CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Irinotecan HCl-trihydraat Fresenius Kabi 20 mg/ml, concentrate for solution for infusion, Fresenius Kabi Oncology Plc, United Kingdom

irinotecan hydrochloride trihydrate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1503/001/MR
Registration number in the Netherlands: RVG 34947

10 September 2009

Pharmacotherapeutic group:	other antineoplastic agents
ATC code:	L01XX19
Route of administration:	intravenous
Therapeutic indication:	advanced colorectal cancer
Prescription status:	prescription only
Date of first authorisation in NL:	14 April 2008
Concerned Member States:	Mutual recognition procedure with AT, BE, DE, NO, SE, SI
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Irinotecan HCl-trihydraat Fresenius Kabi 20 mg/ml, concentrate for solution for infusion, from Fresenius Kabi Oncology Plc. The date of authorisation was on 14 April 2008 in the Netherlands.

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 the 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 metastatic colorectal cancer 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.

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

Irinotecan is a semi-synthetic derivative of camptothecin. This oncolytic agent acts as a specific inhibitor of DNA topoisomerase I. In most tissues, it is metabolised by carboxylesterase to SN-38, which has been shown to be more active than irinotecan in purified topoisomerase I and more cytotoxic than irinotecan against various kinds of murine and human tumour cell lines. Inhibition of DNA topoisomerase I by irinotecan or SN-38 causes single-strand DNA lesions that block the DNA replication fork and are responsible for the cytotoxic effect. This cytotoxic activity has been shown to be time-dependent and was specific to the S phase.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Campto 20 mg/ml (NL RVG 22820) which has been registered in the Netherlands by Pfizer B.V. since 1998. It was first authorised in 1995 in France by Pfizer Holding. In addition, reference is made to Campto 20 mg/ml authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Irinotecan HCl-trihydraat Fresenius Kabi 20 mg/ml is a product in aqueous solution for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

General information
The active substance is irinotecan hydrochloride trihydrate, an established active substance, however not described in the European (Ph.Eur.*), British or United States Pharmacopoeia.
Irinotecan has one chiral centre and is produced in the S-configuration. The trihydrate has a specific crystal form.

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/EMEA 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.

** Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Manufacturing process
The substance is made starting from a significant structural fragment (Camptothecin) derived from a plant species. The manufacturing of irinotecan hydrochloride trihydrate consists of eight steps.
Detailed information on the manufacturing process is included in the EDMF. The drug substance has been adequately characterized. Sufficient information has been provided on the synthesis.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and has been established in-house by the MAH. The specification includes the following parameters: appearance, identification, colour of solution, pH of solution, water content, chromatographic purity, residual solvents, assay, specific optical rotation, sulphated ash, heavy metals, chloride, melting point, UV absorption, and bacterial endotoxins. The analytical methods were described in adequate detail. The HPLC method for assay and purity was adequately validated in line with ICH requirements. As the active substance is not described in recognised compendia, the acceptance limits are based on batch analysis data and justified by referring to frequently used limits for substances in USP or Ph.Eur. monographs. The MAH committed to add a Terminal Sterilization step in the current manufacturing process for the product. The MAH will submit a variation for this change within 6 months after approval of the current required stability information. Batch analytical data demonstrating compliance with the specification have been provided for three pilot scale validation batches and three scaled-up batches of each presentation.

Stability
Stability data on the active substance have been provided for three pilot scaled and three production scaled batches stored at 30°C/65% RH (pilot batches: 36 months; production batches: 3 months) and 40°C/75%RH (6 months). The full scale batches were stored at long term and accelerated conditions during 3 months. Study conditions were in compliance with ICH Guidelines. The batches were stored in an acceptable simulation of the commercial packaging. Based on the data provided, the proposed retest period of 2 years is justified. No special storage condition is required.

Medicinal Product

Composition
Irinotecan HCl-trihydraat Fresenius Kabi 20 mg/ml contains as active substance 20 mg/ml of irinotecan hydrochloride trihydrate, corresponding to 17.33 mg/ml of irinotecan, and is a pale yellow solution, free from visible particles.

The concentrate for solution for infusion is packed in type I amber glass vials with chlorobutyl rubber stopper and aluminium crimp cap with polypropylene flip-off. Each 6 ml glass vial contains 2 ml or 5 ml concentrate for solution for infusion.

The excipients are: sorbitol (E420), lactic acid (E270), sodium hydroxide (E524) (for pH adjustment to 3.5), water for injections.

Pharmaceutical development
The composition was stated to be the same as the composition of the reference product, both qualitatively and quantitatively. The development of the product was satisfactory performed and explained. The excipients used are common in the manufacture of parenteral formulations and the amounts used are within normal ranges. The excipients comply with their Ph.Eur. specifications. These specifications are acceptable. The packaging is usual and suitable for the dosage form. The pH was chosen for optimal chemical stability.

Manufacturing process
The drug product is prepared by dissolving the drug substance and solid excipients in water. The pH is adjusted and the final volume made up. The solution cannot be terminally sterilised and therefore the solution is filtrated through two bacteria-retentive filters prior to aseptic processing.
The manufacturing process is described in sufficient detail and has been validated according to relevant European guidelines. Process validation data on the product have been presented for 3 pilot scale batches of 2 ml vials and for 3 pilot scale batches of 5 ml vials in accordance with the relevant European guidelines. The MAH filed a suitable protocol for full-scale validation, which is identical to the pilot-scale validation. Since the manufacturing process of the product is considered standard, the information is regarded as sufficient. The choice of aseptic work and sterile filtration can be accepted. However, the Swedish authorities were of the opinion that the medicinal product should be terminally sterilised (see post-approval commitment on page 8). The efficacy of the packaging system as a barrier against microbes was shown in a media fill study.

Compatibility with diluents and dosage devices
The reference product is to be diluted with 5% dextrose or 0.9% saline to concentrations of 0.12 mg/ml and 2.8 mg/ml. The same dilutions were made with the test product, and tests showed that these dilutions were stable over 24 hours. Storage took place under ambient room lighting at 15-25°C, and in a (dark) refrigerator.

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, identity, pH, particles, extractable volume, sealing integrity, bacterial endotoxins, sterility, related substances and assay.
Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. All parameters required for the dosage form are included in accordance with the Ph.Eur. monograph on concentrates for parenteral use. Identification of the active substance is done by two analytical methods, which were deemed adequate. The analytical procedures are all described in adequate detail. Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from 6 pilot-scale batches from the proposed production sites have been provided, three on each filling volume, demonstrating compliance with the specification.

Stability tests on the finished product

The drug product has been stored at 25°C/60% RH and 40°C/75% RH. Neither out of specifications nor trends have been observed. The same applies for in-use stability. Sample vials were stored both upright and inverted. Storage under intermediate conditions was also started; these samples were only to be tested if the accelerated samples should show any changes. Since this did not happen, no intermediate test results were included.
The photostability of the solution in the amber vials was tested as required. Clear, colourless glass vials were used for comparison. In these vials degradation was significant. In amber vials the solution was stable.
Stability data on the product has been provided for six pilot scaled batches (three for each volume) stored at 25°/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. No changes were seen. The proposed shelf life of 24 months was granted. Stability data has been provided demonstrating that the product remains stable for 24 hours following dilution, when stored at room temperature and for 48 hours when stored refrigerated and dark.

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 can be excluded.

II.2 Non clinical aspects

This product is a generic formulation of Campto 20 mg/ml, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of irinotecan released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Irinotecan is a well-known active substance with established efficacy and tolerability. However, the indications approved in different member states vary. As in some member states the sought indications have not been approved, these were specified from a clinical point of view. Moreover, there is no harmonized SPC for Irinotecan products.

Irinotecan HCl-trihydraat Fresenius Kabi 20 mg/ml, concentrate for solution for infusion is a parenteral formulation in solution 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 HCl-trihydraat Fresenius Kabi 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.

Discussion on clinical subjects
Irinotecan and palliative chemotherapy
The median OS for patients with unresectable metastasized colorectal cancer (mCRC) who receive supportive care alone is five to six months. Although systemic chemotherapy has not significantly improved five-year survival rates, it is now acknowledged that meaningful improvements in median survival and progression-free survival (PFS) can be achieved. Benefits are most pronounced with oxaliplatin and irinotecan based regimens, usually in with 5-FU or 5-FU like drugs as UFT/tegafur, S1 and capecitabine. As the result, median OS durations consistently reach to approx. 20 months, and even 24 months median survival has been reported.

Although 5-FU/folic acid is effective in MCRC, the combination of irinotecan with 5-FU/folic acid (LV) appeared more effective than 5-FU/LV alone, and this triplet combination now represents a standard first-line treatment option of mCRC. However, most NL oncologists use irinotecan (-based) regimens only in the second-line or higher setting, i.e. after failure of initial oxaliplatin-based therapy. Irinotecan-based regimens are considered initially only in cases in which oxaliplatin is relatively contraindicated (eg, preexisting neuropathy).
Currently the most frequently applied i.v. 5-FU-in-combination-with-irinotecan scheme is known as FOLFIRI (or Douillard regimen). It is not clear yet whether the combination of irinotecan and capecitabine (per os) -instead of 5-FU (i.v.)- is equivalent in view of efficacy and toxicity.
Eventually refractoriness to irinotecan may appear. The possibility that cetuximab might reverse this resistance to irinotecan was suggested from a study with 138 patients with EGFR-expressing mCRC, in which partial response was noted in 15% of patients. Median TTP was 6.5 months. Also the addition of irinotecan to cetuximab in patients with irinotecan-refractory mCRC (n=329) resulted in a statistically significant better RR and TTP when compared to the cetuximab-alone arm, but median survival appeared not different significantly.
Patients expressing polymorphism in the irinotecan metabolising enzyme gene UGT1A1 (at the UGT1A1*28 allele) may encounter more /higher grade AE irinotecan-metabolite SN-38 related neutropenia and diarrea. Whether initial dose reduction is needed for UGT1A1*28 homozygote patients remains unclear thus far.

Irinotecan and adjuvant chemotherapy
Benefit could not be shown for irinotecan as adjuvant drug in several clinical trials. Disadvantages were mostly related to (febrile) neutropenia and treatment related death. Based upon the results from several studies, irinotecan-containing chemotherapy is therefore not considered a standard approach for patients requiring adjuvant chemotherapy for resected colon cancer.

Risk management plan
Irinotecan was first approved in May 1995, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of irinotecan can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Pharmacovigilance system
Several deficiencies were identified during the mutual recognition procedure in the pharmacovigilance system. The MAH therefore committed to ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market. During the transfer of the MA to Fresenius Kabi Oncology Plc, a new Pharmacovigilance system was submitted. The Pharmacovigilance system as described fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Product information

SPC
The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Campto marketed by Pfizer B.V.. The chemical-pharmaceutical sections of the Dutch SPC are an adequate reflection of these product characteristics, otherwise the Dutch SPC is in line with the innovator SPC, with the exclusion of the phrases relating to the co-treatment with bevacizumab (as this indication is patented, see section 4.1 and 4.2).

Readability test
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 test consisted of 15 questions. All questions met the criterion of 81% correct answers. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Irinotecan HCl-trihydraat Fresenius Kabi 20 mg/ml, concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Campto 20 mg/ml. Campto 20 mg/ml 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 SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other irinotecan containing products.

The Board followed the advice of the assessors. Irinotecan HCl-trihydraat Fresenius Kabi 20 mg/ml was authorised in the Netherlands on 14 April 2008.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Irinotecan HCl-trihydraat Fresenius Kabi 20 mg/ml with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 2 December 2008.

A European harmonised birth date has been allocated (05-05-1995) and subsequently the first data lock point for irinotecan is May 2011. The first PSUR will cover the period from December 2008 to May 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 2 December 2013.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to add a Terminal Sterilization step in the current manufacturing process for the product. The MAH will submit a variation for this change within 6 months after approval of the current required stability information. Irinotecan HCl-trihydraat Fresenius Kabi 20 mg/ml will not be on the Swedish market until the variation for a change in manufacturing process, to terminal sterilization, has been completed and approved.

Pharmacovigilance

- The MAH committed to provide the registration authority of Slovenia with a written statement regarding the appointment of a person responsible for pharmacovigilance and a copy of diploma of this person. This issue will be solved before the MA can be granted in Slovenia.

Product information

- The MAH committed not to market the product with the name "Irinotecan advisors 20mg/ml" in Norway, and to submit a variation to change the product name.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HPLC	High Performance Liquid Chromatography
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the name and/or address of a manufacturer of the finished product	NL/H/1503/ 001/IA/001	IA	09-03-2009	23-03-2009	Approval	N
Change in the name of the medicinal product (together with transfer of the MA to Fresenius Kabi Oncology Plc.)	NL/H/1503/ 001/IB/002	IB	09-03-2009	08-04-2009	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; secondary packaging site for all types of pharmaceutical forms	NL/H/1503/ 001/IA/003	IA	11-06-2009	26-06-2009	Approval	N
Change in the name and/or address of a manufacturer of the active substance where no Ph.Eur.Certificate of Suitability is available	NL/H/1503/ 001/IA/005	IA	23-07-2009	6-08-2009	Approval	N
Change in the manufacturer of the active substance of starting material/reagent/intermediate in the manufacturing process of the active substance where no Ph.Eur.Certificate of Suitability is available; new manufacturer (replacement or addition)	NL/H/1503/ 001/IB/006	IB	23-07-2009	22-08-2009	Approval	N
Change in the specification of an active substance or a starting material/intermediate/reagent used in the manufacturing process of the active substance; addition of a new test parameter to the specification of an active substance	NL/H/1503/ 001/IB/007	IB	23-07-2009	22-08-2009	Approval	N