1C-001

NAME OF APPLICANT/PHCR	: CIPLA MEDPRO (PTY) LTD.
PRODUCT PROPRIETARY NAME	: CIPLA-IRINOTECAN 40MG/2ML
DOSAGE FORM	: SOLUTION FOR INFUSION
DOSAGE STRENGTH	: 40MG/2ML

PART 1C LABELLING

a) Package Insert

The under-mentioned information with regard to this medicine shall appear on the scientific package insert. The information shall be presented in the format stipulated: Provided that the Council may authorize any deviation from such information or such format (refer to Regulation 9).

1. Scheduling status
2. Proprietary name and dosage form
3. Composition
4. Pharmacological classification
5. Pharmacological action
   (Pharmacokinetics, pharmacodynamics and summary of clinical studies, where applicable)
6. Indications
7. Contra-indications
8. Warnings
9. Interactions
10. Pregnancy and lactation
11. Dosage and directions for use
12. Side effects and special precautions
13. Known symptoms of overdosage and particulars of its treatment
14. Identification
15. Presentation
16. Storage instructions
17. Registration number
18. Name and business address of the holder of the certificate of registration
19. Date of publication of the package insert

1. Proposed Package Insert **1C-002**

PROPOSED PACKAGE INSERT FOR CIPLA-IRINOTECAN SOLUTION FOR INFUSION

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

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 tumour cell lines. The inhibition of DNA topoisomerase I by irinotecan or SN-38 induces single-strand DNA lesions which block 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 display 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.

Pharmacokinetics:

After a 30 minute intravenous infusion of 100 to 700 mg/m^2 every 3 weeks, irinotecan showed a biphasic or three-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/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 is 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 aminopentanoic acid derivative (APC) and 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.

INDICATIONS:

CIPLA-IRINOTECAN is indicated for the treatment of patients with advanced colorectal cancer with a WHO performance status of 2 or lower:

- In combination with 5-fluorouracil and folinic acid in patients without prior chemotherapy for advanced disease.
- As a single agent in patients who have failed an established 5-fluorouracil-containing treatment regimen.

CONTRA-INDICATIONS:

- 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 **CIPLA-IRINOTECAN** until resolution of the ileus.
- Pregnancy and lactation. Women of childbearing age receiving **CIPLA-IRINOTECAN** 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 **CIPLA-IRINOTECAN** in children have not been established.
- Severe bone marrow failure.
- WHO performance status > 2.

WARNINGS:

CIPLA-IRINOTECAN should be used in patients with a good performance

status of less than 2.

The use of **CIPLA-IRINOTECAN** 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 **CIPLA-IRINOTECAN** be administered only in healthcare institutions with adequately equipped facilities, including an intensive care unit.

In all instances where the use of **CIPLA-IRINOTECAN** 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 **CIPLA-IRINOTECAN**, patients should be aware of the high risk of delayed diarrhoea occurring more than 24 hours after the administration of **CIPLA-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 **CIPLA-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 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 **CIPLA-IRINOTECAN** has been administered. After discharge from the hospital, the patients should obtain the prescribed medicines so that they can treat the diarrhoea as soon as it occurs. In addition, they must inform their physician or the department administering **CIPLA-IRINOTECAN** 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 **CIPLA-IRINOTECAN** 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. **CIPLA-IRINOTECAN** 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 **CIPLA-IRINOTECAN** should be reduced. In patients who experienced severe haemotologic 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. **CIPLA-IRINOTECAN** 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 **CIPLA-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 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 **CIPLA-IRINOTECAN**.

Elderly:

Due to the greater frequency of decreased hepatic, renal or cardiac function in an elderly patient, dose selection with **CIPLA-IRINOTECAN** 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.

INTERACTIONS:

Pharmacokinetic parameters of **CIPLA-IRINOTECAN** 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 antagonised. Loperamide should not be given 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 patient):

The recommended dosage of **CIPLA-IRINOTECAN** 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 patient):

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

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

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

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

  Folinic acid 500 mg/m^2 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.

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

  The recommended dose of **CIPLA-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:

  CIPLA-IRINOTECAN 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:

CIPLA-IRINOTECAN 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 **CIPLA-IRINOTECAN** should be delayed until there has been a full recovery of these effects, especially diarrhoea.

CIPLA-IRINOTECAN 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 **CIPLA-IRINOTECAN**, and 5FU when applicable, should be decreased according to the worst grade of adverse events observed in the prior infusion. Treatment should be delayed by 1 to 2 weeks to allow recovery from treatment-related adverse events.

With the following adverse events a dose reduction of 15 to 20 % should be applied 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:

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

Special Populations:

Patients with Impaired Hepatic Function:

Patients with a bilirubin > 1.5 times the ULN should not be treated with **CIPLA-IRINOTECAN**. In patients with a bilirubin ≤ 1.5 times the upper limit of the normal range (ULN), a dose of 350 mg/m^2 **CIPLA-IRINOTECAN** is recommended. In patients with bilirubin > 1 and ≤ 1.5 times the upper limit of the normal range (ULN), the risk of severe neutropenia is increased. Thus, frequent monitoring of complete blood counts should be conducted in this

patient population.

Patients with Impaired Renal Function:

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

Elderly:

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

Preparation for the Intravenous Infusion Administration:

Aseptically withdraw the required amount of **CIPLA-IRINOTECAN** solution from the vial with a calibrated syringe and inject into a 250 ml infusion bag or bottle containing either 0.9 % sodium chloride solution or 5 % dextrose solution. The infusion should then be thoroughly mixed by manual rotation.

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

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

If any precipitate is observed in the vials, 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.

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

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

The intensity of the major toxicities encountered with **CIPLA-IRINOTECAN** (e.g. leukoneutropenia and diarrhoea) is 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

CIPLA-IRINOTECAN:

Blood and lymphatic system disorders:

Frequent:	Neutropenia is a dose-limiting toxic effect. Anaemia, thrombocytopenia, leucopenia 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 system 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 system 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 infarct, cerebrovascular accident, deep thrombophlebitis, heart arrest, myocardial infarct, myocardial ischaemia, peripheral vascular disorder, pulmonary embolus, sudden death, thrombophlebitis, thrombosis and vascular disorder.

Respiratory system disorders:

Frequent:	Dyspnoea (difficulty in breathing), cough and rhinitis.
Less frequent:	Pneumonia.

Gastrointestinal system 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 increase in amylase and lipase has been reported. Cases of pseudomembranous colitis have been reported, one of which has been documented bacteriologically (*Clostridium difficile*).

Hepatobiliary system 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 metastasis. Transient grade 3 levels were observed and no grade 4 was observed.

Renal and urinary system 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 of serum levels of creatinine have been observed.

Skin and subcutaneous tissue disorders:

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

Musculoskeletal system disorders:

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

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:

This medicine contains sorbitol; it is unsuitable for use in patients with hereditary fructose intolerance.

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 **CIPLA-IRINOTECAN**. Maximum supportive care should be instituted to prevent dehydration due to diarrhoea and to treat any infectious complications.

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 grey rubber stopper and 13 mm aluminium flip-off-tear-off seal containing **CIPLA-IRINOTECAN 40 mg/2 ml.**
CIPLA-IRINOTECAN 100 mg/5 ml:	Carton containing one 5 ml amber, USP type 1 glass vial closed by a 13 mm grey rubber stopper and 13 mm aluminium flip-off-tear-off seal containing **CIPLA-IRINOTECAN 100 mg/5 ml.**

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:

To be allocated.

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

CIPLA MEDPRO (PTY) LTD,

Rosen Heights,

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7530

DATE OF PUBLICATION OF THIS PACKAGE INSERT: