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

b) Patient information leaflet

The under-mentioned information with regard to this medicine shall appear on the patient information leaflet. The information shall be presented in the format stipulated, provided that the Council may authorise any deviation from such information or such format (refer to Regulation 10 of the Act).

1. Scheduling status
2. Proprietary name and dosage form
3. Composition of the medicine, that is, what this medicine contains
4. Approved indication and use, that is, what this medicine is used for
5. Instruction before taking the medicine
6. Instructions on how to take the medicine
7. Side effects
8. Storage and disposal information
9. Presentation
10. Identification
11. Registration number
12. Name and business address of the holder of the certificate of registration
13. Date of publication of the Patient Information Leaflet.

1. Proposed Patient Information Leaflet **1C-044**

1C-024

17/10/2006: P&A recommendation as per MCC letter dated 01/09/2006.

Patient Information Leaflet

Information for the Patient about

CIPLA-IRINOTECAN 40 mg/2 ml
CIPLA-IRINOTECAN 100 mg/5 ml
Solution for Infusion

Read all of this leaflet carefully before you start taking this medicine.

- **Keep this leaflet , you may need to read it again.**
- **If you have further questions please ask your doctor or your pharmacist.**
- **This medicine has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.**

SCHEDULING STATUS:

S4

Ref 1, pg1c-002

PROPRIETARY NAME AND DOSAGE FORM:

CIPLA-IRINOTECAN 40 mg/2 ml Solution for Infusion
CIPLA-IRINOTECAN 100 mg/5 ml Solution for Infusion

Ref 1, pg 1c-002

WHAT CIPLA-IRINOTECAN CONTAIN:

The active substance is irinotecan hydrochloride trihydrate. CIPLA-IRINOTECAN 40 mg/ 2 ml and CIPLA-IRINOTECAN 100 mg/ 5 ml contain 40 mg, and 100 mg irinotecan hydrochloride trihydrate as a concentration of 20 mg/1 ml in an isotonic solution, respectively.

Ref 1, pg 1c-002
Ref 2, pg 3B-001

WHAT CIPLA-IRINOTECAN IS USED FOR:

Ref 1,pg 1c-005

- CIPLA-IRINOTECAN belongs to a class of medicines called cytostatic substances.

- CIPLA-IRINOTECAN is used to treat 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.

Ref 1, pg 1c-005

BEFORE YOU USE CIPLA-IRINOTECAN :

Ref 1,pg 1c-005

Do not take CIPLA-IRINOTECAN if you:

- History of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate or to one of the excipients of CIPLA-IRINOTECAN.
- 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.

Take special care with CIPLA-IRINOTECAN :

Tell your doctor if you have any of the following as you may then require a lower dose or special precautions: — Ref 1,pg 1c-009

- Hepatic impairment.
- Cardiac function impairment.
- Woman of child bearing age taking this medicine

This medicine may contain sorbitol, it is unsuitable for use in patients with hereditary fructose intolerance. — Ref 1, pg 1c-018

Taking CIPLA-IRINOTECAN with food and drinks:

CIPLA-IRINOTECAN should not be given orally and should not be injected intramuscularly or subcutaneously. It is administered by intravenous injection. — Ref 1, pg 1c-011

See **"HOW TO TAKE CIPLA-IRINOTECAN"**.

Use in pregnancy and breast feeding:

The safety of **CIPLA-IRINOTECAN** in pregnancy and lactation has not been established. Thus use in pregnancy and lactation is not recommended. — Ref 1, pg 1c-011

If you are pregnant or breast feeding your baby while taking this medicine, please consult your doctor, pharmacist or other healthcare professional for advice. — Ref 3, pg 1c-054

Use in elderly:

CIPLA-IRINOTECAN appears to pose no exceptional safety problems for healthy elderly patients. — Ref 1, pg 1c-014

Can I drive or operate machinery while taking CIPLA-IRINOTECAN?

CIPLA-IRINOTECAN have not been shown to impair judgement, thinking or motor skills. Be cautious about operating hazardous machinery and driving until you are certain that the medicine does not affect them adversely.

Ref 1, pg 1c-010

Taking other medicines with CIPLA-IRINOTECAN?

See "**BEFORE YOU TAKE CIPLA-IRINOTECAN** "

If you are taking other medicines on a regular basis, use of this medicine with other medicines may cause undesirable interactions.

Please consult your doctor or pharmacist.

Ref 3, pg 1c-054

HOW TO TAKE CIPLA-IRINOTECAN :

Always take CIPLA-IRINOTECAN exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Please consult your doctor before abruptly discontinuing CIPLA-IRINOTECAN as your doctor will advise you on the tapered dose to minimise the risk of discontinuation symptoms.

Ref 3, pg 1c-055

If you take more CIPLA-IRINOTECAN than you should:

In the event of an overdosage (if you take too much), or if someone else has taken your medicine by mistake, you, or this other person, may experience gastro-intestinal symptoms.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. General and supportive measures are recommended. Contact your doctor or pharmacist immediately. If neither is available, seek help at the nearest hospital or poison control centre.

Ref 1,pg 1c-011/12

Ref 3, pg 1c-055

If you forget to take CIPLA-IRINOTECAN

Take CIPLA-IRINOTECAN as prescribed. If you miss a dose of this medicine, take it as soon as possible. However, if you do not remember the missed dose until the next day, skip the missed dose and go back to your regular dosing schedule. Do not take a double dose to compensate for the forgotten individual dose.

Ref 3, pg 1c-055

POSSIBLE SIDE-EFFECTS:

What undesirable effects may CIPLA-IRINOTECAN have?

- CIPLA-IRINOTECAN can have side-effects. As with any medicine, CIPLA-IRINOTECAN may have unintended or undesirable effects.
- The most commonly observed adverse effects are:
  Problems with nausea, vomiting, diarrhoea, neutropenia.
- The occurrence of many frequently observed adverse events is dose related. These generally decrease in intensity and frequency with continued therapy. Check with your doctor as soon as possible if the side-effects persist and become bothersome.

Ref 1,pg 1c-015

The following side-effects have been reported:

Blood and lymphatic system disorders

frequent: Neutropenia is a dose-limiting toxic effect.

Less frequent:	Anaemia, thrombocytopenia.	Ref 1,pg 1c-015
Immune system disorder		
Less frequent:	Chills, malaise.	
Nervous system disorders		Ref 1,pg 1c-015
Frequent:	Dizziness	
Eye disorders		Ref 1, pg 1c-016
Frequent:	Visual disturbances, myosis, lachrymation and increased salivation occurring during or within the first 24 hours after the infusion of CIPLA-IRINOTECAN.	Ref 1, pg 1c-016
These symptoms disappear after atropine administration.		
Respiratory System disorders		
Less frequent:	Dyspnoea (difficulty in breathing),	
Gastrointestinal disorders		Ref 1, pg 1c-016
Frequent:	Nausea, vomiting, diarrhea	
Less frequent:	Dehydration, constipation, intestinal obstruction, ileus, or gastrointestinal haemorrhage, intestinal perforation,	Ref 1,pg 1c-016
Transient increase in amylase and lipase has been reported. Other mild effects include anorexia, abdominal pain and mucositis.		

Uncommon cases of pseudo-membranous colitis have been reported, one of which has been documented bacteriologically (*Clostridium difficile*).

Musculoskeletal System Disorders:

Frequent: Abdominal pain, aesthenia, muscular contraction or cramps and paraesthesia — Ref 1,pg 1c-017

Cardiovascular System Disorders:

Frequent: Hypotension, vasodilation, cardio-circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis. — Ref 1,pg 1c-017

Skin:

Frequent: Sweating

Hypersensitivity reactions: — Ref 1,pg 1c-017

Frequent: Conjunctivitis, rhinitis, Mild cutaneous reactions, allergy and infusion site reactions have been reported, — Ref 1,pg 1c-017

Renal System Disorders:

Frequent: Renal insufficiency

Transient and mild to moderate increases of serum levels of creatinine have been observed. — Ref 1,pg 1c-017

Hepatic System Disorders:

Frequent: Transient and mild to moderate increases in serum levels of either transaminases, — Ref 1,pg 1c-017

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

Ref 1, pg 1c-018

Other:

Alopecia,

Not all side-effects reported for this medicine are included in this leaflet. Should your general health worsen while taking this medicine, please consult your doctor, pharmacist or other healthcare professional for advice.

Ref 1, pg 1c-018

Ref 3, pg 1c-055

STORAGE AND DISPOSING OF CIPLA-IRINOTECAN :

Store this medicine out of reach of children.

Store in a cool dry place below 25 °C. Protect 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 °C or 24 hours under refrigeration at 2 to 8 °C. Discard any unused portion thereafter.

Do not use after the expiry date stated on the packaging material.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems,

Ref 1, pg 1c-019

Ref 3, pg 1c-056

for example toilets.

PRESENTATION OF CIPLA-IRINOTECAN:

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

Ref 1, pg 1c-019

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

IDENTIFICATION OF CIPLA-IRINOTECAN :

Cipla-Irinotecan 40mg/2ml: A clear colourless to pale yellow solution.

Cipla-Irinotecan 100mg/5ml: A clear colourless to pale yellow solution.

Ref 1, pg 1c-018

REGISTRATION NUMBER:

To be allocated.

NAME AND BUSINESS ADDRESS OF THE HOLDER CERTIFICATE OF REGISTRATION:

Ref 1,pg 1c-019

CIPLA MEDPRO (PTY) LTD

Rosen Heights

Pasita Street

Rosen Park, Bellville

7530

Ref 1, pg 1c-019

DATE OF PUBLICATION OF THIS PATIENT LEAFLET:

Ref 1,pg 1c-019

1C-033

17/10/2006: P&A recommendation as per MCC letter dated 01/09/2006.

REFERENCES TO PATIENT INFORMATION LEAFLET

REFERENCES	MRF1 PAGES
1. Proposed PI initially submitted by CIPLA MEDPRO (PTY) LTD.	1C-002
2. MRF 1, Part 3B – Formulation	3B-001
3. Guideline on the requirements for patient information leaflets, May 2004.	1C-034

3. BEFORE YOU <TAKE> <USE> X

[List of information necessary before taking the medicinal product]
[This section must take into account the particular condition of certain categories of users, e.g. children and the elderly (specify the age range, special patient populations, e.g. patients with renal or hepatic impairment.]

[Absolute contraindications]
Do not <take> <use> X:

- <if you are hypersensitive (allergic) to *{active substance}* or any of the other ingredients of X.> *[include reference to residues, excipients, etc, if applicable]*
- <if you ...>

[Information on absolute contraindications, in accordance with the professional Package Insert, should be provided here. This should be in patient understandable language and should be strictly limited to contraindications, including chronic accompanying diseases and contraindications due to interactions with other medicinal products. Other precautions and special warnings should be made in the following subsection.]

[Appropriate precautions for use, special warnings]
Take special care with X:

- <if you ...>
- <when ...>

[Information, in patient-friendly language, on relative contraindications, special warning and appropriate precautions for use should be provided here. Include information on interactions with other medicinal products]

[Interactions with food and drink]
<Taking > <Using> X with food and drink:

[Use by pregnant or breast-feeding women]
Pregnancy and Breast-feeding
[Include information given in the professional Package Insert, in patient-friendly language. The following additional statement must be included:]
<If you are pregnant or breast feeding your baby while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice.>

[Effect on the ability to drive or use machinery]
Driving and using machinery:
<Do not <drive because...>
<Do not operate any tools or machines.>
[Excipient warnings]
Important information about some of the ingredients of X:
[If appropriate, details of those excipients knowledge of which is important for the safe and effective use of the medicinal product]

[Interaction with other medicinal products]
Taking> <Using other medicines with X:
[The following statement must be included:]
<If you are taking other medicines on a regular basis, including complementary or traditional medicines, the use of X with these medicines may cause undesirable interactions. Please consult your doctor, pharmacist or other healthcare professional, for advice.>

4. HOW TO <TAKE> <USE> X

[Instructions for proper use]

[The following 4 items can be combined as one paragraph]

[Dosage]
[The recommended dosage should be included here. The following statements should be included, where applicable:]
<Always take X exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.> <The usual dose is...>

<If you have the impression that the effect of X is too strong or too weak, talk to your doctor or pharmacist.>

[Method and/or route(s) of administration]
[Method of administration: directions for the proper use of the medicinal product; e.g.:]
'Do not swallow',
'Do not chew',
'Shake well before use',
'Allow to reach room temperature before using' *[e.g. insulins]*
[Route(s) of administration must be indicated in patient understandable language]

[Frequency of administration]
[Specify if necessary the appropriate time at which the medicinal product may or must be administered]

[Duration of treatment]
[Specify in which cases it should be limited]

[Symptoms in case of overdosage and actions to be take]
If you <take> <use> more X than you should:
[Description of signs and symptoms of overdosage that the patient is able to recognize and actions to be taken]
[The following statement must be included:]
<In the event of overdosage, consult your doctor or pharmacist. If neither is available, seek help at the nearest hospital or poison control center.>

[Actions to be taken when one or more doses have been missed]
If you forget to take X:
[Provide clear explanations of what should be done following irregular use of the medicinal product, e.g.:]
<Do not take a double dose to make up for forgotten individual doses.>

[Indication of the risk of withdrawal effects]
Effects when treatment with X is stopped:
[Indicate any effects of interruption or ending treatment early, if applicable. Indicate withdrawal effects when the treatment ends, if applicable]

5. POSSIBLE SIDE EFFECTS

[A description of side effects should be provided. Begin this section with:]
<X can have side effects.>

[Describe, if necessary, the actions to be taken. If the patient needs to seek help urgently use the term <immediately>; *for less urgent conditions use the phrase* <as soon as possible>.*]*

[The following statement must be included:]
<Not all side effects reported for this medicine are included in this leaflet. Should your general health worsen while taking this medicine, please consult your doctor, pharmacist or other health care professional for advice.>

6. STORING AND DISPOSING OF X

[Storage conditions and disposal of unused medicine]
[The following statement must be included in this section:]
Keep all medicines out of the reach and sight of children.

[Where applicable, the following statements may be included:]
<Do not store above <25°C> <30°C>> *[Explain ideal storage environment]*
<Store at 2°C – 8°C (in a refrigerator)>
<Store in a freezer>
<Do not <refrigerate> <or> <freeze>>
<Store in the original <package> <container>>
<Keep the container in the outer carton>
<Keep the container tightly closed>
<There are no special storage instructions>

[An additional short explanation of the storage conditions, in patient-friendly terms, should be included when appropriate, e.g.:]
<in order to protect from <light> <moisture>>
<Do not store in bathrooms>
<Do not use after the expiry date stated on the <label> <carton> <bottle> <...>>

[Where applicable, shelf life after reconstitution, dilution or after first opening the container should be indicated]

[Where appropriate, warning against any visible signs of deterioration]
<Do not use X if you notice {description of the visible signs of deterioration}.>

[Information on how to dispose of unused medicine, e.g.:]
<Return all unused medicine to your pharmacist.>
<Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets)>

7. PRESENTATION OF X

[In accordance with information provided in the Package Insert, including the pharmaceutical form, the number, volume or mass per package unit, pack size and a description of the packaging material, e.g. bottle, blister pack, etc.]

8. IDENTIFICATION OF X

[A physical description, e.g. shape, colour, texture, imprint, etc, of the dosage form should be included here in accordance with the Package Insert Information.]

9. REGISTRATION NUMBER/REFERENCE NUMBER

[As in the Package Insert and in accordance with Section 15 of the Act.]

10. NAME AND ADDRESS OF REGISTRATION HOLDER

[As in the Package Insert]

11. DATE OF PUBLICATION

[As in the Package Insert]