**Scheduling status:** S4

**Proprietary names and dosage forms:**

IRINOTECAN 40 OETHMAAN (concentrate for solution for infusion)

IRINOTECAN 100 OETHMAAN (concentrate for solution for infusion)

**Composition:**

Each Irinotecan 40 Oethmaan vial contains: 40 mg Irinotecan hydrochloride trihydrate per 2 ml.

Each Irinotecan 100 Oethmaan vial contains: 100 mg Irinotecan hydrochloride trihydrate per 5 ml.

**Pharmacological classification:**

A 26 Cytostatic agents

**Pharmacological action:**

***Pharmacodynamics:***

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 tumor 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 to be time-dependent and was specific to the S phase.

*In vitro*, irinotecan and SN-38 were found not to be significantly recognised by the P-glycoprotein, and displays cytotoxic activities against doxorubicin and vinblastine resistant cell lines.

Besides the anti-tumour activity of irinotecan, the most relevant pharmacological effect of irinotecan is the inhibition of acetylcholinesterase.

***Pharmacokinetics:***

After a 30-minute intravenous infusion of 100 to 700 mg/m$^2$ every 3 weeks, irinotecan showed a biphasic or three-phase elimination profile. The mean plasma clearance was 15 l/h/m$^2$ and the volume of distribution at

steady state (Vss) quite large: 157 l/m$^2$. 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 recommended dose of 350 mg/m$^2$, the mean irinotecan and SN-38 peak plasma concentrations were 7,7 µg/ml and 56 ng/ml, respectively and were reached at the end of the infusion. The mean area under the curve (AUC) values were 34 µg.h/ml and 451 ng.h/ml, respectively. A large inter-individual variability in pharmacokinetic parameters is generally observed for SN-38.

*In vitro*, the plasma protein binding for irinotecan and SN-38 are 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 via the bile and 22 % in urine. Two metabolic pathways, each representing at least 12 % of the dose, have been identified:

- oxidative metabolism at the terminal piperidine ring by cytochrome P450 3A enzymes, which results in an aminopentoic acid derivative (APC) and a primary amine derivate and
- hydrolysis by carboxylesterases into the 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).

Unchanged irinotecan is the major entity in plasma followed by APC, SN-38 glucuronide and SN-38. Only SN-38 has significant cytotoxic activity and no other circulating metabolites have been detected. 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/m$^2$ irinotecan dose leads to plasma drug exposure comparable to that observed at 350 mg/m$^2$ in cancer patients with normal liver parameters. Co-administration of 5-fluorouracil/folinic acid in the combination regimen does not change the pharmacokinetics of irinotecan.

**Indications:**

IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN 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:**

- History of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate or to one of the excipients of the formulation.
- Chronic inflammatory bowel disease, and/or bowel obstruction or ileus. Patients should not be treated with IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN until resolution of the ileus.
- Pregnancy and lactation. Women of childbearing age receiving IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN should be advised to avoid becoming pregnant and to inform the medical practitioner immediately should this occur.
- Bilirubin > 1,5 times the upper limit of the normal range.
- The safety and efficacy of IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN in children have not been established.
- Severe bone marrow failure.
- WHO performance status > 2.

**Warnings and Special precautions:**

IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN should be used in patients with a good performance status of less than 2.

The use of IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a qualified oncologist. It is strongly recommended that IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN be administered only in healthcare institutions with adequately equipped facilities including an intensive care unit. In all instances where the use of IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN is considered for chemotherapy, it is especially important to ensure that the patient understands the need for sufficiently prolonged antidiarrhoeal treatment and abundant fluid intake. In rare cases where it is predictable that the patient would comply poorly with the guidances for the management of side effects, a strict follow-up of the patient by the medical practitioner or hospitalisation is recommended.

Given the nature and frequency of adverse events the expected benefit must be balanced in case of risk factors especially WHO Performance status ≥ 2 (or Karnofsky Index < 50).

***Delayed diarrhoea:***

Apart from the diarrhoea shortly after the infusion of IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN, patients should be aware of the high risk of delayed diarrhoea occurring more than 24 hours after the administration of IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN 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 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN. Patients should quickly inform their medical practitioner on 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 hyperleukocytosis and those with performance status ≥ 2. 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.
The antidiarrhoeal treatment must be prescribed by the department where IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN 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 medical practitioner or the department administering IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN that diarrhoea is occurring. The currently recommended antidiarrhoeal treatment is 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 case 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/$mm^3$).
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.

***Haematology:***

Weekly monitoring of complete blood cell counts should be performed during IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN treatment. Patients should be aware of the risk of infection and the significance of a fever. Febrile neutropenia (temperature ≥ 38 $^{o}$C and neutrophil count ≤ 1000 cells/mm$^{3}$) should be urgently treated in the hospital with broad-spectrum intravenous antibiotics. IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN administration should be delayed until the neutrophil count is ≥ 1500 cells/mm$^{3}$.

In patients who experience severe asymptomatic neutropenia (< 500 cells/ mm$^{3}$), fever or infections associated with neutropenia, the dose of IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN should be reduced. In patients who experience severe haematologic events, a dose reduction is recommended for subsequent administration. There is an increased risk of infections and haematological toxicity in patients with severe diarrhoea.

***Liver impairment:***

Liver function tests should be performed 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. IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN should 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 and vomiting:***

Prophylactic treatment with an anti-emetic is recommended before each treatment with IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN. 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 an acute cholinergic syndrome appears (defined as early diarrhoea and a group of symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation), atropine sulphate (0,25 mg subcutaneously) should be administered unless clinically contra-indicated. Caution should be exercised in patients with asthma. In patients who experienced an acute cholinergic syndrome, the use of prophylactic

atropine sulphate is recommended with subsequent doses of IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN.

***Elderly:***

Due to the greater frequency of decreased hepatic, renal or cardiac function in an elderly patient, dose selection with IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN should be cautious in this population.

***Effects on ability to drive and use machines:***

Patients should be warned about the potential for dizziness or visual disturbances, and advised not to drive or operate machinery if these symptoms occur.

***Others:***

Contraceptive measures must be taken during and for at least three months after cessation of therapy.

***Special precautions:***

IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN contains sorbitol. Patients with hereditary problems of fructose intolerance should not take this medicine.

**Interactions:**

Pharmacokinetic parameters of IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN combined with 5-fluorouracil-folinic acid are comparable to those observed in monotherapy.
Interaction between irinotecan and neuromuscular blocking agents cannot be ruled out. Medicines with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarising agents may be antagonized. Loperamide should not be given prophylactically.
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.

**Pregnancy and lactation:**

The use of IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN during pregnancy and lactation is not recommended as safety and efficacy have not been established (see “Contra-indications”).

**Dosage and directions for use:**

IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN infusion should be administered into a peripheral or central vein.

***Recommended dosage:***

*In monotherapy (for previously treated patients):*

The recommended dosage of IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN is 350 mg/m$^2$ administered as an intravenous infusion over a 30 to 90 minute period every three weeks.

*In combination therapy (for previously untreated patients):*

Safety and efficacy of IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN in combination with 5-fluorouracil (5FU) and folinic acid (FA) have been assessed with either of the following schedules:

- *IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN plus 5FU/FA in weekly schedule:*

  The recommended dose of IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN is 80 mg/m$^2$ administered as a weekly intravenous infusion over a 30 to 90 minute period, followed by an infusion with folinic acid and then by 5-fluorouracil over 6 weeks. This treatment is followed by one week rest.

  The full dosage regimen is as follows:

  IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN 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 2000 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.

- *IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN plus 5FU/FA in every 2 week schedule:*

  The recommended dose of SANDOZ 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:

IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN 180 mg/m$^2$ intravenous as a 30 to 90 minute infusion on day 1 only.

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

Repeat the cycle every two weeks.

***Dosage adjustments:***

*Delayed dosing:*

IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN should not be administered until the neutrophil count remains above 1500 cells/mm$^3$. In patients who experienced severe neutropenia or severe gastrointestinal adverse events such as diarrhoea, nausea and vomiting, dosing of IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN should be delayed until there has been a full recovery of these effects, especially diarrhoea.

IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN 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. This must be strictly adhered to. At the start of a subsequent infusion of therapy, the dose of IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN, 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 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN 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 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN 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 upper limit of the normal range (ULN) should not be treated with IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN. In patients with a bilirubin ≤ 1,5 times the ULN, a dose of 350 mg/m$^2$ IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN is recommended. In patients with bilirubin > 1 and ≤ 1,5 times the 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 IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN concentrate 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. Mix the infusion thoroughly by manual rotation. IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN infusion solution should be infused into a peripheral or central vein.

IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN 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:***

Drug handling precautions for cytostatic drugs should be followed:

- Only trained personnel should reconstitute the medicine in a designated area.

- IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparin IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN solutions.
- The work surface should be covered with disposable plastic-backed absorbent paper.
- Adequate protective gloves and clothing should be worn.
- If IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN solution or infusion solution should come into contact with the skin, wash immediately and thoroughly with soap and water. If IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN 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:**

The intensity of the major toxicities encountered with IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN (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.

The following adverse reactions have been reported with the use of IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN:

***Blood and lymphatic system disorders:***

Neutropenia is a dose-limiting toxic effect.

*Frequent:* Anaemia, thrombocytopenia.

***Immune system disorder:***

*Frequent:* Chills.

*The following side effect has been reported and frequencies are unknown*: Malaise.

***Nervous system disorder:***

*Frequent:* Dizziness.

***Eye disorders:***

Visual disturbances, myosis, lacrimation and increased salivation occurring during or within the first 24 hours after the infusion of IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN.
These symptoms disappear after atropine administration.

***Respiratory system disorders:***

*Frequent:* Dyspnoea (difficulty in breathing).

***Gastrointestinal disorders:***

*Frequent:* Nausea, vomiting, diarrhoea, constipation. Other mild effects include anorexia, abdominal pain and mucositis.
*Less frequent:* Dehydration.
*The following side effects have been reported and frequencies are unknown:* Intestinal perforation, intestinal obstruction, ileus or gastro-intestinal haemorrhage. Transient increase in amylase and lipase has been reported.
Cases of pseudo-membranous colitis have been reported, one of which has been documented bacteriologically (*Clostridium difficile*).

***Musculoskeletal system disorders:***

*Frequent:* Asthenia.
*The following side effects have been reported and frequencies are unknown:* Muscular contraction or cramps and paraesthesia.

***Cardiovascular system disorders:***

*Frequent:* Hypotension, vasodilation.
*The following side effects have been reported and frequencies are unknown:* Cardio-circulatory failure has been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis.

***Skin and subcutaneous tissue disorders:***

*Frequent:* Sweating.

***Hypersensitivity disorders:***

*Frequent:* Rhinitis.

*The following side effects have been reported and frequencies are unknown:* Conjunctivitis, mild cutaneous reactions, allergy and infusion site reactions have been reported.

***Renal system disorders:***

*Less frequent*: Renal insufficiency.

Transient and mild to moderate increases of serum levels of creatinine have been observed.

***Hepatic system disorders:***

Transient and mild to moderate increases in serum levels of either transaminases, alkaline phosphatase or bilirubin have been observed, in the absence of progressive liver metastasis. Transient serum levels (grade 1 and 2) of either ALT, AST, alkaline phosphatase or bilirubin have been observed, in the absence of progressive liver metastasis. Transient grade 3 were observed and no grade 4 was observed.

***Other:***

*Frequent:* Alopecia.

**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 and diarrhoea. There is no known antidote for IRINOTECAN 40 OETHMAAN AND IRINOTECAN 100 OETHMAAN. Maximum supportive care should be instituted to prevent dehydration due to diarrhoea and to treat any infectious complications.

**Identification:**

Concentrate for solution for infusion: Yellowish clear solution.

Ready-for-use diluted solution: Clear slightly yellow solution without particles.

**Presentations:**

Irinotecan 40 Oethmaan: 2 ml concentrate for solution for infusion packed in 4 ml amber glass vials with fluoropolymer coated bromobutyl rubber stoppers.

Irinotecan 100 Oethmaan: 5 ml concentrate for solution for infusion packed in 7 ml amber glass vials with fluoropolymer coated bromobutyl rubber stoppers.

**Storage instructions:**

Concentrate for solution for infusion: Store at or below 25 ºC. Protect from light. Keep vials in carton until required for use.

Ready-for-use diluted solution: Store for 48 hours under refrigeration (2 to 8 ºC) or 24 hours below 25 ºC. Do not freeze.

KEEP OUT OF THE REACH OF CHILDREN.

**Registration numbers:**

Irinotecan 40 Oethmaan: 41/26/0028

Irinotecan 100 Oethmaan: 41/26/0029

**Name and business address of the holder of the certificates of registration:**

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**Date of publication of this package insert:**

09 December 2008