COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Irinotecan Amarox 20 mg/ml, concentrate for solution for infusion (irinotecan hydrochloride trihydrate)

NL/H/5486/001/DC

Date: 27 March 2023

This module reflects the scientific discussion for the approval of Irinotecan Amarox 20 mg/ml, concentrate for solution for infusion. The procedure was finalised at 12 October 2022. 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
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
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PD	Pharmacodynamics
PK	Pharmacokinetics
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of medicinal Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Irinotecan Amarox 20 mg/ml, concentrate for solution for infusion, from Amarox Pharma B.V.

The product is indicated:

- for the treatment of patients with advanced colorectal cancer:
  - in combination with 5-fluorouracil and folinic acid in patients without prior chemotherapy for advanced disease,
  - as a single agent in patients who have failed an established 5-fluorouracil containing treatment regimen.
- in combination with cetuximab for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing RAS wild-type metastatic colorectal cancer, who had not received prior treatment for metastatic disease or after failure of irinotecan-including cytotoxic therapy (see section 5.1 of the SmPC).
- in combination with 5-fluorouracil, folinic acid and bevacizumab for first-line treatment of patients with metastatic carcinoma of the colon or rectum.
- in combination with capecitabine with or without bevacizumab for first-line treatment of patients with metastatic colorectal carcinoma.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Campto 20 mg/ml concentrate for solution for infusion, authorised on 23 June 1998 by Pfizer B.V. (FR/H/0108/002). Campto has been registered in the Netherlands under RVG 22820 by a mutual recognition procedure.

The concerned member states (CMS) involved in this procedure were Germany and Spain. The market authorisation was granted in these countries as well as in the RMS (The Netherlands).

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Irinotecan Amarox is a pale yellow colour solution, free from visible particles and contains as active substance 20 mg/mL irinotecan hydrochloride trihydrate (equivalent to 17.33 mg/mL irinotecan).

The solution is packed in amber tubular Type-1 glass vials closed with rubber stoppers (for 40mg/2mL, 100mg/5mL, 300mg/15mL, or 500mg/25mL) or amber moulded type-1 glass

vials closed with rubber stoppers (for 750mg/37.5mL). The different volumes can be distinguished due to different colour flip-off seals and different vial sizes.

The excipients are: sorbitol, lactic acid, sodium hydroxide, hydrochloric acid and water for injection.

II.2 Drug Substance

The active substance is irinotecan hydrochloride trihydrate (form B), an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a pale yellow to yellow crystalline powder, slightly soluble in ethanol, water, methanol and in dimethylformamide. Irinotecan hydrochloride trihydrate exhibits isomerism. Form B is used in this current product, which is the active S-isomer. The R-enantiomer is controlled in compliance with the Ph.Eur.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process consists of six stages, namely Stage-I, Stage-II and Stage-III for the synthesis of an advanced intermediate and Stage-I (IRS-I), Stage-II (IRS-II), and Stage-III (IRS) for the synthesis of the active substance, drying and packing. A synthetic scheme and a detailed description of the manufacturing process has been provided by the MAH. Adequate specifications have been adopted for starting materials, solvents and reagents. The substance has adequately been characterised by suitable analytical methods. The details of the manufacturing have been evaluated by the member states during the procedure and are considered confidential.

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. Batch analytical data demonstrating compliance with this specification have been provided for three original scale process batches and three upscale batches. Most quality control tests and results submitted by the MAH are considered confidential.

Stability of drug substance

Stability data on the active substance have been provided for in accordance with applicable European guidelines demonstrating the stability of the active substance for five original scale batches and one upscale batch at 25°C/60% RH up to 60 months, and for four batches at 40°C/75% RH, up to 6 months. Based on the data submitted, a retest period could be granted of 5 years when stored under stated conditions.

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 aim of the development is to develop a product similar to the reference product. The choice of excipients is justified and their functions explained. The MAH has assessed the compatibility of the substance with components used in the manufacturing and packaging. The finished product is a concentrate for solution for intravenous administration. Consequently, there is no requirement to perform bioequivalence studies, or comparable dissolution studies. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. Process validation data have been presented for three full scale batches. The active substance and excipients sorbitol and lactic acid are dissolved in water for injection. The pH is adjusted, if needed, with sodium hydroxide or hydrochloric acid solution. The solution is filtered into vials and then terminally sterilised.

Control of excipients

The excipients comply with Ph. Eur. requirements. These specifications were acceptable.

Microbiological attributes

The excipients are tested for bacterial endotoxins and the drug product underwent controlled microbial tests, in which all results were below the specification limit. The bioburden has been tested on bulk solution prior to sterilization and results have been found within specifications, which is also confirmed by stability tests of the final product. In the manufacturing process, the solution is filtered into vials, which are then sterilised.

Quality control of drug product

The finished product specifications were adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, bacterial endotoxins, test for sterility, pH, related compounds, assay, particulate matter, osmolality, and extractable volume. Limits in the specification have been justified and were considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided and all currently identified sources of nitrosamine impurities have adequately been addressed.

The proposed release and shelf-life limits are identical, except for total related substances and these specifications are acceptable. The analytical methods have been adequately

described and validated. Batch analytical data from the proposed production site have been provided on three full scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three full scale batches per packaging volume at 25°C/60% RH (40 mg/2 mL and 100 mg/5mL for 36 months; 300 mg / 15mL, 750 mg/37.5 mL and 500 mg/25mL for 12 months), and 40°C/75% RH (40 mg/2 mL, 100 mg/5 mL, 300 mg/15mL and 750mg/37.5mL for 6 months; and 500 mg/25mL for 3 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored inverted and upright, in the proposed commercial packaging. Based on the provided data, a shelf life of 2 years was granted.

Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light when stored in the original packaging. When exposed to light outside of the packaging, physico-chemical stability has been demonstrated for up to 3 days.

In-use stability data have been provided following dilution in 5% glucose and 0.9% sodium chloride, demonstrating that the product remains stable for 24 hours at 2-8°C. This is reflected in the SmPC, along with a note that the infusion solutions should be prepared immediately prior to use and infusion should commence as soon as practicable after preparation, in order to reduce microbiological hazard.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE could be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Irinotecan Amarox 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 Irinotecan Amarox is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Campto 20 mg/ml, which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there was no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies were required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Irinotecan hydrochloride trihydrate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Irinotecan Amarox 20 mg/ml, concentrate for solution for infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Irinotecan Amarox is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

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 Irinotecan Amarox.

Table 1. Summary of safety concerns as approved in RMP

Important identified risks	• Delayed diarrhoea • Acute and severe cholinergic syndrome • Interstitial lung disease • Myocardial ischaemic events • Blood disorders including neutropenia, thrombocytopenia, anaemia and febrile neutropenia • Infections • Drug toxicity in patients with reduced uridine diphosphate glucuronosyltransferase (UGT1A1) activity
Important potential risks	• Drug interaction with CYP3A inducers • Drug interaction with CYP3A inhibitors • Interaction between irinotecan and neuromuscular blocking agents • Interaction between irinotecan and oral anticoagulant • Use in elderly population • Use in patients with bowel obstruction
Missing information	• Use in patients with impaired renal function • Use in pregnancy and lactation • Effect on fertility

The member states 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 Campto. Risk management was adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Irinoliquid 20 mg/ml Konzentrat zur Herstellung einer Infusionslösung (AT/H/0256/001/DC) for content and Levetiracetam Hetero 750 mg Film-Coated Tablets (PT/H/515/01-04/DC) for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Irinotecan Amarox 20 mg/ml, concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Campto 20 mg/ml concentrate for solution for infusion. Campto is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study was deemed necessary. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Irinotecan Amarox with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 October 2022.

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
-	-	-	-	-	-