European Commission</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>HPLC</td>
<td>High performance liquid chromatography</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
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<tr>
<td>ID</td>
<td>identification</td>
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<tr>
<td>Int.</td>
<td>integration</td>
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<tr>
<td>IR</td>
<td>infrared</td>
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<tr>
<td>IS</td>
<td>internal standard</td>
</tr>
<tr>
<td>ISR</td>
<td>incurred sample reanalysis</td>
</tr>
<tr>
<td>LC/MS/MS</td>
<td>liquid chromatography with tandem mass spectrometry</td>
</tr>
<tr>
<td>LIMS</td>
<td>laboratory information management system</td>
</tr>
<tr>
<td>LLOQ or LOQ</td>
<td>lower limit of quantitation</td>
</tr>
<tr>
<td>LOD</td>
<td>Loss on Dryying</td>
</tr>
<tr>
<td>µL</td>
<td>microliter</td>
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<td>µm</td>
<td>micron</td>
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<td>min</td>
<td>minute</td>
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<td>Min.</td>
<td>minimum</td>
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<td>mL</td>
<td>milliliter</td>
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<td>mm</td>
<td>millimeter</td>
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<td>n, No., or #</td>
<td>number</td>
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<tr>
<td>NA or N/A</td>
<td>not applicable</td>
</tr>
<tr>
<td>ng</td>
<td>nanogram</td>
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<td>P</td>
<td>period</td>
</tr>
<tr>
<td>Ph.Eur</td>
<td>European Pharmacopoeia</td>
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<td>PLM</td>
<td>plasma</td>
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<td>QC</td>
<td>quality control</td>
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<td>Resp.</td>
<td>response</td>
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<tr>
<td>RT</td>
<td>retention time</td>
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<td>S.D.</td>
<td>standard deviation</td>
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<td>sec</td>
<td>second</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>SOP</td>
<td>standard operating procedure</td>
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<tr>
<td>Split.</td>
<td>splitting</td>
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<td>SRM</td>
<td>selected reaction monitoring</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>STD or Std</td>
<td>calibration standard</td>
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<tr>
<td>Sub.</td>
<td>Subtraction</td>
</tr>
<tr>
<td>TAMC</td>
<td>Total Aerobic Microbial Count</td>
</tr>
<tr>
<td>TYMC</td>
<td>Total combined Yeasts/Moulds Count</td>
</tr>
<tr>
<td>Temp</td>
<td>temperature</td>
</tr>
<tr>
<td>ULOQ</td>
<td>upper limit of quantification</td>
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<tr>
<td>V or v</td>
<td>version</td>
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</table>
1. Background information on the procedure

1.1. Submission of the dossier

The applicant Lucane Pharma submitted on 25 April 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Ucedane, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004 – ‘Generic of a Centrally authorised product’. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 May 2014.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC, and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication: treatment of hyperammonaemia due to N-acetylglutamate synthase primary deficiency.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC); Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Carbaglu instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Carbaglu, 200 mg, Dispersible tablet
- Marketing authorisation holder: Orphan Europe S.A.R.L.
- Date of authorisation: 24/01/2003
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number: EU/1/02/246/001, EU/1/02/246/002 and EU/1/02/246/003

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Carbaglu, 200 mg, Dispersible tablet
- Marketing authorisation holder: Orphan Europe S.A.R.L.
- Date of authorisation: 24/01/2003
- Marketing authorisation granted by:
Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Carbaglu, 200 mg, Dispersible tablet
- Marketing authorisation holder: Orphan Europe S.A.R.L.
- Date of authorisation: 24/01/2003
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number: EU/1/02/246/001, EU/1/02/246/002 and EU/1/02/246/003
- Bioavailability study number(s): LUC06-BIOEQ-2013

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Eleftheria Nikolaidi    Co-Rapporteur: N/A

- The application was received by the EMA on 25 April 2016.
- The procedure started on 19 May 2016.
- The Rapporteur’s first Assessment Report was circulated to all CHMP members on 18 August 2016. The PRAC Rapporteur’s first Assessment Report was circulated to all PRAC members on 19 August 2016.
- During the meeting on 15 September 2016, the CHMP agreed on the consolidated List of Questions to
be sent to the applicant.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 December 2016.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 30 January 2017.
- During the PRAC meeting on 9 February 2017 the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 23 February 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 22 March 2017.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 6 April 2017.
- During the meeting on 21 April 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Ucedane.

2. **Scientific discussion**

2.1. **Introduction**

**About the product**

The proposed product is an immediate release 200 mg dispersible tablets containing carglumic acid as active substance. Carglumic acid is a chemical substance and the dosage form has been developed as generic product to the centrally authorised product Carbaglu 200 mg dispersible tablets containing the same active substance in the same pharmaceutical form.

Carglumic acid (also called N-carbamyl-L-glutamate, or carbamylglutamate) is an orally active deacetylase-resistant synthetic structural N-acetylglutamate (NAG) analogue. NAG, which is formed by the hepatic enzyme N-acetylglutamate synthase (NAGS), is an essential allosteric activator of the enzyme carbamoyl phosphate synthetase 1 (CPS-1). CPS-1 plays an essential role in the urea cycle and converts ammonia into urea which prevents hyperammonaemia. Despite a lower affinity of carbamoyl phosphate synthetase for carglumic acid than for N-acetylglutamate, carglumic acid has been shown in vivo to stimulate carbamoyl phosphate synthetase and to be much more effective than N-acetylglutamate in protecting against ammonia intoxication in rats.

Upon oral administration, Carglumic acid is taken up enterally and replaces NAG in the activation of CPS-1, thus being the definitive therapy for NAGS deficiency (Häberle, 2012; PubChem, 2015).

This application for marketing authorisation is a generic application for Ucedane 200 mg, dispersible tablets, and included a hybrid application for Ucedane 50 mg, dispersible tablets according to Articles 10(1) and 10(3) of Directive 2001/83/EC as amended.
Carglumic acid was first authorised in the EU as Carbaglu dispersible tablets in January 2003. At the time of approval Carbaglu was indicated for the treatment of hyperammonaemia associated with N-acetylglutamate synthase deficiency.

Subsequently, the approved indications for Carbaglu have been extended and is now also authorised for the treatment of hyperammonaemia due to, isovaleric acidaemia, methymalonic acidaemia, or propionic acidaemia.

Ucedane is indicated in treatment of hyperammonaemia due to N-acetylglutamate synthase primary deficiency.

**Proposed posology and method of administration for Ucedane**

**Posology**

Based on clinical experience, the treatment may be started as early as the first day of life. The initial daily dose should be 100 mg/kg, up to 250 mg/kg if necessary.

It should then be adjusted individually in order to maintain normal ammonia plasma levels (see section 4.4).

In the long term, it may not be necessary to increase the dose according to body weight as long as adequate metabolic control is achieved; daily doses range from 10 mg/kg to 100 mg/kg.

**Carglumic acid responsiveness test**

It is recommended to test individual responsiveness to carglumic acid before initiating any long term treatment. As examples:

- In a comatose child, start with a dose of 100 to 250 mg/kg/day and measure ammonia plasma concentration at least before each administration; it should normalise within a few hours after starting Ucedane.

- In a patient with moderate hyperammonaemia, administer a test dose of 100 to 200 mg/kg/day for 3 days with a constant protein intake and perform repeated determinations of ammonia plasma concentration (before and 1 hour after a meal); adjust the dose in order to maintain normal ammonia plasma levels.

**Method of administration**

This medicine is for oral use ONLY (ingestion or via nasogastric tube using a syringe, if necessary).

Based on pharmacokinetic data and clinical experience, it is recommended to divide the total daily dose into two to four intakes to be given before meals or feedings. The breaking of the tablets in halves allows most of the required posology adjustments. It is not possible to administer Ucedane to patients who require dose adjustments of 50 mg. In such cases, other carglumic acid products which allow for these dose adjustments should be used.

The tablets must be dispersed in a minimum of 5-10 mL of water and ingested immediately or administered by fast push through a syringe via a nasogastric tube.

**Type of Application and aspects on development**

The initial application for marketing authorisation was a generic application for Ucedane 200 mg, dispersible tablets, but also included a hybrid application for Ucedane 50 mg, dispersible tablets according to Articles
10(1) and 10(3) of Directive 2001/83/EC as amended. During the procedure the Applicant decided to withdraw the hybrid application for Ucedane 50 mg dispersible tablets.

The reference medicinal product is Carbaglu 200mg tablets by the company Orphan Europe S.A.R.L., originally authorised in the community on 24 January 2003 (marketing authorisation numbers EU/1/02/246/001, EU/1/02/246/002 and EU/1/02/246/003).

Bioequivalence with the product Carbaglu 200mg tablets by the company Orphan Europe S.A.R.L. is claimed. The CHMP Guidelines were followed. The applicant did not receive CHMP Scientific Advice pertinent to the clinical investigation.

### 2.2. Quality aspects

#### 2.2.1. Introduction

The finished product is presented as dispersible tablets containing 200 mg of carglumic acid as active substance.

Other ingredients are microcrystalline cellulose, mannitol, colloidal anhydrous silica, sodium stearyl fumarate, crospovidone type B, copovidone K28.

The product is available in blisters (aluminium/aluminium) packed in cartons as described in section 6.5 of the SmPC.

#### 2.2.2. Active substance

**General information**

The chemical name of the active substance, carglumic acid, is N-Carbamyl-L-glutamic acid corresponding to the molecular formula $C_6H_{10}N_2O_5$.

It has a relative molecular mass 190.16 g/mol and the following structure:

**Figure 1.** Structure of carglumic acid

The molecular structure of carglumic acid was confirmed by proton nuclear magnetic resonance spectroscopy, carbon-13 nuclear magnetic resonance spectroscopy, mass spectrometry with fragmentation study, infrared spectrometry and elemental analysis.
Carglumic acid exists as a white powder or colourless crystals. It is soluble in boiling water, slightly soluble in cold water and practically insoluble in organic solvents (cyclohexane, dichloromethane, ether). The water solubility of carglumic acid at pH 2.0 is 21.0 g/L. It increases rapidly between the pH 3.0 (28.2 g/L) and the pH 5.0 (440.9 g/L). The solubility of carglumic acid in water is stable between pH 6.0 (555.5 g/L) and pH 8.0 (553.9 g/L).

Carglumic acid is prepared from L-glutamic acid. It exhibits stereoisomerism due to the presence of one chiral centre and has one optical isomer; N-carbamoyl-D-glutamic acid. The enantiomeric purity of carglumic acid is controlled routinely by specific optical rotation and chiral HPLC tests.

Polymorphism has not been observed for carglumic acid. Polymorphism studies showed there is no enantiotropic polymorphism of carglumic acid and the crystal structure is orthorhombic. This has been confirmed by X-ray analyses.

**Manufacture, characterisation and process controls**

Information on the manufacture of the active substance was provided via an ASMF procedure. Carglumic acid is synthesized from a commercially available well defined starting material with acceptable specifications.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. The packaging components comply with the EC directive 2002/72/EC and EC 10/2011, as amended, and Ph. Eur. requirements.

**Specification**

The active substance specification includes tests for appearance, identification (IR, HPLC), specific optical rotation (Ph. Eur.), melting point (Ph. Eur.), pH (Ph. Eur.), loss on drying (Ph. Eur.), residue on ignition (Ph. Eur.), heavy metals (Ph. Eur.), D-enantiomer of carglumic acid (HPLC), related substances/impurities (HPLC) and assay (HPLC).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for 3 production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

**Stability**

Stability data on 3 production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for 36 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The following parameters were tested; appearance, identity (IR, HPLC), loss on drying (Ph. Eur.), related substances/impurities (HPLC), D-enantiomer of carglumic acid (HPLC) and assay (HPLC). The analytical
methods used were the same as for release and were stability indicating. All tested parameters were within the specifications.

Results of forced degradation studies performed under stress conditions (in acid medium, alkaline medium, and after exposure to oxidation, light and heat in dry or wet conditions) were also provided on one batch. The results show that carglumic acid is mainly sensitive to acidic medium and heat and moderately sensitive to oxidation when dissolved in water. The resolution of the peak of carglumic acid and its degradation products was satisfactory. The peak purity of carglumic acid was good in every condition and time. The results confirm the HPLC method for purity test and assay of carglumic acid is specific and stability indicative.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months when stored in the proposed container in climatic zones I and II.

### 2.2.3. Finished medicinal product

**Description of the product**

Ucedane dispersible tablets contain 200 mg of carglumic acid.

The tablets are white, oval and biconvex with score line and engraving LL on one side.

Other ingredients are microcrystalline cellulose, mannitol, colloidal anhydrous silica, sodium stearyl fumarate, crospovidone type B, copovidone K28.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report. The final excipients chosen for Ucedane dispersible tablets are different to those of the reference product (Carbaglu), but this is not expected to have a significant impact on the performance of the finished product.

<table>
<thead>
<tr>
<th>Ucedane dispersible tablets</th>
<th>Carbaglu dispersible tablets</th>
</tr>
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<tbody>
<tr>
<td>microcrystalline cellulose</td>
<td>microcrystalline cellulose</td>
</tr>
<tr>
<td>mannitol</td>
<td>sodium laurilsulfate</td>
</tr>
<tr>
<td>crospovidone type B</td>
<td>hypromellose</td>
</tr>
<tr>
<td>copovidone K 28</td>
<td>croscarmellose sodium</td>
</tr>
<tr>
<td>colloidal anhydrous silica</td>
<td>silica colloidal anhydrous</td>
</tr>
<tr>
<td>sodium stearyl fumarate</td>
<td>sodium stearyl fumarate</td>
</tr>
</tbody>
</table>

The formulation and manufacturing process were developed following a step-wise approach aimed at optimising the choice of excipients, the blending steps, the choice of tableting punches, the choice of tableting machine, the breaking strength of the tablets and the scale up to production scale.
In order to be able to deliver appropriate incremental doses to patients it was decided to develop two separate tablet strengths, 200 mg and 50 mg. The proposed Ucedane 200 mg tablets were white, oval and biconvex with score line and engraving LL on one side and the Ucedane 50 mg tablets were white, round and biconvex, with engraving L on one side.

An open-label, two-way cross-over bioequivalence study was performed to compare the pharmacokinetic profile of a single oral dose of Ucedane 200 mg dispersible tablet (test product) with a single oral dose of Carbaglu 200 mg dispersible tablet (reference product). For details of the clinical assessment of this bioequivalence study please refer to section 2.4 of this report.

Comparative dissolution profile testing between Ucedane 200 mg dispersible tablets and Carbaglu 200 mg dispersible tablets used in the bioequivalence study using dissolution medium with various pH values (0.1 N HCl, pH 4.5, pH 6.8) was requested by CHMP and subsequently provided by the applicant. The dissolution profiles of the two products were similar at pH 4.5 and 6.8, as more than 85% was dissolved within 15 minutes for both products. At pH 1.2, more than 85% in average was dissolved within 15 minutes for both products but some individual values were less than 85% at 15 minutes for the reference product. As the bioequivalence study submitted by the Applicant demonstrated the bioequivalence of the two products, it was concluded that the minor observed difference in dissolution profiles of the two products at pH 1.2 did not have any impact on bioavailability and was therefore acceptable.

In parallel to the generic application for Ucedane 200 mg dispersible tablets, the applicant initially proposed the additional strength, Ucedane 50 mg dispersible tablet, as a hybrid application under Article 10(3) of Directive 2001/83/EC, supported by a biowaiver of strength. The hybrid application for Ucedane 50 mg dispersible tablets was subsequently withdrawn by the Applicant before the procedure was finalised.

The Applicant demonstrated that the scoreline on Ucedane 200 mg dispersible tablets allows the tablet to be divided into equal halves (containing 100 mg carglumic acid). The proposed finished product specification includes a routine test for compliance with the Ph. Eur. subdivision of tablets test described in the Tablets monograph (0478).

Following withdrawal of the hybrid application for Ucedane 50 mg dispersible tablets, the applicant proposed that a 50 mg dose could be obtained from a Ucedane 200 mg dispersible tablet either with the help of a knife or a tablet splitter. The CHMP concluded that use of knife or tablet splitter is not considered an appropriate approach for accurate dosing in clinical practice, and that the posology of Ucedane 200 mg dispersible tablets should therefore not include any reference to a 50 mg dose. Nevertheless, in the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends that the applicant should consider performing further pharmaceutical development studies in order to design a product which can deliver a dosing posology of 50 mg increments (e.g. additional score lines on the Ucedane 200 mg tablet to facilitate further subdivision of the tablet halves or development of a separate 50 mg strength of Ucedane dispersible tablets). For details of the clinical assessment of this aspect please refer to section 2.4 of this report.

In order to demonstrate the discriminatory power of the routine QC dissolution method, formulations differing significantly in composition (disintegrant and binder contents) and active substance particle size were tested, however the discriminatory power of the dissolution method could not be demonstrated, despite selecting dissolution conditions that favour discriminatory power (e.g. low pH, stirring speed, earlier sample timepoint). It was concluded that this is probably a consequence of the relatively high solubility and dissolution rate of carglumic acid. The proposed conditions of the dissolution test method were therefore
accepted, in line with the Reflection paper on the dissolution specification for generic oral immediate release products (EMA/332805/2016).

The primary packaging is an aluminium/aluminium blister of 12 tablets per strip. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

**Manufacture of the product and process controls**

The manufacturing process consists of the following main steps:

- preparation of the bulk mixture of active substance and excipients (weighing, sieving and blending steps);
- tableting (compression step);
- packaging (blister packing step).

The process is considered to be a standard manufacturing process. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. Process validation was carried out on three batches at commercial scale. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

**Product specification**

The finished product release specifications include appropriate tests for this kind of dosage form; appearance, identification (IR, HPLC), dissolution (Ph. Eur.), related substances/impurities (HPLC), assay (HPLC), uniformity of dosage units (Ph. Eur.), fineness of dispersion (Ph. Eur.), breakability (Ph. Eur.), disintegration (Ph. Eur.) and microbiology (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The proposed acceptance criteria have been adequately justified the applicant and are in compliance with relevant scientific guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 3 production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

**Stability of the product**

Stability data of 3 batches of finished product stored under long term conditions for 24 months at 30 ºC / 65% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. These validation batches of Ucedane are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for routine stability tests of appearance, dissolution (Ph. Eur.), related substances/impurities (HPLC), assay (HPLC), fineness of dispersion (Ph. Eur.), disintegration (Ph. Eur.) and microbiology (Ph. Eur.). In addition, these validation batches were also tested for uniformity of mass (Ph. Eur.), breakability (Ph. Eur.), breaking strength (Ph. Eur.) and loss on drying (LOD). The analytical procedures used were stability indicating.
In addition to these studies, one batch was exposed to freezing conditions (-20°C for 1 month) and high temperature (60°C ± 5°C for 4 days). The provided results comply with the specifications in all studies and no significant changes have been observed.

Based on the available stability data, the proposed shelf-life of 36 months with no special storage conditions as stated in the SmPC (section 6.3) are acceptable.

*Adventitious agents*

No excipients derived from animal or human origin have been used.

**2.2.4. Discussion on chemical, and pharmaceutical aspects**

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

**2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects**

The quality of Ucedane 200 mg dispersible tablets is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

**2.2.6. Recommendation(s) for future quality development**

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant should consider performing further pharmaceutical development studies in order to design a product which can deliver a dosing posology of 50 mg increments (e.g. additional score lines on the Ucedane 200 mg tablet to facilitate further subdivision of the tablet halves or development of a separate 50 mg strength of Ucedane dispersible tablets).

**2.3. Non-clinical aspects**

**2.3.1. Introduction**

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.
2.3.2. Ecotoxicity/environmental risk assessment

The applicant did not submit a complete Environmental Risk Assessment. This was justified by the applicant as the introduction of Ucedane manufactured by Lucane Pharma is considered unlikely to result in any significant increase in the combined sales volumes for all carglumic acid containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

Nevertheless, a Phase I evaluation was performed to assess the potential environmental exposure of carglumic acid.

The log Kow value of carglumic acid of -1.097 as provided in the material safety data sheet (Sigma-Aldrich) is below the threshold of 4.5, as stipulated in the *EMA Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/44609/2010)*. Therefore, the applicant considered that screening for persistence, bioaccumulation and toxicity was not needed in this Phase I study.

The results of this study are summarised in Table 2.

**Table 2. Summary of main study results**

<table>
<thead>
<tr>
<th>Substance (INN/Invented Name):</th>
<th>Carglumic acid/Ucedane</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS-number:</td>
<td>1188-38-1</td>
</tr>
<tr>
<td><strong>Phase I</strong></td>
<td></td>
</tr>
<tr>
<td>Calculation</td>
<td>Value</td>
</tr>
<tr>
<td>PEC surfacewater, refined (e.g. prevalence, literature)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

2.3.3. Discussion on non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

A valid justification for not submitting a full ERA was given. The estimated PECsurfacewater of 0.001 µg/L for carglumic acid in UCEDANE 200 mg, dispersible tablets is approximately 10-fold below the action limit of 0.01 µg/L as defined in the *'EMA Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use(EMA/CHMP/SWP/44609/2010)'* and thus it was agreed that no further evaluation of the environmental toxicity is needed.

2.3.4. Conclusion on the non-clinical aspects

The CHMP agreed that there are no objections to approval of Ucedane from a non-clinical point of view.
2.4. Clinical aspects

2.4.1. Introduction

This is an application for tablets containing carglumic acid. To support the marketing authorisation application the applicant conducted bioequivalence study with a cross-over design under fasting conditions. This study was the pivotal study for the assessment.

In the initial application, which included a hybrid application for an additional strength of 50 mg tablets, the applicant claimed that a bioequivalence study would not be required as the general biowaiver criteria for the new strength were met. The CHMP however considered that the applicant would have to provide appropriate in vitro dissolution data, and also demonstrate linear pharmacokinetics between the two strengths. The applicant elected not to pursue this and instead chose to withdraw the hybrid application for the 50 mg tablets.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the EMA Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1 Cor**) as well as the EMA Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09), the EMA Carglumic acid dispersible tablets 200 mg product-specific bioequivalence guidance (EMEA/CHMP/315238/2014) and Question number 10 of the Questions & Answers: Positions on specific questions addressed to the Pharmacokinetics Working Party EMEA/618604/2008 Rev13 are of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study.

Table 3. Tabular overview of clinical studies

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Study Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUC06-BIOEQ-2013</td>
<td>An Open-Label, Two-Way Cross-Over Bioequivalnace Study to Compare The Pharmacokinetic Profile Of A Single Oral Dose of LUC-06 (Carglumic Acid) Tablet With A Single Oral Dose Of Carbaglu® (Reference Carglumic Acid) Tablet</td>
</tr>
</tbody>
</table>
2.4.2. Pharmacokinetics

Methods

This was a single oral dose, randomised, open-label, two-way cross-over, bioequivalence study in healthy male and female subjects conducted at a single study centre in the EU. Subjects were randomised to one of two treatment sequences (AB or BA) and received Treatment A (test) and Treatment B (reference) in two different treatment periods (Treatment Period 1 and Treatment Period 2).

Study design

This was a single oral dose, randomised, open-label, two-way cross-over, bioequivalence study in healthy male and female subjects conducted at a single study centre in the EU. Subjects were randomised to one of two treatment sequences (AB or BA) and received Treatment A and Treatment B in two different treatment periods (Treatment Period 1 and Treatment Period 2).

The study consisted of screening (Day -28 to Day -2; 28 days before Treatment Period 1 Day -1); Treatment Period 1 (admission on the morning of Day -1, study medication administration on Day 1, and discharge on Day 3); Treatment Period 2 (admission on Day -1, study medication administration on Day 1, and discharge on Day 3); and follow-up (5 to 10 days after discharge from Treatment Period 2). Treatment Periods 1 and 2 were separated by a wash-out period of at least 7 days up to a maximum of 14 days.

Test and reference products

Ucedane 200mg water-dispersible oral tablet manufactured by LUCANE PHARMA (batch No CPM8317) has been compared to Carbaglu 200mg water-dispersible oral tablet manufactured by Orphan Europe SARL (Batch No: CBC1402).

Population(s) studied

Healthy adult male and female subjects, who had given signed and dated written informed consent, aged 18 to 45 years (both inclusive) with a body mass index of 18 to 28 kg/m2 (both inclusive) and weighing at least 50 kg were included in the study.

Subject disposition is summarised in Figure 2.

In total, 18 subjects were screened and enrolled into the study. All 18 subjects completed the study. All 18 subjects were included in both the PK population as well as the Safety population.

Mean (range) age of subjects was of 30 years (20 to 41). Mean (range) weight and BMI of subjects were 69.2 kg (52.3 to 88.5) and 23.48 kg/m2 (23.12 to 27.47), respectively.
**Analytical methods**

The extracted samples were analyzed for Carglumic acid by LC-MS/MS. The quantitative analysis of the samples was carried out with interpolation of data into the linear regression calibration curve.

The calibration curve for Carglumic acid have been constructed between peak area ratios of analytical to internal Standard (N-Carbamyl-L-Glutamic 1,2-13C2 Acid), and their concentration levels.

A bioanalytical report entitled “Quantitative Determination of LUC-06 in Human Plasma from Study LUC06-BIOEQ-2013 Using Turbo Ion Spray LC/MS/MS” was submitted by the applicant. The objective of this study was to determine LUC-06 concentrations in 612 samples and to perform incurred sample reanalysis (ISR). Repeat analyses were conducted for 20 samples for LUC-06. In accordance with the protocol at least two-thirds of the re-assayed values were within 20.0% of the original result, based on the % Difference between the repeat analysis result and the mean of the two results.

Long term stability of carglumic acid in biological matrix at -70°C was proven for a period that spanned the time from the first study sample collection to the completion of study sample analysis.

**Pharmacokinetic variables**

Blood samples for the determination of carglumic acid in plasma were obtained at pre-determined time points up to 48 hours post-dose in each treatment period. The plasma concentration-time data were used to calculate the following pharmacokinetic (PK) parameters using non-compartmental methods: maximum observed concentration (Cmax), time to maximum observed concentration (tmax), area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUC(0-t)), the area under the plasma concentration-time curve from time zero to time extrapolated to infinity (AUC(0-inf)), and apparent terminal half-life (t1/2).
**Statistical methods**

Plasma carglumic acid concentrations and PK parameters were summarised by treatment using descriptive statistics and graphical presentations.

Bioequivalence between treatments (LUC-06 as a 200 mg water dispersible tablets [test] and Carbaglu as a 200 mg water dispersible tablets [reference]) was assessed using analysis of variance on log-transformed AUC(0-t) and Cmax.

The 90% confidence intervals (CI) for the ratio of geometric least squares means of test and reference treatments were calculated for the natural log-transformed values of Cmax and AUC(0-t) for carglumic acid. Bioequivalence was to be concluded if these 90% CI fell within 80.00% to 125.00%.

The analysis described above for AUC(0-t) and Cmax were repeated for AUC(0-inf). However, no conclusions were to be drawn with regard to bioequivalence from this analysis on AUC(0-inf).

To determine the bioequivalence of LUC-06 (test) and Carbaglu® 200 mg water dispersible tablets (reference) the following assumptions were made.

Assuming an intra-subject variability as 30% and inter-subject CV as 19% in AUC, and no difference between the test and reference treatments in true geometric means, 16 completing subjects in total in a cross over design would yield 80% power to conclude equivalence for AUC under the standard criteria for PK bioequivalence (90% CI for ratio of geometric means contained within the 80% to 125% interval). To account for an assumed 10% early withdrawal rate, 18 subjects were to be enrolled.

**Results**

The results of the bioequivalence study LUC06-BIOEQ-2013 are presented in Tables 4, 5 and 6.

**Table 4.** Pharmacokinetic parameters for carglumic acid (non-transformed values) in Study LUC06-BIOEQ-2013

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Summary Statistics</th>
<th>n</th>
<th>Treatment A</th>
<th>n</th>
<th>Treatment B</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>Mean (SD)</td>
<td>18</td>
<td>370 (138)</td>
<td>18</td>
<td>347 (114)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;(0-t)&lt;/sub&gt; (ng*h/mL)</td>
<td>Mean (SD)</td>
<td>18</td>
<td>3100 (962)</td>
<td>18</td>
<td>3030 (929)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;(0-inf)&lt;/sub&gt; (ng*h/mL)</td>
<td>Mean (SD)</td>
<td>18</td>
<td>3410 (1050)</td>
<td>18</td>
<td>3360 (1070)</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>Median (min – max)</td>
<td>18</td>
<td>2.50 (1.50 – 3.02)</td>
<td>18</td>
<td>2.00 (1.50 – 3.00)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>Mean (SD)</td>
<td>18</td>
<td>21.3 (3.79)</td>
<td>18</td>
<td>20.8 (6.85)</td>
</tr>
</tbody>
</table>

*Notes: max = maximum, min = minimum, SD = standard deviation. Treatment A = 200 mg LUC-06 water-dispersible tablet; Treatment B = 200 mg Carbaglu® water-dispersible tablet.*
### Table 5. Statistical Comparison of Key Pharmacokinetic Parameters (PK Population) in Study LUC06-BIOEQ-2013

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>n</th>
<th>Geometric LS Mean</th>
<th>95% CI</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>A</td>
<td>18</td>
<td>346</td>
<td>(300, 398)</td>
<td>A/B</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>18</td>
<td>331</td>
<td>(287, 381)</td>
<td>104.49 (88.54, 123.32)</td>
</tr>
<tr>
<td>$AUC_{(0-t)}$ (ng*h/mL)</td>
<td>A</td>
<td>18</td>
<td>2950</td>
<td>(2620, 3310)</td>
<td>A/B</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>18</td>
<td>2890</td>
<td>(2570, 3250)</td>
<td>102.00 (88.97, 116.94)</td>
</tr>
<tr>
<td>$AUC_{(0-\infty)}$ (ng*h/mL)</td>
<td>A</td>
<td>18</td>
<td>3250</td>
<td>(2900, 3650)</td>
<td>A/B</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>18</td>
<td>3190</td>
<td>(2840, 3580)</td>
<td>101.85 (89.00, 116.55)</td>
</tr>
</tbody>
</table>

Notes: CI = confidence interval; LS = least squares.
Treatment A = 200 mg LUC-06 water-dispersible tablet;
Treatment B = 200 mg Carbaglu water-dispersible tablet.

### Table 6. Nonparametric Analysis of $t_{\text{max}}$ in Study LUC06-BIOEQ-2013

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>n</th>
<th>Median</th>
<th>95% CI [a]</th>
<th>Treatment Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>A</td>
<td>18</td>
<td>2.50</td>
<td>(2.00, 2.50)</td>
<td>0.25 (-0.03, 0.50) p-value [d] 0.3218</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>18</td>
<td>2.00</td>
<td>(2.00, 2.50)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: CI = confidence interval
Treatment A = 200 mg LUC-06 water-dispersible tablet;
Treatment B = 200 mg Carbaglu water-dispersible tablet.
[a] Calculated using the method of Hahn and Meeker.
[c] Exact Hodges-Lehmann estimate.
[d] p-value from Wilcoxon signed-rank test.

### Safety data

Adverse events (AE) were also recorded in the bioequivalence study described. No serious AEs, treatment-emergent AEs (TEAEs) leading to discontinuation, or severe TEAEs were reported.

In addition, safety laboratory parameters, vital signs, 12-lead electrocardiogram (ECGs) and physical examination were evaluated.

Overall, TEAEs were reported by 7 (38.9%) subjects, 3 (16.7%) subjects after receiving Ucedane and 5 (27.8%) subjects after receiving Carbaglu. With the exception of 1 subject, all subjects reported a single TEAE during the study, either on Ucedane or Carbaglu. The subject with more than 1 TEAE had: fatigue after receiving Ucedane and muscle spasms after receiving Carbaglu. Overall, most subjects had reported TEAEs in the System Organ Class “General Disorders and administration site conditions” (3 [16.7%] subjects) followed
by "Nervous system disorders" (2 [11.1%] subjects). Each Preferred Term was reported for only 1 (5.6%) subject.

A few abnormal ECG assessments were reported but none were judged to be clinically significant by the Investigator. With regards to the ECG outlier values, only 1 subject had an outlier value, which was present at 48 hours post-dose after both treatments.

No abnormal physical examinations were reported.

**Conclusions**

Based on the presented bioequivalence study Ucedane is considered bioequivalent with Carbaglu.

**2.4.3. Pharmacodynamics**

No new pharmacodynamic studies were presented and no such studies are required for this application.

**2.4.4. Post marketing experience**

No post-marketing data are available. The medicinal product has not been marketed in any country.

**2.4.5. Discussion on clinical aspects**

This is a generic application for the marketing authorisation of Ucedane 200 mg tablets which was supported by one bioequivalence study.

The choice of parameters, fed state and sample size for the bioequivalence demonstration are all acceptable for the 200mg dispersible tablets.

Statistical evaluation of the PK parameters and the acceptance ranges for bioequivalence are in accordance with the bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev.1 Cor**). The statistical methods chosen were considered adequate.

The median tmax was comparable between the two treatments (2.50 hours for Ucedane and 2.00 hours for Carbaglu). The range of the observed tmax was approximately the same following administration of the two treatments. The t1/2 was also similar between the two treatments (20.8 hours for Carbaglu and 21.3 hours for Ucedane).

Based on the presented bioequivalence study Ucedane 200 mg tablets are considered bioequivalent with Carbaglu 200 mg tablets.

**2.4.6. Conclusions on clinical aspects**

The application contains an adequate review of published clinical data and bioequivalence has been shown between Ucedane and Carbaglu 200 mg tablets based on the presented bioequivalence study.
2.5. Risk management plan

Safety concerns

Summary of Safety Concerns

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important potential risks</td>
<td>Lack of efficacy</td>
</tr>
<tr>
<td>Missing information</td>
<td>Use in pregnant women</td>
</tr>
<tr>
<td></td>
<td>Patients with cardiac diseases/renal and hepatic impairment</td>
</tr>
</tbody>
</table>

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

<table>
<thead>
<tr>
<th>Safety Concerns</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of efficacy</td>
<td>Medicinal product subject to restricted medical prescription</td>
<td>None proposed</td>
</tr>
<tr>
<td>Use in pregnant women</td>
<td>Proposed text in SmPC section 4.2 “Posology and method of administration”: “Ucedane treatment should be initiated under the supervision of a physician experienced in the treatment of metabolic disorders”. Proposed text in SmPC section 4.6 “Fertility, pregnancy and lactation”: “Pregnancy. For carglumic acid no clinical data on exposed pregnancies are available. Animal studies have revealed minimal developmental toxicity (see section 5.3). Caution should be exercised when prescribing to pregnant women.” Medicinal product subject to restricted medical prescription</td>
<td>None proposed</td>
</tr>
<tr>
<td>Patients with cardiac</td>
<td>Proposed text in SmPC section 4.2 “Posology and method of”</td>
<td></td>
</tr>
</tbody>
</table>
diseases/
renal and hepatic
impairment administration”: “Ucedane treatment should be initiated under the supervision of a physician experienced in the treatment of metabolic disorders”.

Proposed text in SmPC section 4.4 “Special warnings and precautions for use”: “Therapeutic monitoring. Plasma levels of ammonia and amino acids should be maintained within normal limits. As very few data on the safety of carglumic acid are available, systematic surveillance of liver, renal, cardiac functions and haematological parameters is recommended”.

Medicinal product subject to restricted medical prescription

| None proposed |

**Conclusion**

The CHMP and PRAC considered that the risk management plan version 1.1 is acceptable.

**2.6. PSUR submission**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

**2.7. Pharmacovigilance**

**Pharmacovigilance system**

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

**2.8. Product information**

**2.8.1. User consultation**

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *EC Guideline on the readability of the label and package leaflet of medicinal products for human use.*
3. Benefit-risk balance

This application concerns a generic version of carglumic acid tablets. The reference product Carbaglu is indicated for the treatment of hyperammonaemia due to:

- N-acetylglutamate synthase primary deficiency,
- isovaleric acidaemia,
- methymalonic acidaemia,
- propionic acidaemia.

However, the application for Ucedane concerns only treatment of hyperammonaemia due to N-acetylglutamate synthase primary deficiency.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a single oral dose, randomised, open-label, two-way cross-over design in healthy male and female subjects conducted at a single study centre in the EU. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Ucedane met the protocol-defined criteria for bioequivalence when compared with Carbaglu. The point estimates and their 90% confidence intervals for the parameters AUC₀₋₉, AUC₀₋∞, and Cmax were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ucedane is favourable in the following indication:

treatment of hyperammonaemia due to N-acetylglutamate synthase primary deficiency.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).
Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.