

Public Assessment Report

Scientific discussion

Kargluminsyra Waymade (carglumic acid)

SE/H/1956/01/E/01

This module reflects the scientific discussion for the approval of Kargluminsyra Waymade. The Public Assessment Report was written in August 2017 by the previous RMS UK after initial procedure UK/H/5924/001/DC and is attached at the end of this document. RMS transfer from UK to SE was completed February 2019. For information on changes after this date please refer to the module ‘Update’.

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/non approval	Summary/Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)



Public Assessment Report

Decentralised Procedure

Carglumic Acid Waymade 200 mg Dispersible Tablets

(Carglumic acid)

Procedure No: UK/H/5924/001/DC

UK Licence Number: PL 06464/3072

Waymade Plc trading as Sovereign Medical.

LAY SUMMARY

Carglumic Acid Waymade 200 mg Dispersible Tablets (Carglumic acid)

This is a summary of the Public Assessment Report (PAR) for Carglumic Acid Waymade 200 mg Dispersible Tablets (PL 06464/3072; UK/H/5924/001/DC). It explains how Carglumic Acid Waymade 200 mg Dispersible Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Carglumic Acid Waymade 200 mg Dispersible Tablets.

The product will be referred to as Carglumic Acid throughout the remainder of this public assessment report (PAR).

For practical information about using Carglumic Acid, patients should read the package leaflet or contact their doctor or pharmacist.

What is Carglumic Acid and what is it used for?

Carglumic Acid is a 'generic medicine'. This means that Carglumic Acid is similar to a 'reference medicine' already authorised in the European Union (EU) called Carbaglu 200mg dispersible tablets (Orphan Europe SARL, France).

Carglumic Acid can help to eliminate high ammonia levels in the blood. Ammonia is especially toxic for the brain and can lead, in severe cases, to reduced levels of consciousness and to coma.

High levels of ammonia in the blood may be due to:

- the lack of a specific liver enzyme (N-acetylglutamate synthase). Patients with this rare disorder are not able to eliminate nitrogen waste, which builds up after eating protein. This disorder persists throughout the life of the affected patient, requiring lifelong treatment.

How does Carglumic Acid work?

This medicine contains the active substance carglumic acid.

Carglumic acid is very similar in structure to N-acetylglutamate, which activates an enzyme that breaks down ammonia. When ammonia builds up in the blood, it is toxic to the body, especially the brain.

Carglumic acid helps break down ammonia, reducing ammonia blood levels and its toxic effects.

How is Carglumic Acid used?

The pharmaceutical form of this medicine is a dispersible tablet and the route of administration is oral (by mouth).

The patient should always take this medicine exactly as their doctor has instructed them. The patient should check with their doctor or pharmacist if they are not sure.

The usual dose:

The initial daily dose is usually 100 mg per kilogram of body weight, up to a maximum of 250 mg per kilogram of body weight (for example, if the patient weighs 10 kg, they should take 1 g per day, or 5 tablets).

For patients suffering from N-acetylglutamate synthase deficiency, in the long term, the daily dose usually ranges from 10 mg to 100 mg per kilogram of body weight.

The patient's doctor will determine the dose suitable for the patient in order to maintain normal ammonia levels in their blood.

Carglumic Acid should ONLY be given by mouth, or through a feeding tube into the stomach (using a syringe, if necessary).

When the patient is in hyperammonaemic coma, Carglumic Acid is administered by fast push through a syringe via the tube set up to feed them.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of administration, and the duration of treatment.

For further information on how Carglumic Acid is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

What benefits of Carglumic Acid have been shown in studies?

Because Carglumic Acid is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Carbaglu 200mg dispersible tablets (Orphan Europe SARL, France). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Carglumic Acid?

Because Carglumic Acid is a generic medicine and as it is bioequivalent to the reference medicine Carbaglu 200mg dispersible tablets (Orphan Europe SARL, France), its possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Carglumic Acid, see section 4 of the package leaflet available on the MHRA website.

Why was Carglumic Acid approved?

It was concluded that, in accordance with EU requirements, Carglumic Acid has been shown to have comparable quality and to be bioequivalent to Carbaglu 200mg dispersible tablets (Orphan Europe SARL, France). Therefore, the MHRA decided that, as for Carbaglu 200mg dispersible tablets (Orphan Europe SARL, France); the benefits are greater than the risks and recommended that Carglumic Acid can be approved for use.

What measures are being taken to ensure the safe and effective use of Carglumic Acid?

A risk management plan (RMP) has been developed to ensure that Carglumic Acid is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPCs) and the package leaflet for Carglumic Acid including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously.

Other information about Carglumic Acid

Agreement for granting a Marketing Authorisation was given on 24 May 2017 by the UK and EU member states Germany, Spain, France, Italy and Sweden.

A Marketing Authorisation was granted in the UK on 20 June 2017.

The full PAR for Carglumatic Acid follows this summary.

For more information about treatment with Carglumatic Acid read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2017.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Waymade Plc, a marketing authorisation for the medicinal product, Carglumic Acid (PL 06464/3072; UK/H/5924/001/DC). The product is a prescription-only medicine (POM) indicated in the treatment of hyperammonaemia due to N-acetylglutamate synthase primary deficiency.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Germany, Spain, France, Italy and Sweden as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Carbaglu 200mg dispersible tablets which was first granted to Orphan Europe SARL, France on 24 January 2003 (EU/1/02/246/001) via the centralised procedure. The reference medicinal product was granted an orphan designation. The Community register indicates that the orphan designation for the indication "treatment of N-acetylglutamate synthetase (NAGS) deficiency" ended on 28 January 2013. The application is therefore valid.

Carglumic acid is a structural analogue of N-acetylglutamate, which is the naturally occurring activator of carbamoyl phosphate synthetase, the first enzyme of the urea cycle.

Carglumic acid has been shown *in vitro* to activate liver carbamoyl phosphate synthetase. 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. This could be explained by the following observations:

- The mitochondrial membrane is more readily permeable for carglumic acid than for N-acetylglutamate
- Carglumic acid is more resistant than N-acetylglutamate to hydrolysis by aminoacylase present in the cytosol.

One bioequivalence study (conducted under fasting conditions) was submitted to support this application. The applicant has stated that the bioequivalence study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that this is a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure on 24 May 2017. After a subsequent national phase, a licence was granted in the UK on 20 June 2017.

II QUALITY ASPECTS

II.1 Introduction

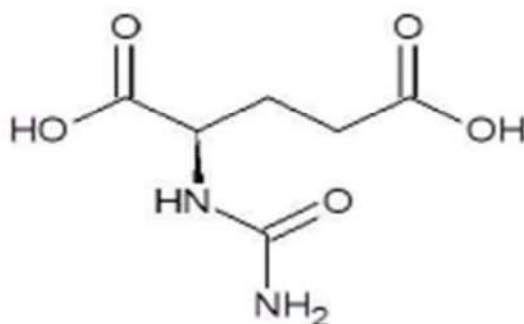
Each dispersible tablet contains 200 mg carglumic acid as the active ingredient. Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, croscarmellose sodium, sodium laurilsulfate, colloidal anhydrous silica and sodium stearyl fumarate.

The finished product is packed into high density polyethylene containers with a child resistant polypropylene cap with a liner and a desiccant unit and is available in pack sizes of 5, 15 or 60 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance

INN: Carglumic acid
Chemical name: N-carbamoyl-L-glutamic acid
Structural formula:



Molecular formula: $C_6H_{10}N_2O_5$
Molecular mass: 190.15 g/mol
Appearance: Off white to white, crystalline powder.
Solubility: Soluble in dimethyl formamide and sparingly soluble in water.

Carglumic acid is the subject of an active substance master file (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate safe, dispersible tablets containing 200 mg carginic acid per tablet, that are generic versions of the reference product Carbaglu 200mg dispersible tablets (Orphan Europe SARL, France). A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing processes have been validated at commercial scale batch size and have shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided which comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the product

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with the storage condition 'This medicinal product does not require any special storage conditions. After first opening of the tablet container: do not refrigerate or freeze.

Keep the container tightly closed in order to protect from moisture'. The in-use shelf life for the container is 1 month after first opening.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of carglumic acid are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Carglumic Acid is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of carglumic acid is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of carglumic acid.

Based on the data provided, Carglumic Acid (Waymade Plc, UK) can be considered bioequivalent to Carbaglu 200mg dispersible tablets (Orphan Europe SARL, France).

IV.2 Pharmacokinetics

In support of this application, the applicant submitted the following bioequivalence study:

STUDY 1

An open label, balanced, randomised, single-dose, two-treatment, two sequence, two-period, crossover bioequivalence study of applicant's test product Carglumic Acid Waymade 200 mg Dispersible Tablets (Waymade Plc, UK) versus the reference product Carbaglu 200mg dispersible tablets (Orphan Europe SARL, France). in healthy, adult, human subjects under fasting conditions.

Treatments were allocated to subjects by carrying out randomisation using statistical techniques. The dose for each subject was calculated by multiplying the subject's weight by 100 mg/kg and then rounding up to the next 200 mg dose.

Each subject was administered one dose each of test and reference product during the study according to the randomisation schedule.

Blood samples were collected for plasma levels before dosing and up to and including 72 hours after each administration. The washout period between the treatment phases was 13 days. The pharmacokinetic results are presented below:

Table: Summary statistics for the pharmacokinetic parameters for carglumic acid are presented below (geometric least squares means, ratio and 90% Confidence Intervals):

Parameters (Units)	Geometric Least Squares Means and it's ratio			Intra subject %CV	90% Confidence Interval	Power (%)
	Test Product (T)	Reference Product (R)	(T/R)%			
C_{max} (ng/mL)	4674.070	4628.067	100.99	27.36	86.76% - 117.56%	78.73
AUC_{0-72} (hr*ng/mL)	33870.421	35878.368	94.40	15.68	86.44% - 103.09%	99.19

C_{max} maximum plasma concentration

AUC_{0-72} area under the plasma concentration-time curve from zero to 72 hours

Study Conclusion

The 90% confidence intervals of the test/reference ratio for AUC and C_{max} values for carglumic acid lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**'. Thus, the data support the claim that the applicant's test product is bioequivalent to the reference product Carbaglu 200mg dispersible tablets (Orphan Europe SARL, France).

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety

No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Carglumic Acid.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:

Summary of safety concerns	
Important identified risks	None
Important potential risks	Medication error (including incorrect route of administration) Off label use
Important missing information	Use in pregnant women Patients with cardiac diseases/renal and hepatic impairment

Routine pharmacovigilance and routine risk minimisation are proposed. No additional pharmacovigilance or additional risk minimisation measures are proposed. Follow up forms are proposed in order to gather follow up information on any cases of pregnancy. This is considered a routine pharmacovigilance activity.

IV.7 Discussion on the clinical aspects

There are no objections to the approval of this application from a clinical viewpoint.

V User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with carglumic acid is considered to have demonstrated the therapeutic value of the compound. The product is bioequivalent to the marketed reference product and the benefit-risk balance is considered similar and positive.

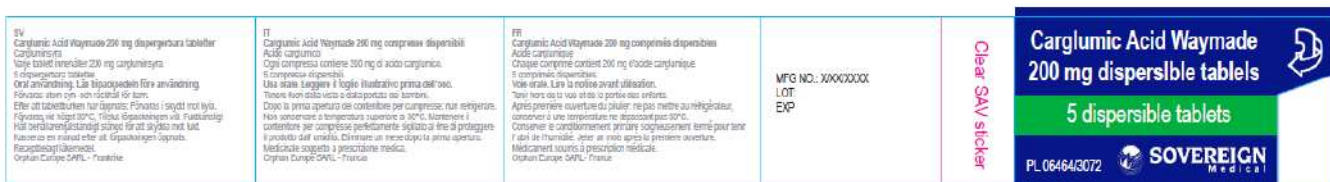
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

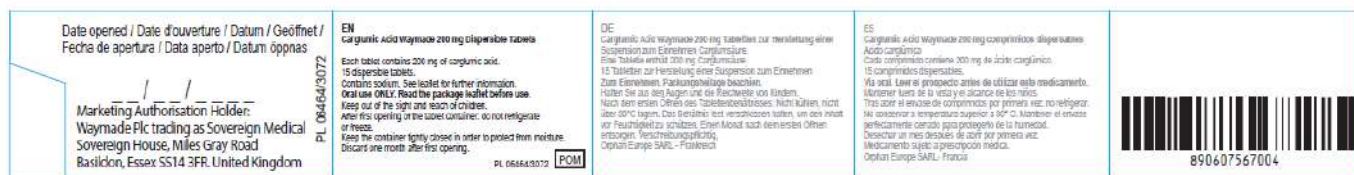
The following labelling is the approved label mock-ups for this medicine:



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Front



SV Carglumic Acid Waymade 200 mg dispergerbare tableter Carglumic Vejs tablet mænkler 200 mg carginlumic. Dispergerbare tableter Oral administration. Læs bagepakkens fersk anvisning. Følg altid den sædvanlige dosering. Dosis: 200 mg 1-2 gange dagligt med eller uden mad. Opbevar på 15-25°C. Holdbarhed: 36 måneder. Hvis du bemærker ændringer i dit urtøj, kontakt din læge. Kænske armbrædder eller indpakkings apparater. Næstapsted: Østermark. Optima Europe S.p.A., Firenze	IT Carglumic Acid Waymade 200 mg compresse disperdibili Acido carginmico Cgli compressi contengono 200 mg di acido carginmico. 15 compresse disperdibili. Uso orale. Leggere il foglio illustrativo prima dell'uso. Tenere fuori dalla vista dei bambini. Dopo la apertura del contenitore per compressi non espongere non conservare a temperatura superiore ai 30°C. Mantenere il contenitore per compressi ben sigillato e in un luogo fresco. La durata di conservazione è di 36 mesi dopo la prima apertura. Medicine soggette a prescrizione medica. Optima Europe S.p.A., Firenze	FR Carglumic Acid Waymade 200 mg comprimés dispersibles Acide carginmique Chaque comprimé contient 200 mg d'acide carginmique. 15 comprimés dispersibles. Voie orale. Lisez la notice avant utilisation. Tenir hors de la vue de la portée des enfants. Après ouverture du contenant ne pas exposer au réchauffement, conserver à une température ne dépassant pas 30°C. Le contenant des comprimés doit être bien fermé et conservé dans un endroit frais. La durée de conservation est de 36 mois après la première ouverture. Médicament soumis à prescription médicale. Optima Europe S.p.A., Firenze	MFG NO.: XXXXXXXXXX LOT: EXP:	Carglumic Acid Waymade 200 mg dispersible tablets 15 dispersible tablets Clear SAs sticker PL 08464/3072  SOVEREIGN MEDICAL
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Date opened / Date d'ouverture / Datum / Geotoff / Fecha de apertura / Data aperto / Datum öppnas Waymade Pfl trading as Sovereign Medical Sovereign House, Miles Gray Road Basildon, Essex S514 3FR, United Kingdom	EN Carglumic Acid Waymade 200 mg Dispersible Tablets Each tablet contains 200 mg of carglumic acid. 60 dispersible tablets. Contains sodium. See leaflet for further information. Only use ONLY if the package leaflet before use. Keep out of the sight and reach of children. After first opening of the tablet container do not refrigerate contents. Keep the container tightly closed in order to protect from moisture. Discard one month after first opening. PL 06464/3072 POM	DE Carglumic Acid Waymade 200 mg Tabletten zur Herstellung einer Suspension zum Lagern Diese Tablette enthält 200 mg Carglúminat. 60 Tabletten zur Herstellung einer Suspension zum Lagern. Zusammensetzung: Packungsbeilage beachten. Nur bei richtiger Anwendung und nach Anweisung des Arztes. Nach dem Öffnen des Tablettbehälters: Nicht kühlen, nicht über 30°C lagern. Das Behälter fest verschlossen halten, um das Inhalt vor Feuchtigkeit zu schützen. Bitte Material nach dem ersten Öffnen entsorgen (Umweltverträglichkeit).	ES Carglumic Acid Waymade 200 mg comprimidos dispersibles Cada comprimido contiene 200 mg de ácido carglúmico. 60 comprimidos dispersibles. Puede contener sodio. Ver la información antes de utilizar este medicamento. Mantener fuera de la vista y el alcance de los niños. Tras abrir el envase de comprimidos no refrigerar, no refrigerar. No conservar a temperatura superior a 30°C. Mantener el envase perfectamente cerrado para protegerlo de la humedad. Después de un mes después de abrir por primera vez. Medicamento sujeto a prescripción médica.
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SV Karglúminsyra Waymade 200 mg dispergerbara tabletter V varje brett innehåller 200 mg karglúminsyra. 60 dispergerbara tabletter. Oral användning. Läs bipacksedeln före användning. Förvara i originalförpackningen. Efter att brettet öppnats bör förpackningen skyddas mot ljus. Förvara vid högst 30°C. Tillslut förpackningen väl. Fuktinläckage ska undvikas. Efter öppnandet ska brettet inte kylas. Kassera en månad efter att brettet öppnats. Receptbelagt läkemedel.	IT Acido carglúmico Waymade 200 mg compresse dispersibili Ogni compressa contiene 200 mg di acido carglúmico. 60 compresse dispersibili. Lec sodio. Leggere il foglio illustrativo prima dell'uso. Tenere fuori dalla vista e dalla portata dei bambini. Dopo la prima apertura del contenitore non refrigerare, non refrigerare. Non conservare a temperatura superiore a 30°C. Utilizzare il contenitore per compressa perfettamente sigillato al fine di proteggerlo dal rischio di umidità. Eliminare un mese dopo la prima apertura. Medicamento soggetto a prescrizione medica.	FR Acide carglúmique Waymade 200 mg comprimés dispersibles Chaque comprimé contient 200 mg d'acide carglúmique. 60 comprimés dispersibles. Rien sodio. Lire la notice avant utilisation. Tenir hors de la vue et de la portée des enfants. Après première ouverture du pilulier ne pas mettre au réfrigérateur, ne pas réfrigérer. Ne conserver à température ne dépassant pas 30°C. Conserver le conditionnement primaire soigneusement fermé pour le protéger de l'humidité. Jeter un mois après la première ouverture. Médicament soumis à prescription médicale. MFG NO.: X/XX/XXXX LOT: EXP	Clear SAV sticker Carglumic Acid Waymade 200 mg Dispersible Tablets 60 dispersible tablets SOVEREIGN MEDICAL
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Annex 1 - Table of content of the PAR update for MRP and DCP**Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report**
(Type II variations, PSURs, commitments)

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/non approval	Assessment report attached
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