SCHEDULING STATUS

S4

1. NAME OF MEDICINE:

IROCAN 40 mg/2 ml (Solution for Infusion)

IROCAN 100 mg/5 ml (Solution for Infusion)

IROCAN 300 mg/15 ml (Solution for Infusion)

IROCAN 500 mg/ 25 ml (Solution for Infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Single-dose vials containing 40 mg, 100 mg, 300 mg or 500 mg irinotecan hydrochloride trihydrate.

Each 1 ml of the solution for infusion contains 20 mg irinotecan hydrochloride trihydrate.

Contains: Sorbitol

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Clear yellow solution for Infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

IROCAN 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 medicine in patients who have failed an established 5-fluorouracil containing treatment regimen.

4.2 Posology and method of administration

Recommended Dosage:

In monotherapy (for a previously treated patient):

The recommended dosage of **IROCAN** is 350 mg/m² administered as an intravenous infusion over a 30- to 90-minute period every three weeks.

***In combination therapy (for a previously untreated patient)**:*

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

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

The recommended dose of **IROCAN** is 80 mg/m² 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:

IROCAN 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.

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

The recommended dose of **IROCAN** is 180 mg/m² 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:

IROCAN 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.

The cycle must be repeated every two weeks.

Dosage Adjustments:

Delayed dosing**:**

IROCAN should not be administered until the neutrophil count remains above 1500 cells/mm3. In patients who experienced severe neutropenia or severe gastrointestinal adverse events such as diarrhoea, nausea and vomiting, dosing of **IROCAN** should be delayed until there has been a full recovery of these effects, especially diarrhoea.

IROCAN 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 **IROCAN**, 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 **IROCAN** 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 **IROCAN** should be continued until there is an objective progression of the disease or an unacceptable toxicity.

Special populations

Patients with Impaired Hepatic Function:

IROCAN is contraindicated in patients with bilirubin levels > 1.5 times the upper limit of the normal range. Liver function tests should be performed at baseline and before each cycle.

Patients with renal impairment:

Irocan is not recommended for use in patients with impaired renal function, as the product has not been studied in this patient group (see sections 4.4 and 5.2).

Elderly: The dose should be chosen carefully in the elderly due to their greater frequency of decreased biological function.

Paediatric population

The safety and efficacy of **IROCAN** in children have not been established. **IROCAN** is contraindicated in patients with severe bone marrow failure

Method of administration

Preparation for the Intravenous Infusion Administration:

The required amount of **IROCAN** solution must be aseptically withdrawn from the vial with a calibrated syringe and injected into a 250 ml infusion bag or bottle containing either 0,9 % sodium chloride solution or 5 % dextrose solution. The infusion should be thoroughly mixed by manual rotation thereafter. **IROCAN** infusion solution should be infused into a peripheral or central vein.

IROCAN 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 medicines.

Do not admix with other medicines.

Recommendations for safe handling:

Medicine handling precautions for cytostatic medicines should be followed:

Only trained personnel should reconstitute the medicine in a designated area.

IROCAN is an antineoplastic medicine and, as with other potentially toxic medicines, caution should be exercised when handling it and preparing **IROCAN** solutions.

The work surface should be covered with disposable plastic-backed absorbent paper.

Adequate protective gloves and clothing should be worn.

If **IROCAN** solution or infusion solution should come into contact with the skin, wash immediately and thoroughly with soap and water. If **IROCAN** 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.

4.3 Contraindications

- History of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate or to one of the excipients of **IROCAN** (see section 6.1)
- Chronic inflammatory bowel disease, and/or bowel obstruction or ileus. Patients should not be treated with **IROCAN** until resolution of the ileus.

- **IROCAN** is contraindicated in pregnancy and lactation. Women of childbearing age receiving **IROCAN** should be advised to avoid becoming pregnant and to inform the treating medical practitioner immediately should this occur.
- Patients with bilirubin levels > 1,5 times the upper limit of the normal range should not use **IROCAN**.
- The safety and efficacy of **IROCAN** in children have not been established.
- **IROCAN** is contraindicated in patients with severe bone marrow failure.
- Patients with a WHO performance status > 2 should not use **IROCAN**.
- Concomitant administration of azole antifungals.
- St John's Wort
- Live attenuated vaccines (see section 4.5).

4.4 Special warnings and precautions for use

IROCAN should be used in patients with a WHO performance status of less than 2.

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

In all instances where the use of **IROCAN** is considered for chemotherapy, it is especially important to ensure that the patient understands the need for sufficiently prolonged antidiarrhoeal treatment and abundant fluid intake. In less frequent cases where it is

predictable 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 medical practitioner 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 **IROCAN**, patients should be aware of the high risk of delayed diarrhoea occurring more than 24 hours after the administration of **IROCAN** and at any time before the next cycle. Patients should inform their medical practitioner of the first liquid stool 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 antidiarrhoeal therapy must be initiated immediately.

This antidiarrhoeal treatment must be prescribed by the department where **IROCAN** 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 medical practitioner or the department administering **IROCAN** that diarrhoea is occurring.

The currently recommended antidiarrhoeal 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. Loperamide should under no circumstances be administered for more than 48 consecutive hours at the above doses, because of the risk of paralytic ileus, nor for less than 12 hours.

In addition to the antidiarrhoeal treatment, a prophylactic broad-spectrum antibiotic should be given when diarrhoea is associated with severe neutropenia (neutrophil count < 500 cells/mm3).

In addition to the antibiotic treatment, hospitalisation is recommended for management of the diarrhoea in the following cases:

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

Loperamide should not be given prophylactically, even in patients who experienced delayed diarrhoea at previous cycles

In patients who experienced severe diarrhoea, a reduction in dose is recommended for subsequent cycles.

Haematology:

Weekly monitoring of complete blood cell counts should be performed during **IROCAN** treatment.

Patients should be aware of the risk of infection and the significance of a fever. Febrile neutropenic (temperature ≥ 38 ºC and neutrophil count ≤ 1000 cells/mm3) should be urgently treated in the hospital with broad spectrum intravenous antibiotics.

IROCAN administration should be delayed until the neutrophil count is ≥1500 cells/mm3.

In patients who experienced severe asymptomatic neutropenia (< 500 cells/mm3), fever or infections associated with neutropenia the dose of **IROCAN** 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, including complete blood counts. **IROCAN** 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. In patients with a bilirubin of < 1,5 times ULN a dose of 350 mg/m^2 is recommended once every 3 weeks (see section 4.2)

Renal Impairment:

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

Nausea and vomiting:

Prophylactic treatment with an anti-emetic is recommended before each treatment with **IROCAN**. 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. These symptoms may disappear after atropine administration. 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 **IROCAN**.

Immunosuppressant effects/increased susceptibility to infections:

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

Respiratory disorders

Interstitial lung disease presenting as lung infiltration may occur during **IROCAN** therapy. Interstitial lung disease can be fatal. Risk factors possibly associated with the development of interstitial lung disease include the use of pneumotoxic medicinal products, radiation therapy and colony stimulating factors. Patients with risk factors should be closely monitored for respiratory symptoms before and during **IROCAN** therapy.

Extravasation

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

Elderly:

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

Chronic inflammatory bowel disease and/or bowel obstruction

Patients must not be treated with **IROCAN** until resolution of the bowel obstruction (see section 4.3).

Renal function:

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

Irradiation therapy:

Patients who have previously received pelvic/abdominal irradiation are at increased risk of myelosuppression following the administration of **IROCAN**. Medical practitioners should use caution in treating patients with extensive prior irradiation (e.g. > 25% of bone marrow irradiated and within 6 weeks prior to start of treatment with **IROCAN**). Dosing adjustment may apply to this population (see section 4.2).

Cardiac disorders:

Myocardial ischaemic events have been observed following irinotecan therapy predominately in patients with underlying cardiac disease, other known risk factors for cardiac disease, or previous cytotoxic chemotherapy (see section 4.8).

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

Vascular disorders:

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

Others:

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

Women of childbearing potential and men have to use effective contraception during and for at least 3 months after treatment (see section 4.6).

Concomitant administration of irinotecan with a strong inhibitor (e.g. ketoconazole) or inducer (e.g. rifampicin, carbamazepine, phenobarbitone, phenytoin) of CYP3A4 may alter the metabolism of irinotecan and should be avoided (see section 4.5).

Paediatric Population:

The safety and efficacy of **IROCAN** in children have not been established.

Sorbitol:

Since **IROCAN** contains sorbitol, it is unsuitable for use in patients with hereditary fructose intolerance.

Sorbitol can also have a laxative effect.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use contraindicated (see section 4.3)

Yellow fever vaccine: Risk of fatal generalised reaction to vaccines

Saint John's Wort: Decrease in the active metabolite of irinotecan, SN-38, plasma levels. In a small pharmacokinetic study (n=5), in which irinotecan 350 mg/m^2 was co-administered with St. John's Wort (*Hypericum perforatum)* 900 mg, a 42% decrease in the active metabolite of irinotecan, SN-38, plasma concentrations was observed. As a result, St. John's Wort should not be administered with **IROCAN**.

Live attenuated vaccines: Risk of generalised reaction to vaccines, possibly fatal. Concomitant use is contraindicated during treatment with **IROCAN** and for 6 months following discontinuation of chemotherapy. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Concomitant use not recommended (see section 4.4)

Concurrent administration of **IROCAN** with a strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) may alter the metabolism of irinotecan which is found in **IROCAN** and should be avoided (see section 4.4):

Strong CYP3A4 and/or UGT1A1 inducing medicinal products: (e.g. rifampicin, carbamazepine, phenobarbital or phenytoin):

Risk of reduced exposure to irinotecan, SN-38 and SN-38 glucuronide and reduced pharmacodynamic effects. Several studies have shown that concomitant administration of CYP3A4-inducing anticonvulsant medicines leads to reduced exposure to irinotecan, SN-38 and SN-38 glucuronide and reduced pharmacodynamic effects. The effects of such anticonvulsant medicines were reflected by a decrease in AUC of SN-38 and SN-38G by 50% or more. In addition to induction of CYP3A4 enzymes, enhanced glucuronidation and enhanced biliary excretion may play a role in reducing exposure to irinotecan and its metabolites. Additionally with phenytoin: Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic medicines.

Strong CYP3A4 inhibitors: (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, protease inhibitors, clarithromycine, erythromycine, telithromycine):

A study has shown that the co-administration of ketoconazole resulted in a decrease in the AUC of APC of 87% and in an increase in the AUC of SN-38 of 109% in comparison to irinotecan given alone.

UGT1A1 inhibitors: (e.g. atazanavir, ketoconazole, regorafenib)

Risk to increase systemic exposure to SN-38, the active metabolite of irinotecan. Medical practitioners should take this into consideration if the combination is unavoidable.

Other CYP3A4 inhibitors: (e.g. crizotinib, idelalisib)

Risk of increase in irinotecan toxicity, due to a decrease in irinotecan metabolism by crizotinib or idelalisib.

Caution for use

Vitamin K antagonists: Increased risk of haemorrhage and thrombotic events in tumoral diseases. If vitamin K antagonists are indicated, an increased frequency in the monitoring of INR (International Normalised Ratio) is required.

Concomitant use to take into consideration

Immunosuppressant agents: (e.g. ciclosporine, tacrolimus): Excessive immunosuppression with risk of lymphoproliferation.

Neuromuscular blocking medicines: Interaction between **IROCAN** and neuromuscular blocking medicines cannot be ruled out. Since **IROCAN** has anticholinesterase activity, medicines with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarising medicines may be antagonised. Excess acetylcholine may impair the muscle relaxant action of the non-depolarising medicines and may impair the return of normal muscle tone at the end of anaesthesia.

Other combinations

5-fluorouracil/folinic acid: Coadministration of 5-fluorouracil/folinic acid in the combination regimen does not change the pharmacokinetics of irinotecan found in **IROCAN**.

Bevacizumab: Results from a dedicated drug-drug interaction trial demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan and its active metabolite SN-38. However, this does not preclude any increase of toxicities due to their pharmacological properties.

Cetuximab: There is no evidence that the safety profile of irinotecan found in **IROCAN** is influenced by cetuximab or vice versa

Loperamide should not be given prophylactically.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing age receiving **IROCAN** should avoid becoming pregnant. Contraceptive measures must be taken during and for at least three months after cessation of therapy

Pregnancy

IROCAN is contraindicated during pregnancy (see section 4.3). It may cause foetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of **IROCAN** in pregnant women. If **IROCAN** is used during pregnancy, or if the patient becomes pregnant, while receiving **IROCAN**, the patient should be apprised of the potential hazard to the foetus.

Breast feeding

IROCAN is contraindicated during lactation (see section 4.3). Patients receiving IROCAN should therefore not breastfeed their infants

Fertility

There are no human data on the effect of **IROCAN** on fertility. In animals' adverse effects of **IROCAN** on the fertility of offspring has been documented (see section 5.3).

4.7 Effects on ability to drive and use machines

There is a potential for dizziness or visual disturbances when **IROCAN** is used. Patients must be advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

SIDE-EFFECTS:

Infections and infestations:

Frequent: Infection

*Less Frequent***:** Sepsis

Blood and lymphatic system disorders:

Frequent: Neutropenia, anaemia, leukopenia, thrombocytopenia, febrile neutropenia

Endocrine disorders:

Less frequent: diaphoresis, increased salivation

Metabolism and nutrition disorders:

Frequent: Decreased weight, dehydration,

hypovolaemia

Less frequent: Hypokalaemia, hypomagnesaemia

Nervous system disorders:

Less frequent: Abnormal gait, confusion, headache, dizziness, cholinergic syndrome

Eye disorders:

Less frequent: Increased lacrimation, miosis

Unknown frequency: conjunctivitis, visual disturbances

Cardiac disorders:

Less frequent: Hypotension, syncope, bradycardia

Frequency unknown: Myocardial ischaemic events have been observed following **IROCAN** therapy.

Vascular disorders:

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

Less frequent: Flushing

Unknown frequency: Vasodilation

Respiratory, thoracic and mediastinal disorders:

Frequent: Dyspnoea

Less frequent: Rhinitis

Gastrointestinal disorders:

Frequent: Delayed diarrhoea, nausea, vomiting, early diarrhoea, abnormal cramping/pain, anorexia, stomatitis, constipation, mucositis

Less frequent: Rectal disorder, GI monilia

Frequency unknown: Intestinal obstruction, ileus, megacolon, gastrointestinal haemorrhage, colitis, including typhlitis, ischaemic and ulcerative colitis, colitis complicated by ulceration, bleeding, ileus or infection, ileus without preceding colitis, intestinal perforation. Symptomatic pancreatitis or asymptomatic elevated pancreatic enzymes have been reported

Hepatobiliary disorders:

Frequent: Hyperbilirubinemia

Skin and subcutaneous disorders:

Frequent: Alopecia

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

Unknown frequency: Sweating

Renal and urinary disorders

Less frequent: Urinary tract infection

Reproductive system and breast disorders

Less frequent: Breast pain

General disorders and administration site conditions

Frequent: Asthenia, fever, pain

Less frequent: Chills, malaise, extravasation, tumour-lysis syndrome

Investigations

Frequent: Increased serum creatinine**,** transaminases increased (ALT and AST), blood bilirubin increased, blood alkaline phosphatase increased

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

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

To contact Innovata Pharmaceuticals (Pty) Ltd.:

Email: regulatory@innovata.co.za

Tel: 086 999 0912

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 **IROCAN**. 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

Class of medicine: Cytostatic medicines, A 26

Mechanism of action:

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 is more active than irinotecan in purified topoisomerase I and more cytotoxic than irinotecan against several murine and human tumour cell lines. The inhibition of DNA topoisomerase I by irinotecan or SN-38 induces single-strand DNA lesions which blocks the DNA replication fork and are responsible for the cytotoxicity. This cytotoxic activity is time-dependent and is 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.

Furthermore, irinotecan has a broad antitumour activity *in vivo* against murine tumour models (P03 pancreatic ductal adenocarcinoma, MA16/C mammary adenocarcinoma, C38 and C51 colon adenocarcinoma) and against human xenografts (Co-4 colon adenocarcinoma, Mx-1 mammary

adenocarcinoma, ST-15 and SC-16 gastric adenocarcinomas). Irinotecan is also active against tumours expressing the P-glycoprotein (vincristine- and doxorubicin-resistant P388 leukemias). Beside the antitumour activity of **IROCAN**, the most relevant pharmacological effect of irinotecan is the inhibition of acetylcholinesterase.

5.2 Pharmacokinetic properties

Absorption

A large interindividual variability in pharmacokinetic parameters is generally observed for SN-38.

Distribution

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

Biotransformation

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 mainly via the bile and 22% in urine.

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

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

• Cytochrome P450 3A enzymes-dependent oxidations resulting in opening of the outer piperidine ring with formation of APC (aminopentanoic acid derivate) and NPC (primary amine derivate) (see section 4.5).

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

Elimination

SN-38 exhibits a biphasic elimination profile with a terminal half-life of about 14 hours**.**

SN-38 is mainly eliminated by glucuronidation, predominantly by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). Irinotecan is partly metabolised by cytochrome P450 isoenzyme CYP3A4 and perhaps CYP3A5. More than 50% of an intravenous dose of irinotecan is excreted as unchanged medicine with 30% in the faeces via the bile and about 20 % in the urine.

Linearity/non-linearity

A population pharmacokinetic analysis of irinotecan has been performed in 148 patients with metastatic colorectal cancer, treated with various schedules and at different doses in phase II trials. Pharmacokinetic parameters estimated with a three-compartment model were similar to those observed in phase I studies. All studies have shown that irinotecan (CPT-11) and SN-38 exposure increase proportionally with CPT-11 administered dose; their pharmacokinetics are independent of the number of previous cycles and of the administration schedule.

Pharmacokinetic/Pharmacodynamic relationship(s)

The intensity of the major toxicities encountered with CAMPTO (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.

5.3. Pre-Clinical safety data

IROCAN and SN-38 have been shown to be mutagenic *in vitro* in the chromosomal aberration test on CHO-cells as well as in the *in vivo* micronucleus test in mice.

However, they have been shown to be devoid of any mutagenic potential in the Ames test.

In rats treated once a week during 13 weeks at the maximum dose of 150 mg/m^2 (which is less than half the human recommended dose), no treatment related tumours were reported 91 weeks after the end of treatment.

Single- and repeated-dose toxicity studies with **IROCAN** have been carried out in mice, rats and dogs. The main toxic effects were seen in the haematopoietic and lymphatic systems. In dogs, delayed diarrhoea associated with atrophy and focal necrosis of the intestinal mucosa was reported. Alopecia was also observed in the dog.

The severity of these effects was dose-related and reversible.

Reproduction

Irinotecan was teratogenic in rats and rabbits at doses below the human therapeutic dose. In rats, pups born to treated animals with external abnormalities showed a decrease in fertility. This was not seen in morphologically normal pups. In pregnant rats there was a decrease in placental weight and in the offspring a decrease in fetal viability and increase in behavioural abnormalities.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients: Sorbitol, lactic acid, water for injection, sodium hydroxide, hydrochloric acid.

6.2 Incompatibilities

None known.

In the absence of compatibility studies, **IROCAN** must not be mixed with other medicines.

6.3 Shelf life

3 years for the unused product. Refer section 6.4 for diluted solution.

6.4 Special Precautions for storage

Single-dose vials of **IROCAN** 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 at or below 25 ºC or 4 days under refrigeration (2 – 8ºC).

Discard any unused portion thereafter. Do not freeze.

6.5 Nature and contents of container

Type 1 amber coloured glass vials containing a clear, slightly yellow solution.

IROCAN 40 mg/2 ml: Carton containing one single-dose type I amber glass vials of **IROCAN** 40 mg/2 ml.

IROCAN 100 mg/5 ml: Carton containing one single-dose, type I amber glass vials of **IROCAN** 100 mg/5ml.

IROCAN 300 mg/15 ml: Carton containing one single-dose, type I amber glass vials of **IROCAN** 300 mg/5 ml

IROCAN 500 mg/25 ml: Carton containing one single-dose, type I amber glass vials of **IROCAN** 500 mg/5 ml

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Innovata Pharmaceuticals

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2092

South Africa

8. REGISTRATION NUMBERS

IROCAN 40 A 50/26/0947

IROCAN 100 A 50/26/0948

IROCAN 300 A 50/26/0949

IROCAN 500 A 50/26/0950

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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