Irinotecan 20 mg/ml Concentrate for Solution for Infusion
PL 33410/0089-90

UKPAR

TABLE OF CONTENTS

Lay Summary Page 2
Scientific Discussion Page 3
Steps taken for assessment Page 11
Steps taken after authorisation – summary
Summary of Product Characteristics Page 12
Product Information Leaflet Page 30
Labelling Page 31
Irinotecan 20 mg/ml Concentrate for Solution for Infusion
PL 33410/0089-90

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted APSLA Limited Marketing Authorisations for the medicinal product Irinotecan 20 mg/ml concentrate for solution for infusion (PL 33410/0089-90) on 04 November 2011. This medicine is only available on prescription from your doctor and is used for the treatment of advanced cancer of the colon and rectum in adults either in combination with other medicines or alone.

Irinotecan 20 mg/ml concentrate for solution for infusion contains the active ingredient, irinotecan hydrochloride trihydrate, which belongs to a group of medicines called cytostatics (anti-cancer medicines).

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Irinotecan 20 mg/ml concentrate for solution for infusion outweigh the risks; hence Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction ....................................................... Page 4
Pharmaceutical assessment ................................. Page 5
Non-clinical assessment ................................ Page 8
Clinical assessment ............................................ Page 9
Overall conclusions and risk assessment .............. Page 10
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted APSLA Limited Marketing Authorisations for the medicinal product Irinotecan 20 mg/ml concentrate for solution for infusion (PL 33410/0089-90) on 04 November 2011. Irinotecan 20 mg/ml concentrate for solution for infusion is a prescription-only medicine (POM).

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 have not received prior treatment for metastatic disease or after failure of irinotecan-including cytotoxic therapy.

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

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

These are duplicate, national, abridged applications (for the same product), submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Campto 40mg/2ml and 100mg/5ml (Pfizer Ltd, UK), which was first authorised in the UK on 17 October 1996.

The active ingredient, irinotecan (as irinotecan hydrochloride trihydrate), is a camptothecin. Irinotecan is metabolised 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.

No new non-clinical or clinical data were submitted, which is acceptable given that the applications were based on being generic medicinal products of an originator product that has been in clinical use for over 10 years. A bioequivalence study was not necessary to support these applications for an aqueous parenteral product (containing the same active substance in the same concentration as the innovator product).

No new or unexpected safety concerns arose during review of the information provided by the applicant and it was judged that the benefits of taking Irinotecan 20 mg/ml concentrate for solution for infusion outweigh the risks; hence Marketing Authorisations have been granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE
INN: Irinotecan hydrochloride trihydrate
Chemical Name: (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H pyrano [3’,4’:6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4’bipiperidine]-1’-carboxylate, monohydrochloride, trihydrate.
Molecular Formula: C\textsubscript{33}H\textsubscript{38}N\textsubscript{4}O\textsubscript{6}·HCl·3H\textsubscript{2}O
Structure

Molecular mass: 677.19
Appearance: A pale yellow to yellow coloured powder, slightly soluble in water and organic solvents.

Irinotecan hydrochloride trihydrate is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in the synthesis of the active substance are not of animal, biological or genetically modified origin.

An appropriate specification is provided for the active substance. Analytical methods have been validated appropriately and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications and Certificates of Analysis have been provided for all packaging used. The primary packaging has been shown to comply with current regulations concerning plastic containers and closures for pharmaceutical use, and with legislation relating to primary packaging in contact with foodstuff.
Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

**DRUG PRODUCT**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients lactic acid, sodium hydroxide, sorbitol (E420), hydrochloric acid and water for injection. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**

The objective of the pharmaceutical development programme was to produce safe, efficacious presentations of a product containing 20 mg/ml of irinotecan hydrochloride trihydrate, which could be considered a generic medicinal product of Campto (40mg/2ml and 100mg/5ml) powder for concentrate for solution for infusion (Pfizer Limited, UK).

The physico-chemical properties of the proposed product and the reference product, Campto, 40mg/2ml and 100mg/5ml (Pfizer Ltd, UK), have been found to be comparable.

Suitable pharmaceutical development data have been provided for these applications.

**Manufacturing Process**

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Control of Finished Product**

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 coloured glass vials, with rubber stoppers and aluminium flip-off tear-off overseals, containing 40mg or 100 mg of irinotecan hydrochloride trihydrate. The product is packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in single pack sizes of 2ml fill volume (40 mg) or 5ml fill volume (100 mg) vials.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials suitable for contact with parenteral products.
Stability
Stability studies were performed in accordance with current guidelines, using batches of the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the unopened vials with the storage conditions, “Keep the vial below 25°C and protect from light”.

After dilution, the following instructions are given concerning shelf-life and storage: “Chemical and physical in-use stability has been demonstrated for 48 hours at 2-8 °C and 24 hours at 15-30 °C following dilution with 5% dextrose and for 24 hours at 15-30 °C following dilution with 0.9% NaCl. From a microbiological point of view, the solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8 °C unless reconstitution/dilution has taken place in controlled and validated aseptic conditions”.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
A bioequivalence study was not necessary to support these applications for an aqueous parenteral product.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet 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.

Marketing Authorisation Application (MAA) Forms
The MAA forms are pharmaceutically satisfactory.

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

Conclusion
The grant of Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of irinotecan hydrochloride trihydrate are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT
The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for the non-submission of an Environmental Risk Assessment As this product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of Marketing Authorisations is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
No new clinical pharmacology data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support these applications. According to CPMP guidelines, bioequivalence studies are not generally required if the test 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).

EFFICACY
The efficacy of irinotecan hydrochloride trihydrate is well-known. No new efficacy data have been submitted with these applications and none are required for applications of this type.

SAFETY
No new safety data have been submitted with these applications and none are required. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of irinotecan hydrochloride trihydrate is well-known.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for this product.

SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPCs, PIL and labels are acceptable from a clinical perspective. The SmPCs are consistent with that for the originator product. The PIL is consistent with the details in the SmPCs and is in line with the current guidelines. The labelling is in line with the current guidelines.

CLINICAL EXPERT REPORT
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

CONCLUSION
The grant of Marketing Authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Irinotecan 20 mg/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.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of irinotecan hydrochloride trihydrate are well-known, no additional data were required.

EFFICACY
No new clinical data were submitted for these applications. A bioequivalence study was not necessary to support these applications for an aqueous parenteral product.

SAFETY
No new safety data were supplied or required for these applications. Irinotecan hydrochloride trihydrate has a well-established safety profile.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with those for the originator product, where appropriate, and consistent with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with irinotecan hydrochloride trihydrate is considered to have demonstrated the therapeutic value of the product. The benefit/risk balance is, therefore, considered to be positive.
Irinotecan 20 mg/ml Concentrate for Solution for Infusion
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STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation applications on 17 June 2010.

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 07 July 2010.

3 Following assessment of the applications the MHRA requested further information relating to the dossier on 04 October 2010 and 22 June 2011.

4 The applicant responded to the MHRA’s requests, providing further information on the dossier on 02 April 2011 and 11 August 2011.

5 The applications were granted on 04 November 2011.
SUMMARY OF PRODUCT CHARACTERISTICS

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
The concentrate contains 20 mg/ml irinotecan hydrochloride, trihydrate (equivalent to 17.33 mg/ml Irinotecan). Vials of Irinotecan contain 40 mg or 100 mg of Irinotecan hydrochloride Trihydrate

Excipient(s):
Sorbitol (E420)

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM
Concentrate for solution for infusion.

A clear, colourless to pale yellow solution

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Irinotecan is indicated for the treatment of patients with advanced colorectal cancer:
• in combination with 5-fluorouracil and folinic acid in patients without prior chemotherapy for advanced disease,
• as a single agent in patients who have failed an established 5-fluorouracil containing treatment regimen.

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 should be infused into a peripheral or central vein.

Recommended dosage:
In monotherapy (for previously treated patient):
The recommended dosage of Irinotecan is 350 mg/m² administered as an intravenous infusion over a 30- to 90- minute period every three weeks. (see sections 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 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 (UNL)) 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 is 350 mg/m²,
• In patients with bilirubin ranging from 1.5 to 3 times the ULN, the recommended dosage of Irinotecan is 200 mg/m²,
• Patients with bilirubin beyond to 3 times the ULN should not be treated with irinotecan (see section 4.3 and section 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 section 4.4 and section 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

Irinotecan is contraindicated in:

• 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 4.4 and 4.6)
• Bilirubin > 3 times the upper limit of the normal range (see section 4.4)
• Severe bone marrow failure.
• WHO performance status ≥ 2.
• Concomitant use with St John's Wort (see section 4.5).

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 concentrate for solution for infusion will only be prescribed in the following cases after the expected benefits have been weighted against the possible therapeutic risks:

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

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

Delayed diarrhoea

Patients should be made aware of the risk of delayed diarrhoea occurring more than 24 hours after the administration of irinotecan and at any time before the next cycle. In monotherapy, the median time of onset of the first liquid stool was on day 5 after the infusion of irinotecan. Patients should quickly inform their physician of its occurrence and start appropriate therapy immediately.

Patients with an increased risk of diarrhoea are those who had a previous abdominal/pelvic radiotherapy, those with baseline hyperleucocytosis, those with performance status ≥2 and women. If not properly treated, diarrhoea can be life-threatening, especially if the patient is concomitantly neutropenic.

As soon as the first liquid stool occurs, the patient should start drinking large volumes of beverages containing electrolytes and an appropriate antidiarrhoeal therapy must be initiated immediately. This antidiarrhoeal treatment will be prescribed by the department where
irinotecan hydrochloride trihydrate 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 hydrochloride trihydrate when/if diarrhoea is occurring.

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

In addition to the anti-diarrhoeal treatment, a prophylactic broad spectrum antibiotic should be given, when diarrhoea is associated with severe neutropenia (neutrophil count < 500 cells/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 treatment with irinotecan. Patients should be aware of the risk of neutropenia and the significance of fever. Febrile neutropenia (temperature> 38°C and neutrophil count $\leq$ 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 "Pharmacokinetic properties" section) 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 concentrate solution for infusion until resolution of the bowel obstruction (see section 4.3).

Patients with Impaired Renal Function
Studies in this population have not been conducted. (see section 4.2 and section 5.2).

Others
Since this Irinotecan contains sorbitol, patients with rare hereditary problems of fructose intolerance should not take this medicine. In frequent cases of renal insufficiency, hypotension or circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis. Contraceptive measures must be taken during and for at least three months after cessation of therapy (see section 4.6).

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 effects of such anticonvulsant drugs was reflected by a decrease in AUC of SN-38 and SN-38G by 50% or more. In addition to induction of cytochrome P450 3A enzymes, enhanced glucuronidation and enhanced biliary excretion may play a role in reducing exposure to irinotecan and its metabolites.

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

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

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

St. John's Wort decreases SN-38 plasma levels. As a result, St. John's Wort should not be administered with irinotecan (see section 4.3).
Coadministration of 5-fluorouracil/folinic acid in the combination regimen does not change the pharmacokinetics of irinotecan.

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.

4.6 Fertility, 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 concentrate for solution for infusion must not be used during pregnancy (see section 4.3 and section 4.4)

Women of child-bearing potential/Contraception:

Women of child-bearing age receiving irinotecan concentrate for solution for infusion should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur (see section 4.3 and section 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%). Therefore also refer to the product information of cetuximab. For information on adverse reactions in combination with bevacizumab, refer to the bevacizumab summary of product characteristics.

The following adverse reactions considered to be possibly or probably related to the administration of irinotecan hydrochloride trihydrate have been reported from 765 patients at the recommended dose of 350 mg/m² in monotherapy, and from 145 patients treated by irinotecan hydrochloride trihydrate in combination therapy with 5FU/FA in every 2 weeks schedule at the recommended dose of 180 mg/m². The most common (≥ 1/10), dose-limiting adverse reactions of irinotecan are delayed diarrhoea (occurring more than 24 hours after administration) and blood disorders including neutopenia, anaemia and thrombocytopenia. Commonly severe transient acute cholinergic syndrome was observed. The main symptoms were defined as early diarrhoea and various other symptoms such as abdominal pain,
conjunctivitis, rhinitis, hypotension, vasodilation, sweating, chills, malaise, dizziness, visual disturbances, myosis, lacrimation and increased salivation occurring during or within the first 24 hours after the infusion of Irinotecan concentrate for solution for infusion. These symptoms disappear after atropine administration (see section 4.4).

**Delayed diarrhoea**
In monotherapy:
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:
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.

**Blood disorders**

**Neutropenia**
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:
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 < 1,000 cells/mm³ including 7.6 % with a neutrophil count < 500 cells/mm³.

Total recovery was usually reached by day 22.

Fever with severe neutropenia was reported in 6.2 % of patients and in 1.7 % of cycles.

Infectious episodes occurred in about 10.3 % of patients (2.5 % of cycles) and were associated with severe neutropenia in about 5.3 % of patients (1.1 % of cycles), and resulted in death in two cases.

In combination therapy:
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 < 1,000 cells/mm³ including 2.7 % with a neutrophil count < 500 cells/mm³.

Total recovery was usually reached within 7 – 8 days.

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 one case.

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

In combination therapy:
Anaemia was reported in 97.2 % of patients (2.1 % with haemoglobin < 8 g/dl).
**Thrombocytopenia**

In monotherapy:
Thrombocytopenia (< 100,000 cells/mm³) was observed in 7.4 % of patients and 1.8 % of cycles with 0.9 % with platelets ≤ 50,000 cells/mm³ and 0.2 % of cycles. Nearly all the patients showed a recovery by day 22.

In combination therapy:
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.

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

Side effects have been summarised in the table below with MedDRA frequencies. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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; not known (cannot be estimated from the available data)

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Frequency</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Very common | | ● Severe delayed diarrhoea
● Severe nausea and vomiting in case of monotherapy |
| Common | | ● Severe nausea and vomiting in case of combination therapy
● Episodes of dehydration (associated with diarrhoea and/or vomiting)
● Constipation relative to irinotecan and/or loperamide |
| Uncommon | | ● Pseudo-membranous colitis (one has been documented bacteriologically: Clostridium difficile)
● Renal insufficiency, hypotension or cardio-circulatory failure as a consequence of dehydration associated with diarrhoea and/or vomiting
● Intestinal obstruction, ileus, gastrointestinal haemorrhage |
| Rare | | ● Colitis, including typhlitis, ischemic and ulcerative colitis
● Intestinal perforation
● Other mild effects include anorexia, abdominal pain and mucositis.
● Symptomatic or asymptomatic pancreatitis |
| **Blood and lymphatic system disorders** | | |
| Very common | | ● Neutropenia (reversible and not cumulative)
● Anaemia
● Thrombocytopenia in case of combination therapy
● Infectious episodes in case of monotherapy |
| Common | | ● Febrile neutropenia
● Infectious episodes in case of combination therapy
● Infectious episodes associated with severe neutropenia resulting in death in three cases
● Thrombocytopenia in case of monotherapy |
<p>| Very rare | | ● One case of peripheral thrombocytopenia with antiplatelet antibodies has been reported. |
| <strong>Skin and subcutaneous tissue disorders</strong> | | |</p>
<table>
<thead>
<tr>
<th>Organ system</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>Side effects</td>
</tr>
<tr>
<td><strong>Very common</strong></td>
<td>• Alopecia (reversible)</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>• Mild cutaneous reactions</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very common</strong></td>
<td>• Fever in the absence of infection and without concomitant severe neutropenia in case of monotherapy</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>• Fever in the absence of infection and without concomitant severe neutropenia in case of combination therapy • Severe transient acute cholinergic syndrome (The main symptoms were defined as early diarrhoea and various other symptoms such as abdominal pain, conjunctivitis, rhinitis, hypotension, vasodilation, sweating, chills, malaise, dizziness, visual disturbances, myosis, lacrimation and increased salivation.) • Asthenia</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>• Infusion site reactions</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very common</strong></td>
<td>• In combination therapy, transient serum levels (grade 1 and 2) of serum transaminases, alkaline phosphatase or bilirubin were observed in the absence of progressive liver metastasis.</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>• In monotherapy, transient and mild to moderate increases in serum levels of either transaminases, alkaline phosphatase or bilirubin were observed in the absence of progressive liver metastasis. • In combination therapy, transient grade 3 serum levels of bilirubin • Transient and mild to moderate increases of serum levels of creatinine</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>• Hypokalemia and hyponatremia</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>• Increases of amylase and/or lipase</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>• Interstitial pulmonary disease presenting as pulmonary infiltrates • Early effects such as dyspnoea</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>• Mild allergic reactions</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>• Anaphylactic/anaphylactoid reactions</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>• Renal insufficiency, hypotension or cardio-circulatory failure have been observed in patients who experienced sepsis.</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>• Hypertension during or following the infusion</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>• Early effects such as muscular contraction or cramps and paraesthesia</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>• Transient speech disorders</td>
</tr>
</tbody>
</table>
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 vincristine 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 leukaemias).

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 hydrochloride trihydrate at 180 mg/m² once every 2 weeks is followed by infusion with folinic acid (200 mg/m² over a 2-hour intravenous infusion) and 5-fluorouracil (400 mg/m² as an intravenous bolus, followed by 600 mg/m² over a 22-hour intravenous infusion). On day 2, folinic acid and 5-fluorouracil are administered at the same doses and schedules. In the weekly schedule, the administration of irinotecan at 80 mg/m² is followed by infusion with folinic acid (500 mg/m² over a 2-hour intravenous infusion) and then by 5-fluorouracil (2300 mg/m² over a 24-hour intravenous infusion) over 6 weeks.
In the combination therapy trial with the 2 regimens described above, the efficacy of irinotecan was evaluated in 198 treated patients:

<table>
<thead>
<tr>
<th>Combined regimens (n=198)</th>
<th>Weekly schedule (n=50)</th>
<th>Every 2 weeks schedule (n=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan hydrochloride trihydrate +5FU/FA</td>
<td>Irinotecan hydrochloride trihydrate +5FU/FA</td>
<td>Irinotecan hydrochloride trihydrate +5FU/FA</td>
</tr>
<tr>
<td><strong>Response rate (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40.8 *</td>
<td>23.1 *</td>
<td>51.2 *</td>
</tr>
<tr>
<td>p value</td>
<td>p=0.045</td>
<td>p=0.005</td>
</tr>
<tr>
<td><strong>Median time to progression (months)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.7</td>
<td>4.4</td>
<td>7.2</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>p=0.001</td>
</tr>
<tr>
<td><strong>Median duration of response (months)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.3</td>
<td>8.8</td>
<td>8.9</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>p=0.043</td>
</tr>
<tr>
<td><strong>Median duration of response and stabilisation (months)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.6</td>
<td>6.2</td>
<td>8.3</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>p=0.003</td>
</tr>
<tr>
<td><strong>Median time to treatment failure (months)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.3</td>
<td>3.8</td>
<td>5.4</td>
</tr>
<tr>
<td>p value</td>
<td>p=0.0014</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Median survival (months)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.8</td>
<td>14.0</td>
<td>19.2</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>p=0.028</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.

<table>
<thead>
<tr>
<th></th>
<th>AVF2107g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arm 1 Irinotecan/5FU/FA + Placebo</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>411</td>
</tr>
<tr>
<td>Overall survival</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 &lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.660</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>Progression-free survival</td>
<td></td>
</tr>
<tr>
<td>Median time (months)</td>
<td>6.2</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>Overall response rate</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></td>
</tr>
<tr>
<td>Duration of response</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>

<sup>a</sup> 5 mg/kg every 2 weeks. <sup>b</sup> Relative to control arm.
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:

<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 FOLFIRI (N=599)</td>
<td>FOLFIRI (N=599)</td>
</tr>
<tr>
<td>ORR % (95%CI)</td>
<td>46.9 (42.9, 51.0)</td>
<td>38.7 (34.8, 42.8)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0038</td>
<td>0.0025</td>
</tr>
<tr>
<td>PFS Hazard Ratio (95% CI)</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>

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

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) 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 Irinotecan was evaluated in 765 patients with documented progression on 5-FU at study entry.

<table>
<thead>
<tr>
<th>Phases III</th>
<th>Irinotecan versus supportive care</th>
<th>Irinotecan versus 5FU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Irinotecan n=183</td>
<td>Supportive care n=90</td>
</tr>
<tr>
<td>Progression Free Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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>

p values: 26.7, 26.7; p=0.03; 32.4, 32.4; p=0.0351; 8.5, 8.5; p=0.0351

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:

<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 95% CI</td>
</tr>
<tr>
<td><strong>Cetuximab + irinotecan</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMR 62202-007</td>
<td>218</td>
<td>50 (22.9)</td>
<td>17.5, 29.1</td>
<td>121 (55.5)</td>
<td>48.6, 62.2</td>
</tr>
<tr>
<td>IMCLCP02-9923</td>
<td>138</td>
<td>21 (15.2)</td>
<td>9.7, 22.3</td>
<td>84 (60.9)</td>
<td>52.2, 69.1</td>
</tr>
<tr>
<td><strong>Cetuximab</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMR 62202-007</td>
<td>111</td>
<td>12 (10.8)</td>
<td>5.7, 18.1</td>
<td>36 (32.4)</td>
<td>23.9, 42.0</td>
</tr>
</tbody>
</table>

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.

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 7.7 µg/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 14 C-labelled drug have shown that more than 50% of an intravenously administered dose of irinotecan is excreted as unchanged drug, with 33% in the faeces mainly via the bile and 22% in urine.
Two metabolic pathways account each for at least 12% of the dose:

- Hydrolysis by carboxylesterase into active metabolite SN-38. SN-38 is mainly eliminated by glucuronidation, and further by biliary and renal excretion (less than 0.5% of the irinotecan dose). The SN-38 glucuronide is subsequently probably hydrolysed in the intestine.
- Cytochrome P450 3A enzymes-dependent oxidations resulting in opening of the outer piperidine ring with formation of APC (aminopentanoic acid derivate) and NPC (primary amine derivate) (see section 4.5).

Unchanged irinotecan is the major entity in plasma, followed by APC, SN-38 glucuronide and SN-38. Only SN-38 has significant cytotoxic activity.

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

5.3 Preclinical safety data

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Lactic acid
- Sodium hydroxide
- Sorbitol (E420)
- Hydrochloric acid
- Water for injection

6.2 Incompatibilities

No incompatibilities are known but only the recommended diluents in section 6.3 should be used.

6.3 Shelf life

The shelf life for unopened vials is 2 years.

Chemical and physical in-use stability has been demonstrated for 48 hours at 2-8°C and 24 hours at 15-30°C following dilution with 5% dextrose and for 24 hours at 15-30°C following dilution with 0.9% NaCl.

From a microbiological point of view, the solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.
6.4 **Special precautions for storage**

Vials of irinotecan concentrate for solution for infusion should be stored below 25°C and protected from light.

For storage condition of the diluted medicinal product, please see section 6.3.

6.5 **Nature and contents of container**

Amber glass vial (type I) with rubber stopper and aluminium flip off seal.

Pack sizes: 2ml vial and 5 ml vials. Available as single pack.

6.6 **Special precautions for disposal**

*Handling*

As with all antineoplastic agents caution should be exercised when handling irinotecan concentrate for solution for infusion. Dilution should be carried out under asceptic 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 for infusion 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 concentrate for solution for infusion*

1. Protective chamber should be used and protective gloves as well as protective gowns 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, 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.

*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**

APSLA Limited,
Bayview House,
49 North Strand Road,
Dublin 3,
Ireland.
8 MARKETING AUTHORISATION NUMBER(S)
PL 33410/0089
PL 34410/0090

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
04/11/2011

10 DATE OF REVISION OF THE TEXT
04/11/2011
UKPAR Irinotecan 20 mg/ml, concentrate for solution for infusion

PL 33410/0089-90

PATIENT INFORMATION LEAFLET

For the treatment of:

1. What This Medication Is

This is a leaflet summarising the patient information contained in the Summary of Product Characteristics (SPC) for the above product. You should read the SPC before taking the medication.

2. Before You Are Given Irinotecan

You should not take this medication if you are allergic to irinotecan or any of its excipients.

3. How To Take Irinotecan

The medication is administered as an intravenous infusion at a dose of 0.15 mg/kg body weight.

4. Possible Side Effects

Common side effects include:

- Nausea and vomiting
- Diarrhea
- Fever
- Fatigue
- Headache
- Infection

Rare side effects include:

- Seizures
- Inflammation of the colon
- Liver damage

5. What To Do If You Forget To Take Your Medication

Do not take a missed dose if you are delayed in starting your treatment.

6. How To Order Another Supply

Contact your doctor to arrange for another supply.

7. Further Information

Contact your doctor for further information.

8. Storage

Store at room temperature.

9. Disposal

Discard any unused medication.

10. Marketing Authorisation Holder

AstraZeneca Pharmaceuticals LP, 6000 Rockland Road, Westborough, MA 01581, USA.

11. Manufacturer and Distributor

AstraZeneca Pharmaceuticals LP, 6000 Rockland Road, Westborough, MA 01581, USA.

12. Guarantee

The guarantee is not available to patients.

13. Further Information

Contact your doctor for further information.

14. Disposal

Discard any unused medication.

15. Patient Information Summary

A summary of the patient information is available from the manufacturer.

16. Description

The medication is administered as an intravenous infusion at a dose of 0.15 mg/kg body weight.

17. How To Order Another Supply

Contact your doctor to arrange for another supply.

18. Further Information

Contact your doctor for further information.

19. Storage

Store at room temperature.

20. Disposal

Discard any unused medication.

21. Marketing Authorisation Holder

AstraZeneca Pharmaceuticals LP, 6000 Rockland Road, Westborough, MA 01581, USA.

22. Manufacturer and Distributor

AstraZeneca Pharmaceuticals LP, 6000 Rockland Road, Westborough, MA 01581, USA.

23. Guarantee

The guarantee is not available to patients.

24. Further Information

Contact your doctor for further information.

25. Storage

Store at room temperature.

26. Disposal

Discard any unused medication.

27. Marketing Authorisation Holder

AstraZeneca Pharmaceuticals LP, 6000 Rockland Road, Westborough, MA 01581, USA.

28. Manufacturer and Distributor

AstraZeneca Pharmaceuticals LP, 6000 Rockland Road, Westborough, MA 01581, USA.

29. Guarantee

The guarantee is not available to patients.

30. Further Information

Contact your doctor for further information.
LABELLING

Please note that the representative labelling for Irinotecan 20 mg/ml concentrate for solution for infusion (PL 33410/0089) is shown below. The labelling details for Irinotecan 20 mg/ml concentrate for solution for infusion (PL 33410/0089) are consistent with these labels, with the exception of the product licence number.