PRESCRIBING INFORMATION
For the use of a registered medical practitioner or a hospital or a laboratory only

IMTUS
(Irinotecan Hydrochloride Trihydrate Concentrate for Solution for Infusion 20mg/mL)

For Intravenous Use Only

Each mL contains:
Irinotecan hydrochloride USP (as trihydrate), 20 mg
Water for Injection USP q.s. to 1 mL

PRODUCT DESCRIPTION :
Before dilution: Pale yellow, clear aqueous solution.
After dilution: Pale yellow, clear aqueous colution.

CLINICAL PHARMACOLOGY
Pharmacodynamics:
Irinotecan is a semisynthetic derivative of camptothecin. It is an antineoplastic agent which acts as a specific inhibitor of DNA topoisomerase I. It is metabolised by carboxylesterase in most tissues to SN-38, which was found to be more active than irinotecan in purified topoisomerase I and more cytotoxic than irinotecan against several murine and human tumour cell lines. The inhibition of DNA topoisomerase I by irinotecan or SN-38 induces single-strand DNA lesions which blocks the DNA replication fork and are responsible for the cytotoxicity. This cytotoxic activity was found time-dependent and was specific to the S phase.
In vitro, irinotecan and SN-38 were not found to be significantly recognised by the P-glycoproteinMDR 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-glycoproteinMDR (vincristine- and doxorubicin-resistant P388 leukaemias).
Beside the antitumour activity of Irinotecan, the most relevant pharmacological effect of irinotecan is the inhibition of acetylcholinesterase.

Pharmacokinetics:
Irinotecan showed a biphasic or thriphasic elimination profile. The mean plasma clearance was 15 L/h/m^2 and the volume of distribution at steady state (Vss): 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 end of the infusion, at the recommended dose of 350 mg/m^2, 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.

In vitro, plasma protein binding for irinotecan and SN-38 was approximately 65% and 95% respectively.

Mass balance and metabolism studies with 14 C-labelled drug have shown that more than 50% of an intravenously administered dose of irinotecan is excreted as unchanged drug, with 33% in the faeces mainly via the bile and 22% in urine.

Two metabolic pathways account each for at least 12% of the dose:

• Hydrolysis by carboxylesterase into active metabolite SN-38, SN-38 is mainly eliminated by glucuronidation, and further by biliary and renal excretion (less than 0.5% of the irinotecan dose) The SN-38 glucuronite is subsequently probably hydrolysed in the intestine.

• Cytochrome P450 3A enzymes-dependent oxidations resulting in opening of the outer piperidine ring with formation of APC (aminopentanoic acid derivate) and NPC (primary amine derivate).

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

Irinotecan clearance is decreased by about 40% in patients with bilirubinemia between 1.5 and 3 times the upper normal limit. In these patients a 200 mg/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.

INDICATIONS AND USAGE
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.

DOSAGE AND ADMINISTRATION
Strictly follow the recommended dosage unless directed otherwise by the physician. All doses of irinotecan should be administered as an intravenous infusion over 30 to 90 minutes.

Single-agent dosage schedules
Single-agent dosage schedules have been extensively studied for metastatic colorectal cancer.

Starting dose
Weekly Dosage Schedule. The recommended single-agent starting dose of irinotecan is 125 mg/m^2. A lower starting dose may be considered (e.g., 100 mg/m^2) for patients with any of the following conditions: prior extensive radiotherapy, performance status of 2, increased bilirubin levels, or gastric cancer. Treatmentshould be given in repeated 6-week cycles, comprising weekly treatment for 4 weeks, followed by a 2-week rest.

Once-Every-2-Week Dosage Schedule. The usual recommended starting dose of irinotecan is 250 mg/m^2 every 2 weeks by intravenous infusion. A lower starting dose may be considered (e.g., 200 mg/m^2) for patients with any of the following conditions: age 65 years and older, prior extensive radiotherapy, performance status of 2, increased bilirubin levels, or gastric cancer.

Once-Every-3-Week Dosage Schedule. The usual recommended starting dose of irinotecan for the once-every-3-week dosage schedule is 350 mg/m^2. A lower starting dose may be considered (e.g., 300 mg/m^2) for patients with any of the following conditions: age 65 years and older, prior extensive radiotherapy, performance status of 2, increased bilirubin levels, or gastric cancer.

Special populations
Elderly
The dose should be chosen carefully in this population due to their greater frequency of decreased biological functions. This population should require more intensive surveillance.

Patients with impaired hepatic function
In patients with hepatic dysfunction, the following starting doses are recommended:

Table 1: Starting Doses in Patients with Hepatic Dysfunction: *Single-agent Weekly Regimen*

Serum Total Bilirubin Concentration	Serum ALT/AST Concentration	Starting Dose, mg/m^2
1.5-3.0 x IULN	≤5.0 x IULN	60
3.1-5.0 x IULN	≤5.0 x IULN	50
<1.5 x IULN	5.1-20.0 x IULN	60
1.5-5.0 x IULN	5.1-20.0 x IULN	40

Table 2: Starting Doses in Patients with Hepatic Dysfunction: *Single-agent Once-Every-3-Week Regimen*

Serum Total Bilirubin Concentration	Starting Dose, mg/m^2
1.5-3.0 x IULN	200
>3.0 x IULN	Not Recommended*

*The safety and pharmacokinetics of irinotecan given once-every-3-weeks have not been defined in patients with bilirubin >3.0 x institutional upper limit of normal (IULN) and this schedule cannot be recommended in these patients.

Patients with impaired renal function

Studies in this population have not been conducted. Therefore, caution should be undertaken in patients with impaired renal function. Irinotecan is not recommended for use in patients on dialysis.

Combination-agent dosage schedules

Starting Dose

Irinotecan in Combination with 5-Fluorouracil (5-FU) and folinic acid (FA). Irinotecan in combination with 5-FU and folinic acid is recommended for use in patients with metastatic colorectal cancer. For all regimens, the dose of folinic acid should be administered immediately after irinotecan, with the administration of 5-FU to occur immediately after receipt of folinic acid. The currently recommended regimens are shown below:

Regimen 1 (6-week cycle with bolus 5-FU/FA): The recommended starting dose is 125 mg/m^2 of irinotecan, 500 mg/m^2 bolus 5-FU, and 20 mg/m^2 bolus folinic acid.

Regimen 2 (6-week cycle with infusional 5-FU/FA): The recommended starting dose is 180 mg/m^2 of irinotecan, 400 mg/m^2 bolus 5-FU, 600 mg/m^2 5-FU infusion, and 200 mg/m^2 folinic acid.

Lower starting doses may be considered for irinotecan (e.g., 100 mg/m^2) and 5-FU (e.g., 400 mg/m^2) for patients with any of the following conditions: age 65 years and older, prior extensive radiotherapy, performance status of 2, increased bilirubin levels, or gastric cancer. Treatment should be given in repeated 6-week cycles, comprising weekly treatment for 4 weeks, followed by a 2-week rest.

Duration of treatment

For both single-agent and combination-agent regimens, treatment with additional cycles of irinotecan may be continued indefinitely in patients who attain a tumor response or in patients whose cancer remains stable. Patients should be carefully monitored for toxicity and should be removed from therapy if unacceptable toxicity occurs that is not responsive to dose modification and routine supportive care.

Dose modification recommendations

The recommended dose modifications during a cycle of therapy and at the start of each subsequent cycle of therapy for single-agent dosage schedules are described in **Table 3**. These recommendations are based on toxicities commonly observed with the administration of irinotecan. For modifications at the start of a subsequent cycle of therapy, the dose of irinotecan should be decreased relative to the initial dose of the previous cycle.

The recommended dose modifications during a cycle of therapy and at the start of each subsequent cycle of therapy for irinotecan, 5-FU, and folinic acid are described in **Table 4**.

All dose modifications should be based on the worst preceding toxicity. A new cycle of therapy should not begin until the toxicity has recovered to Grade 2 or less. Treatment may be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicity. If the patient has not recovered, consideration should be given to discontinuing irinotecan.

Table 3: Recommended Dose Modifications for Single-agent Schedules

A new cycle of therapy should not begin until the granulocyte count has recovered to ≥1500/mm3, and the platelet count has recovered to ≥100,000/mm3, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing irinotecan.

Toxicity NCI Grade[b] (Value)	**During a Cycle of Therapy**	**At the Start of the Next Cycle of Therapy (After Adequate Recovery), Compared with the Starting Dose in the Previous Cyclea**	
	Weekly	**Weekly**	**Once Every 2 or 3 Week**

No toxicity	Maintain dose level	↑ 25 mg/m^2 up to a maximum dose of 150 mg/m^2	Maintain dose level
Neutropenia 1 (1500 to 1999/mm^3)	Maintain dose level	Maintain dose level	Maintain dose level
2 (1000 to 1499/mm^3)	↓ 25 mg/m^2	Maintain dose level	Maintain dose level
3 (500 to 999/mm^3)	Omit dose, then ↓ 25 mg/m^2 when resolved to ≤ Grade 2	↓ 25 mg/m^2	↓ 50 mg/m^2
4 (<500/mm^3)	Omit dose, then ↓ 50 mg/m^2 when resolved to ≤ Grade 2	↓ 50 mg/m^2	↓ 50 mg/m^2
Neutropenic fever (Grade 4 neutropenia & ≥Grade 2 fever)	Omit dose, then ↓ 50 mg/m^2 when resolved	↓ 50 mg/m^2	↓ 50 mg/m^2
Other hematologic toxicities	Dose modifications for leukopenia, thrombocytopenia, and anemia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.		
Diarrhea 1 (2-3 stools/day > pretx[c])	Maintain dose level	Maintain dose level	Maintain dose level
2 (4-6 stools/day > pretx[c])	↓ 25 mg/m^2	Maintain dose level	Maintain dose level
3 (7-9 stools/day > pretx[c])	Omit dose, then ↓ 25 mg/m^2 when resolved to ≤Grade 2	↓ 25 mg/m^2	↓ 50 mg/m^2
4 (≥ 10 stools/day > pretx[c])	Omit dose, then ↓ 50 mg/m^2 when resolved to ≤Grade 2	↓ 50 mg/m^2	↓ 50 mg/m^2
Other non-hematologic toxicities[d] 1	Maintain dose level	Maintain dose level	Maintain dose level
2	↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2

3	Omit dose, then ↓ 25 mg/m^2 when resolved to ≤Grade 2	↓ 25 mg/m^2	↓ 50 mg/m^2
4	Omit dose, then ↓ 50 mg/m^2 when resolved to ≤Grade 2	↓ 50 mg/m^2	↓ 50 mg/m^2

[a] All dose modifications should be based on the worst preceding toxicity.
[b] National Cancer Institute Common Toxicity Criteria.
[c] Pre-treatment
[d] Excludes alopecia, anorexia, asthenia.

Table 4: Recommended Dose Modifications for Irinotecan/5-Fluorouracil/Folinic Acid Combination Schedules

Patients should return to pre-treatment bowel function without requiring antidiarrhea medications for at least 24 hours before the next chemotherapy administration. A new cycle of therapy should not begin until the granulocyte count has recovered to ≥1500/mm^3, and the platelet count has recovered to ≥100,000/mm^3, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing irinotecan.

Toxicity NCI Gradeb (Value)	**During a Cycle of Therapy**	**At the Start of Subsequent Cycles of Therapy**
No toxicity	Maintain dose level	Maintain dose level
Neutropenia 1 (1500 to 1999/mm^3)	Maintain dose level[c]	Maintain dose level[c]
2 (1000 to 1499/mm^3)	↓ 1 dose level[d]	Maintain dose level
3 (500 to 999/mm^3)	Omit dose, then ↓ 1 dose level when resolved to ≤Grade 2	↓ 1 dose level[d]
4 (< 500/mm^3)	Omit dose, then ↓ 2 dose levels when resolved to ≤Grade 2[d]	↓ 2 dose levels
Neutropenic fever (Grade 4 neutropenia & ≥Grade 2 fever)	Omit dose, then ↓ 2 dose levels when resolved	↓ 2 dose levels
Other hematologic toxicities	Dose modifications for leukopenia or thrombocytopenia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	

Diarrhea 1 (2-3 stools/day > pretx[e]) 2 (4-6 stools/day > pretx) 3 (7-9 stools/day > pretx) 4 (≥ 10 stools/day > pretx)	Delay dose until resolved to baseline (bsl), then give same dose Omit dose, then ↓ 1 dose level when resolved to bsl Omit dose, then ↓ 1 dose level when resolved to bsl Omit dose, then ↓ 2 dose levels when resolved to bsl	Maintain dose level Maintain dose level ↓ 1 dose level ↓ 2 dose levels
Other non-hematologic Toxicities[f] 1 2 3 4	Maintain dose level Omit dose, then ↓ 1 dose level when resolved to ≤Grade 1 Omit dose, then ↓ 1 dose level when resolved to ≤Grade 2 Omit dose, then ↓ 2 dose levels when resolved to ≤Grade 2 *For mucositis/stomatitis decrease only 5-FU, not irinotecan.[g]*	Maintain dose level Maintain dose level ↓ 1 dose level ↓ 2 dose levels *For mucositis/stomatitis decrease only 5-FU, not irinotecan.[g]*

[a] Dose modification refers to irinotecan and 5-FU; LV dose remains fixed at 20 mg/m2 (not adjusted).
[b]National Cancer Institute Common Toxicity Criteria.
[c]Refers to initial dose used in previous cycle.
[d]Irinotecan: dose level reductions = 25 mg/m2 decrements; 5-Fluorouracil: dose level reductions = 100 mg/m2 decrements.
[e]Pre-treatment
[f] Excludes alopecia, anorexia, asthenia.
[g] For mucositis/stomatitis decrease only 5-FU, not irinotecan.

Caution For Usage
Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product:

Preparation: Irinotecan must be diluted prior to infusion in 5% dextrose injection, (preferred) or 0.9% sodium chloride injection to a final concentration range of 0.12 to 2.8 mg/mL. Irinotecan is intended for single use only and any unused portion should be discarded. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit. Inspect vial contents for particulate matter and repeat inspection when drug product is withdrawn from vial into syringe. It is recommended that in order to reduce microbiological hazard, the infusion solutions should be prepared immediately prior to use and infusion commenced as soon as practicable after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at room temperature between 15°C to 25°C and 48 hours at 2°C to 8°C when diluted with 5% dextrose injection, and not longer than 24 hours when diluted with 0.9% sodium chloride injection at room temperature

between 15°C to 25°C.

Handling: As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions prepared from irinotecan. The use of gloves is recommended. If irinotecan contacts the skin, wash the skin immediately and thoroughly with soap and water. If irinotecan contacts the mucous membranes, flush thoroughly with water.

Incompatibilities: Other drugs should not be added to the infusion solution.

CONTRAINDICATIONS

Irinotecan Injection is contraindicated in patients with a known hypersensitivity to the drug or its excipients.

WARNINGS AND PRECAUTIONS

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

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

• in patients presenting a risk factor, particularly those with a WHO performance status = 2.

• in the few rare instances where patients are deemed unlikely to observe recommendations regarding management of adverse events (need for immediate and prolonged antidiarrhoeal treatment combined with high fluid intake at onset of delayed diarrhoea). Strict hospital supervision is recommended for such patients.

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

Delayed diarrhoea

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

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

As soon as the first liquid stool occurs, the patient should start drinking large volumes of beverages containing electrolytes and an appropriate antidiarrhoeal therapy must be initiated immediately. This antidiarrhoeal treatment will be prescribed by the department where Irinotecan has been administered. After discharge from the hospital, the patients should obtain the prescribed drugs so that they can treat the diarrhoea as soon as it occurs. In addition, they must inform their physician or the department administering Irinotecan when/if diarrhoea is occurring.

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

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

Haematology

Neutropenia has been significantly higher in patients who received previous pelvic/abdominal irradiation than in those who had not received such irradiation. Patients with baseline serum total bilirubin levels of 1.0 mg/dL or more have also had a significantly greater likelihood of neutropenia than those with bilirubin levels that were less than 1.0 mg/dL.

Weekly monitoring of complete blood cell counts is recommended during Irinotecan treatment. Patients should be aware of the risk of neutropenia and the significance of fever. Febrile neutropenia (temperature > 38°C and neutrophil count ≤ 1,000 cells/mm3) should be urgently treated in the hospital with broad-spectrum intravenous antibiotics.

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

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 Pharmacokinetic) and thus increasing the risk of hematotoxicity in this population. For patients with a bilirubin > 3 times ULN.

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 signs and symptoms such as sweating, abdominal cramping, myosis and salivation), atropine sulphate (0.25 mg subcutaneously) should be administered unless clinically contraindicated (see section Adverse effect).

These symptoms may be observed during or shortly after infusion of irinotecan, are thought to be related to the anticholinesterase activity of the irinotecan parent compound, and are expected to occur more frequently with higher irinotecan doses.

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.

Extravasation

While irinotecan is not a known vesicant, care should be taken to avoid extravasation and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site and application of ice is recommended.

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 recommended dosage).

Chronic inflammatory bowel disease and/or bowel obstruction

Patients must not be treated with Irinotecan until resolution of the bowel obstruction.

Renal function

Increases in serum creatinine or blood urea nitrogen have been observed. There have been cases of acute renal failure. These events have generally been attributed to complications of infection or to dehydration related to nausea, vomiting, or diarrhoea. Rare instances of renal dysfunction due to tumour lysis syndrome have also been reported.

Irradiation therapy

Patients who have previously received pelvic/abdominal irradiation are at increased risk of myelosuppression following the administration of irinotecan. Physicians should use caution in

treating patients with extensive prior irradiation (e.g.>25% of bone marrow irradiated and within 6 weeks prior to start of treatment with irinotecan). Dosing adjustment may apply to this population (see section Recommended dosage).

Cardiac disorders

Myocardial ischaemic events have been observed following irinotecan therapy predominately in patients with underlying cardiac disease, other known risk factors for cardiac disease, or previous cytotoxic chemotherapy (see section Adverse effects).

Consequently, patients with known risk factors should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Vascular disorders

Irinotecan has been rarely associated with thromboembolic events (pulmonary embolism, venous thrombosis, and arterial thromboembolism) in patients presenting with multiple risk factors in addition to the underlying neoplasm.

Immunosuppressant effects/increased susceptibility to infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including irinotecan, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving irinotecan. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Others

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

Infrequent cases of renal insufficiency, hypotension or circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis.

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

Concomitant administration of irinotecan with a strong inhibitor (e.g. ketoconazole) or inducer (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, St John's Wort) of CYP3A4 may alter the metabolism of irinotecan and should be avoided (see section Interaction with other medicaments).

INTERACTION WITH OTHER MEDICAMENTS

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.

Concomitant administration of CYP3A-inducing anticonvulsant drugs (e.g., carbamazepine, phenobarbital or phenytoin) leads to reduced exposure to irinotecan, SN-38 and SN-38 glucuronide and reduced pharmacodynamic effects. The effects of such anticonvulsant drugs was

reflected by a decrease in AUC of SN-38 and SN-38G. 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.
Co-administration of ketoconazole resulted in a decrease in the AUC of APC and in an increase in the AUC of SN-38.
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 Warning and precautions).
St. John's Wort decreases SN-38 plasma levels. As a result, St. John's Wort should not be administered with irinotecan (see section Contraindication).
Coadministration of 5-fluorouracil/folinic acid in the combination regimen does not change the pharmacokinetics of irinotecan.
Atazanavir sulphate. Coadministration of atazanavir sulfate, a CYP3A4 and UGT1A1 inhibitor, has the potential to increase systemic exposure to SN-38, the active metabolite of irinotecan. Physicians should take this into consideration when co-administering these drugs.

Interactions common to all cytotoxics:
The use of anticoagulants is common due to increased risk of thrombotic events in tumoral diseases. If vitamin K antagonist anticoagulants are indicated, an increased frequency in the monitoring of INR (International Normalised Ratio) is required due to their narrow therapeutic index, the high intra-individual variability of blood thrombogenicity and the possibility of interaction between oral anticoagulants and anticancer chemotherapy.

Concomitant use contraindicated
- Yellow fever vaccine: risk of fatal generalised reaction to vaccines

Concomitant use not recommended
- Live attenuated vaccines (except yellow fever): risk of systemic, possible fatal disease (eg- infections). This risk is increased in subjects who are already immunosuppressed by their underlying disease.
Use an inactivated vaccine where this exists (poliomyelitis)
- Phenytoin: Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug or risk of toxicity enhancement due to increased hepatic metabolism by phenytoin

Concomitant use to take into consideration
- Ciclosporine, Tacrolimus: Excessive immunosuppression with risk of lymphoproliferation
There is no evidence that the safety profile of irinotecan is influenced by cetuximab or *vice versa*.

PREGNANCY AND LACTATION
Women of child-bearing potential/ Contraception in males and females

Women of childbearing potential and men have to use effective contraception during and up to 1 month and 3 months after treatment respectively.

Pregnancy

There is no data from the use of irinotecan in pregnant women. Irinotecan has been shown to be embryotoxic and teratogenic in animals. Therefore, based on results from animal studies and the

mechanism of action of irinotecan, Irinotecan should not be used during pregnancy unless clearly necessary.

Breast-feeding

In lactating rats, 14C-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 should be discontinued for the duration of Irinotecan therapy.

ADVERSE REACTIONS

The most common, dose-limiting adverse reactions of irinotecan are delayed diarrhoea (occurring more than 24 hours after administration) and blood disorders including neutropenia, anaemia and thrombocytopenia.

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.

Very commonly severe transient acute cholinergic syndrome was observed.

The main symptoms were defined as early diarrhoea and various other symptoms such as abdominal pain, sweating, myosis and increased salivation occurring during or within the first 24 hours after the infusion of Irinotecan. These symptoms disappear after atropine administration (see section Warning and precautions).

MONOTHERAPY

The following adverse reactions considered to be possibly or probably related to the administration of Irinotecan at the recommended dose of 350 mg/m^2 in monotherapy. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common, common, uncommon, rare, and very rare.

Adverse Reactions Reported with Irinotecan in Monotherapy (350 mg/m^2 every 3 weeks schedule)		
MedDRA System Organ Class	**Frequency Category**	**Preferred Term**
Infections and infestations	Common	Infection
Blood and lymphatic system disorders	Very common	Neutropenia
	Very common	Anaemia
	Common	Thrombocytopenia
	Common	Febrile neutropenia
Metabolism and nutrition disorders	Very common	Decreased appetite
Nervous system disorders	Very common	Cholinergic syndrome
Gastrointestinal disorders	Very common	Diarrhoea
	Very common	Vomiting
	Very common	Nausea
	Very common	Abdominal pain
	Common	Constipation
Skin and subcutaneous tissue disorders	Very common	Alopecia (reversible)
General disorders and administration site conditions	Very common	Mucosal inflammation
	Very common	Pyrexia
	Very common	Asthenia
Investigations	Common	Blood creatinine increased

	Common	Transaminases (SGPT and SGOT) increased
	Common	Bilirubin increased
	Common	Blood alkaline phosphatase increased

COMBINATION THERAPY

Adverse reactions 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 adverse reactions were those expected with cetuximab (such as acneform rash). For information on adverse reactions on irinotecan in combination with cetuximab , also refer to their respective summary of product characteristics.

Adverse drug reactions reported in patients treated with capecitabine in combination with irinotecan in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy include: *Very common, all grade adverse drug reactions*: thrombosis/embolism; *Common, all grade adverse drug reactions:*hypersensitivity reaction, cardiac ischemia/infarction; *Common, grade 3 and grade 4 adverse drug reactions*: febrile neutropenia. For complete information on adverse reactions of capecitabine, refer to the capecitabine summary product of characteristics.

Grade 3 and Grade 4 adverse drug reactions reported in patients treated with capecitabine in combination with irinotecan and bevacizumab in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy include: *Common, grade 3 and grade 4 adverse drug reactions:* neutropenia, thrombosis/embolism, hypertension, and cardiac ischemia/infarction. For complete information on adverse reactions of capecitabine and bevacizumab, refer to the respective capecitabine and bevacizumab summary of product characteristics.

Grade 3 hypertension was the principal significant risk involved with the addition of bevacizumab to bolus Irinotecan/5-FU/FA. In addition, there was a small increase in the grade 3/4 chemotherapy adverse events of diarrhoea and leukopenia with this regimen compared to patients receiving bolus Irinotecan/5-FU/FA alone. For other information on adverse reactions in combination with bevacizumab, refer to the bevacizumab summary of product characteristics.
Irinotecan has been studied in combination with 5-FU and FA for metastatic colorectal cancer.
Safety data of adverse reactions very commonly observed in the blood and the lymphatic system disorders, gastrointestinal disorders, and skin and subcutaneous tissue disorders MedDRA System Organ Classes.
The following adverse reactions considered to be possibly or probably related to the administration of Irinotecan have been reported in combination therapy with 5FU/FA in every 2 weeks schedule at the recommended dose of 180 mg/m^2.

Adverse Reactions Reported with Irinotecan in Combination Therapy (180 mg/m^2 every 2 weeks schedule)		
MedDRA System Organ Class	**Frequency Category**	**Preferred Term**
Infections and infestations	Common	Infection
Blood and lymphatic system disorders	Very common	Thrombocytopenia
	Very common	Neutropenia
	Very common	Anaemia
	Common	Febrile neutropenia

Metabolism and nutrition disorders	Very common	Decreased appetite
Nervous system disorders	Very common	Cholinergic syndrome
Gastrointestinal disorders	Very common	Diarrhoea
	Very common	Vomiting
	Very common	Nausea
	Common	Abdominal pain
	Common	Constipation
Skin and subcutaneous tissue disorders	Very common	Alopecia (reversible)
General disorders and administration site conditions	Very common	Mucosal inflammation
	Very common	Asthenia
	Common	Pyrexia
Investigations	Very common	Transaminases (SGPT and SGOT) increased
	Very common	Bilirubin increased
	Very common	Blood alkaline phosphatase increased

OVERDOSAGE
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 diarrhea. There is no known antidote for overdosage of Irinotecan. Maximum supportive care should be instituted to prevent dehydration due to diarrhea and to treat any infectious complications.

STORAGE AND SHELF LIFE
Before dilution: store below 30°C

After dilution:
Store at room temperature between 15°C to 25°C up to 24 hours and at 2-8°C up to 48 hours when diluted with 5% Dextrose injection at concentration 0.12mg/ml and 2.8mg/ml.
Store at room temperature between 15°C to 25°C up to 24 hours when diluted with 0.9% Sodium chloride injection at concentration 0.12mg/ml and 2.8mg/ml.

PRESENTATION
Single-dose amber glass vials of 2 ml and 5 ml.

Manufactured by :
Emcure Pharmaceutical Limited (Plant-III),
Plot No. P-1 & P-2, I.T- B.T. Park, Phase II,
MIDC, Hinjawadi, Pune –411057 INDIA.

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