

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0361/028/001

Case No: 2051061

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Martindale Pharmaceuticals Ltd

Bampton Road, Harold Hill, Romford, RM3 8UG, United Kingdom

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Irinotecan Martindale Pharma 20 Mg/ML. Concentrate for Solution for Infusion

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **23/04/2010** until **22/04/2015**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Irinotecan Martindale Pharma 20 mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of concentrate contains 20 mg irinotecan hydrochloride trihydrate equivalent to 17.33 mg/ml irinotecan. Each 2 ml or 5ml vial of Irinotecan contains 40 mg or 100 mg of irinotecan hydrochloride trihydrate respectively.

Excipients: Sorbitol (E240)
 Sodium hydroxide

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for Solution for Infusion

Clear, colourless to slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Irinotecan Martindale Pharma[®] 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 metastatic colorectal cancer 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.

4.2 Posology and method of administration

For adults only.

After dilution Irinotecan Martindale Pharma should be infused into a peripheral or central vein.

Recommended dosage

In monotherapy (for previously treated patients)

The recommended dosage of irinotecan hydrochloride trihydrate is 350 mg/m² administered as an intravenous infusion over a 30 – 90 minute period every three weeks (see below ‘Method of administration’ and section 4.4 and 6.6).

In combination therapy (for previously untreated patients)

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

The recommended dose of irinotecan hydrochloride trihydrate is 180 mg/m² administered once every 2 weeks as an intravenous infusion over a 30 – 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 one hour after the end of the cetuximab infusion.

For the posology and method of administration of bevacizumab, refer to the bevacizumab 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 5-FU 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 events a dose reduction of 15 to 20% should be applied for irinotecan hydrochloride trihydrate and/or 5-FU 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 of product characteristics for dose modifications of bevacizumab when administered in combination with Irinotecan/5-FU/FA.

Treatment Duration:

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

Special populations

Patients with impaired hepatic function

In monotherapy: Blood bilirubin levels (up to 3 times the upper limit of the normal range (ULN)) in patients with performance status ≤ 2, should determine the starting dose of Irinotecan. In these patients with hyperbilirubinemia and prothrombin time greater than 50%, the clearance of irinotecan is decreased (see section 5.2) and therefore the risk of haemotoxicity 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 ULN, the recommended dosage of irinotecan hydrochloride trihydrate is 350 mg/m²,
- In patients with bilirubin ranging from 1.5 to 3 times the ULN, the recommended dosage of irinotecan hydrochloride trihydrate is 200 mg/m²,
- Patients with bilirubin beyond 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 with 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).

Children

Irinotecan should not be used in children.

Method of administration

Irinotecan is cytotoxic, for information regarding dilution, and special precautions for disposal and other handling (see section 6.6).

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

Treatment Duration

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

4.3 Contraindications

Irinotecan Martindale Pharma is contraindicated in:

- Chronic inflammatory bowel disease and/or bowel obstruction (see section 4.4).
- History of severe hypersensitivity to irinotecan hydrochloride trihydrate or to any of the excipients.
- Pregnancy and lactation (see section 4.4 and section 4.6).
- Bilirubin > 3 times the ULN (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, refer to the product information for these medicinal products.

4.4 Special warnings and precautions for use

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

Given the nature and incidence of adverse events, Irinotecan will only be prescribed in the following cases after the expected benefits have been weighed 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 section 5.1) may be considered in patients who need a closer follow-up or who are at a 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 hydrochloride trihydrate. Patients should quickly inform their physician of its occurrence and start appropriate therapy immediately.

Patients with an increased risk of diarrhoea are those who have 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 dose 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 antidiarrhoeal 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 $> 38^{\circ}\text{C}$ and neutrophil count ≤ 1000 cells/mm³) should be urgently treated in the hospital with broad-spectrum intravenous antibiotics.

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

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

Liver impairment

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

Weekly monitoring of complete blood counts should be conducted in patients with bilirubin ranging from 1.5 to 3 times ULN, due to decrease of the clearance of irinotecan (see section 5.2) and thus increasing the risk of haematotoxicity in this population. Irinotecan should not be administered to 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 (250 micrograms subcutaneously) should be administered unless clinically contraindicated (see section 4.8). Caution should be exercised in patients with asthma. In patients who experienced an acute and severe cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent doses of irinotecan.

Respiratory disorders

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

Elderly

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

Patients with bowel obstruction

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

Patients with impaired renal function

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

Others

Since Irinotecan contains sorbitol, it is unsuitable for 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 were 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).

Co-administration 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 /5-FU/FA alone and in combination with bevacizumab. Concentrations of SN-38, the active metabolite of irinotecan, were analysed in a subset of patients (approximately 30 per treatment arm). Concentrations of SN-38 were on average 33% higher in patients receiving irinotecan/5-FU/FA in combination with bevacizumab compared with irinotecan/5-FU/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/5-FU/FA in combination with bevacizumab.

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

4.6 Pregnancy and lactation

Pregnancy

There is no information on the use of irinotecan in pregnant women. Irinotecan has been shown to be embryotoxic, foetotoxic and teratogenic in rabbits and rats. Therefore irinotecan must not be used during pregnancy (see section 4.3 and section 4.4).

Women of child-bearing potential

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

Contraceptive measures must be taken by women of child-bearing age, and also by male patients, during and for at least three months after cessation of therapy.

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 5-FU/FA in every 2 weeks schedule at the recommended dose of 180 mg/m².

Frequency estimate:

- Very common ($\geq 1/10$)
- Common ($\geq 1/100$, $< 1/10$)
- Uncommon ($\geq 1/1,000$, $< 1/100$)
- Rare ($\geq 1/10,000$, $< 1/1,000$)
- Very rare ($< 1/10,000$)

Gastrointestinal disorders

Delayed diarrhoea

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

In monotherapy:

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

In combination therapy:

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

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

Nausea and vomiting

In monotherapy:

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

In combination therapy:

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

Dehydration

Common: Episodes of dehydration associated with diarrhoea and/or vomiting.

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

Other gastrointestinal disorders

Common: Constipation relative to irinotecan and/or loperamide has been observed, shared between :

- in monotherapy : in less than 10% of patients
- in combination therapy : 3.4% of patients.

Uncommon: Intestinal obstruction, ileus, or gastrointestinal haemorrhage

Rare: Colitis, including typhlitis, ischemic and ulcerative colitis and intestinal perforation.

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

Other mild effects include anorexia, abdominal pain and mucositis.

Blood and lymphatic system disorders

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

In monotherapy:

Very Common: Neutropenia was observed in 78.7% of patients and was severe (neutrophil count <500 cells/mm³) in 22.6% of patients. Of the evaluable cycles, 18% had a neutrophil count below 1,000 cells/mm³ including 7.6% with a neutrophil count <500 cells/mm³. Total recovery was usually reached by day 22.

Anaemia was reported in about 58.7% of patients (8% with haemoglobin <80 g/l and 0.9% with haemoglobin <65 g/l). Infectious episodes occurred in about 10.3% of patients (2.5% of cycles)

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

In combination therapy:

Very Common: Neutropenia was observed in 82.5% of patients and was severe (neutrophil count <500 cells/mm³) in 9.8 % of patients. Of the evaluable cycles, 67.3 % had a neutrophil count below 1,000 cells/mm³ including 2.7% with a neutrophil count <500 cells/mm³. Total recovery was usually reached within 7-8 days. Anaemia was reported in 97.2% of patients (2.1% with haemoglobin <80 g/l).

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

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

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

Very rare:

One case of peripheral thrombocytopenia with antiplatelet antibodies has been reported.

Infections and Infestations

Uncommon: Renal insufficiency, hypotension or cardio-circulatory failures have been observed in patients who experienced sepsis.

General disorders and administration site conditions

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

*Common:**Acute cholinergic syndrome*

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

Asthenia was severe in less than 10% of patients treated in monotherapy and in 6.2% of patients treated in combination therapy. The causal relationship to irinotecan has not been clearly established.

Fever in the absence of infection and without concomitant severe neutropenia, occurred in 6.2% of patients treated in combination therapy.

Uncommon: Mild infusion site reactions have been reported.

Cardiac disorders

Rare: Hypertension during or following the infusion.

Respiratory, thoracic and mediastinal disorders

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

Skin and subcutaneous tissue disorders

Very common: Reversible alopecia.

Uncommon: Mild cutaneous reactions.

Immune system disorders

Uncommon: Mild allergy reactions

Rare: Anaphylactic/anaphylactoid reactions.

Musculoskeletal and connective tissue disorders

Rare: Early effects such as muscular contraction or cramps and paresthesia have been reported.

Investigations

Very Common: In combination therapy transient increases in serum levels (grades 1 and 2) of either ALT (alanine aminotransferase) , AST (aspartate aminotransferase) , alkaline phosphatase or bilirubin were observed in 15%, 11%, 11% and 10% of the patients, respectively, in the absence of progressive liver metastasis.

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

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

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

Very Rare: Increases of amylase and/or lipase.

Nervous system disorders

Very rare: Transient speech disorders associated with infusion of irinotecan.

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: Other antineoplastic agents

ATC code: L01 XX19

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 of 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 antitumour 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 antitumour activity of irinotecan, the most relevant pharmacological effect is the inhibition of acetylcholinesterase.

Clinical data

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

	Phase III					
	Irinotecan versus supportive care			Irinotecan versus 5-FU		
	Irinotecan hydrochloride trihydrate	Supportive care	p values	Irinotecan hydrochloride trihydrate	5-FU	p values
	n = 183	n = 90		n = 127	n = 129	
Progression Free Survival at 6 months (%)	N/A	N/A		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

N/A: Not 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 medial time to progression was 17 weeks and median survival was 10 months. A similar safety profile has been observed in the weekly-dosage schedule in 193 patients at the starting dose of 125 mg/m², compared to the every 3-week-dosage schedule. The median time of onset of the first liquid stool was on day 11.

In combination therapy: A phase III study was performed in 385 previously untreated metastatic colorectal cancer patients treated with either every 2 weeks schedule (see section 4.2) or weekly schedule regimens. In the every 2 weeks schedule, on day 1, the administration of irinotecan hydrochloride trihydrate at 180 mg/m² once every two 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 hydrochloride trihydrate at 80 mg/m² is followed by infusion with folinic acid (500 mg/m² over a 2-hour intravenous infusion) and then by 5-flourouracil (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 hydrochloride trihydrate + 5-FU/FA	5- FU/FA	Irinotecan hydrochloride trihydrate + 5-FU/FA	5- FU/FA	Irinotecan hydrochloride trihydrate + 5-FU/FA	5- FU/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	

5-FU: 5-flourouracil
NS: Not Significant

FA: folinic acid
*): 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 5-FU/FA and 25.6% in patients treated by 5-FU/FA alone. The incidence of severe neutropenia (neutrophil count < 500 cells/mm³) was 5.8% in patients treated by irinotecan in combination with 5-FU/FA and 2.4% in patients treated by 5-FU/FA alone.

Additionally, median time to definitive performance status deterioration was significantly longer in irinotecan combination group than 5-FU/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/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 with cetuximab: 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 majority of whom had a Karnofsky performance status ≥ 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 the studies are summarised in the table below:

Study	N	ORR		DCR		PFS (months)		OS (months)	
		n (%)	95%CI	n (%)	95%CI	Median	95% CI	Median	95%CI
Cetuximab + irinotecan									
EMR 62 202-007	218	50 (22.9)	17.5, 29.1	121 (55.5)	48.6, 62.2	4.1	2.8, 4.3	8.6	7.6, 9.6
IMCL CP01-9923	138	21 (15.2)	9.7, 22.3	84 (60.9)	52.2, 69.1	2.9	2.6, 4.1	8.4	7.2, 10.3
Cetuximab									
EMR 62 202-007	111	12 (10.8)	5.7, 18.1	36 (32.4)	23.9, 42.0	1.5	1.5, 2.0	6.9	5.6, 9.1

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).

In combination with bevacizumab: A phase III randomised, double-blind, active-controlled clinical trial evaluated bevacizumab in combination with irinotecan/5-FU/FA as first-line treatment for metastatic carcinoma of the colon or rectum (Study AVF2107g). The addition of bevacizumab to the combination of irinotecan/5-FU/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 of Study AVF2107g are summarised in the table below:

	AVF2107g	
	Arm 1 Irinotecan/5-FU/FA	Arm 2 Irinotecan/5-FU/FA Avastin ^a

	Placebo	
Number of Patients	411	402
Overall survival		
Median time (months)	15.6	20.3
95% Confidence Interval	14.29 – 16.99	18.46 – 24.18
Hazard ratio ^b		0.660
p-value		0.00004
Progression-free survival		
Median time (months)	6.2	10.6
Hazard ratio		0.54
p-value		0.0001
Overall response rate		
Rate (%)	34.8	
95% CI	30.2 – 39.6	
p-value		
Duration of response		
Median time (months)	7.1	
25 – 75 percentile (months)	4.7 – 11.8	

^a5 mg/kg every 2 weeks. ^bRelative to control arm

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 distribution at steady state (V_{ss}): 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 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 derivative) and NPC (primary amine derivative) (see section 4.5).

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

Irinotecan clearance is decreased by about 40% in patients with bilirubinemia between 1.5 and 3 times the ULN. In these patients a 200 mg/m² irinotecan dose leads to plasma drug exposure comparable to that observed at 300 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 in the in vivo micronucleus test in mice. However, they have 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 haemopoietic 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 (E240)
Lactic acid
Water for injections
Sodium hydroxide (for pH-adjustment)

6.2 Incompatibilities

Irinotecan must not be mixed with other medicinal products, except those mentioned in section 6.6 (see also section 4.2).

6.3 Shelf Life

Vial before opening: 2 years

After opening: The content of the vial should be used immediately after the first breakage of vial.

After dilution: Chemical and physical in-use stability of the drug product after dilution in the recommended solutions for infusion (see section 6.6) has been demonstrated for 24 hours at 15 – 30°C and 48 hours at 2 – 8°C.

From a microbiological point of view, unless the method of opening and dilution preclude the risk of microbial contamination, the product should be used immediately after dilution. If not used immediately, in-use storage times and conditions are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

Do not freeze.

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

6.5 Nature and contents of container

Amber glass vial (type I) with flouoresin laminated rubber stopper, the stopper is covered with a crimped-on aluminium cap equipped with a flip-off polypropylene seal.

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

6.6 Special precautions for disposal

Handling

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

Instructions for dilution

Irinotecan Martindale Pharma[®] is intended for intravenous infusion only after diluting prior to administration in the recommended diluents, either 0.9% sodium chloride solution or 5% glucose solution for infusion. Aseptically withdraw the required amount of irinotecan 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 Martindale Pharma[®]:

- (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, tubes and residuals of cytostatics should be considered as hazardous waste and should undergo disposal according to local guidelines for the handling of HAZARDOUS WASTE.
- (3) Follow the instructions below in case of spillage:
 - protective clothing should be worn,
 - broken glass should be collected and placed in the container for HAZARDOUS WASTE,
 - contaminated surfaces should be flushed properly with copious amounts of cold water,
 - the flushed surfaces should then be wiped thoroughly and the materials used for wiping should be disposed as HAZARDOUS WASTE
- (4) In the event of irinotecan contact with the skin, the area should be rinsed with plenty of running water and then washed with soap and water. In case of contact with mucous membranes wash the contacted area thoroughly with water. If you have any discomfort, contact a doctor.
- (5) In case of contact of irinotecan with eyes, wash them thoroughly with plenty of water. Contact an ophthalmologist immediately.

Disposal

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

7 MARKETING AUTHORISATION HOLDER

Martindale Pharmaceuticals Limited
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8 MARKETING AUTHORISATION NUMBER

PA 361/28/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd April 2010

10 DATE OF REVISION OF THE TEXT