Applicant : Eurolab (Pty) Ltd
Proprietary name : Irinotas & Irinotas 100
Dosage form and strength : Solution for infusion 40 mg & 100 mg
Date of submission : 22 November 2024
Approval date : 11 February 2025

APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: **S4**

1 NAME OF THE MEDICINE

IRINOTAS 40 mg/2 mL (Solution for Infusion)

IRINOTAS 100 mg/5 mL (Solution for Infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Single-dose vials containing 40 mg or 100 mg Irinotecan hydrochloride trihydrate.

Each 1 mL contains 20 mg Irinotecan hydrochloride trihydrate.

Excipients with known effect:

Each 1 mL contains 45 mg sorbitol

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for Infusion

A pale yellow, clear solution, free from particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

IRINOTAS 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.

4.2 Posology and method of administration

Recommended Dosage:

In monotherapy (for previously treated patients):

The recommended dosage of IRINOTAS 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 IRINOTAS in combination with 5-fluorouracil (5FU) and folinic acid (FA) have been assessed with either of the following schedules:

- **IRINOTAS plus 5FU/FA in weekly schedule:**

The recommended dose of IRINOTAS 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 rest.

The full dosage regimen is as follows:

IRINOTAS 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 i.v. as a 2-hour infusion, followed by 5-fluorouracil 2000 mg/m^2 i.v. as a 24- hour infusion, on Day 1 and then weekly for 6 weeks. The treatment is to be repeated every 7 weeks.

- **IRINOTAS plus 5FU/FA in every 2 weeks schedule:**

The recommended dose of IRINOTAS 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:

IRINOTAS 180 mg/m^2 i.v as a 30 to 90 minute infusion on Day 1 only. Folinic acid 200 mg/m^2 i.v. as a 2-hour infusion, followed by 5-fluorouracil 400 mg/m^2 i.v. bolus, followed by 5-fluorouracil 600 mg/m^2 i.v. as a 22-hour infusion. The folinic acid and 5-fluorouracil are repeated for two consecutive days.

Repeat the cycle every two weeks.

Dosage Adjustments:

Delayed Dosing:

IRINOTAS should not be administered until the neutrophil count remains above 1 500 cells/mm^3. In patients who experienced severe neutropenia or severe gastrointestinal adverse events such as diarrhoea, nausea and vomiting, dosing of IRINOTAS should be delayed until there has been a full recovery of these effects, especially diarrhoea. IRINOTAS 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 IRINOTAS, 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 IRINOTAS 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 (grade 3-4).

Treatment Duration:

Treatment with IRINOTAS 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 IRINOTAS. In patients with a bilirubin ≤ 1,5 times the upper limit of the normal range (ULN), a dose of 350 mg/m^2 IRINOTAS 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 hepatic, renal, or cardiac function.

4.3 Contraindications

- History of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate or to any of the excipients of the formulation**.**
- Chronic inflammatory bowel disease, and/or bowel obstruction or ileus. Patients should not be treated with IRINOTAS until resolution of the ileus.
- Pregnancy and lactation. Women of childbearing age receiving IRINOTAS should be advised to avoid becoming pregnant and to inform the treating physician immediately should this occur.
- Bilirubin > 1.5 times the upper limit of the normal range.
- The safety and efficacy of IRINOTAS in children has not been established.
- Severe bone marrow failure.
- WHO performance status > 2.
- Concomitant administration of azole antifungals, St. John's Wort.

4.4 Special warnings and precautions for use

IRINOTAS should be used in patients with a good performance status of less than 2.

The use of IRINOTAS 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 IRINOTAS be administered only in healthcare institutions with adequately equipped facilities, including an intensive care unit. In all instances where the use of IRINOTAS is considered for chemotherapy, it is especially important to ensure that the patient understands the need for sufficiently prolonged anti-diarrhoeal 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 treating physician 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 IRINOTAS, patients should be aware of the high risk of delayed diarrhoea occurring more than 24 hours after the administration of IRINOTAS 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 IRINOTAS.

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 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 anti-diarrhoeal therapy must be initiated immediately. The anti-diarrhoeal treatment must be prescribed by the department where IRINOTAS 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 IRINOTAS that diarrhoea is occurring. The currently recommended anti-diarrhoeal 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 anti-diarrhoeal treatment, a prophylactic broad spectrum antibiotic should be given when diarrhoea is associated with severe neutropenia (neutrophil count <500 cells/mm^3). In addition to the antibiotic treatment, hospitalisation is recommended for management of the diarrhoea in the following cases:

- Diarrhoea associated with fever,
- Severe diarrhoea (requiring intravenous hydration),
- Diarrhoea persisting beyond 48 hours following the initiation of high-dose loperamide therapy.

Loperamide should not be given prophylactically, even in patients who experienced delayed diarrhoea at previous cycles. In patients who experienced severe diarrhoea, a reduction in dose is recommended for subsequent cycles.

Haematology:

Weekly monitoring of complete blood cell counts should be performed during IRINOTAS treatment. Patients should be aware of the risk of infection and the significance of a fever. Febrile neutropenia (temperature ≥ 38 °C and neutrophil count ≤ 1000 cells/mm^3) should be urgently treated in the hospital with broad-spectrum intravenous antibiotics. IRINOTAS administration should 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 IRINOTAS should be reduced. In patients who experienced 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. IRINOTAS 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 IRINOTAS. 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, lachrymation, myosis and salivation), atropine sulphate (0,25 mg subcutaneously) should be administered unless clinically contraindicated. 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 IRINOTAS.

Immunosuppressant effects/increased susceptibility to infections:

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

Elderly:

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

Others:

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

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic parameters of IRINOTAS 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.

Antineoplastic agents: The adverse effects of IRINOTAS such as myelosuppression and diarrhoea, is expected to be exacerbated by other antineoplastic agents having a similar adverse-effect profile.

Dexamethasone: Lymphocytopenia has been reported in patients receiving Irinotecan, and it is possible that the administration of dexamethasone as antiemetic prophylaxis may have enhanced the likelihood of lymphocytopenia. Hyperglycaemia has been observed in patients with a history of diabetes mellitus or evidence of glucose intolerance prior to administration of Irinotecan. It is probable that dexamethasone, given as antiemetic prophylaxis, contributed to hyperglycaemia in some patients.

Laxatives: Laxative use during therapy with IRINOTAS is expected to worsen the incidence or severity of diarrhoea.

Diuretics: Dehydration secondary to vomiting and/or diarrhoea may be induced by IRINOTAS. The medical practitioner may wish to withhold diuretics during dosing with IRINOTAS and during periods of active vomiting or diarrhoea.

Anticonvulsants: Concomitant administration of CYP3A enzyme-inducing anticonvulsant medicines (e.g. carbamazepine, phenobarbital or phenytoin) leads to reduced exposure to the active metabolite SN-38.
Consideration should be given to starting or substituting non-enzyme inducing anticonvulsants at least one week prior to initiation of IRINOTAS therapy in patients requiring anticonvulsant treatment.

Azole antifungals: IRINOTAS clearance is greatly reduced in patients receiving concomitant azole antifungals, leading to increased exposure to the active metabolite, SN-38. Azole antifungals should be discontinued at least 1 week prior to starting IRINOTAS therapy and should not be administered during IRINOTAS therapy (see section 4.3).

St. John's Wort (Hypericum perforatum): Exposure to the active metabolite of IRINOTAS is reduced in patients taking concomitant St. John's Wort. St. John's Wort should be discontinued at least 1 week prior to the first cycle of IRINOTAS, and should not be administered during IRINOTAS therapy (see Section 4.3).

Atazanavir sulphate: Coadministration of atazanavir sulphate, a CYP3A4 and UGT1A1 inhibitor has the potential to increase systemic exposure to SN-38, the active metabolite of IRINOTAS.
Atazanavir should not be used with IRINOTAS.

Bevacizumab: In one study, irinotecan plasma 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. 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Male patients treated with IRINOTAS should be advised to use highly effective contraception, until the end of relevant systemic exposure to the genotoxic compound including potential genotoxic metabolites plus an additional 3 months after exposure (i.e. five half-lives after the last dose, plus 60-75 days for sperm production plus 10-14 days for the transport to epididymis).

Female patients and female sexual partners of male patients receiving IRINOTAS, should be advised to avoid becoming pregnant and to use highly effective contraception, until the end of relevant systemic exposure to the genotoxic compound including potential genotoxic metabolites plus an additional 6 months after exposure (i.e. five half-lives after the last dose) plus 6 months (which covers the growth and maturation phase of folliculogenesis).

Pregnancy and lactation

The use of IRINOTAS during pregnancy and lactation is not recommended as safety and efficacy have not been established (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, and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

Side effects have been reported but frequencies are unknown:

The intensity of the major toxicities encountered with IRINOTAS (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 IRINOTAS:

Blood and lymphatic system disorders

Frequent: Leukopenia, neutropenia is a dose-limiting toxic effect.

Anaemia, thrombocytopenia.

Immune system disorders

Frequency unknown: Chills, malaise.

Nervous system disorders

Less frequent: Dizziness, abnormal gait, confusion, headache.

Eye disorders

Less frequent: Myosis, lachrymation and increased salivation occurring during or within the first 24 hours after the infusion of IRINOTAS. These symptoms disappear after atropine administration.

Frequency unknown: Visual disturbances, conjunctivitis

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea (difficulty in breathing)

Less frequent: Rhinitis

Gastrointestinal disorders

Frequent: Nausea, vomiting, diarrhoea, dehydration, constipation, intestinal obstruction, ileus, or gastrointestinal haemorrhage, intestinal perforation, transient increase in amylase and lipase has been reported.

Other mild effects include anorexia, abdominal pain and mucositis.

Less frequent: Rectal disorder, GI monilia, uncommon cases of pseudo-membranous colitis have been reported, one of which has been documented bacteriologically (*Clostridium difficile*).

Metabolism and nutrition disorders

Frequent: Decreased weight, dehydration, hypovolaemia

Less frequent: hypokalaemia, hypomagnesaemia

Musculoskeletal system disorders:

Frequency unknown: Abdominal pain, aesthenia, muscular contraction or cramps and paraesthesia

Cardiovascular system disorders:

Frequent: venous and arterial thromboembolic events which includes– angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep vein thrombophlebitis, heart arrest, myocardial infarct, embolus, sudden death, thrombophlebitis, thrombosis, vascular disorder

Less frequent: Hypotension, flushing, syncope, bradycardia

Frequency unknown: vasodilation and cardio-circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis.

Skin and subcutaneous tissue disorders:

Frequent: Alopecia

Less frequent: rash, cutaneous signs such as dry skin, pruritus, skin discolouration

Frequency unknown: Sweating

Infections and infestations

Frequent: Infection

Less frequent: Sepsis

Hepatobiliary disorders

Frequent: Hyperbilirubinaemia

Endocrine disorders

Less frequent: diaphoresis, increased salivation

Hypersensitivity reactions:

Less frequent: Rhinitis

Frequency unknown: Conjunctivitis, rhinitis, mild cutaneous reactions, allergy and infusion site reactions have been reported.

Reproductive system and breast disorders

Less frequent: breast pain

Renal system disorders:

Renal insufficiency

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

Investigations

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

Less frequent: increased serum alkaline phosphatase, increased GGTP (gamma-glutamyl transpeptidase), increase in amylase, increase in lipase

Hepatic system disorders:

Frequency unknown: 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 (grades 1 and 2) of either SGPT, SGOT, 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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website, or to Eurolab (Pty) Ltd. by email: drug-safety@eurolab.co.za. By reporting side effects, you can help provide more information on the safety of IRINOTAS.

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 diarrhoea. There is no known antidote for IRINOTAS. 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

A 26 Cytostatic agents

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

5.2 Pharmacokinetic properties

After a 30 minute-intravenous infusion of 100 to 700 mg/m^2 every 3 weeks, irinotecan showed a biphasic or tri-phasic 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/mł and 56 ng/mł, respectively and were reached at the end of the infusion. The mean area under the curve (AUC) values were 34 µg.h/mł and 451 ng.h/mł, 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 14C-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 aminopentanoic 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 bilirubinaemia 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. (International System of Units)

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactic acid

Sorbitol

Sodium hydroxide

Hydrochloric acid 37 %

Water for injection

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

36 months

6.4. Special precautions for storage

Single-dose vials of **IRINOTAS** solution for infusion should be stored at or below 25 °C and protected from light.

After dilution in either 0,9 % sodium chloride or 5 % dextrose, the diluted solution is stable for 24 hours at a temperature below 25 ºC or 4 days under refrigeration (2-8 ºC). Discard any unused portion thereafter. Do not freeze.

6.5 Nature and contents of container

IRINOTAS 40: Carton containing one single-dose 2 ml~~l~~L USP type 1 amber tubular glass vial, with a grey rubber stopper and an orange flip-off aluminium seal. (International System of Units)

IRINOTAS 100: Carton containing one single-dose 5 ml~~l~~L USP type 1 amber tubular glass vial, with a grey rubber stopper and an orange or red flip-off aluminium seal. (International System of Units)

6.6 Special precautions for disposal and other handling

Preparation for the intravenous infusion administration:

Aseptically withdraw the required amount of IRINOTAS solution from the vial with a calibrated syringe and inject into a 250 mL infusion bag or bottle containing either 0,9 % sodium chloride solution or 5 % dextrose solution. The infusion should then be thoroughly mixed by manual rotation. IRINOTAS infusion solution should be infused into a peripheral or central vein. IRINOTAS 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.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd.

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8 REGISTRATION NUMBER

IRINOTAS 40: 41/26/1004

IRINOTAS 100: 44/26/0025

9 DATE OF FIRST AUTHORISATION

IRINOTAS 40: 17 April 2009

IRINOTAS 100: 12 June 2009

10 DATE OF REVISION OF THE TEXT

11 February 2025