Public Assessment Report

Decentralised Procedure

IRINOTECAN 20MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

UK/H/1294/001/DC
UK licence no: PL 31304/0003

SymPhar Sp.z.o.o
IRINOTECAN 20MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

LAY SUMMARY

On 20th November 2009, the UK granted a licence for the medicinal product Irinotecan 20mg/ml Concentrate for Solution for Infusion (PL 31304/0003). This licence was granted via the decentralised procedure (UK/H/1294/001/DC), with the UK as reference member state (RMS) and Poland as concerned member state (CMS).

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

The active ingredient irinotecan hydrochloride trihydrate 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 Concentrate for Solution outweigh the risks, hence a Marketing Authorisation has been granted.
TABLE OF CONTENTS

Module 1: Information about initial procedure Page 3
Module 2: Summary of Product Characteristics Page 4
Module 3: Product Information Leaflets Page 22
Module 4: Labelling Page 24
Module 5: Scientific Discussion Page 34
   1 Introduction
   2 Quality aspects
   3 Non-clinical aspects
   4 Clinical aspects
   5 Overall conclusions
Module 6 Steps taken after initial procedure
## Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Irinotecan Hydrochloride 20mg/ml Concentrate for Solution for Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic application, Article 10.1</td>
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<tr>
<td><strong>Active Substance</strong></td>
<td>Irinotecan hydrochloride trihydrate</td>
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<td><strong>Form</strong></td>
<td>Solution for injection 20mg/ml</td>
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<td><strong>Strength</strong></td>
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<tr>
<td><strong>MA Holder</strong></td>
<td>SymPhar Sp.z.o.o, ul Wloska 1L, Warsaw, PL 00-777, Poland</td>
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<td>Day 210 – 19th October 2009</td>
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Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Irinotecan 20 mg/ml concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance: irinotecan (as hydrochloride, trihydrate).

The concentrate contains 20 mg/ml Irinotecan hydrochloride Trihydrate (equivalent to 17.33 mg/ml Irinotecan). Vials of Irinotecan 20 mg/ml concentrate for solution for infusion contain 40 mg or 100 mg of Irinotecan hydrochloride Trihydrate.

Excipient(s):
Sorbitol

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Concentrate for solution for infusion.
Clear, yellowish to pale yellow coloured solution with pH between 3.0 and 3.8.

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.

Irinotecan in combination with cetuximab is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer who had not received prior treatment for metastatic disease or after failure of irinotecan-including cytotoxic therapy (please see section 5.1).

Irinotecan in combination with 5-fluorouracil, folinic acid and bevacizumab is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum.

Irinotecan in combination with capecitabine with or without bevacizumab is indicated for first-line treatment of patients with metastatic colorectal carcinoma.

4.2 Posology and method of administration
For adults only. After dilution Irinotecan 20 mg/ml concentrate for solution for infusion should be infused into a peripheral or central vein.

Recommended dosage:
In monotherapy (for previously treated patient):
The recommended dosage of Irinotecan 20 mg/ml concentrate for solution for infusion is 350 mg/m² administered as an intravenous infusion over a 30-to 90-minute period every three weeks (see section 4.4 and 6.6).

In combination therapy (for previously untreated patient):
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 every 2 weeks schedule
The recommended dose of Irinotecan 20 mg/ml concentrate for solution for infusion 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.

For the posology and method of administration of concomitant cetuximab, refer to the product information for this medicinal product. Normally, the same dose of irinotecan is used as administered
in the last cycles of the prior irinotecan-containing regimen. Irinotecan must not be administered earlier than 1 hour after the end of the cetuximab infusion.

For the posology and method of administration of bevacizumab, refer to the bevacizumab summary product of characteristics.

For the posology and method of administration of capecitabine combination, please see section 5.1 and refer to the appropriate sections in the capecitabine summary of product characteristics.

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). Recommendations for dose modifications of cetuximab when administered in combination with irinotecan must be followed according to the product information for this medicinal product.

Refer to the bevacizumab summary product of characteristics for dose modifications of bevacizumab when administered in combination with irinotecan/5FU/FA.

In combination with capecitabine for patients 65 years of age or more, a reduction of the starting dose of capecitabine to 800 mg/m² twice daily is recommended according to the summary of product characteristics for capecitabine. Refer also to the recommendations for dose modifications in combination regimen given in the summary of product characteristics for capecitabine.

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 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 20 mg/ml concentrate for solution for infusion is 350 mg/m². In patients with bilirubin ranging from 1.5 to 3 times the ULN, the recommended dosage of Irinotecan 20 mg/ml concentrate for solution for infusion is 200 mg/m². Patients with bilirubin beyond 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).
Paediatric patients:
Irinotecan should not be used in children.

4.3 Contraindications
Chronic inflammatory bowel disease and/or bowel obstruction (see section 4.4).
History of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate or to one of the excipients.
Pregnancy and lactation (see section 4.6 and 4.4).
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)

For additional contraindications of cetuximab or bevacizumab or capecitabine, refer to the product information for these medicinal products.

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 anti-diarrhoeal 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 every-3-week-dosage schedule. However, the weekly-dosage schedule (see section 5.1) 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 ≥ 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 anti-diarrhoeal therapy must be initiated immediately. This anti-diarrhoeal 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 anti-diarrhoeal 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/mm³).
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 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 decrease of the clearance of irinotecan (see section 5.2) and thus 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 the 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 5.1).
Others
Since this medicinal contains sorbitol, it is unsuitable in hereditary fructose intolerance.

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.

Effective contraceptive measures must be taken by treated men and by treated women of child-bearing age, 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, drugs with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarising drugs may be antagonised.

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 effect 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-fluouracil/folinic acid in the combination regimen does not change the pharmacokinetics of irinotecan.

There is no evidence that the safety profile of irinotecan is influenced by cetuximab or vice versa.

In one study, irinotecan concentrations were similar in patients receiving irinotecan/5FU/FA alone and in combination with bevacizumab. Concentrations of SN-38, the active metabolite of irinotecan, were analyzed in a subset of patients (approximately 30 per treatment arm). Concentrations of SN-38 were on average 33% higher in patients receiving irinotecan/5FU/FA in combination with bevacizumab compared with irinotecan/5FU/FA alone. Due to high inter-patient variability and limited sampling, it is uncertain if the increase in SN-38 levels observed was due to bevacizumab. There was a small increase in diarrhoea and leukopenia adverse events. More dose reductions of irinotecan were reported for patients receiving irinotecan/5FU/FA in combination with bevacizumab.

Patients who develop severe diarrhoea, leukopenia, or neutropenia with the bevacizumab and irinotecan combination should have irinotecan dose modifications as specified in section 4.2 Posology and method of administration.
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, $^{14}$C-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

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

Undesirable effects detailed in this section refer to irinotecan. There is no evidence that the safety profile of irinotecan is influenced by cetuximab or vice versa. In combination with cetuximab, additional reported undesirable effects were those expected with cetuximab (such as acneform rash 88%).

For information on adverse reactions on irinotecan in combination with cetuximab, also refer to their respective summaries of product characteristics.

For information on adverse reactions in combination with bevacizumab, refer to the bevacizumab summary product of characteristics.

Adverse drug reactions reported in patients treated with capecitabine in combination with irinotecan in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy include: Very common, all grade adverse drug reactions: thrombosis/embolism; Common, all grade adverse drug reactions: hypersensitivity reaction, cardiac ischemia/infarction; Common, grade 3 and grade 4 adverse drug reactions: febrile neutropenia. For complete information on adverse reactions of capecitabine, refer to the capecitabine summary product of characteristics. Grade 3 and Grade 4 adverse drug reactions reported in patients treated with capecitabine in combination with irinotecan and bevacizumab in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy include: Common, grade 3 and grade 4 adverse drug reactions: neutropenia, thrombosis/embolism, hypertension, and cardiac ischemia/infarction. For complete information on adverse reactions of capecitabine and bevacizumab, refer to the respective capecitabine and bevacizumab summary product of characteristics.

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.

Frequency estimate: 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).
Gastrointestinal disorders

Delayed diarrhoea
Diarrhoea (occurring more than 24 hours after administration) is a dose-limiting toxicity of irinotecan.

In monotherapy:
Very common: Severe diarrhoea was observed in 20% of patients who follow recommendations for the management of diarrhoea. Of the evaluable cycles, 14% have severe diarrhoea. The median time of onset of the first liquid stool was on day 5 after the infusion of irinotecan.

In combination therapy:
Very common: Severe diarrhoea was observed in 13.1% of patients who follow recommendations for the management of diarrhoea. Of the evaluable cycles, 3.9% have severe diarrhoea.

Uncommon: Cases of pseudo-membranous colitis have been reported, one of which has been documented bacteriologically (Clostridium difficile).

Nausea and vomiting
In monotherapy:
Very common: Nausea and vomiting were severe in approximately 10% of patients treated with antiemetics.

In combination therapy:
Common: A lower incidence of severe nausea and vomiting was observed (2.1% and 2.8% of patients respectively).

Dehydration
Common: Episodes of dehydration associated with diarrhoea and/or vomiting have been reported.
Uncommon: Cases of renal insufficiency, hypotension or cardiov-circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting.

Other gastrointestinal disorders
Common: Constipation relative to irinotecan and/or loperamide has been observed, shared between:
in monotherapy: in less than 10% of patients
in combination therapy: 3.4% of patients.

Uncommon: Intestinal obstruction, ileus, or gastrointestinal haemorrhage
Rare: Colitis, including typhlitis, ischemic and ulcerative colitis and intestinal perforation.

Cases of symptomatic or asymptomatic pancreatitis have been associated with irinotecan therapy.

Other mild effects include anorexia, abdominal pain and mucositis.

Blood and lymphatic system disorders
Neutropenia is a dose-limiting toxic effect. Neutropenia was reversible and not cumulative; the median day to nadir was 8 days whatever the use in monotherapy or in combination therapy.

In monotherapy:
Very common: Neutropenia was observed in 78.7% of patients and was severe (neutrophil count <500 cells/mm³) in 22.6% of patients. Of the evaluable cycles, 18% had a neutrophil count below 1,000 cells/mm³ including 7.6% with a neutrophil count <500 cells/mm³.

Total recovery was usually reached by day 22.

Anaemia was reported in about 58.7% of patients (8% with haemoglobin <8 g/dl and 0.9% with haemoglobin <6.5 g/dl).

Infectious episodes occurred in about 10.3% of patients (2.5% of cycles).

Common: Fever with severe neutropenia was reported in 6.2% of patients and in 1.7% of cycles.
Infectious episodes associated with severe neutropenia occurred in about 5.3% of patients (1.1% of cycles), and resulted in death in 2 cases.
Thrombocytopenia (<100,000 cells/mm³) was observed in 7.4% of patients and 1.8% of cycles with 0.9% with platelets count ≤ 50,000 cells/mm³ and 0.2% of cycles. Nearly all the patients showed a recovery by day 22.

**In combination therapy:**

*Very common:* Neutropenia was observed in 82.5% of patients and was severe (neutrophil count <500 cells/mm³) in 9.8% of patients.

Of the evaluable cycles, 67.3% had a neutrophil count below 1,000 cells/mm³ including 2.7% with a neutrophil count <500 cells/mm³.

Total recovery was usually reached within 7-8 days.

Anaemia was reported in 97.2% of patients (2.1% with haemoglobin <8 g/dl).

Thrombocytopenia (<100,000 cells/mm³) was observed in 32.6% of patients and 21.8% of cycles. No severe thrombocytopenia (<50,000 cells/mm³) has been observed.

*Common:* Fever with severe neutropenia was reported in 3.4% of patients and in 0.9% of cycles.

Infectious episodes occurred in about 2% of patients (0.5% of cycles) and were associated with severe neutropenia in about 2.1% of patients (0.5% of cycles), and resulted in death in 1 case.

*Very rare:* One case of peripheral thrombocytopenia with antiplatelet antibodies has been reported in the post-marketing experience.

**Infection and Infestation**

*Uncommon:* Cases of renal insufficiency, hypotension or cardio-circulatory failure have been observed in patients who experienced sepsis.

**General disorders and infusion site reactions**

*Very common:* Fever in the absence of infection and without concomitant severe neutropenia, occurred in 12% of patients treated in monotherapy.

*Common:* **Acute cholinergic syndrome** Severe transient acute cholinergic syndrome was observed in 9% of patients treated in monotherapy and in 1.4% of patients treated in combination therapy. The main symptoms were defined as early diarrhoea and various other symptoms such as abdominal pain, conjunctivitis, rhinitis, hypotension, vasodilatation, sweating, chills, malaise, dizziness, visual disturbances, myosis, lachrimation and increased salivation occurring during or within the first 24 hours after the infusion of irinotecan. These symptoms disappear after atropine administration (see section 4.4).

Asthenia was severe in less than 10% of patients treated in monotherapy and in 6.2% of patients treated in combination therapy. The causal relationship to irinotecan has not been clearly established. Fever in the absence of infection and without concomitant severe neutropenia, occurred in 6.2% of patients treated in combination therapy.

*Uncommon:* Mild infusion site reactions have been reported.

**Cardiac disorders**

*Rare:* Hypertension during or following the infusion.

**Respiratory, thoracic and mediastinal disorders**

*Uncommon:* Interstitial pulmonary disease presenting as pulmonary infiltrates. Early effects such as dyspnoea have been reported (see section 4.4).

**Skin and subcutaneous tissue disorders**

**Immune system disorders**
*Uncommon:* Mild allergy reactions

*Rare:* Anaphylactic/anaphylactoid reactions.

**Musculoskeletal and connective tissue disorders**
*Rare:* Early effects such as muscular contraction or cramps and paresthesia have been reported.

**Investigations**
*Very common:* In combination therapy transient serum levels (grades 1 and 2) of either SGPT, SGOT, alkaline phosphatase or bilirubin were observed in 15%, 11%, 11% and 10% of the patients, respectively, in the absence of progressive liver metastasis.

*Common:* In monotherapy, transient and mild to moderate increases in serum levels of either transaminases, alkaline phosphatase or bilirubin were observed in 9.2%, 8.1% and 1.8% of the patients, respectively, in the absence of progressive liver metastasis. Transient and mild to moderate increases of serum levels of creatinine have been observed in 7.3% of the patients.

In combination therapy transient grade 3 serum level of bilirubin were observed in 1% of the patients. No grade 4 was observed.

*Rare:* Hypokalemia and hyponatremia mostly related with diarrhoea and vomiting.

*Very rare:* Increases of amylase and/or lipase.

**Nervous system disorders**
*Very rare:* Transient speech disorders associated with irinotecan infusions.

### 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: Cytostatic topoisomerase I inhibitor. ATC Code: L01XX19

**Experimental data**
Irinotecan is a semi-synthetic derivative of camptothecin. 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 tumors expressing the P-glycoprotein MDR (vincristine-and doxorubicin-resistant P388 leukaemia's).

Beside the antitumor activity of irinotecan, the most relevant pharmacological effect of irinotecan is the inhibition of acetylcholinesterase.
**Clinical data**

In combination therapy for the first-line treatment of metastatic colorectal carcinoma

In combination therapy with Folinic Acid and 5-Fluorouracil: 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></td>
<td>5FU/FA</td>
<td>Irinotecan +5FU/FA</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>40.8*</td>
<td>51.2*</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>7.2</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>8.9</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>8.3</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>5.4</td>
</tr>
<tr>
<td>p value</td>
<td>p=0.0014</td>
<td>NS</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>16.8</td>
<td>19.2</td>
</tr>
<tr>
<td>p value</td>
<td>p=0.028</td>
<td>NS</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.

In combination therapy with bevacizumab: A phase III randomised, double-blind, active-controlled clinical trial evaluated bevacizumab in combination with irinotecan/5FU/FA as first-line treatment for metastatic carcinoma of the colon or rectum (Study AVF2107g). The addition of bevacizumab to the combination of irinotecan/5FU/FA resulted in a statistically significant increase in overall survival. The clinical benefit, as measured by overall survival, was seen in all pre-specified patient subgroups, including those defined by age, sex, performance status, location of primary tumour, number of organs involved, and duration of metastatic disease. Refer also to the bevacizumab summary of product characteristics. The efficacy results of Study AVF2107g are summarized in the table below.
**AVF2107g**

<table>
<thead>
<tr>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan/5FU/FA + Placebo</td>
<td>Irinotecan/5FU/FA + Avastin*</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>411</td>
</tr>
<tr>
<td><strong>Overall survival</strong></td>
<td></td>
</tr>
<tr>
<td>Median time (months)</td>
<td>15.6</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>14.29 – 16.99</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.660</td>
</tr>
<tr>
<td>p-value</td>
<td>0.00004</td>
</tr>
<tr>
<td><strong>Progression-free survival</strong></td>
<td></td>
</tr>
<tr>
<td>Median time (months)</td>
<td>6.2</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.54</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Overall response rate</strong></td>
<td></td>
</tr>
<tr>
<td>Rate (%)</td>
<td>34.8</td>
</tr>
<tr>
<td>95% CI</td>
<td>30.2 – 39.6</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0036</td>
</tr>
<tr>
<td><strong>Duration of response</strong></td>
<td></td>
</tr>
<tr>
<td>Median time (months)</td>
<td>7.1</td>
</tr>
<tr>
<td>25–75 percentile (months)</td>
<td>4.7 – 11.8</td>
</tr>
</tbody>
</table>

* 5 mg/kg every 2 weeks. 

**In combination therapy with cetuximab:**

EMR 62 202-013: This randomised study in patients with metastatic colorectal cancer who had not received prior treatment for metastatic disease compared the combination of cetuximab and irinotecan plus infusional 5 fluorouracil/folinic acid (5-FU/FA) (599 patients) to the same chemotherapy alone (599 patients). The proportion of patients with KRAS wild-type tumours from the patient population evaluable for KRAS status comprised 64%. The efficacy data generated in this study are summarised in the table below: CI = confidence interval, FOLFIRI = irinotecan plus infusional 5-FU/FA, ORR = objective response rate (patients with complete response or partial response), PFS = progression-free survival time.

<table>
<thead>
<tr>
<th>Variable/statistic</th>
<th>Overall population</th>
<th>KRAS wild-type population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cetuximab plus</td>
<td>FOLFIRI (N=599)</td>
</tr>
<tr>
<td></td>
<td>FOLFIRI (N=599)</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% (95%CI)</td>
<td>46.9</td>
<td>(42.9, 51.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(59.3)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0038</td>
<td>0.0025</td>
</tr>
<tr>
<td>PFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard</td>
<td>0.85 (0.726, 0.998)</td>
<td>(0.68 (0.501, 0.934)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0479</td>
<td>0.0167</td>
</tr>
</tbody>
</table>

**In combination therapy with capecitabine:**

Data from a randomised, controlled phase III study (CAIRO) support the use of capecitabine at a starting dose of 1000 mg/m² for 2 weeks every 3 weeks in combination with irinotecan for the first-line treatment of patients with metastatic colorectal cancer. 820 Patients were randomized to receive either sequential treatment (n=410) or combination treatment (n=410). Sequential treatment consisted of first-line treatment with capecitabine (1250 mg/m² twice daily for 14 days), second-line irinotecan (350 mg/m² on day 1), and third-line combination of capecitabine (1000 mg/m² twice daily for 14 days) with oxaliplatin (130 mg/m² on day 1). Combination treatment consisted of first-line treatment of capecitabine (1000 mg/m² twice daily for 14 days) combined with irinotecan (250 mg /m² on day 1) (XELIRI) and second-line capecitabine (1000 mg/m² twice daily for 14 days).
mg/m² twice daily for 14 days) plus oxaliplatin (130 mg/m² on day 1). All treatment cycles were
administered at intervals of 3 weeks. In first-line treatment the median progression-free survival in the
intent-to-treat population was 5.8 months (95%CI, 5.1 - 6.2 months) for capecitabine monotherapy and
7.8 months (95%CI, 7.0-8.3 months) for XELIRI (p=0.0002). Data from an interim analysis of a
 multicentre, randomised, controlled phase II study (AIO KRK 0604) support the use of capecitabine at
a starting dose of 800 mg/m² for 2 weeks every 3 weeks in combination with irinotecan and
bevacizumab for the first-line treatment of patients with metastatic colorectal cancer. 115 patients were
randomised to treatment with capecitabine combined with irinotecan (XELIRI) and bevacizumab:
capecitabine (800 mg/m² twice daily for two weeks followed by a 7-day rest period), irinotecan (200
mg/m² as a 30 minute infusion on day 1 every 3 weeks), and bevacizumab (7.5 mg/kg as a 30 to 90
minute infusion on day 1 every 3 weeks); a total of 118 patients were randomised to treatment with
capecitabine combined with oxaliplatin plus bevacizumab: capecitabine (1000 mg/m² twice daily for
two weeks followed by a 7-day rest period), oxaliplatin (130 mg/m² as a 2 hour infusion on day 1 every
3 weeks), and bevacizumab (7.5 mg/kg as a 30 to 90 minute infusion on day 1 every 3 weeks).
Progression-free survival at 6 months in the intent-to-treat population was 80% (XELIRI plus
bevacizumab) versus 74 % (XELOX plus bevacizumab). Overall response rate (complete response plus
partial response) was 45 % (XELOX plus bevacizumab) versus 47 % (XELIRI plus bevacizumab).

In monotherapy for the second-line treatment of metastatic colorectal carcinoma:
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
CAMPTO was evaluated in 765 patients with documented progression on 5-FU at study entry.

<table>
<thead>
<tr>
<th>Phases III</th>
<th>CAMPTO versus supportive care</th>
<th>CAMPTO versus 5FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAMPTO n=183</td>
<td>Supportive care n=90</td>
<td>p values</td>
</tr>
<tr>
<td>CAMPTO n=127</td>
<td>5FU n=129</td>
<td>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 with cetuximab after failure of Irinotecan-including cytotoxic therapy
The efficacy of the combination of cetuximab with irinotecan was investigated in two clinical studies.
A total of 356 patients with EGFR-expressing metastatic colorectal cancer who had recently failed
irinotecan-including cytotoxic therapy and who had a minimum Karnofsky performance status of 60,
but the majority of whom had a Karnofsky performance status of ≥80 received the combination
treatment.

EMR 62 202-007: This randomised study compared the combination of cetuximab and irinotecan (218
patients) with cetuximab monotherapy (111 patients).
IMCL CP02-9923: This single arm open-label study investigated the combination therapy in 138 patients. The efficacy data from these studies are summarised in the table below: CI = confidence interval DCR = disease control rate (patients with complete response, partial response, or stable disease for at least 6 weeks) ORR = objective response rate (patients with complete response or partial response) OS = overall survival time PFS = progression-free survival

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>ORR</th>
<th>DCR</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>95%CI</td>
<td>n (%)</td>
<td>95%CI</td>
<td>Median</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median</td>
<td>Median</td>
</tr>
<tr>
<td>Cetuximab + irinotecan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMR 62202007</td>
<td>218</td>
<td>50</td>
<td>17.5</td>
<td>4.1</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>(22.9)</td>
<td>9.7</td>
<td>(55.5)</td>
<td>2.84.3</td>
<td>7.210.3</td>
</tr>
<tr>
<td>IMCL CP029923</td>
<td>138</td>
<td>21</td>
<td>84</td>
<td>2.9</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>(15.2)</td>
<td>22.3</td>
<td>(60.9)</td>
<td>2.64.1</td>
<td>7.210.3</td>
</tr>
<tr>
<td>Cetuximab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMR 62202007</td>
<td>111</td>
<td>12</td>
<td>36</td>
<td>1.5</td>
<td>6.9</td>
</tr>
<tr>
<td></td>
<td>(10.8)</td>
<td>(32.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The efficacy of the combination of cetuximab with irinotecan was superior to that of cetuximab monotherapy, in terms of objective response rate (ORR), disease control rate (DCR) and progression-free survival (PFS). In the randomised trial, no effects on overall survival were demonstrated (hazard ratio 0.91, p = 0.48).

**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 56 ng/ml, respectively, and the mean area under the curve (AUC) values were 34 µg.h/ml and 451 ng.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 SN38 glucuronite 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.

Irinotecan clearance is decreased by about 40% in patients with bilirubinemia between 1.5 and 3 times the upper limit of normal. 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
- Lactic acid
- Sodium hydroxide (for pH adjustment)
- Hydrochloric acid (for pH adjustment)
- Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

2 years

The irinotecan solution should be used immediately after dilution as it contains no antibacterial preservative. If dilution is performed under strict aseptic conditions (e.g. on Laminar Air Flow bench) irinotecan solution should be used (infusion completed) within 12 hours at room temperature or 24 hours if stored 2°-8°C after the first breakage.

It is recommended, however, that in order to reduce microbiological hazard, the infusion solutions should be prepared immediately prior to use and infusion commenced as soon as practicable after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user

6.4 Special precautions for storage

For storage conditions of the diluted medicinal product, see section 6.3. This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

5 ml amber type-I tubular glass vial with bromobutyl rubber stopper and flip off seal.

Pack size:
- 1 vial 2 ml fill volume
- 5 vials 2 ml fill volume
- 1 vial 5 ml fill volume
- 5 vials 5 ml fill volume
6.6 Special precautions for disposal

Handling
As with all antineoplastic agents, caution should be exercised when handling Irinotecan. Dilution should be carried out under aseptic conditions by trained personnel in a designated area. Precautions should be taken to avoid contact with the skin and mucous membranes.

Instructions for dilution
Irinotecan concentrate for solution for infusion is intended for intravenous infusion only after diluting prior to administration in the recommended diluents, either 0.9 % Sodium chloride solution for infusion or 5% glucose solution for infusion. Aseptically withdraw the required amount of Irinotecan concentrate for solution from the vial with a calibrated syringe and inject into a 250 ml infusion bag or bottle. The infusion should be thoroughly mixed by manual rotation.

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

Protection instructions for preparation of Irinotecan solution for infusion.
1. Protective chamber should be used and protective gloves as well as protective gown should be worn. If there is no protective chamber available mouth cover and goggles should be used.
2. Opened containers, like injection vials and infusion bottles and used cannulae, syringes, catheters, tubes, and residuals of cytostatics should be considered as hazardous waste and undergo disposal according to local guidelines for the handling of HAZARDOUS WASTE.
3. Follow the instructions below in case of spillage: protective clothing should be worn - broken glass should be collected and placed in the container for HAZARDOUS WASTE - contaminated surfaces should be flushed properly with copious amounts of cold water - the flushed surfaces should then be wiped thoroughly and the materials used for wiping should be disposed as HAZARDOUS WASTE
4. In the event of Irinotecan contact with the skin, the area should be rinsed with plenty of running water and then washed with soap and water. In case of contact with mucous membranes, wash the contacted area thoroughly with water. If you have any discomfort, contact a doctor.
5. In case of contact of Irinotecan with eyes, wash them thoroughly with plenty of water. Contact an ophthalmologist immediately.

Disposal
All items used for preparation, administration or otherwise coming into contact with irinotecan should undergo disposal according to local guidelines for the handling of cytotoxic compounds.

7 MARKETING AUTHORISATION HOLDER
SymPhar Sp.z.o.o
ul Wloska 1
WARSAW
PL00-777

8 MARKETING AUTHORISATION NUMBER(S)
PL 31304/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/11/2009

10 DATE OF REVISION OF THE TEXT
20/11/2009
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Irinotecan 20 mg/ml concentrate for solution for infusion.

The name of your medicine is irinotecan 20 mg/ml concentrate for solution for infusion, which will be referred to as 'Irinotecan 20 mg/ml concentrate for solution for infusion' or 'Irinotecan 20 mg/ml concentrate for solution for infusion solution' throughout this leaflet.

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Irinotecan 20 mg/ml concentrate for solution for infusion is and what it is used for
2. Before you use Irinotecan 20 mg/ml concentrate for solution for infusion
3. How you are given Irinotecan 20 mg/ml concentrate for solution for infusion
4. Possible side effects
5. How to store Irinotecan 20 mg/ml concentrate for solution for infusion
6. Further information

1. WHAT IRINOTECAN 20 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION IS AND WHAT IT IS USED FOR

Irinotecan 20 mg/ml concentrate for solution for infusion belongs to a group of medicines called cytostatics (anti-cancer medicines).

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

2. BEFORE YOU ARE GIVEN IRINOTECAN 20 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

Do not use Irinotecan 20 mg/ml concentrate for solution for infusion if:
- You are allergic (hypersensitive) to irinotecan or any of the other ingredients of Irinotecan 20 mg/ml concentrate for solution for infusion
- You have any other bowel disease or a history of bowel obstruction
- You are pregnant or breast-feeding
- You have high levels of bilirubin (a waste blood product)
- You have severe bone marrow failure
- You are taking the natural remedy St John's wort (Hypericum perforatum - used for depression)
- You are in a poor general health (evaluated by an international standard).

Take special care with Irinotecan 20 mg/ml concentrate for solution for infusion
This medicine is intended for adults only. Check with your doctor if this medicine has been prescribed for use in a child.

Special care is also needed in elderly patients.
As irinotecan is an anti-cancer medicine it will be administered to you in a special unit and under the supervision of a doctor qualified in the use of anti-cancer medicines. The unit’s personnel will explain to you what you need to take special care of during and after the treatment. This leaflet may help you to remember that:

1) **The first 24 hours after administration of irinotecan**

During administration of irinotecan (30-90 min.) and shortly after administration you may experience some of the following symptoms:
- diarrhoea
- swelling
- abdominal pain
- watering eyes
- visual disturbance
- excessive mouth watering

The medical term for these symptoms is acute cholinergic syndrome which can be treated (with atropine). If you have any of these symptoms immediately tell your doctor who will give you any treatment necessary.

2) **From the day after treatment with irinotecan until next treatment**

During this period you may experience various symptoms, which may be serious and require immediate treatment and close supervision.

**Diarrhoea**

If your diarrhoea starts more than 24 hours after administration of irinotecan ("delayed diarrhoea") it may be serious. It is often seen about 5 days after administration. The diarrhoea should be treated immediately and kept under close supervision. Immediately after the first liquid stools do the following:

(a) Take any anti-diarrhoeal treatment that the doctor has given you, exactly as he/she has told you. The treatment may not be changed without consulting the doctor. Recommended anti-diarrhoeal treatment is loperamide (4 mg for the first intake and then 2 mg every 2 hours, also during the night). This should be continued for at least 12 hours after the last liquid stools. The recommended dosage of loperamide may not be taken for more than 48 hours.

(b) Drink large amounts of water and rehydration fluids, immediately (i.e. water, soda water, fizzy drinks, soup or oral rehydration therapy)

(c) Immediately inform your doctor who is supervising the treatment, and tell him/her about the diarrhoea. If you are not able to reach the doctor, contact the unit at the hospital supervising the irinotecan treatment. It is very important that they are aware of the diarrhoea.

You must immediately tell the doctor, or the unit supervising the treatment, if:
- you have nausea and vomiting as well as diarrhoea
- you have any fever as well as the diarrhoea
- you still have diarrhoea 48 hours after starting the diarrhoea treatment

Note: Do not take any treatment for diarrhoea other than that given to you by your doctor and the fluids described above. Follow the doctor’s instructions. The anti-diarrhoeal treatment should not be used to prevent a further episode of diarrhoea, even though you have experienced delayed diarrhoea at previous cycles.

**Fever**

If the body temperature increases over 38°C it may be a sign of infection, especially if you also have diarrhoea. If you have any fever (over 36°C) contact your doctor or the unit immediately so that they can give you any treatment necessary.

**Nausea and vomiting**

If you have nausea and/or vomiting contact your doctor or the unit immediately

**Neutropenia**
Irinoctecan may cause a decrease in the number of some of your white blood cells, which play an important role in fighting infections. This is called neutropenia. Neutropenia is often seen during treatment with Irinoctecan and is reversible. Your doctor should arrange for you to have regular blood tests to monitor these white blood cells. Neutropenia is serious and should be treated immediately and carefully monitored.

Breathing difficulties
If you have any breathing difficulties contact your doctor immediately.

Impaired liver function
Before treatment with Irinoctecan is started and before every following treatment cycle the liver function should be monitored (by blood tests).

If you have one or more of the symptoms mentioned, after you have returned home from the hospital, you should immediately contact the doctor or the unit supervising the Irinoctecan treatment.

Impaired kidney function
As this medicine has not been tested in patients with kidney problems, please check with your doctor if you have any kidney problems.

Taking other medicines
Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines, including medicines obtained without a prescription, as they may interact with Irinoctecan 20 mg/ml concentrate for solution for infusion. This is especially important of:
- muscle relaxants, e.g. suxamethonium
- medicines for the treatment of epilepsy (e.g. carbamazepine, phenobarbital or phenytoin)
- ketoconazole (used to treat fungal infections)
- rifampicin (an antibiotic)
- the natural remedy St John’s Wort (a treatment for depression)

This is also valid for herbal medicines, strong vitamins and minerals.
If you require an operation, please tell your doctor or anaesthetist that you are using this medicine, as it may alter the effect of some medicines used during surgery.

It may still be all right for you to be given Irinoctecan 20 mg/ml concentrate for solution for infusion and your doctor will be able to decide what is suitable for you.

Pregnancy and breast-feeding
You must not receive Irinoctecan 20 mg/ml concentrate for solution for infusion if you are pregnant. Tell your doctor if you are pregnant, think you could be pregnant, or could become pregnant.
Contraceptive measures must be taken by both male and female patients of reproductive age during and for at least three months after cessation of therapy. If you become pregnant during this period you must immediately inform your doctor.
You should not breast-feed while you are treated with Irinoctecan 20 mg/ml concentrate for solution for infusion.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Irinoctecan 20 mg/ml concentrate for solution for infusion may make you feel dizzy or cause visual disturbances within 24 hours after administration of the product. If this happens to you do not drive or use any tools or machines.

Important information about some of the ingredients of Irinoctecan 20 mg/ml concentrate for solution for infusion
Irinoctecan 20 mg/ml concentrate for solution for infusion solution contains sorbitol. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW YOU ARE GIVEN IRINOCTECAN 20 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION
Dosage
Irinotecan 20 mg/ml concentrate for solution for infusion is for adults only and will be given to you by a doctor or nurse. Irinotecan 20 mg/ml concentrate for solution for infusion solution is infused into a vein.

The usual dose when used alone in patients who have been treated before is 350 mg/m² (square meter of body area) given as an infusion over a 30 to 90 minute period every three weeks.

The usual dose for patients who have not been treated before is 180 mg/m² (square meter of body area) given once every 2 weeks as an infusion over a 30 to 90 minute period, followed by infusion with folinic acid and 5-fluorouracil (other cancer treatments).

Altered dosages
- The dose of Irinotecan 20 mg/ml concentrate for solution for infusion may be reduced if you suffer side effects.
- The dose of Irinotecan 20 mg/ml concentrate for solution for infusion may be reduced if you have a liver disorder.
- The dose of Irinotecan 20 mg/ml concentrate for solution for infusion may be altered if it is used with other chemotherapy.
- The dose should be chosen carefully in elderly; more intense surveillance is required.
- Irinotecan 20 mg/ml concentrate for solution for infusion is not recommended for patients with kidney disorders.
- Treatment is continued until the cancer gets worse or the side effects are unacceptable.

If you receive more Irinotecan 20 mg/ml concentrate for solution for infusion than you should Irinotecan 20 mg/ml concentrate for solution for infusion will be given to you by a doctor or nurse who is familiar with this type of treatment so the chance is very small to be given an overdose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Irinotecan 20 mg/ml concentrate for solution for infusion can cause side effects, although not everybody gets them.

Your doctor will discuss these side effects with you and explain the risks and benefits of your treatment. Some of these side effects must be treated immediately, see also information in section "Take special care with Irinotecan".

Very common side effects (more than 1 in 10 patients):
- Blood disorders:
  - Decreased number of a certain type of white blood cells (neutropenia) which increases the risk of infections.
  - Decreased number of red blood cells (anaemia) which can make the skin pale and cause weakness and breathlessness.
  - In combination therapy, decreased number of blood platelets (thrombocytopenia) which increases the risk of bruising and bleeding.
  - In monotherapy, fever and infections.
  - Delayed severe diarrhoea.
  - In monotherapy, nausea and vomiting.
  - Hair loss (the hair grows again after end of treatment).
  - In combination therapy transient serum levels of some liver enzymes (AST, ALT, alkaline phosphatase) or bilirubin.

Common side effects (less than 1 in 10 patients but more than 1 in 100):
- Severe transient acute cholinergic syndrome: the main symptoms are defined as early diarrhoea and various other symptoms such as abdominal pain; red, sore, itching or weeping eyes (conjunctivitis); running nose (rhinitis); low blood pressure; widening of the blood vessels; sweating, chills; a feeling of general discomfort and illness; dizziness; visual disturbances;
pupil contraction; watering eyes and increased salivation, occurring during or within the first 24 hours after the infusion of irinotecan.

- In monotherapy, decreased number of blood platelets (thrombocytopenia) which increases the risk of bruising and bleeding
- In combination therapy, fever and infections.
- Infections associated with a severe decrease in the number of a certain type of white blood cells (neutropenia) resulting in death in 3 cases.
- Fever associated with a severe decrease in the number of a certain type of white blood cells.
- In combination therapy, severe nausea (feeling sick) and vomiting (being sick).
- Loss of water (dehydration), commonly associated with diarrhoea and/or vomiting.
- Constipation.
- Fatigue (severe weakness).
- In monotherapy, increased levels of some liver enzymes (transaminases, alkaline phosphatase) or bilirubin.
- Increase of creatinine in the blood.
- In combination therapy, transient severe (grade 3) increase in serum levels of bilirubin.

Uncommon side effects (less than 1 in 100 patients but more than 1 in 1000):

- Mild allergic reactions causing skin rash including red itchy skin, urticaria, conjunctivitis, rhinitis.
- Mild skin reactions; mild reactions at the infusion site.
- Early effects such as breathing difficulties.
- Lung disease (interstitial pulmonary disease) presenting as shortness of breath, dry cough and inspiratory crackles.
- Intestinal blockage.
- Gastrointestinal bleeding.
- Abdominal pain and inflammation, causing diarrhoea (a condition known as pseudomembranous colitis)
- Kidney problems (renal insufficiency), low blood pressure or cardio-circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting or sepsis.

Rare side effects (less than 1 in 1000 patients but more than 1 in 10,000):

- Severe allergic reactions (anaphylactic/anaphylactoid reactions) causing swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing). If this happens you should tell your doctor immediately.
- Early effects such as muscular contraction or cramps and numbness (paresthesia).
- Inflammation of the large bowel (colitis including typhilitis, ischemic and ulcerative colitis) causing abdominal pain.
- Intestinal perforation, loss of appetite (anorexia), abdominal pain, inflammation of the mucous membranes.
- Inflammation of the pancreas (pancreatitis) which may cause upper abdominal pain.
- Increased blood pressure during and following administration.
- Decreased levels of potassium and sodium in the blood, mostly related to diarrhoea and vomiting.

Very rare side effects (less than 1 in 10,000 patients):

- Bruising or bleeding easily due to your body destroying its own blood platelets (peripheral thrombocytopenia with antiplatelet antibodies [one case]).
- Transient speech disorders.
- Increase in levels of some digestive enzymes which break down sugars and fats.

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

5. HOW TO STORE IRINOTECAN 20 MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

This medicinal product does not require any special storage conditions.
The irinotecan solution should be used immediately after dilution as it contains no antibacterial preservative. If dilution is performed under strict aseptic conditions (e.g. laminar air flow bench) irinotecan solution should be used (infusion completed) within 12 hours at room temperature or 24 hours if stored 2-8°C after the first breakage.

Irinotecan 20 mg/ml concentrate for solution for infusion should be kept out of the reach and sight of children.

Do not use irinotecan 20 mg/ml concentrate for solution for infusion after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month.

Do not use irinotecan 20 mg/ml concentrate for solution for infusion if you notice any particles in the solution or if there are any other visible signs of deterioration.

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

6. FURTHER INFORMATION

What irinotecan 20 mg/ml concentrate for solution for infusion contains:

The active substance is irinotecan (as hydrochloride trihydrate).

Each vial filled with 2 ml Irinotecan hydrochloride Trihydrat 20 mg/ml contains 40mg irinotecan hydrochloride trihydrate equivalent to 34.68mg irinotecan.

Each vial filled with 5 ml Irinotecan hydrochloride Trihydrat 20 mg/ml contains 100mg irinotecan hydrochloride trihydrate equivalent to 86.68mg irinotecan.

The other ingredients are: sorbitol, lactic acid, sodium hydroxide, hydrochloric acid, water for injection

What irinotecan 20 mg/ml concentrate for solution for infusion looks like and contents of the pack

Irinotecan 20 mg/ml concentrate for solution for infusion is a clear, yellowish coloured solution. Irinotecan 20 mg/ml concentrate for solution for infusion 20 mg/ml is available in boxes containing a single or five amber type-I tubular glass vial with bromobutyl rubber stopper and flip off seal.

Pack size:
1 vial 2 ml fill volume
5 vials 2ml fill volume

1 vial 5 ml fill volume
5 vials 5ml fill volume

Not all pack sizes may be marketed.

Marketing Authorisation Holder
SymPhar Sp. z o.o.
ul. Wiloska 1, Warsaw, Poland

Manufacturer Tecnimed – Sociedade Técnico-Medicinal, SA
Quinta da Corca, Caixaria
2565-187 Dois Portos
Portugal
SymPhar sp. z o.o.
ul. Włoska 1
00-777 Warsaw
Poland

This medicinal product is authorised in the Member States of the EEA under the following names:

UK: Irinotecan 20 mg/ml concentrate for solution for infusion
PL: Symtecan 20 mg/ml

This leaflet was last revised in
03 Nov 09
Irinotecan 20 mg/ml concentrate for solution for infusion 20 mg/ml concentrate for solution for infusion.

The following information is intended for medical or healthcare professionals only:

**Instruction for use – Cytotoxic**

**Handling of Irinotecan**

As with all antineoplastic agents, caution should be exercised when handling Irinotecan. Dilution should be carried out under aseptic conditions by trained personnel in a designated area. Precautions should be taken to avoid contact with the skin and mucous membranes.

**Protection instructions for preparation of irinotecan solution for infusion**:

1. Protective chamber should be used and protective gloves as well as protective gown should be worn. If there is no protective chamber available, mouth cover and goggles should be used.

2. Opened containers, like injection vials and infusion bottles and used cannulae, syringes, catheters, tubings, and residues of cytostatics should be considered as hazardous waste and undergo disposal according to local guidelines for the handling of HAZARDOUS WASTE.

3. Follow the instructions below in case of spillage:
   - protective clothing should be worn
   - broken glass should be collected and placed in the container for HAZARDOUS WASTE.
   - Contaminated surfaces should be flushed properly with copious amounts of cold water.
   - the flushed surfaces should then be wiped thoroughly and the materials used for wiping should be disposed as HAZARDOUS WASTE.

4. In the event of Irinotecan contact with the skin, the areas should be rinsed with plenty of running water and then washed with soap and water. In case of contact with mucous membranes, wash the contacted area thoroughly with water. If you have any discomfort, contact a doctor.

5. In case of contact of Irinotecan with eyes, wash them thoroughly with plenty of water contact an ophthalmologist immediately.

**Preparation of infusion solution**

Irinotecan concentrate for solution for infusion is intended for intravenous infusion only after diluting prior to administration in the recommended diluents, either 0.9 % Sodium chloride solution for infusion or 5 % glucose solution for infusion. Aseptically withdraw the required amount of irinotecan concentrate for solution from the vial with a calibrated syringe and inject into a 250 ml infusion bag or bottle. The infusion should be thoroughly mixed by manual rotation. If any precipitate is observed in the vials or after reconstitution, the product should be discarded according to standard procedures for cytotoxic agents. Irinotecan should not be delivered as an intravenous bolus or an intravenous infusion shorter than 30 minutes or longer than 90 minutes.

**Disposal**

All items used for preparation, administration or otherwise coming into contact with Irinotecan should undergo disposal according to local guidelines for the handling of cytotoxic compounds.
Module 4
Labelling

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Tubular glass vials with rubber closure, sealed

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

Irinotecan 20 mg/ml concentrate for solution for infusion.

Irinotecan hydrochloride, trihydrate
For intravenous infusion after dilution.

2. METHOD OF ADMINISTRATION

[not applicable]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 mg/2 ml

6. OTHER

SymPhar Sp. z o.o.
Ul. Wloska 1, Warsaw, Poland
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Tubular glass vials with rubber closure, sealed

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

Irinotecan 20 mg/ml concentrate for solution for infusion.

Irinotecan hydrochloride, trihydrate.

For intravenous infusion after dilution.

2. METHOD OF ADMINISTRATION

[not applicable]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg/5 ml

6. OTHER

SynPhar Sp. z o.o.
Ul. Wloska 1, Warsaw, Poland
1. NAME OF THE MEDICINAL PRODUCT

Irinotecan 20 mg/ml concentrate for solution for infusion.

Irinotecan hydrochloride, trihydrate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of concentrate contains 20 mg irinotecan hydrochloride trihydrate (equivalent to 17.35 mg irinotecan).

Each 2 ml vial contains 40 mg of irinotecan hydrochloride trihydrate (equivalent to 34.66 mg irinotecan).

3. LIST OF EXCIPIENTS

Excipients:
sorbitol, lactic acid, sodium hydroxide, hydrochloric acid, water for injection

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

1 x 2 ml, 5 x 2 ml  1 x 5 ml, 5 x 5 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous infusion after dilution.

Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic agent

8. EXPIRY DATE

EXP

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

Any unused product or waste material should be disposed of in accordance with local requirements.

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

SymPhar Sp. z o.o.
Ul.Włośka 1, Warsaw, Poland

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 31304/0003

13. **BATCH NUMBER**

Batch

14. **GENERAL CLASSIFICATION FOR SUPPLY**

- [To be completed nationally]-

15. **INSTRUCTIONS ON USE**

[not applicable]

16. **INFORMATION IN BRAILLE**

Braille is not applicable for medicines only intended for administration by health care professionals (Guideline on the packaging information of medicinal products for human use authorized by the community - March 2007; Notice to Applicants Volume 2C - Medicinal Products for Human Use - Regulatory Guidelines of The Rules governing Medicinal Products in the European Community)
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
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</thead>
<tbody>
<tr>
<td>Carton box</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Irinotecan 20 mg/ml concentrate for solution for infusion.
Irinotecan hydrochloride, trihydrate

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

1 ml of concentrate contains 20 mg irinotecan hydrochloride trihydrate (equivalent to 17.33 mg irinotecan).
Each 5 ml vial contains 100 mg of irinotecan hydrochloride trihydrate (equivalent to 86.65 mg irinotecan).

3. **LIST OF EXCIPIENTS**

Excipients:
sorbitol, lactic acid, sodium hydroxide, hydrochloric acid, water for injection

4. **PHARMACEUTICAL FORM AND CONTENTS**

Concentrate for solution for infusion
1 x 2ml, 5 x 2ml
In 5 ml, 5 x 5ml

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For intravenous infusion after dilution
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

Cytotoxic agent

8. **EXPIRY DATE**

EXP

9. **SPECIAL STORAGE CONDITIONS**


10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**
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SymPhar Sp. z o.o.
Ul.Wloka 1, Warsaw, Poland

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 31504/0003

13. **BATCH NUMBER**

Batch

14. **GENERAL CLASSIFICATION FOR SUPPLY**

[To be completed nationally]

15. **INSTRUCTIONS ON USE**

[not applicable]

16. **INFORMATION IN BRAILLE**

Braille is not applicable for medicines only intended for administration by health care professionals (Guideline on the packaging information of medicinal products for human use authorised by the Community - March 2007; Notice to Applicants Volume 2C - Medicinal Products for Human Use - Regulatory Guidelines of The Rules governing Medicinal Products in the European Community)
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
On 19th October 2009, Poland and the UK agreed to grant a marketing authorisation to Symphar SP ZOO for the medicinal product Irinotecan 20mg/ml Concentrate for Solution. The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS – UK/H/1294/001/DC). After the national phase, a licence was granted in the UK on 20th November 2009 (PL 31304/0003).

This application was made under Article 10.1 of Directive 2001/83 EC for Irinotecan 20mg/ml Concentrate for Solution, containing the known active substance irinotecan hydrochloride trihydrate. The reference medicinal products for this application are Campto 40mg/2ml Concentrate for Solution for Infusion (PL 00057/0626). These applications were first granted in the UK to May and Baker on 17th October 1996, but following a change of ownership in March 2003 these changed marketing authorisation holder to Aventis Pharma Limited. A second change of ownership changed the marketing authorisation holder to Pfizer Limited, where they are currently held.

Irinotecan, a Camptothecin, is licensed for first-line use in patients with advanced or metastatic colorectal cancer (either alone or in combination with fluorouracil and folinic acid/ Cetuximab/Bevacizumab [see specific indications in the SPC]). Irinotecan is administered intravenously at doses ranging from 180-350 mg/m² over a 30-90 minute period. It 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.

The drug product Irinotecan corresponds to the current EU definition for generic medicinal product because it complies with the criteria of having the same qualitative and quantitative composition in terms of active substance, and the same dosage form.

The proposed product is developed using an approved drug substance that 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.

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.

An acceptable justification for not submitting a European Risk Management Plan has been provided. Other documentation relating to pharmacovigilance system has been provided.

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’ issued by the inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those non-Community sites.

II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th><strong>Name of the product in the Reference Member State</strong></th>
<th>Irinotecan Hydrochloride 20mg/ml Concentrate for Solution for Infusion</th>
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<tr>
<td><strong>Name(s) of the active substance(s) (USAN)</strong></td>
<td>Irinotecan hydrochloride trihydrate</td>
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<td><strong>Pharmacotherapeutic classification (ATC code)</strong></td>
<td>Cytostatic topoisomerase I inhibitor (L01 XX19)</td>
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<td><strong>Pharmaceutical form and strength(s)</strong></td>
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<td>Poland</td>
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<td><strong>Marketing Authorisation Number(s)</strong></td>
<td>PL 31304/0003</td>
</tr>
<tr>
<td><strong>Name and address of the authorisation holder</strong></td>
<td>Symphar SP ZOO, Ul wloska 1L, Warsaw, PL 00-777</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Irinotecan hydrochloride trihydrate
Chemical Names: [1,4'-Bipiperidine]-l'-carboxylic acid (4S) - 4,11-diethyl-3 ,4, 12,14-tetrahydro-4-hydroxy-3,14-dioxo-1 H- pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester.Hydrochloride Trihydrate

7-ethyl- 10- [4-(1-piperidino)- 1 -piperidino]carboxyloxy camptothecin Hydrochloride Trihydrate

(+)-7-ethyl- 10-hydroxycamptothecine 10-[1 ,4'-bipiperidine]-l'-carboxylate Hydrochloride Trihydrate


Structure:

Molecular formula: C₃₃H₃₈N₄O₆.HCl.3H₂O
Molecular weight: 677.19
Physical form: A light yellow to yellow coloured powder, sparingly soluble in methanol and water.

Irinotecan hydrochloride trihydrate is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. No materials of animal or human origin are used in the production of the active substance.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. All impurities have been appropriately characterised and certificates of analysis have been provided for any working standards used. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications for all materials used in the active substance packaging have been provided. The primary packaging meets the requirements for materials in contact with food.
Appropriate stability data have been generated, from studies carried out in accordance with ICH conditions. A suitable retest period has been set, based on the stability data provided.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of pharmaceutical excipients sorbitol E420, lactic acid, sodium hydroxide, hydrochloric acid and water for injections. All excipients are controlled to their respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients. None of the excipients used contain materials of animal or human origin.

**Pharmaceutical Development**

Suitable pharmaceutical development data have been provided for this application.

**Manufacture**

A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results appear satisfactory.

**Finished product specification**

The finished product specification is satisfactory. Test methods have been described and 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 finished product is supplied in 5ml Type I amber glass vial, which is closed with a chlorobutyl rubber stopper and an aluminium flip-off seal. Pack sizes are 1x2ml or 1x5ml packs.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidelines concerning materials in contact with parenteral products.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years has been set when the product is unopened, with no specific storage conditions for the unopened product.

It has been stipulated that the contents of the vial should be used immediately after opening. However, the following instructions are also given concerning storage of the product after dilution:

*The irinotecan solution should be used immediately after dilution as it contains no antibacterial preservative. If dilution is performed under strict aseptic conditions (e.g. on Laminar Air Flow bench) irinotecan solution should be used (infusion completed) within 12 hours at room temperature or 24 hours if stored 2°C-8°C after the first breakage.*
It is recommended, however, that in order to reduce microbiological hazard, the infusion solutions should be prepared immediately prior to use and infusion commenced as soon as practicable after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling
The SPC, PIL and labelling are pharmaceutically satisfactory. The marketing authorisation holder has committed to submitting mock-ups of the patient information leaflet and labels to the MHRA before marketing the product in the UK.

The applicant has submitted results of PIL user testing. 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.

MAA Form
The MAA form is pharmaceutically satisfactory.

Expert Report
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

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

III.2 PRE-CLINICAL ASPECTS
PHARMACODYNAMICS
Since irinotecan is an established drug, only an overview will be presented here.

Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I, which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent re-ligation of these single-strand breaks. Current research suggests that the cytotoxicity of Irinotecan is related to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA and either Irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-38 is formed from Irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is approximately 1000 times as potent as Irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumour cell lines. However, the plasma area under the concentration versus time curve (AUC) values for SN-38 are 2% to 8% of Irinotecan and SN-38 is 95% bound to plasma proteins compared to approximately 50% for Irinotecan. The precise contribution of SN-38 to the activity of Irinotecan is thus unknown. Both Irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the two forms such that an acid pH promotes the formation of the lactone, while a more basic pH favours the hydroxy acid anion form.

Irinotecan was active in carcinoma xenograft models.
The non-clinical overview also includes consideration of the potential for gastrointestinal side effects and mechanisms of resistance to Irinotecan.

**PHARMACOKINETICS**

The area under the plasma concentration-time curve (AUC) of Irinotecan increased 47-fold over the 20-fold increase in dose from 2 to 40mg/kg. Kidneys, adrenals, thyroid, lung, pancreas, pituitary, and liver were exposed to the highest levels of radiolabel following a single 10mg/kg dose of camptothecin-labelled Irinotecan.

Irinotecan was metabolised by rats, mice, dogs, monkey and human tissues to the active metabolite SN-38. The primary route of elimination for both rats and dogs was biliary via faeces, accounting for 67% to 77% of the administered dose. Urinary excretion accounted for 22% to 27% of the dose. The pharmacokinetic indices suggested that the $C_{\text{max}}$ of irinotecan is closely related to the incidence and severity of adverse reactions, such as myelosuppression and acute/delayed-onset diarrhoea.

**TOXICOLOGY**

Irinotecan’s toxicities are similar to those caused by other chemotherapeutic agents, such as bone marrow suppression, gastrointestinal toxicity, teratogenicity, mutagenicity, potential antigenicity and carcinogenicity.

Acute toxicity in rodents consists of tremors, convulsions, respiratory distress and death. The acute toxicity of Irinotecan after a single oral dose was 8- to 10-fold less than for a single intravenous dose.

Repeated-dose toxicity studies showed that Irinotecan caused vomiting, anorexia, alopecia, diarrhoea, soft stools, anaemia, leucopaenia, and thrombocytopenia. Irinotecan has an effect on tissues with high proliferative activity, such as bone marrow, thymus gland, spleen, lymph nodes and testes.

Local tolerance was acceptable in a series of experiments.

**EXCIPIENTS**

The excipients are commonly used in injectable formulations and comply with the European, the British or the United States Pharmacopoeiae. Hydrochloric acid or sodium hydroxide is used to adjust the pH.

**IMPURITIES**

A suitable justification has been provided for the limits of all impurities in the specifications. All limits comply with the ICH guidelines.

**ENVIRONMENTAL RISK ASSESSMENT**

There is no environmental risk assessment statement included in the application. This is acceptable for a generic product. The applicant has concluded that there is no need for a risk management plan. However, they have compiled the proposed SPC on the basis of the innovator product (Campto [Pfizer]), and a review of the current literature, which was conducted specifically to identify new/emerging safety issues and any recommendations made by regulatory authorities in relation to issues or adverse drug reactions that are not currently listed on the SPC of the innovator brand. However, no concerns were identified.

**SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

The SPC is satisfactory from a preclinical viewpoint.
NON-CLINICAL EXPERT REPORT
The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the preclinical aspects of the dossier.

OVERALL CONCLUSION ON THE NON-CLINICAL PART
The applicant has provided an adequate review of the available non-clinical data. The pattern of toxicity seen with irinotecan is consistent with its anti-cancer actions. There were no new non-clinical data identified in the literature review that would change the risk-benefit analysis for irinotecan.

III.3 CLINICAL ASPECTS
Pharmacokinetics
No new data have been submitted and none are required for an application of this type.

Irinotecan 20mg/ml Concentrate for Solution for Infusion is the generic version of Campto 20mg/ml (concentrate for solution for infusion). The use of the reference product is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredient, irinotecan hydrochloride trihydrate.

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).

Pharmacodynamics
No new data have been submitted and none are required for an application of this type.

Clinical efficacy
No new data have been submitted and none are required for an application of this type.

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.

Supportive trials include:

- Monotherapy studies with Irinotecan in colorectal cancer (Rougier et al., 1997; Tsavaris et al., 2002; Schoemaker et al., 2004; Hartmann et al., 2004; Van Cutsem et al., 2005).
- Randomised comparative studies of Irinotecan in colorectal cancer (Cunningham et al., 1999; van Cutsem et al., 1999; Douillard et al., 2000; Fuchs et al., 2003; Cunningham et al., 2004; Hurwitz et al., 2004).
- Studies of Irinotecan in combination with Fluorouracil in colorectal cancer (Glimelius et al., 2002; Vamvakas et al., 2002; Bouzid et al 2003; Moehler et al., 2003; Souglakos et al., 2005; Barcelo et al., 2006).
- Studies of Irinotecan in combination with Cetuximab in colorectal cancer (Vincenzi et al., 2006).
- Studies of Irinotecan in combination with Bevacizumab in colorectal cancer (Giantonio et al., 2006).

Clinical safety
Irinotecan has an acceptable adverse events profile. No novel safety data are supplied or required for this generic application. Irinotecan has a well established side-effect profile and is generally well-tolerated. The applicant has provided a review of clinical trials published in
the literature confirming the safety of Irinotecan. Side-effects include cholinergic symptoms, fatigue, nausea, vomiting, diarrhoea, anaemia, thrombocytopenia and neutropenia.

*Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and labelling*  
The SPC, PIL and labelling are medically satisfactory and consistent with those for the reference products.

*Clinical Expert Report*  
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

*MAA Form*  
The MAA Form is medically satisfactory.

*Clinical Conclusion*  
A Marketing Authorisation may be granted.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Irinotecan 20mg/ml Concentrate for Solution for Infusion are 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
The preclinical data submitted have not revealed any evidence of potential risks to human health from treatment with Irinotecan 20mg/ml Concentrate for Solution for Infusion beyond those already described.

EFFICACY
No new data have been submitted and none are required for an application of this type.

Irinotecan 20mg/ml Concentrate for Solution for Infusion is the generic version of Campto 20mg/ml (concentrate for solution for infusion). The use of the reference product is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredient, irinotecan hydrochloride trihydrate.

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No new safety data are supplied or required for this generic application. Irinotecan has a well-established side-effect profile and is generally well-tolerated.

The SPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s product and the innovator product are interchangeable. 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.
Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

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