CBG MEB

Public Assessment Report

Scientific discussion

Irinotecan Koanaa 20 mg/ml concentrate for solution for infusion

(irinotecan hydrochloride trihydrate)

NL/H/3753/001/DC

Date: 5 October 2017

This module reflects the scientific discussion for the approval of Irinotecan Koanaa 20 mg/ml. The procedure was finalised on 8 June 2017. 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
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of 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 Koanaa 20 mg/ml concentrate for solution for infusion from Koanaa Healthcare Limited.

The product has the following indications:

- Irinotecan 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.
- Irinotecan in combination with cetuximab is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer, who had not received prior treatment for metastatic disease or after failure of irinotecan-including cytotoxic therapy.
- Irinotecan in combination with 5-fluorouracil, folinic acid and bevacizumab is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum.
- Irinotecan in combination with capecitabine with or without bevacizumab is indicated for first-line treatment of patients with metastatic colorectal carcinoma.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Campto 20 mg/ml (NL Licence RVG 22820) has been registered in the Netherlands since 1998 by Pfizer B.V.

The concerned member states (CMS) involved in this procedure were Austria, France, Germany, Ireland, Malta, Romania and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Irinotecan Koanaa 20 mg is a pale yellow coloured clear aqueous solution, free from visible particles. with pH 3.0 to 3.8 and osmolality 250 – 350 mOsmol/kg.

One ml of concentrate contains 20 mg irinotecan hydrochloride trihydrate equivalent to 17.33 mg irinotecan.

The product is packed in:

- 40 mg/2 ml: type I flint amber colored glass vial, with a rubber stopper (bromo butyl omniflex plus coated rubber stopper) and sealed with an aluminium flip-off Dark blue colour seals.
- 100 mg/5 ml: type I flint amber colored glass vial, with a rubber stopper (bromo butyl omniflex plus coated rubber stopper) and sealed with an aluminium flip-off Light blue colour seals.
- 300 mg/15 ml: type I flint amber colored glass vial, with a rubber stopper (bromo butyl omniflex plus coated rubber stopper) and sealed with an aluminium flip-off Dark blue colour seals.

The excipients are: sorbitol (E420), lactic acid (E270), sodium hydroxide (E524) (for pH adjustment), hydrochloric acid (E507) (for pH adjustment), water for injections.

II.2 Drug Substance

The active substance is irinotecan hydrochloride trihydrate, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). A monograph in the United States Pharmacopoeia (USP) is available. The active substance is a pale yellow crystalline powder, which is soluble in dimethyl sulphoxide, sparingly soluble in water, slightly soluble in ethanol and chloroform, and insoluble in acetone. The water content is 8.0 to 9.0% w/w. Two asymmetric carbons are present in the molecule. The active substance displays polymorphism; polymorphic form B is used.

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 of the drug substance is described in four stages. The synthesis processes, starting materials, solvents and reagents have been included in the description. The active substance has been adequately characterized.

Quality control of drug substance
The drug substance specification of the MAH is in line with the specifications of the ASMF-holder. Analysis data have been provided for three batches of the drug substance, tested by the drug product manufacturer, demonstrating compliance with the drug substance specification.

Stability of drug substance
Stability data on the active substance at accelerated (40°C/75% RH) and long-term (25°C/60% RH) conditions have been provided for batches of different batch sizes. No changes or trends in the tested parameters were observed at both long-term and accelerated conditions. The claimed retest period of 48 months and storage conditions "Preserve in tight containers protected from light and store below 25°C" are acceptable.

II.3 Medicinal Product

Pharmaceutical development
Selection of active substance and excipients was based on the innovator product. Development studies included optimisation of the sequence of addition of excipients and drug substance, pH optimization, filling volume, tubing compatibility and selection, impact of terminal sterilization on the drug product, photostability and a freeze thaw study. The choice of sterilisation process has been justified; the product is filtered and terminally sterilized. The drug product does not contain a preservative and is tested for sterility and bacterial endotoxins at release. As this generic product is a concentrate for solution for infusion containing the same active substance in the same concentration as the currently authorised product, this product is exempt from bioequivalence study with the reference product.

Manufacturing process
The concentrate for solution for infusion is manufactured by compounding, sterile filtration, filling, stoppering and sealing of vials, and terminal sterilization. The process is a standard manufacturing process and has been adequately validated according to relevant European guidelines. Adequate process validation data on commercial size batches have been provided.

Control of excipients
The excipients comply with Ph. Eur. requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, pH, color of solution, light transmission, extractable volume, osmolality, particulate contamination, assay, related substances,

bacterial endotoxins and sterility. The release and shelf-life limits for all tests are the same. The specification is acceptable. Analytical methods were adequately described. Validation has been carried out. The stability indicating nature of the methods for assay and related substances has been demonstrated. Batch analysis data from the proposed production site have been provided on three commercial scale batches, demonstrating compliance with the release specifications.

Stability of drug product
Stability studies at accelerated (40°C/75% RH, 6 months) and long-term (25°C/60% RH) conditions were performed on three batches in the primary packaging material, stored in inverted and upright position. 24 months stability data at long-term conditions have been provided for these batches. No significant changes were observed in any of the parameters tested. The proposed shelf-life of 2 years and the storage condition "This medicinal product does not require any special storage conditions" are acceptable. Photostability has been demonstrated. The shelf-life and storage after opening and further dilution claimed in the SmPC is in accordance with the provided stability data. Chemical and physical in-use stability has been demonstrated for 24 hours at 5ºC and 25ºC in LDPE containers.

Specific measures for 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 can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Irinotecan Koanaa 20 mg/ml 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 Koanaa 20 mg/ml 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Campto, which is available on the European market. 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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Irinotecan is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Irinotecan Koanaa 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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Irinotecan Koanaa 20 mg/ml 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 Koanaa.

- Summary table of safety concerns as approved in RMP

Important identified risks	Delay diarrhea Blood disorders (including neutropenia, thrombocytopenia, anaemia and febrile neutropenia) Myocardial ischaemic events Acute and severe cholinergic syndrome Interstitial pulmonary disease Infections Drug toxicity in patients with reduced uridine diphosphate glucuronosyltransferase (UGT1A1) activity
Important potential risks	Interaction between irinotecan and neuromuscular blocking agents Interaction between irinotecan and oral anticoagulant Use in elderly population Use in patients with bowel obstruction Interaction with CYP3A4 inducers Interaction with CYP3A4 inhibitors
Missing information	Use in pregnancy and lactation Effect on fertility Use in patients with impaired renal function

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. No new clinical studies were conducted. The MAH demonstrated essential similarity based on quality attributes. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

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 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 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

Irinotecan Koanaa 20 mg/ml concentrate for solution for infusion from has a proven chemical-pharmaceutical quality and is a generic form of Campto 20 mg/ml. 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 is deemed necessary.

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 Koanaa 20 mg/ml concentrate for solution for infusion with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 June 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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