# UKPAR

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LAY SUMMARY

The Medicines Healthcare products Regulatory Agency granted TechnoPharm Ltd a Marketing Authorisation (licence) for the medicinal product Irinotecan 20mg/ml Solution for Infusion (PL 20176/0052) on the 11th May 2009. The licence subsequently underwent a change of ownership to TEVA UK Limited on the 10th June 2009, as PL 00289/1393. This is a prescription-only medicine (POM).

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

The active ingredient irinotecan hydrochloride belongs to a group of medicines called cytostatics (anti-cancer medicines).

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Irinotecan Hydrochloride 20mg/ml Solution for Infusion outweigh the risks; hence a Marketing Authorisation has been granted.
IRINOTECAN 20MG/ML SOLUTION FOR INFUSION
PL 00289/1393

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal products Irinotecan Hydrochloride 20mg/ml Solution for Infusion (PL 20176/0052) on 11th May 2009. The licence subsequently underwent a change of ownership to TEVA UK Limited on the 10th June 2009, as PL 00289/1393. This is a prescription-only medicine (POM).

This is a national application for Irinotecan Hydrochloride 20mg/ml Solution for Infusion submitted under Article 10.1 of Directive 2001/83/EC, as amended, which have been shown to be generic medicinal product of Campto 40mg/2ml (PL 00057/0626) and 100mg/5ml (PL 00057/0627) concentrate for solution for infusion, authorised to Pfizer Ltd on 5th November 2004 following two change of ownerships originating to May and Baker Limited [PL00012/0302 (40mg/2ml) and PL00012/0303 (100mg/5ml)], dated in 17 October 1996. The reference product has therefore been authorised in the EU for more than 10 years.

The product contains the active ingredient irinotecan hydrochloride trihydrate, an antineoplastic agent of the topoisomerase I inhibitor class. It is a semisynthetic derivative of camptothecin, obtained from the branches of Mappia foetida tree. I.

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. 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.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Irinotecan Hydrochloride trihydrate
INN: Irinotecan Hydrochloride trihydrate

Structure:

Description: Pale yellow to yellow crystalline powder
Molecular formula: C_{33}H_{38}N_{4}O_{6}.HCl.3H_{2}O
Relative molecular mass: 677.19

Physical form: White or almost white, crystalline powder, bitter taste
Molecular formula: C_{17}H_{27}N_{3}O_{4}S
Molecular weight: 369.5
Steroisomerism/chirality: one chiral centre (racemic mixture)

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting material and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance irinotecan hydrochloride trihydrate.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification.

An adequate retest period has been defined based on conducted stability studies.

DRUG PRODUCT
Other ingredients
Other ingredients consist of pharmaceutical excipients, namely sorbitol, lactic acid, sodium hydroxide, hydrochloric acid and water for injections. All excipients used comply with their respective Ph Eur monograph. Satisfactory certificates of analysis have been provided for
all excipients. The only excipient used that contains material of animal or human origin is lactic acid. A satisfactory certificate of suitability has been provided for lactic acid.

**Impurity profiles**
Impurity profiles of the drug product were found to be similar to those for the reference product, Campto.

**Manufacture**
A detailed description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on two batches per strength of product and the results are satisfactory.

**Finished product specification**
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container Closure System**
The product is presented in a Type I amber glass vial, with a bromobutyl stopper capped by a flip-off aluminium cap with a polypropylene cover. Specifications and certificates of analysis for the packaging types used have been provided. These are satisfactory. The product is packaged in sizes of 40mg/2ml and 100mg/5ml.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24months (unopened) has been set. Storage conditions are to “Store in the original package, in order to protect from light”, which is satisfactory. For specific storage conditions after opening please refer to the SPC and leaflet.

**Patient Information Leaflet**
This is satisfactory. The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Bioequivalence**
No new data have been submitted and none are required for this application. According to CPMP guidelines, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98, subpoint 5.1.6, Parenteral solutions).
ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics
This is consistent with that of the reference product and is satisfactory.

MAA forms
This is satisfactory.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

The requirements for a generic medicinal product for the proposed products have been met with respect to qualitative and quantitative content of the active substance and pharmaceutical form.
PRECLINICAL ASSESSMENT

This application is a generic medicinal product of Campto 40mg/2ml and Campto 100mg/5ml (Pfizer Ltd, which have been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with this application and none are required for an application of this type.
CLINICAL ASSESSMENT

1.1 CLINICAL BACKGROUND
Irinotecan Hydrochloride Trihydrate is an antineoplastic agent of the topoisomerase I inhibitor class. It is a semisynthetic derivative of camptothecin, obtained from the branches of Mappia foetida tree. Irinotecan is rapidly esterified in vivo to SN-38, an active metabolite that contributes to the antitumor activity of the drug.

Irinotecan is considered to have a well-established use and a favourable risk: benefit profile in the intended indications, and there is sufficient published literature supporting the claim of well-established use with proven efficacy.

1.2 INDICATIONS

The Applicant has stated the following:

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.

Assessor’s comment:
The indications sought for this generic irinotecan solution for infusion are consistent with those approved for the reference medicinal product in the UK.

1.3 DOSE AND DOSE REGIMEN

The Applicant’s dosing recommendations are as reiterated below:

For adults only.

Irinotecan solution for infusion should be infused into a peripheral or central vein.

Recommended dosage:

In monotherapy (for previously treated patients):

The recommended dosage of Irinotecan is 350 mg/m² administered as an intravenous infusion over a 30 to 90 minute period every three weeks (see sections 6.6 and 4.4).

In combination therapy (for previously untreated patients):

Safety and efficacy of Irinotecan in combination with 5-fluorouracil (5FU) and folinic acid (FA) have been assessed with the following schedule (see section 5.1):
Irinotecan plus 5FU/FA in once every 2 weeks schedule.

The recommended dose of Irinotecan is 180 mg/m² administered once every 2 weeks as an intravenous infusion over a 30 to 90 minute period, followed by infusion with folinic acid and 5-fluorouracil.

**Dosage adjustments:**

Irinotecan should be administered after appropriate recovery of all adverse events to grade 0 or 1 NCI-CTC grading (National Cancer Institute Common Toxicity Criteria) and when treatment-related diarrhoea is fully resolved.

At the start of a subsequent infusion of therapy, the dose of Irinotecan, and 5FU when applicable, should be decreased according to the worst grade of adverse events observed in the prior infusion. Treatment should be delayed by 1 to 2 weeks to allow recovery from treatment-related adverse events.

With the following adverse events a dose reduction of 15 to 20 % should be applied for Irinotecan and/or 5FU when applicable:

- haematological toxicity (neutropenia grade 4, febrile neutropenia (neutropenia grade 3-4 and fever grade 2-4), thrombocytopenia and leukopenia (grade 4)),
- non haematological toxicity (grade 3-4).

**Treatment Duration:**

Treatment with Irinotecan should be continued until there is an objective progression of the disease or an unacceptable toxicity.

**Special populations:**

**Patients with Impaired Hepatic Function:**

In monotherapy: Blood bilirubin levels (up to 3 times the upper limit of the normal range (ULN)) in patients with performance status ≤ 2, should determine the starting dose of Irinotecan. In these patients with hyperbilirubinemia and prothrombin time prolonged by greater than 50%, the clearance of irinotecan is decreased (see section 5.2) and therefore the risk of hematoxotoxicity is increased. Thus, weekly monitoring of complete blood counts should be conducted in this patient population.

- In patients with bilirubin up to 1.5 times the upper limit of the normal range (ULN), the recommended dosage of Irinotecan is 350 mg/m².
- In patients with bilirubin ranging from 1.5 to 3 times the ULN, the recommended dosage of Irinotecan is 200 mg/m².
- Patients with bilirubin greater than 3 times the ULN should not be treated with Irinotecan (see sections 4.3 and 4.4).

No data are available in patients with hepatic impairment treated by Irinotecan in combination.

**Patients with Impaired Renal Function:**

Irinotecan is not recommended for use in patients with impaired renal function, as studies in this population have not been conducted (see sections 4.4 and 5.2).
Elderly:
No specific pharmacokinetic studies have been performed in elderly. However, the dose should be chosen carefully in this population due to their greater frequency of decreased biological functions. This population should require more intense surveillance (see section 4.4).

Assessor’s comment:
These dosing recommendations are consistent with those for the reference medicinal product.

1.4 GCP ASPECTS
Not applicable

1.5 ORPHAN MEDICINAL PRODUCTS
Not applicable

1.6 PAEDIATRIC DEVELOPMENT PROGRAMME
Not applicable

1.7 SCIENTIFIC ADVICE
No scientific advice sought.

1.8 LEGAL STATUS
POM

2 CLINICAL PHARMAKOLOGY

2.1 PHARMACOKINETICS
No novel PK data are supplied or required for this application

2.2 BIOEQUIVALENCE
No bioequivalence data have been submitted or are required for this application.

2.3 PHARMACODYNAMICS
No novel efficacy or safety data are supplied or required for this application.

3 EFFICACY
No novel clinical data are supplied or required for this application.

4 SAFETY
No novel clinical data are supplied or required for this application.

5 EXPERT REPORTS
The Clinical Overview provides an adequate review of the relevant literature, and has been written by a suitably qualified person.
6 PRODUCT LITERATURE

6.1 SPC
The SPC is medically fine.

6.2 PATIENT INFORMATION LEAFLET
The PIL is medically satisfactory.

6.3 LABEL
The label is medically satisfactory.

6.4 APPLICATION FORM
The MAA form is medically satisfactory.

7 OVERALL CONCLUSION
No new clinical data have been submitted or are required for this generic irinotecan solution for infusion.

A marketing authorisation is recommended for this application.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Irinotecan 20mg/ml Solution for Infusion is well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
No bioequivalence data were submitted and none are required for an application of this type.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with irinotecan hydrochloride trihydrate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
IRINOTECAN 20MG/ML SOLUTION FOR INFUSION
PL 00289/1393

STEPS TAKEN FOR ASSESSMENT

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 26\textsuperscript{th} May 2006.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 8\textsuperscript{th} August 2006.</td>
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<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 30\textsuperscript{th} October 2006, 24\textsuperscript{th} September 2007 and 18\textsuperscript{th} December 2007, and further information relating to the quality dossiers on 9\textsuperscript{th} September 2006, 27\textsuperscript{th} July 2007 and 18\textsuperscript{th} February 2008.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 16\textsuperscript{th} May 2007, 18\textsuperscript{th} November 2007, and 18\textsuperscript{th} December 2007 for the clinical sections, and again on 16\textsuperscript{th} May 2007, 27\textsuperscript{th} July 2007, and 25\textsuperscript{th} September 2008 for the quality sections.</td>
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<td>The application was determined on 11\textsuperscript{th} May 2009.</td>
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IRINOTECAN 20MG/ML SOLUTION FOR INFUSION
PL 00289/1393

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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<tr>
<td>10th June 2009</td>
<td>Cancellation</td>
<td>Cancellation of licence (PL 20176/0052)</td>
<td>Approved 10th June 2009</td>
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<tr>
<td>10th June 2009</td>
<td>Change of Ownership</td>
<td>Change of Ownership to PL 00289/1393</td>
<td>Approved 10th June 2009</td>
</tr>
<tr>
<td>17th June 2009</td>
<td>Label &amp; Leaflets</td>
<td>Self Certification submitted under Article 61 (3) change category 9 &amp; 19.</td>
<td>Approved 17th June 2009</td>
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IRINOTECAN 20MG/ML SOLUTION FOR INFUSION
PL 00289/1393

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Irinotecan 20mg/ml Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
The concentrate contains 20 mg/ml irinotecan hydrochloride, trihydrate (equivalent to 17.33 mg/ml irinotecan). Each vial of 2 ml contains 40 mg and each vial of 5 ml contains 100 mg of irinotecan hydrochloride, trihydrate.

Excipients:
Each ml of solution contains 45mg sorbitol (E420)
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Concentrate for solution for infusion.
Light yellow or yellow solution.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC 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.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
For adults only.
Irinotecan solution for infusion should be infused into a peripheral or central vein.

Recommended dosage:
- In monotherapy (for previously treated patients):
The recommended dosage of Irinotecan is 350 mg/m² administered as an intravenous infusion over a 30 to 90 minute period every three weeks (see sections 6.6 and 4.4).
- In combination therapy (for previously untreated patients):
Safety and efficacy of Irinotecan in combination with 5-fluorouracil (5FU) and folinic acid (FA) have been assessed with the following schedule (see section 5.1):
Irinotecan plus 5FU/FA in once every 2 weeks schedule.
The recommended dose of Irinotecan is 180 mg/m² administered once every 2 weeks as an intravenous infusion over a 30 to 90 minute period, followed by infusion with folinic acid and 5-fluorouracil.

Dosage adjustments:
Irinotecan should be administered after appropriate recovery of all adverse events to grade 0 or 1 NCI-CTC grading (National Cancer Institute Common Toxicity Criteria) and when treatment-related diarrhoea is fully resolved.
At the start of a subsequent infusion of therapy, the dose of Irinotecan, and 5FU when applicable, should be decreased according to the worst grade of adverse events observed in the prior infusion. Treatment should be delayed by 1 to 2 weeks to allow recovery from treatment-related adverse events.

With the following adverse events a dose reduction of 15 to 20% should be applied for Irinotecan and/or 5FU when applicable:

- haematological toxicity (neutropenia grade 4, febrile neutropenia (neutropenia grade 3-4 and fever grade 2-4), thrombocytopenia and leukopenia (grade 4)),
- non haematological toxicity (grade 3-4).

**Treatment Duration:**

Treatment with Irinotecan should be continued until there is an objective progression of the disease or an unacceptable toxicity.

**Special populations:**

**Patients with Impaired Hepatic Function:**

In monotherapy: Blood bilirubin levels (up to 3 times the upper limit of the normal range (ULN)) in patients with performance status ≤ 2, should determine the starting dose of Irinotecan. In these patients with hyperbilirubinemia and prothrombin time prolonged by greater than 50%, the clearance of irinotecan is decreased (see section 5.2) and therefore the risk of hematotoxicity is increased. Thus, weekly monitoring of complete blood counts should be conducted in this patient population.

- In patients with bilirubin up to 1.5 times the upper limit of the normal range (ULN), the recommended dosage of Irinotecan is 350 mg/m².
- In patients with bilirubin ranging from 1.5 to 3 times the ULN, the recommended dosage of Irinotecan is 200 mg/m².
- Patients with bilirubin greater than 3 times the ULN should not be treated with Irinotecan (see sections 4.3 and 4.4).

No data are available in patients with hepatic impairment treated by Irinotecan in combination.

**Patients with Impaired Renal Function:**

Irinotecan is not recommended for use in patients with impaired renal function, as studies in this population have not been conducted (see sections 4.4 and 5.2).

**Elderly:**

No specific pharmacokinetic studies have been performed in elderly. However, the dose should be chosen carefully in this population due to their greater frequency of decreased biological functions. This population should require more intense surveillance (see section 4.4).

**4.3 CONTRAINDICATIONS**

Hypersensitivity to the active substance or to any of the excipients.

Chronic inflammatory bowel disease and/or bowel obstruction (see section 4.4).

Pregnancy and lactation (see sections 4.4 and 4.6).

Bilirubin > 3 times the upper limit of the normal range (see section 4.4).

Severe bone marrow failure.

WHO performance status > 2.

Concomitant use with St John's Wort (see section 4.5).

Contraindications for other medicinal products also apply, when combined with Irinotecan.
4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The use of Irinotecan should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a physician qualified in the use of anticancer chemotherapy.

Given the nature and incidence of adverse events, Irinotecan will only be prescribed in the following cases after the expected benefits have been weighted against the possible therapeutic risks:

- In patients presenting a risk factor, particularly those with a WHO performance status = 2.
- In the few rare instances where patients are deemed unlikely to observe recommendations regarding management of adverse events (need for immediate and prolonged antidiarrhoeal treatment combined with high fluid intake at onset of delayed diarrhoea). Strict hospital supervision is recommended for such patients.

When Irinotecan is used in monotherapy, it is usually prescribed with the once every 3 week dosage schedule. However, the weekly dosage schedule (see section 5) may be considered in patients who may need a closer follow-up or who are at particular risk of severe neutropenia.

Delayed diarrhoea

Patients should be made aware of the risk of delayed diarrhoea occurring more than 24 hours after the administration of Irinotecan and at any time before the next cycle. In monotherapy, the median time of onset of the first liquid stool was on day 5 after the infusion of Irinotecan. Patients should quickly inform their physician of its occurrence and start appropriate therapy immediately. Patients with an increased risk of diarrhoea are those who had a previous abdominal/pelvic radiotherapy, those with baseline hyperleucocytosis, those with performance status $\geq 2$ and women. If not properly treated, diarrhoea can be life-threatening, especially if the patient is concomitantly neutropenic.

As soon as the first liquid stool occurs, the patient should start drinking large volumes of beverages containing electrolytes and an appropriate antidiarrhoeal therapy must be initiated immediately. This antidiarrhoeal treatment will be prescribed by the department where Irinotecan has been administered. After discharge from the hospital, the patients should obtain the prescribed drugs so that they can treat the diarrhoea as soon as it occurs. In addition, they must inform their physician or the department administering Irinotecan when/if diarrhoea is occurring.

The currently recommended antidiarrhoeal treatment consists of high doses of loperamide (4 mg for the first intake and then 2 mg every 2 hours). This therapy should continue for 12 hours after the last liquid stool and should not be modified. In no instance should loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours.

In addition to the anti-diarrhoeal treatment, a prophylactic broad spectrum antibiotic should be given, when diarrhoea is associated with severe neutropenia (neutrophil count < 500 cells/mm$^3$).

In addition to the antibiotic treatment, hospitalisation is recommended for management of the diarrhoea, in the following cases:

- Diarrhoea associated with fever.
- Severe diarrhoea (requiring intravenous hydration).
- Diarrhoea persisting beyond 48 hours following the initiation of high dose loperamide therapy.

Loperamide should not be given prophylactically, even in patients who experienced delayed diarrhoea at previous cycles.

In patients who experienced severe diarrhoea, a reduction in dose is recommended for subsequent cycles (see section 4.2).
Haematology

Weekly monitoring of complete blood cell counts is recommended during Irinotecan treatment. Patients should be made aware of the risk of neutropenia and the significance of fever. Febrile neutropenia (temperature >38°C and neutrophil count ≤1,000 cells/mm³) should be urgently treated in the hospital with broad-spectrum intravenous antibiotics.

In patients who experienced severe haematological events, a dose reduction is recommended for subsequent administration (see section 4.2).

There is an increased risk of infections and haematological toxicity in patients with severe diarrhoea. In patients with severe diarrhoea, complete blood cell counts should be performed.

Liver impairment

Liver function tests should be performed at baseline and before each cycle.

Weekly monitoring of complete blood counts should be conducted in patients with bilirubin ranging from 1.5 to 3 times ULN, due to the decreased clearance of Irinotecan (see section 5.2) increasing the risk of hematotoxicity in this population.

For patients with a bilirubin > 3 times ULN (see section 4.3).

Nausea and vomiting

A prophylactic treatment with antiemetics is recommended before each treatment with Irinotecan. Nausea and vomiting have been frequently reported. Patients with vomiting associated with delayed diarrhoea should be hospitalised as soon as possible for treatment.

Acute cholinergic syndrome

If acute cholinergic syndrome appears (defined as early diarrhoea and various other symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation), atropine sulphate (0.25 mg subcutaneously) should be administered unless clinically contraindicated (see section 4.8). Caution should be exercised in patients with asthma. In patients who experienced an acute and severe cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent doses of Irinotecan.

Respiratory disorders

Interstitial pulmonary disease presenting as pulmonary infiltrates is uncommon during irinotecan therapy. Interstitial pulmonary disease can be fatal. Risk factors possibly associated with the development of interstitial pulmonary disease include use of pneumotoxic drugs, radiation therapy and colony stimulating factors. Patients with risk factors should be closely monitored for respiratory symptoms before and during irinotecan therapy.

Elderly

Due to the greater frequency of decreased biological functions, in particular hepatic function, in elderly patients, dose selection with Irinotecan should be cautious in this population (see section 4.2).

Patients with bowel obstruction

Patients must not be treated with Irinotecan until resolution of the bowel obstruction (see section 4.3).

Patients with Impaired Renal Function

Studies in this population have not been conducted. (see sections 4.2 and 5.2).

Others

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Infrequent cases of renal insufficiency, hypotension or circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis.

Contraceptive measures must be taken during and for at least three months after cessation of therapy.
Concomitant administration of irinotecan with a strong inhibitor (e.g. ketoconazole) or inducer (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, St John's Wort) of CYP3A4 may alter the metabolism of irinotecan and should be avoided (see section 4.5).

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Interaction between irinotecan and neuromuscular blocking agents cannot be ruled out. Since irinotecan has anticholinesterase activity it may prolong the neuromuscular blocking effects of suxamethonium and may antagonise the neuromuscular blockade of non-depolarising drugs.

Several studies have shown that concomitant administration of CYP3A-inducing anticonvulsant drugs (e.g., carbamazepine, phenobarbital or phenytoin) leads to reduced exposure to irinotecan, SN-38 and SN-38 glucuronide and reduced pharmacodynamic effects. The effects of such anticonvulsant drugs was reflected by a decrease in AUC of SN-38 and SN-38G by 50% or more. In addition to induction of cytochrome P450 3A enzymes, enhanced glucuronidation and enhanced biliary excretion may play a role in reducing exposure to irinotecan and its metabolites.

A study has shown that the co-administration of ketoconazole resulted in a decrease in the AUC of APC of 87% and in an increase in the AUC of SN-38 of 109% in comparison to irinotecan given alone.

Caution should be exercised in patients concurrently taking drugs known to inhibit (e.g., ketoconazole) or induce (e.g., rifampicin, carbamazepine, phenobarbital or phenytoin) drug metabolism by cytochrome P450 3A4. Concurrent administration of irinotecan with an inhibitor/inducer of this metabolic pathway may alter the metabolism of irinotecan and should be avoided (see section 4.4).

In a small pharmacokinetic study (n=5), in which irinotecan 350 mg/m² was co-administered with St. John's Wort (Hypericum perforatum) 900 mg, a 42% decrease in the active metabolite of irinotecan, SN-38, plasma concentrations was observed.

St. John's Wort decreases SN-38 plasma levels. As a result, St. John's Wort should not be administered with irinotecan (see section 4.3).

Coadministration of 5-fluorouracil/folinic acid in the combination regimen does not change the pharmacokinetics of irinotecan.

4.6 PREGNANCY AND LACTATION

Pregnancy:

There is no information on the use of Irinotecan in pregnant women.

Irinotecan has been shown to be embryotoxic, foetotoxic and teratogenic in rabbits and rats. Therefore, Irinotecan must not be used during pregnancy (see sections 4.3 and 4.4).

Women of child-bearing potential:

Women of child-bearing age receiving Irinotecan should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur (see sections 4.3 and 4.4).

Lactation:

In lactating rats, ¹⁴C-irinotecan was detected in milk. It is not known whether irinotecan is excreted in human milk. Consequently, because of the potential for adverse reactions in nursing infants, breast-feeding must be discontinued for the duration of Irinotecan therapy (see section 4.3).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Irinotecan has moderate influence on the ability to drive and use machines.
Patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of Irinotecan, and advised not to drive or operate machinery if these symptoms occur.

4.8 UNDESIRABLE EFFECTS

The following adverse reactions considered to be possibly or probably related to the administration of irinotecan have been reported from 765 patients at the recommended dose of 350 mg/m² in monotherapy, and from 145 patients treated by irinotecan in combination therapy with 5FU/FA in every 2 weeks schedule at the recommended dose of 180 mg/m².

The most serious and/or most frequently occurring adverse events of irinotecan, both in monotherapy and in combination therapy, were gastrointestinal (diarrhoea, nausea, vomiting constipation), haematological (neutropenia, anaemia, thrombocytopenia), fever, asthenia, Acute Cholinergic Syndrome, infections and alopecia.

The frequencies in the following table are defined using the following convention:
- very common (≥1/10);
- common (≥1/100 to <1/10);
- uncommon (≥1/1,000 to 1/100);
- rare (≥1/10,000 to 1/1,000);
- very rare (<1/10,000);
- Incidence not stated (cannot be estimated from the available data).

Further details are given after this table.

<table>
<thead>
<tr>
<th>MedDRA System Organ Classes</th>
<th>Very Common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
<th>Very Rare (&lt;1/10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>8 INFECTIONS AND INFESTATIONS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>• Infectious Episodes¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination Therapy</td>
<td>• Infectious Episodes¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BLOOD AND LYMPHATIC SYSTEM DISORDERS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>• Neutropenia</td>
<td>• Neutropenia with fever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Anaemia</td>
<td>• Thrombocytopenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination Therapy</td>
<td>• Neutropenia</td>
<td>• Neutropenia with fever</td>
<td></td>
<td>• Autoimmune Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Anaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Thrombocytopenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>10 IMMUNE SYSTEM DISORDERS</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td></td>
<td></td>
<td></td>
<td>• Allergic reactions</td>
<td></td>
</tr>
<tr>
<td>Combination Therapy</td>
<td></td>
<td></td>
<td></td>
<td>• Anaphylactic/anaphylactoid reactions</td>
<td></td>
</tr>
<tr>
<td><strong>METABOLISM AND NUTRITION DISORDERS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>• Dehydration²</td>
<td>• Anorexia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination Therapy</td>
<td>• Dehydration²</td>
<td>• Anorexia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2 NERVOUS SYSTEM DISORDERS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td></td>
<td></td>
<td></td>
<td>• Transient</td>
<td></td>
</tr>
<tr>
<td>MedDRA System Organ Classes</td>
<td>Very Common (≥1/10)</td>
<td>Common (≥1/100 to &lt;1/10)</td>
<td>Uncommon (≥1/1,000 to &lt;1/100)</td>
<td>Rare (≥1/10,000 to &lt;1/1,000)</td>
<td>Very Rare (&lt;1/10,000)</td>
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<td>-------------------------------</td>
<td>-------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Combination Therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>speech disorders</td>
</tr>
</tbody>
</table>

**VASCULAR DISORDERS**

<table>
<thead>
<tr>
<th>Combination Therapy</th>
<th>Monotherapy</th>
<th>Common Therapy</th>
<th>Uncommon Therapy</th>
<th>Rare Therapy</th>
<th>Very Rare Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hynopension³</td>
<td>Cardio-circulatory failure³</td>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**14 RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS**

<table>
<thead>
<tr>
<th>Combination Therapy</th>
<th>Monotherapy</th>
<th>Common Therapy</th>
<th>Uncommon Therapy</th>
<th>Rare Therapy</th>
<th>Very Rare Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dyspnoea</td>
<td>Dyspnoea</td>
<td>Interstitial pulmonary disease</td>
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<td></td>
</tr>
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</table>

**GASTROINTESTINAL DISORDERS**

<table>
<thead>
<tr>
<th>Combination Therapy</th>
<th>Monotherapy</th>
<th>Common Therapy</th>
<th>Uncommon Therapy</th>
<th>Rare Therapy</th>
<th>Very Rare Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diarrhoea³</td>
<td>Abdominal pain</td>
<td>Severe nausea</td>
<td>Mucositis</td>
<td>Pseudomembranous colitis</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>Severe vomiting</td>
<td>Constipation⁵</td>
<td>Intestinal obstruction</td>
<td>Colitis⁶</td>
</tr>
<tr>
<td></td>
<td>Mucositis</td>
<td>Severe nausea</td>
<td>Severe vomiting</td>
<td>Constipation⁵</td>
<td>Intestinal perforation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colitis⁶</td>
<td></td>
<td>Colitis⁶</td>
<td></td>
</tr>
</tbody>
</table>

**16 SKIN AND SUBCUTANEOUS TISSUE DISORDERS**

<table>
<thead>
<tr>
<th>Combination Therapy</th>
<th>Monotherapy</th>
<th>Common Therapy</th>
<th>Uncommon Therapy</th>
<th>Rare Therapy</th>
<th>Very Rare Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alopecia</td>
<td>Cutaneous reactions</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**RENAL AND URINARY DISORDERS**

<table>
<thead>
<tr>
<th>Combination Therapy</th>
<th>Monotherapy</th>
<th>Common Therapy</th>
<th>Uncommon Therapy</th>
<th>Rare Therapy</th>
<th>Very Rare Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Renal insufficiency³</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**General Disorders and Administration Site Conditions**

<table>
<thead>
<tr>
<th>Combination Therapy</th>
<th>Monotherapy</th>
<th>Common Therapy</th>
<th>Uncommon Therapy</th>
<th>Rare Therapy</th>
<th>Very Rare Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fever³</td>
<td>Acute Cholinergic Syndrome⁹</td>
<td>Severe asthenia</td>
<td>Infusion Site Reactions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe asthenia</td>
<td>Fever³</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combination Therapy</th>
<th>Monotherapy</th>
<th>Common Therapy</th>
<th>Uncommon Therapy</th>
<th>Rare Therapy</th>
<th>Very Rare Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute Cholinergic Syndrome⁹</td>
<td>Severe asthenia</td>
<td>Fever³</td>
<td>Infusion Site Reactions</td>
<td></td>
</tr>
<tr>
<td>MedDRA System Organ Classes</td>
<td>Very Common (≥1/10)</td>
<td>Common (≥1/100 to &lt;1/10)</td>
<td>Uncommon (≥1/1000 to &lt;1/100)</td>
<td>Rare (≥1/10,000 to &lt;1/1000)</td>
<td>Very Rare (&lt;1/10,000)</td>
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</tr>
<tr>
<td><strong>18 9 INVESTIGATIONS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Serum transaminases increase</td>
<td>• Serum alkaline phosphatase increase</td>
<td>• Serum bilirubin increase</td>
<td>• Serum creatinine increase</td>
<td></td>
</tr>
</tbody>
</table>
| Combination Therapy         | • Serum SGOT increase (Grades 1 and 2) | • Serum SGPT increase (Grades 1 and 2) | • Serum alkaline phosphatase increase (Grades 1 and 2) | • Serum bilirubin increase (Grade 3) | • Hypokalemia \(^2\)  
|                             | • Serum bilirubin increase (Grades 1 and 2) | • Serum bilirubin increase (Grades 1 and 2) | • Serum bilirubin increase (Grades 1 and 2) | • Hyponatremia \(^2\)  
|                             | • Amylase and/or lipase increase | • Amylase and/or lipase increase | • Amylase and/or lipase increase | • Amylase and/or lipase increase |                       |

1 With or without severe neutropenia.
2 Commonly associated with diarrhoea and/or vomiting.
3 Due to dehydration associated with diarrhoea and/or vomiting, or sepsis.
4 Can be severe, delayed and associated with fever.
5 Associated with irinotecan and/or loperamide
6 Including typhlitis, and ischemic or ulcerative colitis.
7 Symptomatic or asymptomatic
8 Fever, in the absence of infection and severe neutropenia.
9 Main symptoms defined as early diarrhoea, abdominal pain, conjunctivitis, rhinitis, hypotension, vasodilation, sweating, chills, malaise, dizziness, visual disturbances, myosis, lacrimation, increased salivation occurring during or within the first 24 hours after infusion. Symptoms disappear after atropine administration.

**4.9 OVERDOSE**

There have been reports of overdosage at doses up to approximately twice the recommended therapeutic dose, which may be fatal. The most significant adverse reactions reported were severe neutropenia and severe diarrhoea. There is no known antidote for Irinotecan.
Maximum supportive care should be instituted to prevent dehydration due to diarrhoea and to treat any infectious complications.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents (topoisomerase I inhibitor), ATC code: L01XX19

Experimental data

Irinotecan is a semi-synthetic derivative of irinotecan hydrochloride tryihydratethecin. It is an antineoplastic agent which acts as a specific inhibitor of DNA topoisomerase I. It is metabolised by carboxylesterase in most tissues to SN-38, which was found to be more active than irinotecan in purified topoisomerase I and more cytotoxic than irinotecan against several murine and human tumour cell lines. The inhibition of DNA topoisomerase I by irinotecan or SN-38 induces single-strand DNA lesions which blocks the DNA replication fork and are responsible for the cytotoxicity. This cytotoxic activity was found time-dependent and was specific to the S phase.

*In vitro*, irinotecan and SN-38 were not found to be significantly recognised by the P-glycoprotein MDR, and displays cytotoxic activities against doxorubicin and vinblastine resistant cell lines.

Furthermore, irinotecan has a broad antitumor activity *in vivo* against murine tumour models (P03 pancreatic ductal adenocarcinoma, MA16/C mammary adenocarcinoma, C38 and C51 colon adenocarcinomas) and against human xenografts (Co-4 colon adenocarcinoma, Mx-1 mammary adenocarcinoma, ST-15 and SC-16 gastric adenocarcinomas). Irinotecan is also active against tumours expressing the P-glycoprotein MDR (vincristine- and doxorubicin-resistant P388 leukaemias).

Beside the antitumor activity of Irinotecan, the most relevant pharmacological effect of irinotecan is the inhibition of acetylcholinesterase.

Clinical data

In monotherapy:

Clinical phase II/III studies were performed in more than 980 patients in the every 3 week dosage schedule with metastatic colorectal cancer who failed a previous 5-FU regimen. The efficacy of Irinotecan was evaluated in 765 patients with documented progression on 5-FU at study entry.

<table>
<thead>
<tr>
<th>Phases III</th>
<th>Irinotecan versus supportive care</th>
<th>Irinotecan versus 5FU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n=183 n=90 p values</td>
</tr>
<tr>
<td>Progression Free Survival at 6 months (%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Survival at 12 months (%)</td>
<td>36.2 *</td>
<td>13.8</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>9.2*</td>
<td>6.5</td>
</tr>
</tbody>
</table>

NA : Non Applicable

* : Statistically significant difference
In phase II studies, performed on 455 patients in the every 3-week dosage schedule, the progression free survival at 6 months was 30% and the median survival was 9 months. The median time to progression was 18 weeks.

Additionally, non-comparative phase II studies were performed in 304 patients treated with a weekly schedule regimen, at a dose of 125 mg/m² administered as an intravenous infusion over 90 minutes for 4 consecutive weeks followed by 2 weeks rest. In these studies, the median time to progression was 17 weeks and median survival was 10 months. A similar safety profile has been observed in the weekly-dosage schedule in 193 patients at the starting dose of 125 mg/m², compared to the every 3-week-dosage schedule. The median time of onset of the first liquid stool was on day 11.

In combination therapy:
A phase III study was performed in 385 previously untreated metastatic colorectal cancer patients treated with either every 2 weeks schedule (see section 4.2) or weekly schedule regimens. In the every 2 weeks schedule, on day 1, the administration of Irinotecan at 180 mg/m² once every 2 weeks is followed by infusion with folinic acid (200 mg/m² over a 2 hour intravenous infusion) and 5-fluorouracil (400 mg/m² as an intravenous bolus, followed by 600 mg/m² over a 22 hour intravenous infusion). On day 2, folinic acid and 5-fluorouracil are administered at the same doses and schedules. In the weekly schedule, the administration of Irinotecan at 80 mg/m² is followed by infusion with folinic acid (500 mg/m² over a 2 hour intravenous infusion) and then by 5-fluorouracil (2300 mg/m² over a 24 hour intravenous infusion) over 6 weeks.

In the combination therapy trial with the 2 regimens described above, the efficacy of Irinotecan was evaluated in 198 treated patients:

<table>
<thead>
<tr>
<th>Combined regimens (n=198)</th>
<th>Weekly schedule (n=50)</th>
<th>Every 2 weeks schedule (n=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan +5FU/FA</td>
<td>5FU/FA</td>
<td>Irinotecan +5FU/FA</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>40.8 *</td>
<td>23.1 *</td>
</tr>
<tr>
<td>p value</td>
<td>p&lt;0.001</td>
<td>p=0.045</td>
</tr>
<tr>
<td>Median time to progression (months)</td>
<td>6.7</td>
<td>4.4</td>
</tr>
<tr>
<td>p value</td>
<td>p&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Median duration of response (months)</td>
<td>9.3</td>
<td>8.8</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>p=0.043</td>
</tr>
<tr>
<td>Median duration of response and stabilisation (months)</td>
<td>8.6</td>
<td>6.2</td>
</tr>
<tr>
<td>p value</td>
<td>p&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Median time to treatment failure (months)</td>
<td>5.3</td>
<td>3.8</td>
</tr>
<tr>
<td>p value</td>
<td>p=0.0014</td>
<td>NS</td>
</tr>
<tr>
<td>Median survival</td>
<td>16.8</td>
<td>14.0</td>
</tr>
</tbody>
</table>
5FU: 5-fluorouracil
FA: folinic acid
NS: Non Significant
*: As per protocol population analysis

In the weekly schedule, the incidence of severe diarrhoea was 44.4% in patients treated by Irinotecan in combination with 5FU/FA and 25.6% in patients treated by 5FU/FA alone. The incidence of severe neutropenia (neutrophil count < 500 cells/mm³) was 5.8% in patients treated by Irinotecan in combination with 5FU/FA and in 2.4% in patients treated by 5FU/FA alone.

Additionally, median time to definitive performance status deterioration was significantly longer in Irinotecan combination group than in 5FU/FA alone group (p=0.046).

Quality of life was assessed in this phase III study using the EORTC QLQ-C30 questionnaire. Time to definitive deterioration constantly occurred later in the Irinotecan groups. The evolution of the Global Health Status/Quality of life was slightly better in Irinotecan combination group although not significant, showing that efficacy of Irinotecan in combination could be reached without affecting the quality of life.

**Pharmacokinetic/Pharmacodynamic data**

The intensity of the major toxicities encountered with Irinotecan (e.g., leukoneutropenia and diarrhoea) are related to the exposure (AUC) to parent drug and metabolite SN-38. Significant correlations were observed between haematological toxicity (decrease in white blood cells and neutrophils at nadir) or diarrhoea intensity and both irinotecan and metabolite SN-38 AUC values in monotherapy.

### 5.2 PHARMACOKINETIC PROPERTIES

In a phase I study in 60 patients with a dosage regimen of a 30-minute intravenous infusion of 100 to 750 mg/m² every three weeks, irinotecan showed a biphasic or triphasic elimination profile. The mean plasma clearance was 15 L/h/m² and the volume of distribution at steady state (Vss): 157 L/m². The mean plasma half-life of the first phase of the triphasic model was 12 minutes, of the second phase 2.5 hours, and the terminal phase half-life was 14.2 hours. SN-38 showed a biphasic elimination profile with a mean terminal elimination half-life of 13.8 hours. At the end of the infusion, at the recommended dose of 350 mg/m², the mean peak plasma concentrations of irinotecan and SN-38 were 7.7µg/ml and 56ng/ml, respectively, and the mean area under the curve (AUC) values were 34µg.h/ml and 451ng.h/ml, respectively. A large interindividual variability in pharmacokinetic parameters is generally observed for SN-38.

A population pharmacokinetic analysis of irinotecan has been performed in 148 patients with metastatic colorectal cancer, treated with various schedules and at different doses in phase II trials. Pharmacokinetic parameters estimated with a three compartment model were similar to those observed in phase I studies.

All studies have shown that irinotecan (CPT-11) and SN-38 exposure increase proportionally with CPT-11 administered dose; their pharmacokinetics are independent of the number of previous cycles and of the administration schedule.

*In vitro*, plasma protein binding for irinotecan and SN-38 was approximately 65% and 95% respectively.

Mass balance and metabolism studies with ¹⁴C-labelled drug have shown that more than 50% of an intravenously administered dose of irinotecan is excreted as unchanged drug, with 33% in the faeces mainly via the bile and 22% in urine.

Two metabolic pathways account each for at least 12% of the dose:
Hydrolysis by carboxylesterase into active metabolite SN-38, SN-38 is mainly eliminated by glucuronidation, and further by biliary and renal excretion (less than 0.5% of the irinotecan dose). The SN-38 glucuronide is subsequently probably hydrolysed in the intestine.

Cytochrome P450 3A enzymes-dependent oxidations resulting in opening of the outer piperidine ring with formation of APC (aminopentanoic acid derivate) and NPC (primary amine derivate) (see section 4.5).

Unchanged irinotecan is the major entity in plasma, followed by APC, SN-38 glucuronide and SN-38. Only SN-38 has significant cytotoxic activity and no other circulating metabolites have been detected.

Irinotecan clearance is decreased by about 40% in patients with bilirubinaemia between 1.5 and 3 times the upper normal limit. In these patients a 200 mg/m² irinotecan dose leads to plasma drug exposure comparable to that observed at 350 mg/m² in cancer patients with normal liver parameters.

5.3 PRECLINICAL SAFETY DATA
Irinotecan and SN-38 have been shown to be mutagenic in vitro in the chromosomal aberration test on CHO-cells as well as in the in vivo micronucleus test in mice. However, they have been shown to be devoid of any mutagenic potential in the Ames test.

In rats treated once a week during 13 weeks at the maximum dose of 150 mg/m² (which is less than half the human recommended dose), no treatment related tumours were reported 91 weeks after the end of treatment.

Single- and repeated-dose toxicity studies with Irinotecan have been carried out in mice, rats and dogs. The main toxic effects were seen in the haematopoietic and lymphatic systems. In dogs, delayed diarrhoea associated with atrophy and focal necrosis of the intestinal mucosa was reported. Alopecia was also observed in the dog. The severity of these effects was dose-related and reversible.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Sorbitol (E420)
Lactic acid
Sodium hydroxide (to adjust pH)
Hydrochloric acid (to adjust pH)
Water for injections.

6.2 INCOMPATIBILITIES
None known.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 SHELF LIFE
Unopened vials: 24 months.
Diluted solution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. When protected from light chemical and physical in-use stability has been demonstrated for 48 hours at both 25°C and 2 to 8°C.

From a microbiological view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.
6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions.
Store in the original package, in order to protect from light.
For storage conditions of the diluted medicinal product, see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER
Irinotecan 40 mg/2ml: One Type I amber glass vial, with a bromobutyl stopper capped by a flip-off aluminium cap with a polypropylene cover.
Irinotecan 100mg/5ml: One Type I amber glass vial, with a bromobutyl stopper capped by a flip-off aluminium cap with a polypropylene cover.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
As with other antineoplastic agents, Irinotecan must be prepared and handled with caution.
The use of glasses, mask and gloves is required.
If Irinotecan solution or infusion solution should come into contact with the skin, wash immediately and thoroughly with soap and water. If Irinotecan solution or infusion solution should come into contact with the mucous membranes, wash immediately with water.
Preparation for the intravenous infusion administration:
As with any other injectable drugs, the Irinotecan solution must be prepared aseptically. The solution contains no antibacterial preservative therefore the dilution should be performed under strict aseptic conditions (e.g. on Laminar Air Flow bench) (See section 6.3).
If any precipitate is observed in the vials or after reconstitution, the product should be discarded according to standard procedures for cytotoxic agents.
Aseptically withdraw the required amount of Irinotecan solution from the vial with a calibrated syringe and inject into a 250 ml infusion bag or bottle containing either 0.9% sodium chloride solution or 5% dextrose solution. The infusion should then be thoroughly mixed by manual rotation.
Disposal:
All materials used for dilution and administration should be disposed of according to hospital standard procedures applicable to cytotoxic agents.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Teva UK Limited
Brampton Road
Hampden Park
Eastbourne
East Sussex
BN22 9AG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/1393

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/05/2009
10 DATE OF REVISION OF THE TEXT

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)
IRINOCAN 20MG/ML SOLUTION FOR INFUSION
PL 00289/1393

PATIENT INFORMATION LEAFLET

IRINOCAN 20mg/ml Solution for Infusion PL 00289/1393

UKPAR

This leaflet contains information for the patient on the medicinal product Irinotecan 20mg/ml Solution for Infusion (PL 00289/1393)

What Irinotecan is and what it is used for
Irinotecan is a medicine belonging to a group of medicines known as antineoplastic agents (antineoplastic chemotherapy). It is used for the treatment of various cancers such as colorectal cancer, lung cancer, breast cancer, and cancer of the head and neck. It is usually prescribed in combination with other medicines for best results.

Before you are given Irinotecan

Before you are given Irinotecan, please read the information leaflet carefully. This may help you to understand how the medicine works.

How to take Irinotecan

Irinotecan is usually given by injection into veins (intravenous) or under the skin (subcutaneous). You will be told how to do this.

Possible side effects

Irinotecan can cause side effects, although not everyone gets them. Some of these side effects may be serious. Therefore, it is important to follow the instructions carefully and report any side effects to your doctor.

If you have any problems or concerns, please contact your doctor.

Handling instructions

Irinotecan solution or infusion solutions should only be used in conjunction with appropriate personal protective equipment. The use of gloves, masks, and gowns is required.

Further information

Further information on Irinotecan 20mg/ml Solution for Infusion PL 00289/1393 is available from the manufacturer or your local hospital pharmacy.
UKPAR

Irinotecan 20mg/ml Solution for Infusion

PL. 00289/1393

- If you have diarrhea starts more than 24 hours after the infusion (delayed diarrhea).
- Any fever, and particularly if you also have diarrhea.
- Feeling and being sick.
- Breathing difficulties.

The following side effects have been observed in patients treated with irinotecan:

Very common (these effects may occur in more than 1 in 10 people):

- Decrease in white blood cells. Irinotecan may cause a temporary decrease in the number of some of your white blood cells which fight infections. This is called neutropenia. If you have a fever this may mean you have an infection associated with neutropenia. If you have a fever you must contact your doctor or nurse immediately.
- Decrease in red blood cells, which can make the skin pale and cause weakness or breathlessness.
- Decrease in platelets (involved in blood clotting), which increases risk of bleeding or bruising.
- Diarrhoea, which starts more than 24 hours after your infusion. Delayed diarrhoea. If diarrhoea starts after 24 hours following your treatment you should immediately take the anti-diarrhoeal treatment that the doctor has given you exactly as he or she has told you.
- You should also drink large amounts of rehydration fluids e.g. water, salt and water, fizzy drinks, soup or oral rehydration therapy. You must also tell your doctor immediately if you still have diarrhoea 48 hours after starting the anti-diarrhoeal treatment. If you experience early diarrhoea, do not use the anti-diarrhoeal treatment that your doctor has given you for delayed diarrhoea.
- Feeling and being sick. You must tell your doctor immediately if you feel or are sick.
- Infections.
- Temporary hair loss.
- Fever. If you have any fever this may be an indication of infection associated with 5 reduction in the number of your white blood cells (neutropenia) and you should contact your doctor immediately for treatment.
- Increases in liver enzymes in the blood. Your doctor may want to monitor your liver function.
- Dehydration.

Common (these effects may occur in more than 1 in 100 people):

- Early onset diarrhoea starts less than 24 hours after your infusion and may be accompanied by the following symptoms: swelling; stomach cramps, water retention, visual disturbance, dermatitis, widening of the blood vessels, and low blood pressure, feeling unequal, excessive mouth watering, conjunctivitis, runny nose. These symptoms are associated with a syndrome called acute cholinergic syndrome. If you experience diarrhoea less than 24 hours after your infusion, tell your doctor immediately.
- Constipation.
- Increases in creatinine levels in the blood (which reflect how your kidneys are working).
- Weakness (lack of energy).

Uncommon (these effects may occur in more than 1 in 1000 people):

- Allergic reactions.
- Scarring of the lungs, which can cause breathing difficulties. You should contact your doctor or nurse immediately if you have breathing difficulties.
- Severe diarrhoea ( pseudomembranous colon).
- Bowel obstruction, abdominal pain, swelling from part of the gut.
- Kidney problems.
- Low blood pressure, which may cause dizziness or light-headedness.
- Pain or redness close to or at the injection site during the infusion.
- Skin rash:
  - Condition of the heart and circulation with shortness of breath and swelling of the feet or legs due to oedema associated with diarrhoea and/ or vomiting, or serious infection (cardio-circulatory failure).

Rare (these effects may occur in less than 1 in 1000 people):

- Pancratoses, which may cause abdominal pain.
- Bowel perforation (loss of appetite, stomach ache, sore red mouth).
- High blood pressure.
- A severe allergic reaction, symptoms of which may include difficulty breathing, dizziness, collapse and swelling of the lips, tongue and other tissues.
- Increases in sodium and potassium levels in your blood usually due to vomiting and diarrhoea.
- Bowel inflammation.
- Very rare (these effects may occur in less than 1 in 10000 people):
  - Increase in anaemia and lipase levels in the blood. These are natural enzymes in your body used for digestion.
  - Temporary speech difficulties.

The occurrence of the following side effects cannot be estimated from the information available:

- Sense of taste.
- Pains and neuralgia.

If any of the above side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

How to store irinotecan

You will not be asked to store your medicine. It will be brought to you ready to be administered straight away. Your doctor, nurse or pharmacist should ensure that irinotecan is kept out of the reach and sight of children.

Your doctor, nurse or pharmacist will ensure that the vial is stored in the original package, in order to protect it from light. They will also ensure that you do not receive irinotecan after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste, your doctor, nurse or pharmacist will dispose of medicines no longer required. These measures will help to protect the environment.

Further information

What irinotecan contains:

- The active substance is irinotecan hydrochloride, trihydrate.
- The other ingredients are sorbitol (E420), lactic acid, sodium hydroxide or hydrochloric acid (to adjust pH), water for injections.

What irinotecan looks like and contents of pack:

Irinotecan 20mg/ml solution for infusion is a light yellow or yellow solution and comes in vials containing 40mg/2ml or 100mg/5ml of irinotecan. The vials are supplied in cartons of one (1).

Marketing Authorisation Holder:

TEVA UK Limited, Eartham, BN22 9QA

Manufacturer:

PLIVA - Lachema a.s.
Cirkva 1
571 33 RVO
Czech Republic

This leaflet was last revised in June 2009.
PL 00289/1503
87555-A
IRINOTECAN 20MG/ML SOLUTION FOR INFUSION
PL 00289/1393

LABEL

OUTER CARTON

The concentrate contains 20mg/ml irinotecan hydrochloride, trihydrate.
Each 2ml vial contains 40mg irinotecan hydrochloride, trihydrate.
Also contains sodium hydroxide or hydrochloric acid (to adjust pH) and water
for injection.
Read the package leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

BOTTLE LABEL

Irinotecan 20mg/ml Solution for infusion irinotecan hydrochloride, trihydrate
for intravenous use after dilution

40mg/2ml

Each vial contains 40mg irinotecan hydrochloride, trihydrate.
Further information on the package leaflet.