PACKAGE INSERT

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

MYLAN IRINOTECAN 40 mg/2 ml (concentrate for solution for infusion)

MYLAN IRINOTECAN 100 mg/5 ml (concentrate for solution for infusion)

COMPOSITION:

MYLAN IRINOTECAN 40 mg/2 ml: Each single-dose 4 ml vial contains 40 mg irinotecan hydrochloride trihydrate per 2 ml (40 mg/2 ml).

Inactive ingredients: sorbitol, lactic acid, sodium hydroxide and water for injection.

MYLAN IRINOTECAN 100 mg/5 ml: Each single-dose 10 ml vial contains 100 mg irinotecan hydrochloride trihydrate per 5 ml (100 mg/5 ml).

Inactive ingredients: sorbitol, lactic acid, sodium hydroxide and water for injection.

PHARMACOLOGICAL CLASSIFICATION:

A 26 – Cytostatic agents

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

Irinotecan is an antineoplastic agent and is a semisynthetic derivative of camptothecin.

Irinotecan and its active metabolite, SN-38, inhibit the action of DNA topoisomerase 1. Irinotecan and SN-38 bind to the topoisomerase 1-DNA complex and blocks the DNA replication fork, resulting in double-strand DNA breakage and cell death (cytotoxicity).

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

Although SN-38 is approximately 2 to 2000 times more potent than the parent compound in various *in vitro* cytotoxicity assays, the precise contribution of the metabolite to the activity of irinotecan in humans is not known because its protein binding is significantly higher, and its area under the plasma concentration-time curve (AUC) is much lower, than those of irinotecan.

Pharmacokinetics:

Distribution:

The volume of distribution (Vol_D) of the terminal elimination phase for irinotecan is 110 liters per square meter of body surface area.

Protein binding:

Irinotecan – Moderate (30 to 68 %) primarily to albumin.

SN-38 metabolite – Very high (95 %) primarily to albumin.

Biotransformation:

Primarily hepatic, via carboxylase-mediated cleavage of the carbamate bond. Conversion to the active metabolite (SN-38) is rapid. SN-38 undergoes conjugation to form a glucuronide metabolite, which is 50 to 100 times less active than SN-38. The disposition of irinotecan in humans is not completely clear.

Irinotecan and SN-38 both undergo reversible, pH-dependent conversion between their two forms, an active lactone and an inactive hydroxyl acid. Whereas only the lactone form is present at an acidic pH, the hydroxyacid form predominates at physiological pH.

Half-life:

Terminal:

Irinotecan: Mean, 6 to 12 hours (5,5 hours in patients younger than 65 years of age and 6 hours in older patients).

SN-38 metabolite: Mean, 10 to 20 hours.

Time to peak concentration:

SN-38 metabolite – Peak plasma concentrations occur within 1 hour after administration of a 90-minute infusion.

Peak plasma concentration:

Following a dose of 125 mg per square meter of body surface area (mg/m^2):

Irinotecan: 1660 ± 797 nanograms per ml.

SN-38 metabolite: 26,3 ± 11,9 nanograms per ml.

Elimination:

Renal: 11 to 20 % of a dose as unchanged irinotecan; < 1 % of a dose as SN-38; 1 to 3 % of a dose as SN-38 glucuronide.

Combined billiary and renal.

Total systemic clearance of irinotecan: 13,3 ± 6,01 litres per hour per square meter of body surface area after a 125 mg/m^2 dose.

INDICATIONS:

MYLAN IRINOTECAN is indicated for the treatment of patients with advanced colorectal cancer with a WHO performance status of 2 or lower.

- 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.

CONTRA-INDICATIONS:

MYLAN IRINOTECAN is contra-indicated in patients with:

- Hypersensitivity to **MYLAN IRINOTECAN** or any of the ingredients of the formulation**.**
- Bowel obstruction or ileus. Treatment should only be started with **MYLAN IRINOTECAN** after resolution of the ileus.
- Bone marrow depression, pre-existing or treatment related.
- Severe bone marrow failure.
- Chronic inflammatory bowel disease.
- Bilirubin > 1,5 times the upper limit of the normal range.
- WHO performance status > 2.
- Concomitant use with St. John's Wort.
- Pregnancy and lactation.
- Children.

WARNINGS:

MYLAN IRINOTECAN should be used only by a doctor experienced with cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

It must be ensured that the patient understands the necessity for sufficiently prolonged antidiarrhoeal treatment and sufficient fluid intake.

A strict follow-up of the patient by the treating doctor or hospitalisation is recommended where it is predictable that there would be poor compliance by the patient with the guidance for the management of side effects.

Given the nature and frequency of side effects, the expected benefit must balance in case of risk factors, especially WHO Performance status ≥ 2 (or Karnofsky index < 50).

Diarrhoea:

Patients should be aware that, apart from diarrhoea shortly after infusion, there is a high risk of delayed diarrhoea, which could occur more than 24 hours after the infusion of **MYLAN IRINOTECAN**, and at any time before the next cycle.

The doctor should quickly be informed of the occurrence and appropriate treatment must be started immediately.

At an increased risk to develop diarrhoea are patients who had a previous abdominal/pelvic radiotherapy, patients with a baseline hyperleukocytosis and patients with performance status ≥ 2. Diarrhoea can be life-threatening if not properly treated, and more so if the patient is also neutropenic.

Once the first liquid stool occurs, patients should start drinking large volumes of beverages containing electrolytes and a suitable antidiarhoeal therapy must be started immediately.

This antidiarrhoeal therapy must be prescribed by the facilities where **MYLAN IRINOTECAN** has been administered. The patients should get the prescribed medicines when they are discharged from hospital, as they must treat the diarrhoea as soon as it starts. They must also inform their doctor or the facilities where treatment was received that diarrhoea is occurring.

The antidiarrhoeal treatment recommended is loperamide 4 mg, for the first intake, and then 2 mg every 2 hours. This treatment must continue for 12 hours after the last liquid stool and must not be changed. Loperamide must not be taken for more than 48 consecutive hours at these doses, as there is a risk of paralytic ileus.

A prophylactic broad spectrum antibiotic should be given, in addition to the antidiarrhoeal treatment, when diarrhoea is associated with severe neutropenia (neutrophil count < 500 cells/mm^3).

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

- Severe diarrhoea which requires intravenous hydration.
- Diarrhoea associated with fever.
- Diarrhoea for more than 48 hours after the start of high-dose loperamide treatment.

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

A reduction in dose is recommended for subsequent cycles in patients who experienced severe diarrhoea.

Haematology:

Monitoring on a weekly basis of the complete blood cell counts should be performed during **MYLAN IRINOTECAN** treatment.

Patients must be made aware of the risk of infection and the significance thereof. Febrile neutropenia (temperature ≥ 38 ^{o}C and neutrophil count ≤ 1 000 cells/mm^3) must urgently be treated in hospital with broad spectrum intravenous antibiotics.

Treatment with **MYLAN IRINOTECAN** must be delayed until the neutrophil count is ≥ 1 500 cells/mm^3.

In patients who experienced severe asymptomatic neutropenia (< 500 cells/mm^3), fever or infections associated with neutropenia, the dose of **MYLAN IRINOTECAN** must be reduced.

A dose reduction is recommended for subsequent administration in patients who experienced severe haematological events.

Patients with severe diarrhoea have an increased risk of infections and haematological toxicity.

Liver:

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

Patients with impaired liver function (bilirubin > 1,0 and ≤ 1,5 times the upper limit of the normal range [ULN] and transaminases 5 times ULN) are at greater risk of developing severe neutropenia or febrile neutropenia and should be closely monitored. **MYLAN IRINOTECAN** must not be used in patients with a bilirubin > 1,5 times the ULN and the patients with bilirubin > ULN should be followed with caution.

Nausea & Vomiting:

It is recommended that patients should receive prophylactic treatment with an anti-emetic before each treatment, as nausea and vomiting have been reported. If patients have vomiting associated with delayed diarrhoea, they should be hospitalised soonest possible for treatment.

Acute Cholinergic Syndrome:

In case of an acute cholinergic syndrome (defined as early diarrhoea and symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation), atropine sulphate (0,25 mg subcutaneously) should be administered unless contra-indicated. Caution is necessary in patients with asthma. In patients experiencing an acute cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent doses of **MYLAN IRINOTECAN.**

Elderly:

Because of the greater frequency of decreased renal, hepatic and cardiac functions in elderly patients, the dosage should be carefully considered.

Risk benefit should be considered in the following medical conditions:

- Chickenpox, existing or recent.
- Herpes zoster infections.
- Pre-existing infection. Recovery may be impaired.
- Bone marrow depression, pre-existing or treatment related.
- Hepatic impairment.
- Pulmonary disease or impairment.
- Caution should also be observed in patients who have had previous cytotoxic therapy or radiation therapy.

INTERACTIONS:

Pharmacokinetic parameters of irinotecan combined with 5-fluorouracil-folinic acid are comparable to those observed with monotherapy.

An interaction between **MYLAN IRINOTECAN** and neuromuscular blocking medication cannot be ruled out.

Medication with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarising medications may be antagonised.

Loperamide should not be prescribed prophylactically.

The use of St. John's Wort during **MYLAN IRINOTECAN** therapy has been found to decrease plasma concentrations of SN-38, the active metabolite of irinotecan.

PREGNANCY AND LACTATION:

MYLAN IRINOTECAN is contra-indicated in pregnancy and lactation.

Patients should be informed of effects on the foetus if **MYLAN IRINOTECAN** is used during pregnancy or if a patient becomes pregnant while using it.

Safety and efficacy of **MYLAN IRINOTECAN** have not been established in children.

During treatment and for at least three months after cessation of therapy, contraceptive measures should be taken.

DOSAGE AND DIRECTIONS FOR USE:

Dosage in monotherapy (for previously treated patients):

The recommended dosage of **MYLAN IRINOTECAN** is 350 mg/m^2 administered as an intravenous infusion over a 30- to 90-minute period every three weeks.

Combination therapy (for previously untreated patients):

MYLAN IRINOTECAN plus 5FU/FA in weekly schedule:

The recommended dose of **MYLAN IRINOTECAN** is 80 mg/m^2 administered as a weekly intravenous infusion over a 30- to 90-minute period, followed by infusion with folinic acid and then by 5-fluorouracil over 6 weeks. This treatment is followed by one week's rest.

Dosage regimen:

MYLAN IRINOTECAN 80 mg/m^2 as a 30- to 90-minute infusion on day 1 and then weekly for 6 weeks.

Folinic acid 500 mg/m^2 IV as a 2-hour infusion, followed by 5-fluorouracil 2 000 mg/m^2 IV as a 24 hour infusion, on day 1 and then weekly for 6 weeks.

The treatment is to be repeated every 7 weeks.

MYLAN IRINOTECAN plus 5FU/FA in every 2 week schedule:

The recommended dose of **MYLAN IRINOTECAN** is 180 mg/m^2 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.

The Full Dosage Regimen is as follows:

MYLAN IRINOTECAN 180 mg/m^2 IV as a 30- to 90-minute infusion on day 1 only.

Folinic acid 200 mg/m^2 IV as a 2-hour infusion, followed by 5-fluorouracil 400 mg/m^2 IV bolus, followed by 5-fluorouracil 600 mg/m^2 IV as a 22-hour infusion. The folinic acid and 5-fluorouracil are repeated for two consecutive days.

The cycle is repeated every two weeks.

Delayed dosing – Dosage adjustments:

MYLAN IRINOTECAN should not be administered until the neutrophil count remains above 1 500 cells/mm^3. In patients who experienced severe neutropenia or severe gastro-intestinal adverse effects such as diarrhoea, nausea and vomiting, dosing of **MYLAN IRINOTECAN** must be delayed until there has been a full recovery of these effects, especially diarrhoea.

MYLAN IRINOTECAN should be administered after appropriate recovery of all adverse effects to grade 0 or 1 NCI-CTC grading (National Cancer Institute Common Toxicity Criteria) and when treatment-related diarrhoea is fully resolved. This must be strictly adhered to.

At the start of a subsequent infusion of therapy, the dose of **MYLAN 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 side effects.

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

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

Duration of Treatment:

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

Special Populations:

Patients with Impaired Hepatic Function:

Patients with a bilirubin > 1,5 times the ULN should not be treated with **MYLAN IRINOTECAN**. In patients with a bilirubin ≤ 1,5 times the upper limit of the normal range (ULN), a dose of 350 mg/m^2 **MYLAN IRINOTECAN** is recommended. In patients with bilirubin > 1 and ≤ 1,5 times the upper limit of the normal range (ULN), the risk of severe neutropenia is increased. Thus, frequent monitoring of complete blood counts should be conducted in this patient population.

Patients with Impaired Renal Function:

No specific pharmacokinetic studies have been performed in patients with renal impairment.

Elderly:

No specific pharmacokinetic studies have been performed in the elderly. However, the dose should be chosen carefully in this population due to their greater frequency of decreased hepatic, renal or cardiac function.

Preparation for the Intravenous Infusion Administration:

Aseptically withdraw the required amount of **MYLAN 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 % glucose solution. The infusion should then be thoroughly mixed by manual rotation.

MYLAN IRINOTECAN infusion solution should be infused into a peripheral or central vein.

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

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

Do **NOT** admix with other medications.

Recommendations for Safe Handling:

Handling precautions for cytostatic medicines should be followed:

- Only trained personnel should reconstitute the medicine in a designated area.
- **MYLAN IRINOTECAN** is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing **MYLAN IRINOTECAN** solutions.
- The work surface should be covered with disposable plastic-backed absorbent paper.
- Adequate protective gloves and clothing should be worn.
- If **MYLAN IRINOTECAN** solution or infusion should come into contact with the skin, wash immediately and thoroughly with soap and water. If **MYLAN IRINOTECAN** solution or infusion solution should come into contact with the eyes or mucous membranes, wash immediately and thoroughly with water.
- The cytotoxic preparations must not be handled by pregnant staff.
- Adequate care and precautions should be taken in the disposal of items used to reconstitute the medicine.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:

Blood and Lymphatic System Disorders:

Frequent: Leukopenia, neutropenia, thrombocytopenia, neutropenic infection, anaemia, arterial thrombosis, thrombophlebitis, embolus.

Less frequent: Haemorrhage, neutropenic fever.

Immune System Disorders:

Less frequent: Allergic reactions including anaphylactoid reactions

Nervous System Disorders:

Frequent: Headache, insomnia, somnolence, vertigo.

Less frequent: Confusion, malaise, dizziness.

Cardiac Disorders:

Frequent: Mechanical cardiac dysfunction, dysrhythmias, hypotension, ischaemia, thromboembolic events including angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, embolus in lower extremities, heart arrest, myocardial infarct, myocardial ischaemia, peripheral vascular disorders, pulmonary embolus.

Less frequent: Vasodilation.

Respiratory, Thoracic and Mediastinal Disorders:

Frequent: Dyspnoea, cough.

Less frequent: Pneumonia, rhinitis.

Gastro-intestinal Disorders:

Frequent: Nausea, vomiting, diarrhoea, possibly preceded by abdominal cramps and/or sweating, abdominal enlargement, cramps and pain, anorexia and weight loss, constipation, dyspepsia, flatulence, mucositis, stomatitis.

Less frequent: Intestinal obstruction, ileus or gastro-intestinal haemorrhage, pseudo-membranous colitis, intestinal perforation.

Frequency not known: Colitis.

Hepato-biliary Disorders:

Frequent: Jaundice, hepatomegaly.

Skin and Subcutaneous Tissue Disorders:

Frequent: Skin rash, hand and foot syndrome (blistering, peeling, redness and/or swelling of palms and hands and bottoms of feet), alopecia.

Musculoskeletal, Connective Tissue and Bone Disorders:

Frequent: Back pain, asthenia, paraesthesia.

Less frequent: Muscular contraction, cramps.

Renal and Urinary Disorders:

Frequent: Oedema.

Less frequent: Renal impairment or acute renal failure.

General Disorders and Administration Site Conditions:

Frequent: Accidental injury, syncope, fever, chills.

Less frequent: Severe transient acute cholinergic syndrome with symptoms such as abdominal pain, conjunctivitis, sweating, chills, visual disturbances, myosis, lacrimation and increased salivation. Dehydration and infusion site reactions. These symptoms may be treated with atropine administration.

Investigations:

Alkaline phosphatase and aspartate aminotransferase may be increased especially in patients with hepatic metastases. Increased amylase, lipase and bilirubin levels. Haemoglobin concentration, leukocyte count and platelet count may be decreased.

Special Precautions:

Avoid immunisations unless approved by a doctor.

It is important to monitor the infusion site for inflammation and to avoid extravasation: flush site with sterile water, apply ice if extravasation occurs.

Since this formulation contains sorbitol, it is unsuitable in hereditary fructose intolerance.

Effects on Ability to Drive and use of Machines:

Patients should be warned about the potential for dizziness or visual disturbances, and they should be advised not to drive or operate machinery if this occurs.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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, leukopenia and diarrhoea.

There is no known antidote for **MYLAN IRINOTECAN**. Maximum supportive care should be instituted to prevent dehydration due to diarrhoea and to treat any infectious complications.

IDENTIFICATION:

Amber coloured vials containing a clear, pale yellow sterile solution and packaged into an outer carton.

PRESENTATION:

MYLAN IRINOTECAN 40 mg/2 ml: Carton containing an amber coloured Type I Ph Eur glass vial with a nominal volume of 4 ml, a 13 mm dark grey chlorobutyl rubber stopper and a 13 mm red aluminium flip-off seal.

MYLAN IRINOTECAN 100 mg/5 ml: Carton containing an amber coloured Type I Ph Eur glass vial with a nominal volume of 10 ml, a 20 mm dark grey chlorobutyl rubber stopper and a 20 mm yellow aluminium flip-off seal.

1, 5, 10 or 20 vials are packed in a cardboard carton. Not all pack sizes may be marketed.

STORAGE CONDITIONS:

Keep in the carton until required for use.

Single-dose vials of **MYLAN IRINOTECAN** should be stored at or below 25 °C and protected from light.

After dilution in either 0,9 % sodium chloride or 5 % glucose, the diluted solution is stable for 6 hours at a temperature at or below 25 °C or 24 hours under refrigeration (2-8 °C) protected from light. Discard any unused portion thereafter.

Do not freeze.

KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS:

MYLAN IRINOTECAN 40 mg/2 ml: 43/26/0349

MYLAN IRINOTECAN 100 mg/5 ml: 43/26/0348

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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