

SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM):

CIPLA-IRINOTECAN 40 mg/2 ml

(solution for infusion).

CIPLA-IRINOTECAN 100 mg/5 ml

(solution for infusion).

COMPOSITION:

CIPLA-IRINOTECAN 40 mg/2 ml: Each 1 millilitre contains 20 mg irinotecan hydrochloride trihydrate.

CIPLA-IRINOTECAN 100 mg/5 ml: Each 1 millilitre contains 20 mg irinotecan hydrochloride trihydrate.

Inactive ingredients include lactic acid, sodium hydroxide and sorbitol.

PHARMACOLOGICAL CLASSIFICATION:

A 26 Cytostatic agents.

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

Irinotecan, an antineoplastic agent, is a semi-synthetic derivative of camptothecin. It is a specific inhibitor of DNA topoisomerase I. In most tissues carboxylesterase metabolises irinotecan to SN-38, which was shown to be more active than irinotecan in purified topoisomerase I and which demonstrated increased cytotoxicity compared to irinotecan against several murine and human tumour cell lines.

Inhibition of DNA topoisomerase I by irinotecan or SN-38 causes single-strand DNA lesions that block the DNA replication fork and which are responsible for the cytotoxic effects. Irinotecan's cytotoxic activity was demonstrated to be time dependent and was specific to the S-phase.

In vitro test results showed that irinotecan and SN-38 were not significantly recognised by P-glycoprotein. Also, irinotecan and SN-38 demonstrated cytotoxic activities against cell lines that were resistant to doxorubicin and vinblastine.

In addition to its anti-tumour activity, the most relevant pharmacological effect of irinotecan is inhibition of acetylcholinesterase.

Pharmacokinetics:

Following a 30-minute intravenous infusion of 100 to 700 mg/m² every 3 weeks, irinotecan demonstrates a biphasic or triphasic elimination profile. Mean plasma clearance is 15 L/h/m² and at steady state the volume of distribution (Vss) is quite large, namely 157 L/m². Mean plasma half-life during the first phase of the triphasic model is 12 minutes, while it is 2.5 hours during the second phase and 14.2 hours during the terminal phase. SN-38 demonstrates a biphasic elimination profile with a mean terminal elimination half-life of 13.8 hours. At the recommended dose of 350 mg/m², the mean irinotecan peak plasma concentration is 7.7 µg/ml and that of SN-38 is 56 ng/ml, which will be reached at the end of the infusion. For irinotecan the mean area under the curve (AUC) is 34 µg.h/ml and for SN-38 it is 451 ng.h/ml. SN-38 generally demonstrates a large inter-individual variability in pharmacokinetic parameters.

In vitro test results show that plasma protein binding is approximately 65 % for irinotecan and 95 % for SN-38. Mass balance and metabolism studies with ¹⁴C-labelled agent have shown that in excess of 50 % of an intravenously administered dose of irinotecan is excreted as unchanged compound, with 33 % in the faeces via the bile and 22 % in urine. Two metabolic pathways, of which each represents at least 12 % of the dose, are recognised. Firstly, cytochrome P450 3A enzymes are responsible for oxidative metabolism at the terminal piperidine ring. This gives rise to an aminopentanoic acid derivative (APC) and primary amine derivative. Secondly, carboxylesterases perform hydrolysis that results in the active metabolite SN-38. Elimination of SN-38 is mainly through glucuronidation and further by biliary and renal excretion (less than 0.5 % of the irinotecan dose).

The major entity in plasma is unchanged irinotecan followed by APC, SN-38 glucuronide and SN-38. SN-38 is the only metabolite that possesses significant cytotoxic activity. No other circulating metabolites have been identified.

In patients with bilirubinaemia between 1,5 and 3 times the upper limit of normal, irinotecan clearance is decreased by approximately 40 %. In these patients a 200 mg/m² irinotecan dose results in plasma irinotecan exposure comparable to that seen at 350 mg/m² in cancer patients with normal liver parameters.

Concomitant administration of 5-fluorouracil/folinic acid in the combination regimen does not cause any changes in the pharmacokinetics of irinotecan.

INDICATIONS:

CIPLA-IRINOTECAN is indicated for the treatment of advanced colorectal cancer in patients with a World Health Organisation (WHO) performance status equal to or less than 2:

- In combination with 5-fluorouracil and folinic acid in patients who have not received prior chemotherapy for advanced disease.
- As a single agent in patients who have failed to respond to an established 5-fluorouracil-containing treatment regimen.

CONTRA-INDICATIONS:

CIPLA-IRINOTECAN is contra-indicated in patients:

- With a history of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate or to one of the excipients in the formulation.
- With chronic inflammatory bowel disease, and/or bowel obstruction or ileus. Patients should not receive **CIPLA-IRINOTECAN** until resolution of the ileus.
- Who are pregnant or breast feeding their infants. If **CIPLA-IRINOTECAN** is prescribed to women of childbearing age, they should be advised to avoid becoming pregnant and to immediately inform their treating doctor in the event of pregnancy.
- With bilirubin levels > 1,5 times the upper limit of normal.
- With severe bone marrow failure.
- With WHO performance status > 2.

The safety and efficacy of **CIPLA-IRINOTECAN** in children have not been established.

WARNINGS:

CIPLA-IRINOTECAN should be given to patients with a good performance status of less than 2.

CIPLA-IRINOTECAN should only be administered in units specialised in the administration of cytotoxic chemotherapy and it should only be given under the supervision of a qualified oncologist. It is strongly advised that **CIPLA-IRINOTECAN** be given only in healthcare institutions with adequately equipped facilities, including an intensive care unit.

In all instances where **CIPLA-IRINOTECAN** is considered for chemotherapy, it is extremely important to ensure that the patient fully comprehends the need for sufficiently prolonged anti-diarrhoeal treatment and abundant fluid intake. In rare instances where it is foreseen that the patient would comply poorly with the guidance for the management of side-effects, a strict follow-up of the patient by the treating doctor or hospitalisation is recommended.

Given the nature and frequency of adverse reactions, the expected benefit must be weighed against risk factors, especially WHO Performance status ≥ 2 (or Karnofsky Index < 50).

Delayed diarrhoea:

Apart from diarrhoea shortly after a **CIPLA-IRINOTECAN** infusion, patients should be informed of the high risk of delayed diarrhoea developing more than 24 hours after the administration of **CIPLA-IRINOTECAN** and at any time before the next cycle. With single agent therapy, the median time to onset of the first liquid stool was on day 5 after the **CIPLA-IRINOTECAN** infusion. Patients should promptly inform their treating doctor of its occurrence and immediately initiate appropriate therapy.

The following factors increase the risk of diarrhoea: previous abdominal/pelvic radiotherapy, baseline hyperleukocytosis and performance status ≥ 2.

If not appropriately treated, diarrhoea can be life-threatening, especially in the presence of concomitant neutropenia. The moment the first liquid stool occurs, the patient should begin drinking large volumes of beverages containing electrolytes and a suitable anti-diarrhoeal therapy must be started immediately.

The department administering **CIPLA-IRINOTECAN** must prescribe the anti-diarrhoeal treatment regime. Following discharge from hospital, patients should obtain the prescribed medicines to enable them to treat the diarrhoea as soon as it develops. In addition, they must inform their treating doctor or the department where they receive **CIPLA-IRINOTECAN** that they have diarrhoea. The currently recommended anti-diarrhoeal regime is 4 mg loperamide initially and then 2 mg every 2 hours. This treatment should be maintained for 12 hours after the last liquid stool and should not be modified. Under no circumstances should loperamide be administered for more than 48 consecutive hours at these dosages, due to the risk of paralytic ileus, nor should it be taken for less than 12 hours.

When diarrhoea is associated with severe neutropenia (neutrophil count < 500 cells/mm³), a prophylactic broad-spectrum antibiotic should be administered in addition to the anti-diarrhoeal treatment.

Hospitalisation, in addition to antibiotic therapy, is advised for the management of diarrhoea in the following instances:

- Diarrhoea associated with fever.
- Severe diarrhoea (requiring hydration with intravenous fluids).
- Diarrhoea continuing beyond 48 hours after the initiation of high-dose loperamide therapy.

Loperamide should not be administered prophylactically, even in patients who developed delayed diarrhoea during previous cycles. In patients who suffered severe diarrhoea, a dose reduction is advised for subsequent cycles.

Haematology:

Complete blood cell counts should be monitored weekly during treatment with **CIPLA-IRINOTECAN**. Patients should be informed of the risk of infection and the significance of a fever. Febrile neutropenia (temperature ≥ 38 °C and neutrophil count ≤ 1000 cells/mm³) requires urgent treatment with broad-spectrum intravenous antibiotics in hospital. Treatment with **CIPLA-IRINOTECAN** should be delayed until the neutrophil count is ≥ 1500 cells/mm³.

The **CIPLA-IRINOTECAN** dose should be reduced in patients who develop severe asymptomatic neutropenia (< 500 cells/mm³), fever or infections associated with neutropenia. In patients who develop severe haematological events, a dose reduction is advised for subsequent administration. Patients with severe diarrhoea have an increased risk of infections and haematological toxicity.

Liver impairment:

Liver function tests are required at baseline and prior to each cycle.

Patients with impaired liver function [bilirubin > 1,0 and ≤ 1,5 times the upper limit of normal (ULN) and transaminases 5 times ULN] have an increased risk of developing severe neutropenia or febrile neutropenia and require close monitoring. **CIPLA-IRINOTECAN** should not be given to patients with a bilirubin 1,5 times ULN and patients with bilirubin > ULN should be followed with caution.

Nausea and vomiting:

Prophylactic treatment with an anti-emetic is advised prior to each **CIPLA-IRINOTECAN** administration. Nausea and vomiting occur frequently. Patients who develop vomiting in association with delayed diarrhoea should be hospitalised as soon as possible for treatment.

Acute cholinergic syndrome:

If an acute cholinergic syndrome develops (defined as early diarrhoea and a cluster 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 is required in patients with asthma. In patients who developed an acute cholinergic syndrome, the use of prophylactic atropine sulphate is advised with subsequent doses of **CIPLA-IRINOTECAN**.

Elderly:

Due to the greater frequency of impaired hepatic, renal or cardiac function in the elderly, careful dose selection with **CIPLA-IRINOTECAN** is required in this population.

Effects on ability to drive and use machines:

CIPLA-IRINOTECAN may cause dizziness or visual disturbances and patients should be warned about such possibilities. They should be advised not to drive or operate machinery if these side-effects occur.

Others:

Contraceptive measures are required during and for at least three months after cessation of therapy.

INTERACTIONS:

Pharmacokinetic parameters of **CIPLA-IRINOTECAN** administered in combination with 5-fluorouracil-folinic acid are comparable to those observed during monotherapy.

It is not possible to rule out interactions between irinotecan and neuromuscular blocking agents. Medicines which possess anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and may antagonise the neuromuscular blockade of non-depolarising agents.

Loperamide should not be administered prophylactically.

PREGNANCY AND LACTATION:

The use of **CIPLA-IRINOTECAN** during pregnancy and lactation is not recommended as safety and efficacy have not been established (see "**CONTRA-INDICATIONS**").

DOSAGE AND DIRECTIONS FOR USE:

Recommended dosage:

In monotherapy (for previously treated patients):

The recommended dosage of **CIPLA-IRINOTECAN** is 350 mg/m² given as an intravenous infusion over 30 to 90 minutes every three weeks.

In combination therapy (for previously untreated patients):

Safety and efficacy of **CIPLA-IRINOTECAN** administered in combination with 5-fluorouracil (5FU) and folinic acid (FA) have been evaluated with either of the following schedules:

• CIPLA-IRINOTECAN plus 5FU/FA in weekly schedule:

The recommended dose of **CIPLA-IRINOTECAN** is 80 mg/m² given as a weekly intravenous infusion over 30 to 90 minutes, followed by infusion with folinic acid and then by 5-fluorouracil over 6 weeks. Following this the patient is given a week's rest. The full dosage regimen is as follows:

- **CIPLA-IRINOTECAN** 80 mg/m² given over 30 to 90 minutes on day 1 and then weekly for 6 weeks.
- Folinic acid 500 mg/m² as a 2-hour intravenous infusion, followed by 5-fluorouracil 2000 mg/m² as a 24-hour intravenous infusion on day 1 and then weekly for 6 weeks. The treatment should be repeated every 7 weeks.

• CIPLA-IRINOTECAN plus 5FU/FA in every 2 weeks schedule:

The recommended dose of **CIPLA-IRINOTECAN** is 180 mg/m² given once every 2 weeks as an intravenous infusion over 30 to 90 minutes, followed by infusion with folinic acid and 5-fluorouracil.

The full dosage regimen is as follows:

- **CIPLA-IRINOTECAN** 180 mg/m² over 30 to 90 minutes as an intravenous infusion on day 1 only.
- Folinic acid 200 mg/m² as a 2-hour intravenous infusion, followed by 5-fluorouracil 400 mg/m² intravenous bolus, followed by 5-fluorouracil 600 mg/m² as an intravenous infusion over 22 hours. The folinic acid and 5-fluorouracil are repeated for two successive days.

The cycle is repeated every two weeks.

Dosage adjustments:

Delayed dosing:

Patients should not receive **CIPLA-IRINOTECAN** until the neutrophil count remains above 1500 cells/mm³. In patients who develop severe neutropenia or severe gastrointestinal adverse reactions, such as diarrhoea, nausea and vomiting, dosing of **CIPLA-IRINOTECAN** should be postponed until there has been a full recovery of these events, especially diarrhoea.

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

At the onset of a subsequent infusion, the dose of **CIPLA-IRINOTECAN** and 5FU, when applicable, should be reduced according to the worst grade of adverse events observed during the preceding infusion. Treatment should be postponed with 1 to 2 weeks to allow recovery from treatment-related adverse effects.

With the emergence of the following adverse events a dose reduction of 15 to 20 % is required for **CIPLA-IRINOTECAN** and/or 5FU when applicable:

- Haematological toxicity [neutropenia grade 4, febrile neutropenia (neutropenia grade 3 – 4 and fever grade 2 – 4), thrombocytopenia and leucopenia (grade 4)].
- Non-haematological toxicity (grade 3 – 4).

Treatment duration:

Therapy with **CIPLA-IRINOTECAN** should be maintained until there is an objective progression of the disease or an unacceptable toxicity.

Special populations:

Patients with impaired liver function:

Patients with bilirubin > 1,5 times ULN should not receive **CIPLA-IRINOTECAN**. In patients with bilirubin ≤ 1,5 times ULN, a dose of 350 mg/m² **CIPLA-IRINOTECAN** is advised. Patients with bilirubin > 1 and ≤ 1,5 times ULN have an increased risk of severe neutropenia. Thus complete blood counts should be frequently monitored in this patient population.

Patients with impaired renal function:

No specific pharmacokinetic studies have been conducted in patients with impaired renal function.

Elderly:

No specific pharmacokinetic studies have been conducted in elderly individuals. However, the dose should be chosen carefully in this population due to the greater frequency of liver, kidney or cardiac dysfunction.

Preparation for the intravenous infusion administration:

Use a calibrated syringe to aseptically withdraw the required amount of **CIPLA-IRINOTECAN** solution from the vial and inject into a 250 ml infusion bag or bottle containing 0,9 % sodium chloride solution or, alternatively, 5 % dextrose solution. Mix the infusion thoroughly by rotating it manually.

CIPLA-IRINOTECAN infusion solution should be administered into a peripheral or central vein.

CIPLA-IRINOTECAN should not be administered as an intravenous bolus or infused over a period shorter than 30 minutes or longer than 90 minutes.

If any precipitate is noted in the vials, the product should be disposed of according to standard procedures for cytotoxic agents.

Do not admix with other medicines.

Recommendations for safe handling:

Handling precautions for cytostatic medicines should be followed:

- Only trained staff should reconstitute the medicine in a designated area.
- **CIPLA-IRINOTECAN** is an antineoplastic agent and, similar to other potentially toxic compounds, caution is required when handling and preparing **CIPLA-IRINOTECAN** solutions.
- Disposable plastic-backed absorbent paper should be placed over the work surface.
- It is necessary to wear adequate protective gloves and clothing.
- If **CIPLA-IRINOTECAN** solution or infusion solution should come into contact with the skin, use soap and water to wash immediately and thoroughly. If **CIPLA-IRINOTECAN** solution or infusion solution should come into contact with the eyes or mucous membranes, use water to wash immediately and thoroughly.
- Pregnant staff should not handle the cytotoxic preparation.
- Adequate care and precautions are required in the disposal of items used to reconstitute this medicine.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-Effects:

The intensity of the major toxicities due to **CIPLA-IRINOTECAN** (e.g. leucopenutropenia and diarrhoea) is related to the exposure (AUC) to the parent compound and metabolite SN-38. Significant correlations were found between haematological toxicity (decrease in white blood cell counts and neutrophil counts 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 **CIPLA-IRINOTECAN**:

Blood and lymphatic system disorders:

Frequent: Neutropenia (a dose-limiting toxic effect), anaemia, thrombocytopenia, leukopenia, and neutropenic infection.

Less frequent: Haemorrhage and neutropenic fever.

Immune system disorders:

Frequent: Chills, fever, and infection.

The following side-effects have been reported and frequencies are unknown: Malaise.

Neuropsychiatric disorders:

Frequent: Dizziness, headache, insomnia, somnolence, syncope, and vertigo.

Less frequent: Confusion.

Eye disorders:

The following side-effects have been reported and frequencies are unknown:

Visual disturbances, myosis, lacrimation and increased salivation occurring during or within the first 24 hours after the infusion of **CIPLA-IRINOTECAN**. These symptoms disappear after atropine administration.

Cardiovascular disorders:

Frequent: Hypotension, vasodilation and cardio-circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis. Also mechanical cardiac dysfunction, dysrhythmias, oedema, ischaemia, thrombo-embolic events, including angina pectoris, arterial thrombosis, cerebral infarction, cerebrovascular accident, deep thrombophlebitis, heart arrest, myocardial infarction, myocardial ischaemia, peripheral vascular disorder, pulmonary embolus, sudden death, thrombophlebitis, thrombosis, and vascular disorder.

Respiratory, thoracic and mediastinal disorders:

Frequent: Dyspnoea (difficultly in breathing), cough and rhinitis.

Less frequent: Pneumonia.

Gastrointestinal disorders:

Frequent: Diarrhoea, abdominal cramps or pain, anorexia, constipation, nausea, vomiting and mucositis. Also abdominal enlargement, ascites, stomatitis, dyspepsia, and flatulence.

Less frequent: Dehydration.

The following side-effects have been reported and frequencies are unknown:

Intestinal obstruction, ileus, gastrointestinal haemorrhage and intestinal perforation. Transient increases in amylase and lipase have been reported. Cases of pseudomembranous colitis have been reported, one of which has been documented bacteriologically (*Clostridium difficile*).

Hepatobiliary disorders:

Frequent: Jaundice and hepatomegaly.

The following side-effects have been reported and frequencies are unknown:

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

Skin and subcutaneous tissue disorders:

Frequent: Sweating, alopecia, hand-and-foot syndrome, and skin rash.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Asthenia and back pain.

The following side-effects have been reported and frequencies are unknown:

Muscular contraction or cramps and paraesthesia.

Renal and urinary disorders:

Less frequent: Renal impairment or acute renal failure.

The following side-effects have been reported and frequencies are unknown:

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

Hypersensitivity reactions:

Less frequent: Conjunctivitis, rhinitis, mild cutaneous reactions, allergy (including anaphylactoid reactions) and infusion site reactions have been reported.

General disorders:

Frequent: Accidental injury and weight loss.

Special Precautions:

CIPLA-IRINOTECAN contains sorbitol; it is not suitable for use in patients with hereditary fructose intolerance.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdosage at doses up to approximately twice the recommended therapeutic dose, which may be fatal, has been reported. Severe neutropenia and diarrhoea were the most significant adverse events reported. **CIPLA-IRINOTECAN** does not have any known antidote. Maximum supportive care is required to prevent dehydration due to diarrhoea and to treat any complications from infections.

IDENTIFICATION:

CIPLA-IRINOTECAN 40 mg/2 ml: A clear, colourless to pale yellow solution.

CIPLA-IRINOTECAN 100 mg/5 ml: A clear, colourless to pale yellow solution.

PRESENTATION:

CIPLA-IRINOTECAN 40 mg/2 ml: Carton containing one 5 ml amber, USP type 1 glass vial closed by a 13 mm rubber stopper and 13 mm aluminium flip-off-tear-off seal

CIPLA-IRINOTECAN 100 mg/5 ml: Carton containing one 5 ml amber, USP type 1 glass vial closed by a 13 mm rubber stopper and 13 mm aluminium flip-off-tear-off seal

STORAGE INSTRUCTIONS:

Store in a cool, dry place below 25 °C. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

After dilution in either 0,9 % sodium chloride or 5 % dextrose, the diluted solution is stable for 24 hours at a temperature below 25 °C or 24 hours under refrigeration at 2 to 8 °C. Discard any unused portion thereafter.

REGISTRATION NUMBERS:

CIPLA-IRINOTECAN 40 mg/2 ml: 41/26/0049

CIPLA-IRINOTECAN 100 mg/5 ml: 41/26/0050

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

CIPLA MEDPRO (PTY) LTD.

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DATE OF PUBLICATION OF THIS PACKAGE INSERT:

May 2011

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