COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Hydroxycarbamide Devatis 500 mg, hard capsules (hydroxycarbamide)

NL License RVG: 133698

Date: 11 May 2026

This module reflects the scientific discussion for the approval of Hydroxycarbamide Devatis 500 mg, hard capsules. The procedure was finalised on 15 January 2026. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CML	Chromic Myeloid Leukaemia
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ET	Essential Thrombocythaemia
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PV	Polycythaemia Vera
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Hydroxycarbamide Devatis 500 mg, hard capsules, from Devatis GmbH.

The product is indicated for:

- treatment of patients with chronic myeloid leukaemia (CML) in the chronic or accelerated phase of the disease
- treatment of patients with essential thrombocythaemia (ET) and polycythaemia **vera (PV)** with a high risk for thromboembolic complications.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this national procedure, similarity is proven between the new product and the innovator product Hydrea 500 mg hard capsules (NL RVG 06387) from Bristol-Myers Squibb) which is no longer marketed (historic reference product). To demonstrate similarity, a bio-equivalence study has been performed with the innovator from the UK market. Since this study was carried out pre-Brexit, this study can be accepted in support of the application.

Similarity assessment

According to Article 8(1) of Regulation (EC) No 141/2000, no marketing authorisation can be granted for a product similar to an orphan medicinal product for a period of ten years, when this concerns a similar medicinal product with the same therapeutic indication(s). A similarity assessment has been performed between Hydroxycarbamide Devatis and the current orphan products authorised in the EU. These orphan products are:

Table 1. Similarity assessment

Product name	Drug substance	Marketing Authorisation number	Orphan designation number	Orphan status (on date)	Indication(s)
Scemblix	asciminib	EU/1/22/1670/001-005	EU/3/20/2261	Active 24-3-2020	Chromic myeloid leukaemia
Daurismo	glasdegib	EU/1/20/1451/001-004	EU/3/17/1923	Active 16-10-2017	Treatment of acute myeloid leukaemia
Mylotarg	gemtuzumab ozogamicin	EU/1/18/1277/001	EU/3/00/005	Active 18-10-2000	Treatment of acute myeloid leukaemia
Xospata	gilteritinib	EU/1/19/1399/001	EU/3/17/1961	Active 17-1-2018	Treatment of acute myeloid leukaemia
Vyxeos	daunorubicin and cytarabine	EU/1/18/1308/001-02 and EU/1/18/1308/005	EU/3/11/942	Active 11-1-2012	Treatment of acute myeloid leukaemia

Rydapt	midostaurin	EU/1/17/1218/001-002	EU/3/04/214	Active 29-7-2004	Treatment of acute myeloid leukaemia
Tibsovo	ivosidenib	EU/1/23/1728/001	EU/3/16/1802	Active 12-12-2016	Treatment of acute myeloid leukaemia
Inrebic	fedratinib	EU/1/20/1514/001	EU/3/10/810	Active 26-11-2010	Essential thrombocythaemia Polycythaemia vera
Omjjara -	momelotinib	EU/1/23/1782/001-003	EU/3/11/887	Active 5-8-2011	Essential thrombocythaemia Polycythaemia vera

The assessment included the comparison of the therapeutic indication(s), mechanism of action and principal (molecular) structure features. The similarity assessment report was completed in August 2025, concluding the above mentioned products were not similar to the test product with regard to the mechanism of action and principal molecular structure.
Regarding the therapeutic indications, it can be concluded that there are differences in the therapeutic indications, however some common indications are defined as follow:

- Hydroxycarbamide and Scemblix - a treatment of chronic myeloid leukaemia.
- Hydroxycarbamide and Daurismo, Mylotarg, Xospata, Vyxeos liposomal, Rydapt, Tibsovo – - a treatment of acute chronic myeloid leukaemia.
- Hydroxycarbamide and Inrebic, Omjjra - a treatment of treatment essential thrombocythaemia or polycythaemia vera.

Differences are related to the combination therapy, diagnosis stage (newly diagnosed) gene mutations specificity, patient groups, use as second-line treatment and other indications.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Scemblix, Daurismo, Mylotarg, Xospata, Vyxeos, Rydapt, Tibsovo, Inrebic and Omjjara with their respective indications does not prevent the granting of the marketing authorisation of Hydroxycarbamide Devatis 500 mg hard capsules.

II. QUALITY ASPECTS

II.1 Introduction

Hydroxycarbamide Devatis is a hard gelatine capsule, with an opaque light green cap and opaque pink body, filled with white to almost white crystalline powder. Each capsule contains as active substance 500 mg of hydroxycarbamide.

The excipients are:
Capsule fill: - lactose monohydrate, citric acid (E330), disodium phosphate (E339) and magnesium stearate.

Capsule shell: - gelatine, titanium dioxide (E171), erythrosin (E127), indigotine (E132) and quinoline yellow (E104).

The hard capsules are packed in blister packs of clear polyvinyl chloride (PVC)/Aclar film or polyamide (PA)/aluminium/PVC, sealed with aluminium foil. The blister packs are packed in carton boxes.

II.2 Drug Substance

The active substance is hydroxycarbamide, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder, freely soluble in water and practically insoluble in ethanol (96%). It shows polymorphism. A test for the polymorphic form is included in the drug substance specification. Furthermore, it has been demonstrated experimentally that the test product used in the bioequivalence (BE) study contains the same polymorphic form as the reference product.

Two CEP procedures are used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with additional in-house requirements for particle size, polymorphic form and microbiological quality. The specification is acceptable.. Batch analytical data demonstrating compliance with this specification have been provided for three batches of drug substance from each manufacturer.

Stability of drug substance

Stability data on the active substance in site I have been provided for 19 batches stored at 25°C/60% RH (up to 60 months) and for 6 batches stored at 40°C/75% RH (6 months). The batches were stored in accordance with applicable European guidelines. The stability data show no clear trends or changes in any of the tested parameters or storage conditions. Based on the data submitted, a retest period could be granted of five years when stored under the stated conditions.

The active substance in site II is stable for four years when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. The main development studies described are the characterisation of the reference product, formulation optimisation studies, manufacturing process development and dissolution method development. The choice of the Quality Control (QC) dissolution method has been justified. It is demonstrated that the drug substance from both proposed suppliers is of the same crystal form. The pharmaceutical development of the product has been adequately performed.

A bioequivalence (BE) study has been performed versus the reference product. The test batch used in the BE study was manufactured according to the final formulation and manufacturing process at a representative scale. Comparative dissolution testing at 3 pHs and in QC medium according to the applicable guidelines was performed complementary to the bioequivalence study. High variability is seen for the test product, but not for the reference product, at the initial time points. This observation is reasonably explained by variability in disintegration time of the gelatin capsule and as the *in vivo* results prevail, the issue is not further pursued.

Manufacturing process

The product is manufactured using conventional manufacturing techniques. The main steps of the manufacturing process are weighing of the raw materials, manual sieving, blending, capsule filling and packaging. The manufacturing process has been described in sufficient detail. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three pilot scale batches and three full scale batches.

Control of excipients

The excipients comply with Ph.Eur., in-house requirements (capsules), or with Regulation EC 231/2012 (colourants). Additional functionality related characteristics have been discussed and are included in the excipient specifications where relevant. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, capsule filling weight, identity, water, dissolution, assay, urea, related substances, uniformity of dosage units, and microbial controls. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three pilot scale batches and six full scaled batches from the proposed production site have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for three production scaled batches per blister packaging, stored at 25°C/60% RH (36 or 24 months, depending on the packaging) and at 40°C/75% (6 months). A commitment has been given that the ongoing stability study at 25°C/60% will be completed up to 36 months for both blister package forms. The stability was tested in accordance with applicable European guidelines. All results were in compliance with the shelf-life specification. Photostability studies confirmed that the product is not sensitive to light. On basis of the data submitted, a shelf life was granted of 36 months. The labelled storage conditions are '*Store in the original blister package for protection against moisture.'*.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for gelatine and lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Hydroxycarbamide Devatis has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made:

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Hydroxycarbamide Devatis is intended for generic substitution, this will not lead to an increased exposure to the environment. Although noted that the innovator product is not marketed in NL anymore, the product at issue will be a substitute for other authorised generics. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Hydrea which is not available on the European market any more. Reference is made to the preclinical data obtained with the innovator product. 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. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Hydroxycarbamide is a well-known active substance with established efficacy and tolerability A clinical overview has been provided, which is based on scientific literature. The MEB agreed that no further clinical studies are required, besides one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Hydroxycarbamide Devatis 500 mg, hard capsules (ADOH B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product Hydrea 500 mg hard capsules (E R Squibb&Sons Ltd, United Kingdom).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Bioequivalence studies

Design

A single-dose, open-label, randomised, two-period, crossover comparative bioequivalence study was carried out under fasted conditions in 30 healthy postmenopausal female subjects, aged 49-64 years. Each subject received a single dose (500 mg) of one of the two hydroxycarbamide formulations. The tablet was orally administered with 200 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 18 and 24 hours after administration of the products.

The design of the study is acceptable.

Hydroxycarbamide may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of hydroxycarbamide. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
All included 30 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of hydroxycarbamide, 500 mg under fasted conditions.

Treatment N=30	**AUC_{0-24} (µg h/mL)**	**$AUC_{0-\infty}$ (µg /mL)**	**C_{max} (µg/mL)**	**t_{max} (h)**
Test	58.73 ± 11.12	60.19 ± 11.11	15.18 ± 3.57	0.5 (0.33 – 1.5)
Reference	58.07 ± 9.97	59.51 ± 9.94	16.98 ± 3.88	0.5 (0.33 – 1.25)
***Ratio (90% CI)**	1.01 (0.99 – 1.03)	--	0.89 (0.83 – 0.96)	--

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 24 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-24} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Hydroxycarbamide Devatis is considered bioequivalent with Hydrea.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, 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 Hydroxycarbamide Devatis. At the time of approval, the most recent version of the RMP was version 0.1 dated30 April 2024.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Hydrea. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 PL was Dutch. The test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Hydroxycarbamide Devatis 500 mg, hard capsules has a proven chemical-pharmaceutical quality and is a generic form of Hydrea 500 mg hard capsules. Hydrea is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Hydroxycarbamide Devatis with the reference product, and have therefore granted a marketing authorisation. The national procedure was finalised with a positive outcome on 15 January 2026.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
1198379	• National transfer MAH • "Change in the (invented) name of the medicinal product - for Nationally Authorised products"	Yes	01-05-2026	Approved	N.A.