Public Assessment Report

Decentralised

Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion

UK/H/1006/001/DC

UK licence no: PL 00289/1018

Teva UK Ltd

LAY SUMMARY

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

This is a summary of the public assessment report (PAR) for Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion (PL 00289/1018). It explains how Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion.

For practical information about using Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion, patients should read the package leaflet or contact their doctor or pharmacist.

What is Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion and what is it used for?

Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion is a 'generic medicine'. This means that Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion is similar to 'reference medicines' already authorised in the UK called Campto 40 mg/2 ml and 100 mg/5 ml concentrate for solution for infusion (Aventis Pharma; PL 04425/0351 and Pfizer Ltd, UK; PL 00057/0627).

Irinotecan hydrochloride 20 mg/ml is used for the treatment of advanced cancer of the colon and rectum in adults, either in a combination with other medicines or alone.

How is Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion used?

Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion is given by infusion into the veins over a period of 30 to 90 minutes.

The amount of Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion given will depend on the age, size, general medical condition and any other treatment the patient may have received for cancer. The body surface area in square metres (m^2) will be calculated by a doctor. The duration of the treatment will depend on how the patient is responding to treatment.

This medicine can only be obtained on prescription from a doctor.

For further information on how Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion is used, please see the Summary of Product Characteristics and the package leaflet available on the MHRA website.

How does Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion work?

Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion contains the active ingredient irinotecan hydrochloride trihydrate, which belongs to a group of medicines called cytostatics (anti-cancer medicines). This medicine kills cancer cells by interfering with the genetic material DNA, which is necessary for their growth and reproduction.

How has Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion been studied?

No clinical studies were conducted as Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion are generic medicines that are given by infusion and contain the same active substance as the reference medicines, Campto 40 mg/2 ml and 100 mg/5 ml concentrate for solution for infusion (Aventis Pharma; PL 04425/0351 and Pfizer Ltd; PL 00057/0627).

What are the benefits and risks of Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion?
As Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion is a generic medicine and is considered to be bioequivalent to the reference products, their benefits and risks are taken as being the same as those of the reference products.

Why is Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion approved?
It was concluded that, in accordance with EU requirements, Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion has been shown to have comparable quality and to be comparable to the reference products. Therefore, the view was that, as for Campto 40 mg/2 ml and 100 mg/5 ml concentrate for solution for infusion (Aventis Pharma; PL 04425/0351 and Pfizer Ltd, UK; PL 00057/0627), the benefit outweighs the identified risks.

What measures are being taken to ensure the safe and effective use of Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion?
A satisfactory pharmacovigilance system has been provided, which fulfils the requirements and provides adequate evidence that the applicant 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.

Other information about Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion
Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Norway, Poland, Portugal, Slovenia, Slovak Republic, Spain, Sweden, The Netherlands and the UK agreed to grant a Marketing Authorisation for Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion on 9th March 2008. A Marketing Authorisation was granted in the UK on 19th February 2008 (PL 00289/1018).

The full PAR for Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion follows this summary. For more information about treatment with Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in November 2014.

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Module 1

Information about initial procedure

Product Name	Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion
Type of Application	Article 10(1), Generic application
Active Substance	Irinotecan hydrochloride trihydrate
Form	Concentrate for solution for infusion
Strength	20 mg/ml
MA Holder	Teva UK Limited Brampton Road, Hampden Park, Eastbourne, BN22 9AG, United Kingdom
RMS	UK
CMSs	Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Norway, Poland, Portugal, Slovenia, Slovak Republic, Spain, Sweden and The Netherlands
Procedure Number	UK/H/1006/001/DC
Timetable	Day 210: 09th March 2008

Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

Module 4

Labelling

PARTICULARS TO APPEAR ON THE OUTER AND IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion
irinotecan hydrochloride trihydrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Sorbitol, Lactic acid, Sodium hydroxide, Hydrochloric acid, Water for injection

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion.
1 vial / pack
40 mg/ 2 ml
100 mg/ 5 ml
300 mg/15 ml
500 mg/ 25 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution only
Please read the enclosed package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytostatic agent

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the vial in the outer carton in order to protect from light.
After first opening the content of the vial should be diluted and used immediately

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

If any precipitate is observed in the vials or after dilution, the product should be discarded according to standard procedures for cytotoxic agents.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

TEVA UK Limited, Eastbourne, BN22 9AG

12. MARKETING AUTHORISATION NUMBER(S)

PL 00289/1018

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by the doctor

16. INFORMATION IN BRAILLE

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

GLASS VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion
irinotecan hydrochloride trihydrate

2. METHOD OF ADMINISTRATION

For intravenous use after dilution only

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 mg/2 ml
100 mg/5 ml
300 mg/ 15 ml
500 mg/ 25 ml

6. OTHER

NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER:

TEVA UK Ltd, Eastbourne, BN22 9AG

POM

PL 00289/1018

Module 5

Scientific discussion during initial procedure

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion, in the treatment of advanced colorectal cancer, is approvable.

EXECUTIVE SUMMARY
Problem statement
This decentralised application concerns a generic version of irinotecan hydrochloride trihydrate submitted under Article 10(1) of Directive 2001/83/EC, as amended. Campto 40 mg/2 ml and 100 mg/5 ml (concentrate for solution for infusion) are the originator products, which have been marketed by Aventis Pharma (PL 04425/0351) and Pfizer Ltd, UK (PL 00057/0627).

With the UK as the Reference Member State in this Decentralised Procedure, Teva Pharma B.V. applied for Marketing Authorisations for Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion in Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Norway, Poland, Portugal, Slovenia, Slovak Republic, Spain, Sweden and The Netherlands.

About the product
Irinotecan, a Camptothecin, is licensed for first-line use in patients with advanced or metastatic colorectal cancer (in combination with fluorouracil and folinic acid) or as second-line monotherapy when fluorouracil-based therapy has failed. Irinotecan is administered intravenously at doses ranging from 180-350 mg/m^2 over a 30-90 minute period. Irinotecan is metabolized to SN-38 in the presence of hepatic or gastrointestinal carboxylesterases. SN-38 is 100-1000 fold more cytotoxic than Irinotecan. Irinotecan and SN-38 form a cleavable drug-topoisomerase I-DNA complex, which results in lethal double stranded DNA breaks. DNA strand breaks lead to activation of apoptosis and cell death. Diarrhoea is the most common adverse event and may cause life threatening hypovolaemia in severe late onset cases. Myelosuppression (neutropenia) is also a frequent dose-limiting adverse event and septic deaths have been reported.

The drug product Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion corresponds to the current EU definition for essential similarity because it complies with the criteria of having the same qualitative and quantitative composition in terms of active substance (20 mg Irinotecan hydrochloride trihydrate/ ml) and the same dosage form (Concentrate for solution for infusion). The proposed product is developed using an approved drug substance which is to be administered as an aqueous intravenous solution containing the same drug substance in the same concentration. Therefore a bioequivalence study is not required in support of this application.

General comments on the submitted dossier
The application is in accordance with Article 10(1) of Directive 2001/83/EC, as amended. The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory quality, non-clinical

and clinical overviews have been submitted. They represent an adequate summary of the dossier.

A formal Environmental Risk Assessment has not been performed as the product is intended for generic substitution. Hence no increase in environmental risk is to be expected compared to that of the reference product. Readability testing of the Patient Information Leaflet has been conducted and the applicant supplied the readability testing on the Patient Information leaflet agreed during the procedure.

General comments on compliance with GMP and GLP

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

SCIENTIFIC OVERVIEW AND DISCUSSION

QUALITY ASPECTS

Drug substance

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to irinotecan hydrochloride trihydrate are of sufficient quality in view of the present European regulatory requirements. The active substance irinotecan hydrochloride trihydrate is not reported in any international pharmacopoeia. The drug substance specification for drug substance is generally acceptable. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest period of 36 months is acceptable.

Drug Product

The development of the product has been described, the choice of excipients is justified and their functions explained. The other ingredients of the product are sorbitol, lactic acid, sodium hydroxide, hydrochloric acid and water for injection. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on three 5000 vials and 2000 vials for 40 mg/2 ml and 100 mg/5 ml presentations respectively. The batch analysis results show that the finished products meet the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. Full validation data for each presentation at commercial scale has been provided. The proposed shelf-life of 2 years is acceptable.

NON-CLINICAL ASPECTS

Critical evaluation of the Non-Clinical Overview and Summary

The pharmacodynamic, pharmacokinetic and toxicological properties of irinotecan hydrochloride trihydrate are well known. As the compound is a widely used, well known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on a literature review is thus appropriate.

Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion is stated to be essentially similar to Campto 40 mg/2 ml concentrate for solution for infusion marketed by Pfizer Ltd, UK which was authorised in September 1995. The reference product has therefore been authorised in the EU for at least 10 years. Irinotecan hydrochloride trihydrate is an antineoplastic agent of the topoisomerase I inhibitor class.

The non-clinical overview is an acceptable overview of some of the published literature. It is acceptable in view of the well-known properties of the compound. The overview refers to ten documents including published literature dated up to 2005.
Section 5.3 of the SmPC is acceptable.

Conclusions

There are no objections to approval of Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion from a non-clinical point of view.

CLINICAL ASPECTS

Bioequivalence studies
No new pharmacokinetic or pharmacodynamic data were submitted with this application and none were required, as per the *Notes for guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1 **) which state that if the test product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived, if the excipients contained in it do not affect gastrointestinal transit, absorption, solubility or *in-vivo* stability of the active substance.

Pharmacodynamics

No novel pharmacodynamic data are supplied or required for this application. The pharmacodynamic claims in the SmPC are appropriately consistent with the innovator product.

Clinical Efficacy

No novel efficacy data are supplied or required for this generic application. However, the applicant has provided a review of clinical trials published in the literature confirming the efficacy of Irinotecan. The clinical overview describes several clinical trials which have established Irinotecan as one of the most active drugs in first and second line treatment of colorectal cancer. Irinotecan has an acceptable adverse events profile (Rothenberg et al., 2001, Kohne et al., 2005, Falcone et al., 2001, Vanhoefer et al., 2001, Saltz et al., 2001, Douillard et al., 2000, Teufel et al., 2004, Rothenberg et al., 1999, Rougier et al., 1998).

Clinical Safety

No novel safety data are supplied or required for this generic application. However, the applicant has provided a review of clinical trials published in the literature confirming the safety of Irinotecan hydrochloride trihydrate. No new safety data have been identified.

BENEFIT RISK ASSESSMENT

The use of irinotecan hydrochloride trihydrate is well established. It has recognised efficacy and acceptable safety. With regards to the current application, sufficient clinical information has been submitted which includes adequate review of published clinical data. The claim of essential similarity can be accepted. Overall the benefit risk analysis is considered favourable and approval is recommended.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

The following table lists some non-safety updates to the Marketing Authorisation for this product that have been approved by the MHRA since the product was first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

Date submitted	Application type	Scope	Outcome
08/09/2014	VAR Medical Type IB	To change the name of the medicinal product in the UK only from Irinotecan Teva 20 mg/ml concentrate for solution for infusion to Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion. Consequentially, sections 1, 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 5.1, 6.3, 6.5, the label and leaflet have been updated.	22/10/2014

Annex 1

Reference: **PL 00289/1018 - application 0056**

Product: **Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion.**

MAH: **TEVA UK LIMITED**

Active Ingredient: **Irinotecan hydrochloride trihydrate**

Reason:
To change the name of the medicinal product in the UK only from Irinotecan Teva 20 mg/ml concentrate for solution for infusion to Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion. Consequentially, sections 1, 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 5.1, 6.3, 6.5, the label and leaflet have been updated.

Supporting evidence:
- Cover letter and AF
- Updated SmPC fragments, label and PL

Evaluation
The scope of this variation is a name change in the UK only from:
- Irinotecan Teva 20 mg/ml concentrate for solution for infusion
  to
- Irinotecan hydrochloride 20 mg/ml concentrate for solution for infusion.

The use of a generic name in the UK is accepted.

The content of irinotecan corresponds to 20 mg/ml of irinotecan hydrochloride trihydrate – the quantity of drug substance is NOT factored for the anhydrous hydrochloride salt.

However this is also the case for a number of other generic products; PL 04515/0227 (Hospira) and PL 04416/1029 (Sandoz). There is one generic product names as “irinotecan concentrate for solution for infusion”, however all have essentially the same composition. No product includes the trihydrate within the product name.

In light of this and to maintain consistency, the proposed name “Irinotecan hydrochloride concentrate for solution for infusion” is accepted.

NOTE: Mock-ups have not been provided as this product is not currently marketed in the UK. An appropriate commitment to submit these for approval prior to initiation of marketing has been provided.

Conclusion
The variation was approved on 22nd October 2014 and the updated SmPC fragments, PIL and labelling have been incorporated into this Marketing Authorisation. The proposed changes are acceptable.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) Updated

Following approval of the variation on 22nd October 2014 the SmPC was updated. In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.

PATIENT INFORMATION LEAFLET (PIL) - Updated

Following approval of the variation on 22nd October 2014 the PIL was updated. In accordance with Directive 2010/84/EU the Patient Information Leaflet (PIL) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.