Public Assessment Report

Irinotecan 20mg/ml Solution for Infusion

Irinotecan hydrochloride trihydrate

PL 18727/0007

Dabur Oncology PLC

Table of Contents

	Page
Lay Summary	2
Scientific Discussion	3
Overall Conclusion And Risk Benefit/Analysis	9
Steps Taken During Assessment	10
Steps Taken After Assessment	11
Summary of Product Characteristics	12
Labels and Leaflet	29

Lay Summary

The MHRA has granted Dabur Oncology PLC a market authorisation (licence) for the medicinal product Irinotecan 20mg/ml Solution for Infusion (PL 18727/0007) on 16th March 2007.

Irinotecan is a prescription only medicine and is indicated for the treatment of patients with advanced colorectal cancer:

1. in combination with 5-fluorouracil and folinic acid in patients without prior chemotherapy for advanced disease,

2. as a single agent in patients who have failed an established 5-fluorouracil containing treatment regimen.

The product contains the active ingredient Irinotecan hydrochloride trihydrate which acts as an antineoplastic agent of the topoisomerase I inhibitor class.

Irinotecan 20mg/ml Solution for Infusion was considered to be a generic medical product of the reference products Campto 40mg/2ml (PL00057/0626) and 100mg/5ml (PL00057/0627) concentrate for solution for infusion, authorised to Pfizer Ltd.

Scientific Discussion

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Irinotecan 20mg/ml Solution for Infusion (PL 18727/0007) on 16th March 2007.

Irinotecan 20mg/ml Solution for Infusion was claimed to be a generic medical product of Campto 40mg/2ml (PL00057/0626) and 100mg/5ml (PL00057/0627) concentrate for solution for infusion, authorised to Pfizer Ltd., dated 05 November 2004 under Article 10(1) of Directive 2001/83/EC. The EEA reference product Campto 20mg/ml Concentrate for Solution for Infusion was first authorised in France, 05 May 1995.

Irinotecan contains the active ingredient Irinotecan hydrochloride trihydrate which is an antineoplastic agent of the topoisomerase I inhibitor class. It is a semisynthetic derivative of camptothecin, obtained from the branches *of Mappia foetida* tree. Irinotecan is rapidly esterified *in vivo* to SN-38, an active metabolite that contributes to the antitumor activity of the drug.

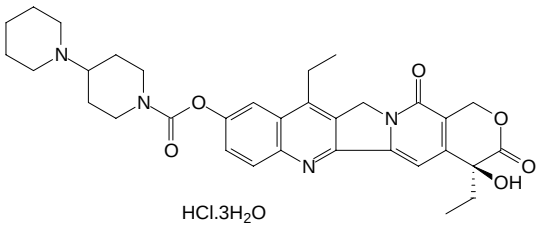
Irinotecan is considered to have a well-established use and a favourable risk: benefit profile in the intended indications, and there is sufficient published literature supporting the claim of well-established use with proven efficacy.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

General information

Structure:



INN:	Irinotecan hydrochloride
Description:	Pale yellow to yellow crystalline powder
Molecular formula:	$C_{33}H_{38}N_4O_6.HCl.3H_2O$
Relative molecular mass:	677.19

An appropriate specification has been provided.

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

Irinotecan hydrochloride trihydrate is stored in appropriate packaging. The drug substance is packed in double LDPE bags in a designed isolator, placed in a HDPE bottle wrapped with parafilm and placed in a fibreboard drum. The specifications and typical analytical test reports are provided and are satisfactory.

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

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 24 months.

DRUG PRODUCT

Other Ingredients

The other ingredients of the drug product are sorbitol, lactic acid, sodium hydroxide and water for injection. All the excipients are controlled to Ph Eur monographs. Specifications and satisfactory certificates of analysis are provided. Satisfactory TSE declarations are provided for lactic acid, sodium hydroxide and sorbitol.

Dissolution and impurity profiles

Stability studies of Irinotecan 20 mg/ml Solution for Infusion have been conducted after dilution with the infusion solutions 5 % dextrose injection and 0.9% sodium chloride injection, at room temperature (15 °C to 25 °C, ambient lighting conditions) and at 2 to 8 °C, protected from light. Impurity profiles were found to be similar to those for the reference product, and a shelf life of 24 hours at ambient temperature (15 °C to 25 °C), ambient lighting conditions, and 48 hours at 2 °C to 8 °C, protected from light, were demonstrated with both diluents.

Manufacture

A description and flow-chart of the manufacturing method has been provided.
In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification

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

Container Closure System

The product is packed in 6 ml, sterile glass amber/brown single-dose vials closed with sterile rubber stoppers and sealed with aluminium caps provided with orange PP covers. Satisfactory specifications and dimensions of the primary packaging materials have been provided.
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months was approved. Storage conditions are “Store below 25°C”, “store in the original packaging” and “protect from light”.

ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A Marketing Authorisation was granted.

PRE-CLINICAL ASSESSMENT

Since the pharmaco-toxicological properties of irinotecan are known, no new non-clinical data is required and none has been submitted.

MEDICAL ASSESSMENT

CLINICAL PHARMACOLOGY

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

Pharmacokinetic properties

In a phase I study in 60 patients with a dosage regimen of a 30-minute intravenous infusion of 100 mg/m² 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.

Bioequivalence

As the product is an aqueous solution for injection no bioequivalence study was required.

Efficacy

Efficacy is reviewed in the Clinical Expert Report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

Safety

Safety is reviewed in the Clinical Expert Report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

Expert Report
The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

Summary Of Product Characteristics
This is satisfactory.

Patient Information Leaflet
This is satisfactory.

Conclusions
Marketing authorisations should be granted for these products.

Overall Conclusion and Risk/Benefit Analysis

Quality

The important quality characteristics of Irinotecan 20mg/ml 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.

Pre-Clinical

No new pre-clinical data were provided and none were required.

Clinical

Due to the pharmacological form of the product no bioequivalence study was required. No novel efficacy or safety data are supplied or required for this application. The PD claims within the SPC are appropriately consistent with the UK reference product SPC

Risk/Benefit Analysis

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit is, therefore, considered to be positive.

Steps Taken During Assessment

1	The MHRA received the application on 14th June 2006.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 6th July 2006.
3	Following assessment of the application, the MHRA requested further information from the applicant regarding the quality assessment on 19th September 2006 and on the medical assessment on 23rd October 2006 and 28th February 2007.
4	The applicant provided further information in regard to the quality assessment on 7th January 2007 and on the medical assessment on 7th January 2007 and 12th March 2007.
5	The application was determined on 16th March 2007.

Steps Taken after Assessment

None

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Irinotecan 20 mg/ml Solution for Infusion
Irinotecan 40 mg/2 ml Solution for Infusion
Irinotecan 100 mg/5 ml Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The solution contains 20 mg/ml irinotecan hydrochloride trihydrate (equivalent to 17.33 mg/ml irinotecan). Each vial of 2 ml contains 40 mg and each vial of 5 ml contains 100 mg of irinotecan hydrochloride trihydrate.

For a full list of excipients, see section 6.1 << List of Excipients>>.

3 PHARMACEUTICAL FORM

Solution for Infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Irinotecan is indicated for the treatment of patients with advanced colorectal cancer:

- in combination with 5-fluorouracil and folinic acid in patients without prior chemotherapy for advanced disease,
- as a single agent in patients who have failed an established 5-fluorouracil containing treatment regimen.

4.2 Posology and method of administration

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

Recommended dosage

In monotherapy (for previously treated 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 « Instructions for Use/Handling » and « Special Warnings and Special Precautions for Use » sections).

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 « Pharmacodynamic properties »):

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.

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

Treatment Duration

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

Special populations

Patients with Impaired Hepatic Function: In monotherapy: Blood bilirubin levels (up to 3 times the upper limit of the normal range (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 “Pharmacokinetic properties” section) 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 « Contraindications » and « Special Warnings and Special Precautions for Use » sections).

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 « Special Warnings and Special Precautions for Use » and « Pharmacokinetic Properties »).

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 « Special Warnings and Special Precautions for Use »).

4.3 Contraindications

Chronic inflammatory bowel disease and/or bowel obstruction (see « Special Warnings and Special Precautions for Use »).

History of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate or to one of the excipients of Irinotecan.

Pregnancy and lactation (see « Pregnancy and Lactation » and « Special Warnings and Special Precautions for Use » sections).

Bilirubin >3 times the upper limit of the normal range (see « Special warnings and Special Precautions for Use » section).

Severe bone marrow failure.

WHO performance status >2

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

4.4 Special warnings and precautions for use

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

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

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

When Irinotecan is used in monotherapy, it is usually prescribed with the every-3-week-dosage schedule. However, the weekly-dosage schedule (see « Pharmacological properties ») 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 has been administered. After discharge from the hospital, the patients should obtain the prescribed drugs so that they can treat the diarrhoea as soon as it occurs. In addition, they must inform their physician or the department administering Irinotecan when/if diarrhoea is occurring.

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

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

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

- Diarrhoea associated with fever,
- Severe diarrhoea (requiring intravenous hydration),

- Diarrhoea persisting beyond 48 hours following the initiation of high-dose loperamide therapy.

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

In patients who experienced severe diarrhoea, a reduction in dose is recommended for subsequent cycles (see « Posology and Method of Administration » section).

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 « Posology and Method of Administration » section).

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 « Contraindications » section).

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 « Undesirable Effects » section). 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 « Posology and Method of Administration » section).

Patients with bowel obstruction

Patients must not be treated with Irinotecan until resolution of the bowel obstruction (see « Contraindications »).

Patients with Impaired Renal Function

Studies in this population have not been conducted. (see « Posology and Method of Administration » and « Pharmacokinetic Properties »).

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

4.5 Interaction with other medicinal products and other forms of interaction

Interaction between irinotecan and neuromuscular blocking agents cannot be ruled out. Since Irinotecan has anticholinesterase activity, 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/m^2 was co-administered with St. John's Wort (Hypericum perforatum) 900 mg, a 42% decrease in the active metabolite of irinotecan, SN-38, plasma concentrations was observed.

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

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

4.6 Pregnancy and lactation

Pregnancy

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

Irinotecan has been shown to be embryotoxic, foetotoxic and teratogenic in rabbits and rats. Therefore, Irinotecan must not be used during pregnancy (see « Contraindications » and « Special Warnings and Special Precautions for Use »).

Women of childbearing potential

Women of childbearing age receiving Irinotecan should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur (see « Contraindications » and « Special Warnings and Special Precautions for Use»).

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 « Contraindications »).

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

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

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

The frequencies in the following table are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to 1/100); rare (≥1/10,000 to 1/1,000); very rare (<1/10,000).

Further details are given after this table.

MedDRA System Organ Classes	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					
Monotherapy	– Diarrhoea[1] – Abdominal pain – Severe nausea – Severe vomiting	– Mucositis – Constipation[2]	– Pseudo-membranous colitis – Intestinal obstruction – Ileus – Gastrointestinal haemorrhage	– Colitis[3] – Intestinal perforation	
Combination Therapy	– Diarrhoea[1] – Abdominal pain – Mucositis	– Severe nausea – Severe vomiting – Constipation[2]	– Pseudo-membranous colitis – Intestinal obstruction – Ileus – Gastrointestinal haemorrhage	– Colitis[3] – Intestinal perforation	
Blood and Lymphatic System Disorders					
Monotherapy	– Neutropenia – Anaemia	– Neutropenia with fever – Thrombocytopenia			
Combination Therapy	– Neutropenia – Anaemia – Thrombocytopenia	– Neutropenia with fever			Autoimmune Thrombocytopenia
General Disorders and Administration Site Conditions					
Monotherapy	– Fever[4]	– Acute Cholinergic Syndrome – Severe asthenia	– Infusion Site Reactions		
Combination Therapy		– Acute Cholinergic Syndrome – Severe asthenia – Fever[4]			
Infections and Infestations					
Monotherapy	– Infectious Episodes[5]				
Combination Therapy		– Infectious – Episodes[5]			
Metabolism and Nutrition Disorders					
Monotherapy	– Dehydration[6]	– Anorexia			
Combination Therapy	- Dehydration[6] - Anorexia				
Vascular Disorders					
Monotherapy			– Hypotension[7] – Cardio-circulatory failure[7]	– Hypertension	
Combination Therapy					
Renal and urinary disorders					
Monotherapy			– Renal insufficiency[7]		
Combination Therapy					

Respiratory, Thoracic and Mediastinal Disorders					
Monotherapy	- Dyspnoea		– Interstitial pulmonary disease		
Combination Therapy		- Dyspnoea			
Skin and Subcutaneous Tissue Disorders					
Monotherapy	– Alopecia		– Cutaneous reactions		
Combination Therapy					
Immune System Disorders					
Monotherapy			– Allergic reactions	– Anaphylactic reactions	
Combination Therapy					
Investigations					
Monotherapy		– Serum transaminases increase – Serum alkaline phosphatase increase – Serum bilirubin increase – Serum creatinine increase		– Hypokalemia – Hyponatremia	– Amylase and/or lipase increase
Combination Therapy	– Serum SGOT increase (Grades 1 and 2) – Serum SGPT increase (Grades 1 and 2) – Serum alkaline phosphatase increase (Grades 1 and 2) – Serum bilirubin increase (Grades 1 and 2)	– Serum bilirubin increase (Grade 3)			
Nervous System Disorders					
Monotherapy					– Transient speech disorders
Combination Therapy					

[1] Can be severe, delayed and associated with fever.
[2] Associated with irinotecan and/or loperamide
[3] Including typhlitis, and ischemic or ulcerative colitis.
[4] Fever, in the absence of infection and severe neutropenia.
[5] With or without severe neutropenia.
[6] Commonly associated with diarrhoea and/or vomiting.
[7] Due to dehydration associated with diarrhoea and/or vomiting, or sepsis.

Gastrointestinal disorders

Delayed diarrhoea

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

In monotherapy

Severe diarrhoea was observed in 20% of patients who follow recommendations for the management of diarrhoea. Of the evaluable cycles, 14% have a 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 a severe diarrhoea.

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

Blood 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

Neutropenia was observed in 78.7% of patients and was severe (neutrophil count <500 cells/mm^3) in 22.6% of patients. Of the evaluable cycles, 18% had a neutrophil count below 1,000 cells/mm^3 including 7.6% with a neutrophil count <500 cells/mm^3.

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 2 cases.

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

Thrombocytopenia (<100,000 cells/mm^3) was observed in 7.4% of patients and 1.8% of cycles with 0.9% with platelets count ≤50,000 cells/mm^3 and 0.2% of cycles.

Nearly all the patients showed a recovery by day 22.

In combination therapy

Neutropenia was observed in 82.5% of patients and was severe (neutrophil count <500 cells/mm^3) in 9.8% of patients.

Of the evaluable cycles, 67.3% had a neutrophil count below 1,000 cells/mm^3 including 2.7% with a neutrophil count <500 cells/mm^3.

Total recovery was usually reached within 7 to 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 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.

One case of peripheral autoimmune thrombocytopenia has been reported in the post-marketing experience.

General disorders and infusion site reactions

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, lacrimation and increased salivation occurring during or within the first 24 hours after the infusion of Irinotecan. These symptoms disappear after atropine administration (see « Special Warning and Special Precautions for Use »).

Respiratory disorders

Interstitial pulmonary disease presenting as pulmonary infiltrates is uncommon during irinotecan therapy. Early effects such as dyspnoea have been reported (see section 4.4).

Skin and subcutaneous tissue disorders

Alopecia was very common and reversible.

Musculoskeletal disorders

Early effects such as muscular contraction or cramps have been reported.

Nervous system disorders

Paresthesia has been reported.

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

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 tumours 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 acetyl cholinesterase.

Clinical data

In monotherapy

Clinical phase II/III studies were performed in more than 980 patients in the every 3-week dosage schedule with metastatic colorectal cancer who failed a

previous 5-FU regimen. The efficacy of Irinotecan was evaluated in 765 patients with documented progression on 5-FU at study entry.

	Phases III					
	Irinotecan versus supportive care			Irinotecan versus 5FU		
	Irinotecan	Supportive care		Irinotecan	5FU	
	n=183	n=90	p values	n=127	n=129	p values
Progression Free Survival at 6 months (%)	NA	NA		33.5 *	26.7	p=0.03
Survival at 12 months (%)	36.2 *	13.8	p=0.0001	44.8 *	32.4	p=0.0351
Median survival (months)	9.2*	6.5	p=0.0001	10.8*	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 therapy

A phase III study was performed in 385 previously untreated metastatic colorectal cancer patients treated with either every 2 weeks schedule (see « Posology and method of administration ») 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:

	Combined regimens (n=198)		Weekly schedule (n=50)		Every 2 weeks schedule (n=148)	
	Irinotecan +5FU/FA	5FU/FA	Irinotecan +5FU/FA	5FU/FA	Irinotecan +5FU/FA	5FU/FA
Response rate (%)	40.8 *	23.1 *	51.2 *	28.6 *	37.5 *	21.6 *
p value	p<0.001		p=0.045		p=0.005	
Median time to progression (months)	6.7	4.4	7.2	6.5	6.5	3.7
p value	p<0.001		NS		p=0.001	
Median duration of response (months)	9.3	8.8	8.9	6.7	9.3	9.5
p value	NS		p=0.043		NS	
Median duration of response and stabilisation (months)	8.6	6.2	8.3	6.7	8.5	5.6
p value	p<0.001		NS		p=0.003	
Median time to treatment failure (months)	5.3	3.8	5.4	5.0	5.1	3.0
p value	p=0.0014		NS		p<0.001	
Median survival (months)	16.8	14.0	19.2	14.1	15.6	13.0
p value	p=0.028		NS		p=0.041	

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/mm^3) was 5.8% in patients treated by Irinotecan in combination with 5FU/FA and in 2.4% in patients treated by 5FU/FA alone.

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

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

Pharmacokinetic/Pharmacodynamic data

The intensity of the major toxicities encountered with Irinotecan (e.g., leukoneutropenia and diarrhoea) is 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 mg/m² 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 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 normal limit. In these patients a 200 mg/m² irinotecan dose leads to plasma drug exposure comparable to that observed at 350 mg/m² in cancer patients with normal liver parameters.

5.3 Preclinical safety data

Irinotecan and SN-38 have been shown to be mutagenic *in vitro* in the chromosomal aberration test on CHO-cells as well as in the *in vivo* micronucleus test in mice.

However, they have been shown to be devoid of any mutagenic potential in the Ames test.

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

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

The severity of these effects was dose-related and reversible.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sorbitol
lactic acid
water for injections and
sodium hydroxide (to adjust to pH 3.5)

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

The shelf-life of unopened vials is 24 months.

The Irinotecan solution should be used immediately after reconstitution, as it contains no antibacterial preservative. If reconstitution and dilution are performed under strict aseptic conditions (e.g. on Laminar Air Flow bench) Irinotecan solution should be used (infusion completed) within 24 hours at room temperature or 48 hours if stored 2 °C to 8 °C after the first breakage.

6.4 Special precautions for storage

Store below 25 °C. Keep vial in the outer carton.

For storage conditions of the diluted medicinal product see section 6.3.

6.5 Nature and contents of container

Irinotecan 40 mg/2 ml and 100 mg/5 ml Solution for Infusion:
6 ml amber type – I tubular glass vials stoppered with 20 mm grey elastomeric closures sealed with 20 mm aluminium flip off overseals.

6.6 Special precautions for disposal

As with other antineoplastic agents, Irinotecan must be prepared and handled with caution. The use of glasses, mask and gloves is required.

If Irinotecan solution or infusion solution should come into contact with the skin, wash immediately and thoroughly with soap and water. If Irinotecan solution or infusion solution should come into contact with the mucous membranes, wash immediately with water.

Preparation for the intravenous infusion administration

As with any other injectable drugs, THE IRINOTECAN SOLUTION MUST BE PREPARED ASEPTICALLY (see « Shelf-life »).

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

Aseptically withdraw the required amount of Irinotecan solution from the vial with a calibrated syringe and inject into a 250 ml infusion bag or bottle containing either 0.9% sodium chloride solution or 5% dextrose solution. The infusion should then be thoroughly mixed by manual rotation.

Disposal

All materials used for dilution and administration should be disposed of according to hospital standard procedures applicable to cytotoxic agents.

7 MARKETING AUTHORISATION HOLDER

DABUR ONCOLOGY PLC.,
Lion Court, Farnham Road,
Bordon, Hampshire,
GU35 0NF, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 18727/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/03/2007

10 DATE OF REVISION OF THE TEXT

16/03/2007

Labels and Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

IRINOTECAN 20 mg/ml SOLUTION FOR INFUSION
(40 mg/2 ml and 100 mg/5 ml Vials)

(IRINOTECAN HYDROCHLORIDE TRIHYDRATE)

Read all of this leaflet carefully before you are given Irinotecan
- 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 is and what it is used for
2. Before you are given Irinotecan
3. How Irinotecan is given
4. Possible side effects
5. How to store Irinotecan
6. Further information

1. WHAT IRINOTECAN IS AND WHAT IT IS USED FOR

Irinotecan belongs to a group of medicines called cytostatics (anti-cancer medicines).
Irinotecan is normally used for the treatment of cancer of the colon or rectum.
However, your doctor may prescribe Irinotecan for other reasons.
If you need any further information on your condition, please ask your doctor.

2. BEFORE YOU ARE GIVEN IRINOTECAN

You should not be given Irinotecan:
- If you have any other bowel disease or a history of bowel obstruction.
- If you have had a severe allergic reaction to Irinotecan in the past.
- If you are pregnant, planning to become pregnant, or breast feeding.
- If you have any liver problems.
- If you have severe bone marrow failure.
- If you are in bed or sitting in a chair for more than half the day or all the time; and you need some help or a lot of help in looking after yourself.
- If you are treated with St John's Wort.

Take special care with Irinotecan:

- You should tell your doctor if you had prior radiotherapy, especially to your abdomen or pelvis, as this can increase your risk of having diarrhoea with irinotecan treatment. You should also tell your doctor if you have had radiotherapy to the lungs, or have taken drugs which have had toxic effects on your lungs as this can increase the likelihood of experiencing respiratory symptoms during treatment with irinotecan. Your doctor should monitor you closely if you have had any of these treatments.
- You should inform your doctor if you have symptoms like inability to pass stools or flatus (suggestive of bowel obstruction). Irinotecan should not be given in patients with these symptoms.

- If you are elderly the dose of irinotecan should be carefully chosen and you should be closely monitored by your doctor.
- You should take contraceptive measures during and for at least three months after treatment has stopped.
- If you suffer from an inherited condition called **fructose intolerance**, tell your doctor or hospital pharmacist before you are given Irinotecan. Irinotecan contains **sorbitol**, which is unsuitable for people who cannot tolerate fructose.
- Your doctor should perform blood tests to check your liver and bone marrow function before you start treatment.

Taking other medicines:
Please tell your doctor or pharmacist if you are taking:
- Antiepileptic drugs (e.g. carbamazepine, phenobarbital or phenytoin).
- Antifungal drugs (e.g. ketoconazole).
- Neuromuscular blocking agents (e.g. suxamethonium)
- Medicines like rifampicin or other prescription medicines.
- Any non-prescription medicines that you may have bought yourself, in particular St Johns' Wort.

Pregnancy and Breast Feeding:
If you are pregnant or planning to become pregnant, tell your doctor or hospital pharmacist immediately, as you should not receive Irinotecan during pregnancy.
You should not breast feed while you are being treated with Irinotecan. Do not restart breast feeding until your doctor tells you it is safe to do so.

Driving and using machines:
Do not drive or operate machinery as Irinotecan may make you feel dizzy or cause visual disturbances.

3. HOW IRINOTECAN IS GIVEN

Irinotecan will be given as an infusion into your veins over a period of 30 to 90 minutes. The amount of Irinotecan you are given will depend on your age, size and general medical condition. It will also depend on any other treatment you may have received for your cancer. Your doctor will calculate your body surface area in square metres (m^2).
- If you have previously been treated with 5-fluorouracil you will normally be treated with Irinotecan alone starting with a dose of 350 mg/m^2 every 3 weeks
- If you have not had previous chemotherapy you will normally receive 180 mg/m^2 Irinotecan every two weeks. This will be followed by folinic acid and 5-fluorouracil.

These dosages may be adjusted by your doctor depending on your condition and any side-effects you may have.

- Your doctor will perform regular blood tests after giving you irinotecan. Irinotecan may cause a decrease in the number of your white blood cells, which play an important role in fighting infections. Irinotecan may also affect you liver function, so your doctor will also arrange for you to have liver function tests at regular intervals while receiving treatment with irinotecan.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Irinotecan 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. Please read the following instructions carefully and follow them if you have any of the side-effects listed.

Tell your doctor immediately if you notice any of the following:
- If your diarrhoea starts less than 24 hours after the infusion ("early diarrhoea").
- If your diarrhoea starts more than 24 hours after the infusion ("delayed diarrhoea").
- Any fever, and particularly if you also have diarrhoea.
- Nausea and vomiting.
- Breathing difficulties.

The most common side effects (in more than 1 in 10 patients) are:
- **DIARRHOEA**, WHICH STARTS MORE THAN 24 HOURS AFTER THE INFUSION (**"DELAYED DIARRHOEA"**). YOU SHOULD **IMMEDIATELY** TAKE ANY ANTI-DIARRHOEAL TREATMENT THAT THE DOCTOR HAS GIVEN YOU EXACTLY AS HE HAS TOLD YOU. IF YOU ARE UNSURE OF WHAT THIS IS, ASK YOUR DOCTOR OR NURSE. DRINK LARGE AMOUNTS OF REHYDRATION FLUIDS, **IMMEDIATELY** (I.E. WATER, SODA WATER, FIZZY DRINKS, SOUP OR ORAL REHYDRATION THERAPY).
- **NAUSEA AND VOMITING**. IF YOU HAVE NAUSEA AND VOMITING CONTACT YOUR DOCTOR **IMMEDIATELY.**
- **FEVER**. IF YOU HAVE ANY FEVER THIS MAY BE AN INDICATION OF INFECTION ASSOCIATED WITH A REDUCTION IN THE NUMBER OF YOUR WHITE BLOOD CELLS (NEUTROPENIA) AND YOU SHOULD CONTACT YOUR DOCTOR **IMMEDIATELY** FOR TREATMENT.
- Constipation.
- Reduction in white blood cells, which play an important role in fighting infections. This is called neutropenia.
- Reduction in blood platelets, which increases risk of bleeding or bruising.
- Reduction in red blood cells, which can make the skin pale and cause weakness or breathlessness.
- Hair loss.
- Signs of infection.
- High levels of liver enzymes and bilirubin.

Common side effects (in more than 1 in 100, but in less than 1 in 10 patients) are:
- **DIARRHOEA**, WHICH STARTS LESS THAN 24 HOURS AFTER THE INFUSION (**"EARLY DIARRHOEA"**). YOU SHOULD CONTACT YOUR DOCTOR OR NURSE **IMMEDIATELY** AND THEY WILL GIVE YOU A SUITABLE TREATMENT.
  IF YOU HAVE "EARLY DIARRHOEA" DO NOT USE ANY ANTI-DIARRHOEAL TREATMENT THAT YOUR DOCTOR HAS GIVEN YOU FOR "DELAYED DIARRHOEA".
  THIS "EARLY DIARRHOEA" MAY BE ACCOMPANIED BY OTHER SYMPTOMS SUCH AS
  - SWEATING
  - ABDOMINAL CRAMPS
  - WATERING EYES
  - CONJUNCTIVITIS
  - RUNNY NOSE
  - CHILLS
  - VISUAL PROBLEMS
  - DIZZINESS
  - LOW BLOOD PRESSURE
  - FEELING UNWELL
  - EXCESSIVE MOUTH WATERING
- Stomach pain.
- Inflammation of the lining of the mouth.

- Fatigue.
- Dehydration.
- Loss or lack of appetite.

Uncommon side effects (in more than 1 in 1,000 but in less than 1 in 100 patients) are:
- SCARRING OF THE LUNGS, WHICH CAUSE **DIFFICULTY IN BREATHING**. IF YOU HAVE ANY BREATHING DIFFICULTIES CONTACT YOUR DOCTOR **IMMEDIATELY**.
- Bowel obstruction.
- Gastrointestinal bleeding.
- Pain or redness close to or at the injection site during the infusion.
- Kidney problems, low blood pressure or collapse in patients dehydrated due to diarrhoea, vomiting or infection.
- Allergic skin reactions.

Rare side effects (in more than 1 in 10,000 but in less than 1 in 1,000 patients) are:
- Inflammation of intestine.
- Intestinal perforation.
- High blood pressure.
- Severe allergic reactions.
- Muscular cramps
- Altered sensation of skin such as tingling, pricking or numbness.
- Low blood levels of potassium which can cause abnormal heart rhythm.
- Low blood levels of sodium which can cause tiredness and confusion, muscle twitching, fits or coma.

Very rare side effects (less than 1 in 10,000 patients) are:
- Transient speech disorders

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

Always keep Irinotecan in a safe place and out of the reach and sight of children.

Expiry Date
Irinotecan must not be used after the expiry date, which is stated on the vial and carton. In both places it is given as "Expiry:" followed by the month and year.

Storing your medicine
Store below 25 °C. Keep vial in the outer carton.

Once the concentrate has been diluted for infusion the solution can be kept for 24 hours at room temperature (15 °C to 25 °C) or for 48 hours in a refrigerator (2 °C to 8 °C).

6. FURTHER INFORMATION

What Irinotecan contains
The active substance is Irinotecan Hydrochloride Trihydrate.
The other ingredients are sorbitol, lactic acid, water for injections and sodium hydroxide (to adjust to pH 3.5).

What Irinotecan looks like and contents of the pack
It is available as a concentrate, which should be diluted before infusion and comes in two sizes:
• 40 mg of irinotecan hydrochloride trihydrate in 2 ml
• 100 mg of irinotecan hydrochloride trihydrate in 5 ml

Irinotecan 40 mg/2 ml and 100 mg/5 ml solution for infusion are available in cartons containing a single vial.

Marketing Authorisation Holder and Manufacturer
Dabur Oncology Plc., Lion Court, Farnham Road, Bordon,
Hampshire, GU35 0NF, United Kingdom,
Tel: +44 (0) 1420 477115, Fax: +44 (0) 1420 477047, email: info@daburoncology.com

Date of revision: March 2007

The following information is for health professionals only:

INSTRUCTIONS FOR USE / HANDLING, PREPARATION AND DISPOSAL GUIDE FOR USE WITH IRINOTECAN 20 MG/ML SOLUTION FOR INFUSION

USE/HANDLING

As with other neoplastic agents, Irinotecan must be prepared and handled with caution. The use of glasses, masks and gloves is required. If Irinotecan solution or infusion solution should come in contact with the skin, wash immediately and thoroughly with soap and water. If Irinotecan solution or infusion solution should come into contact with the mucous membranes, wash immediately with water.

PREPARATION FOR THE INTRAVENOUS SOLUTION

As with any other injectable drugs, the Irinotecan solution must be prepared aseptically.

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

Aseptically withdraw the required amount of Irinotecan solution from the vial with a calibrated syringe and inject into a 250 ml infusion bag or bottle containing either 0.9% sodium chloride or 5% dextrose solution. The infusion should then be thoroughly mixed by manual rotation.

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

Irinotecan should not be delivered as an intravenous bolus or an intravenous infusion shorter than 30 minutes or longer than 90 minutes.

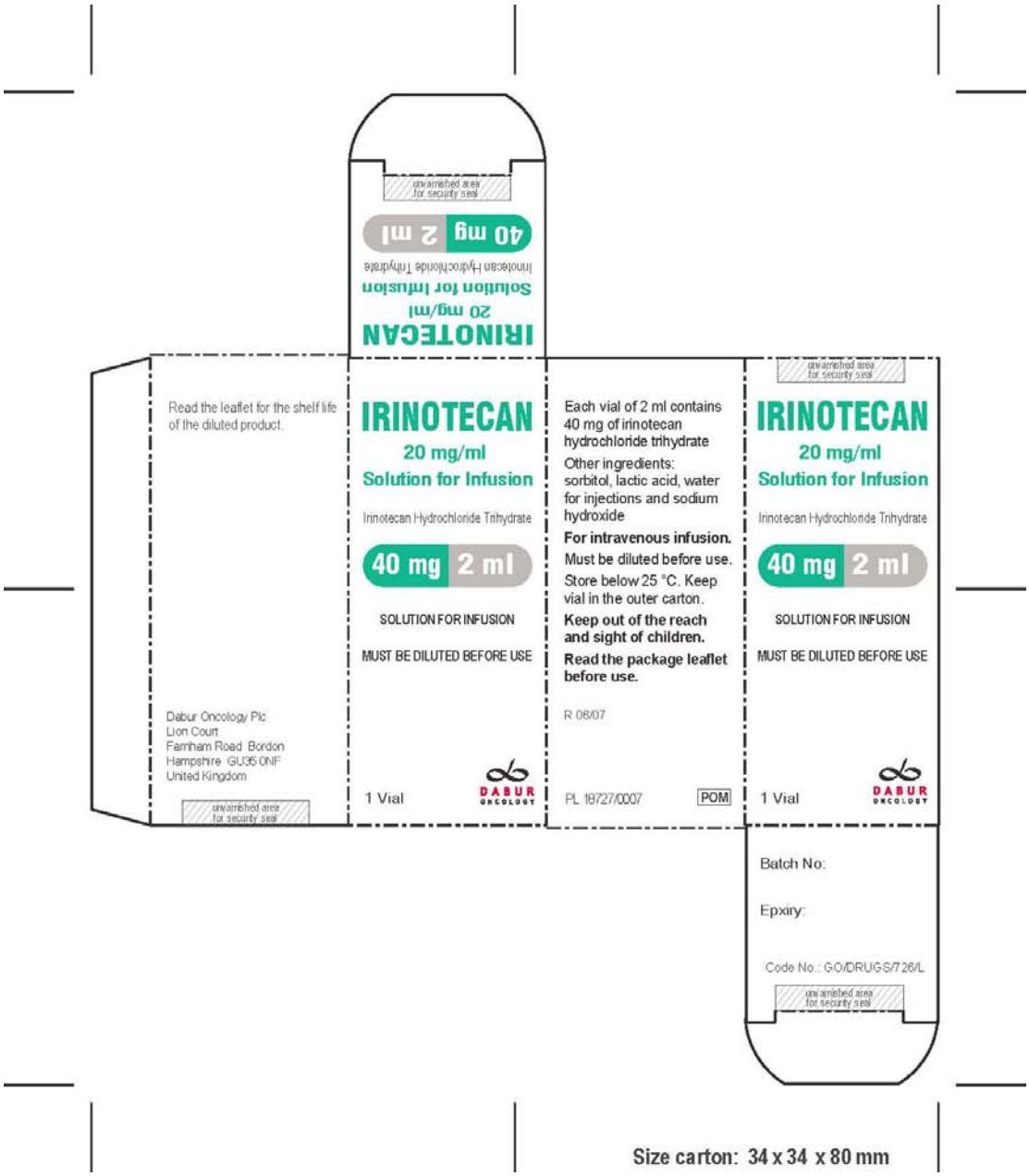
DISPOSAL

All materials used for dilution and administration should be disposed of according to hospital standard procedures applicable to cytotoxic agents.

Mock-Up of Vial Label
Irinotecan 20 mg/ml Solution for Infusion
(40 mg in 2 ml)

Mock-Up of Vial Label
Irinotecan 20 mg/ml Solution for Infusion
(100 mg in 5 ml)

Mock-Up of Vial Carton Label
Irinotecan 20 mg/ml Solution for Infusion
(40 mg in 2 ml)



Mock-Up of Vial Carton Label
Irinotecan 20 mg/ml Solution for Infusion
(100 mg in 5 ml)