LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Oribamide
(hydroxycarbamide)

SE/H/1828/01/DC

This module reflects the scientific discussion for the approval of Oribamide. The procedure was finalised on 2019-03-01. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Oribamide, 500 mg, capsule, hard, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orifarm Generics A/S, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, FI and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Hydrea, 500 mg, capsule, hard, authorised in UK since 1986, with E.R. Squibb & Sons Limited as marketing authorisation holder.

The reference product used in the bioequivalence study is Hydrea, 500 mg, capsule, hard, from UK with E.R. Squibb & Sons Limited as marketing authorisation holder.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Oribamide, 500 mg, capsule with the reference product Hydrea, 500 mg, capsule.

Pharmacokinetic properties of the active substance
Hydroxyurea is readily absorbed from the gastrointestinal tract; peak plasma concentrations are reached within 0.5-2 hours. The effect of food on the absorption of hydroxyurea has not been determined. There are no restrictions with respect to food in the SmPC of the originator. Hydroxyurea crosses the blood-brain barrier. The volume of distribution at steady sate after i.v. hydroxyurea was about 40-50L. The metabolism of Hydroxyurea has not been thoroughly studied in humans. Hydroxyurea is eliminated partly via renal excretion. The contribution of this route of elimination to the total elimination of hydroxyurea is unclear since the fractions of the given dose recovered in urine ranged from 9% to 95%. The terminal half-life is about 3 hours.

Study 561/16
Methods
This was a single-dose, two-way crossover study conducted in 30 healthy volunteers, comparing Oribamide, 500 mg, capsule with the reference product Hydrea, 500 mg , capsule under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of hydroxyurea were determined with an HPLC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 15 Nov 2016 and 29 Nov 2016.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for hydroxyurea, n=30.

Treatment	AUC_{0-t} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	**58.73±11.12**	**15.18±3.57**	**0.68 0.33-1.50**
Reference	**58.07±9.97**	**16.98±3.88**	**0.61 0.33-1.25**
***Ratio (90% CI)**	**100.86 (99.13-102.62)**	**89.18 (82.89-95.96)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, Oribamide, 500 mg, capsule is considered bioequivalent with Hydrea, 500 mg, capsule.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 Risk Management Plan

The Applicant has submitted an updated risk management plan version 1.0 (dated 27 September 2018), 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 Oribamide.

Safety specification
The summary of safety concerns as proposed in the RMP:

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

The summary of safety concerns is considered acceptable.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.

The submitted Risk Management Plan, version 1.0 signed 27 September 2018 is considered acceptable.

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 RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Hydroxyurea medac SE/H/231/01/IB/10 for content. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Oribamide, is found adequate. There are no objections to approval of Oribamide, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.

The benefit/risk ratio is considered positive and Oribamide, 500 mg, capsule, hard is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Oribamide, 500 mg, capsule, hard was positively finalised on 20190301.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

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