Package Insert

SCHEDULING STATUS: **S4**

PROPRIETARY NAME AND DOSAGE FORM:

HYCAMTIN® 0,25 mg Hard Capsules

HYCAMTIN® 1 mg Hard Capsules

COMPOSITION:

HYCAMTIN 0,25 mg: Each hard capsule contains topotecan hydrochloride equivalent to 0,25 mg topotecan free base.

HYCAMTIN 1 mg: Each hard capsule contains topotecan hydrochloride equivalent to 1 mg topotecan free base.

List of excipients: Hydrogenated vegetable oil, glyceryl monostearate, gelatin, titanium dioxide. Black printing ink comprising black iron oxide (E172), shellac, anhydrous ethanol, propylene glycol, isopropyl alcohol, butanol, concentrated ammonia solution and potassium hydroxide.

1 mg capsules also contain red iron oxide.

PHARMACOLOGICAL CLASSIFICATION:

A 26 Cytostatic agents

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

The anti-tumour activity of topotecan involves the inhibition of topoisomerase-I, an enzyme intimately involved in DNA replication as it relieves the torsional strain introduced ahead of the moving replication fork. Topotecan inhibits topoisomerase-I by stabilising the covalent complex of enzyme and strand-cleaved DNA which is an intermediate of the catalytic mechanism.

Pharmacokinetics:

***Absorption*:**

Oral topotecan is well absorbed with peak plasma concentrations occurring between 1 to 2 hours following oral administration.

Following a high-fat meal, the extent of exposure was similar in the fed and fasted state while T_{max} was delayed from 1,5 to 3 hours (topotecan lactone) and from 3 to 4 hours (total topotecan).

Distribution:

Following oral administration, the plasma concentrations decline bi-exponentially. The pharmacokinetics of oral topotecan are dose proportional. There is little or no accumulation of either formulation of topotecan with repeated daily dosing, and there is no evidence of a change in the pharmacokinetics with multiple dosing.

The binding of topotecan to plasma proteins was low (35 %) and its distribution between blood cells and plasma was homogeneous.

Metabolism:

A major route of inactivation of topotecan is a reversible pH-dependent ring opening to the inactive carboxylate form.

Metabolism accounts for less than 10 % of the elimination of topotecan. An N-desmethyl metabolite was found in urine, plasma, and faeces.

Following oral administration the mean metabolite: parent AUC ratio was less than 10 % for both total topotecan and topotecan lactone. An O-glucuronide of topotecan and N-desmethyl topotecan has been identified in the urine.

In vitro, topotecan did not inhibit human cytochrome P450 enzymes CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A, or CYP4A nor did it inhibit the human cytosolic enzymes dihydropyrimidine dehydrogenase or xanthine oxidase.

Elimination:

The pharmacokinetics of topotecan after oral administration have been evaluated in cancer patients following doses of 1,2 to 3,1 mg/m^2 and 4 mg/dose administered daily for 5 days. Oral topotecan exhibits a mean terminal half-life of approximately 3,0 to 6,0 hours.

Overall recovery of medicine-related material following five daily doses of topotecan was 49 % to 71 % of the administered oral dose. Approximately 20 % was excreted as total topotecan and 2 % was excreted as N-desmethyl topotecan in the urine. Faecal elimination of total topotecan accounted for 33 % while faecal elimination of N-desmethyl topotecan was 1,5 %. Overall, the N-desmethyl metabolite

contributed a mean of less than 6 % (range 4-8 %) of the total medicine related material accounted for in the urine and faeces.

Special Patient Populations:

In a population study, a number of factors including age, weight and ascites had no significant effect on clearance.

Renal impairment:

Patients with small cell lung carcinoma who participated in oral topotecan clinical trials had a serum creatinine less than or equal to 133 µmol/ℓ (1,5 mg/dl) or a creatinine clearance (Cl_{cr}) of greater than or equal to 60 ml/min. Dosing recommendations for patients receiving oral topotecan with Cl_{cr} less than 60 ml/min have not been established.

Hepatic impairment:

Pharmacokinetics of topotecan capsules have not been specifically studied in patients with impaired hepatic function.

INDICATIONS:

HYCAMTIN hard capsules are indicated for the palliative treatment of small cell lung carcinoma, as a second-line chemotherapeutic agent in patients who have relapsed after an initial response to treatment with first-line chemotherapeutic agents.

CONTRA-INDICATIONS:

HYCAMTIN is contra-indicated in patients who

- have a history of severe hypersensitivity reactions to topotecan and/or its excipients
- are pregnant or breastfeeding (see PREGNANCY AND LACTATION)
- already have severe bone marrow depression prior to starting first course, as evidenced by baseline neutrophils less than 1,5 x 10^9/ℓ and/or a platelet count of less than or equal to 100 x 10^9/ℓ.

WARNINGS:

HYCAMTIN should be initiated under the direction of a medical practitioner experienced in the use of cytotoxic agents.

Haematological toxicity is dose-related and full blood count including platelets should be monitored regularly (see DOSAGE AND DIRECTIONS FOR USE).

HYCAMTIN can cause severe myelosuppression. Myelosuppression leading to sepsis and fatalities due to sepsis have been reported in patients treated with HYCAMTIN (see SIDE EFFECTS AND SPECIAL PRECAUTIONS).

HYCAMTIN-induced neutropenia can cause neutropenic colitis. Fatalities due to neutropenic colitis have been reported in clinical trials with HYCAMTIN. In patients presenting with fever, neutropenia, and a compatible pattern of abdominal pain, the possibility of neutropenic colitis should be considered.

Dose adjustment may be necessary if HYCAMTIN is administered in combination with other cytotoxic agents (see INTERACTIONS).

Diarrhoea, including severe diarrhoea requiring hospitalisation, has been reported during treatment with oral HYCAMTIN. The incidence of diarrhoea has been reported to be greater in patients receiving oral HYCAMTIN compared to those receiving HYCAMTIN i.v. Additionally, in patients with relapsing small cell lung cancer, greater than 65 years of age, there is substantially higher risk of severe diarrhoea and subsequent hospitalisation than in patients less than 65 years of age.

Communication with patients prior to medicine administration regarding diarrhoea and proactive management of all signs of diarrhoea is important. Medical practitioners are advised to follow guidelines that describe the aggressive management of this event. This includes use of anti-diarrhoeal agents, administration of fluids and electrolytes and interruption or discontinuation of therapy with oral HYCAMTIN. Diarrhoea related to oral HYCAMTIN can occur at the same time as medicine-related neutropenia and its sequelae.

INTERACTIONS:

Myelosuppression is enhanced when HYCAMTIN is used in combination with other cytotoxic agents (e.g. paclitaxel or etoposide) thereby necessitating dose reduction.

However, in combining with platinum agents (e.g. cisplatin or carboplatin), there is a distinct sequence-dependent interaction depending on whether the platinum agent is given on day 1 or 5 of the HYCAMTIN dosing.

Topotecan does not inhibit human cytochrome P450 enzymes (see Pharmacokinetics).

Topotecan is a substrate for both ABCG2 (BCRP) and ABCB1 (P-glycoprotein). Inhibitors of ABCB1 and ABCG2 (e.g. elacridar) administered with oral HYCAMTIN increased topotecan exposure.

Cyclosporin A (an inhibitor of ABCB1, ABCC1 [MRP-1], and CYP3A4) with oral HYCAMTIN increased topotecan AUC.

Patients should be carefully monitored for adverse events when oral HYCAMTIN is administered with a medicine known to inhibit ABCG2 or ABCB1 (see Pharmacokinetics).

The pharmacokinetics of topotecan were generally unchanged when co-administered with ranitidine.

PREGNANCY AND LACTATION:

Pregnancy:

HYCAMTIN has been shown to be both embryotoxic and foetotoxic in preclinical studies. HYCAMTIN may cause foetal harm when administered to pregnant women and therefore is contra-indicated during pregnancy. Women should be advised to avoid becoming pregnant during therapy with HYCAMTIN and to inform the treating medical practitioner immediately should this occur (see CONTRA-INDICATIONS).

Lactation:

HYCAMTIN is contra-indicated during breastfeeding.

DOSAGE AND DIRECTIONS FOR USE:

Prior to administration of the first course of HYCAMTIN, patients must have a baseline neutrophil count of more than or equal to 1,5 x 10^9/ℓ, a platelet count of more than or equal to 100 x 10^9/ℓ and a haemoglobin level of more than or equal to 9 g/dl (after transfusion if necessary).

The hard capsule(s) must be swallowed whole, and must not be chewed, crushed or divided.

HYCAMTIN hard capsules may be taken with or without food.

Initial dose:

The recommended dose of HYCAMTIN hard capsules is 2,3 mg/m^2 daily for five consecutive days every 21 days.

Subsequent doses:

For patients who experience Grade 3 or 4 diarrhoea, the HYCAMTIN capsules dose should be reduced by 0,4 mg/m^2/day for subsequent courses (see WARNINGS). Patients with Grade 2 diarrhoea may need to follow the same dose modification guidelines.

HYCAMTIN should not be re-administered unless the neutrophil count is more than or equal to 1 x 10^9/ℓ, the platelet count is more than or equal to 100 x 10^9/ℓ, and the haemoglobin level is more than or equal to 9 g/dl (after transfusion if necessary).

Patients who experience severe neutropenia (neutrophil count less than or equal to 0,5 x 10^9/ℓ) for seven days or more, or severe neutropenia associated with fever or infection, or who have had treatment delayed due to neutropenia, should be treated as follows:

either

- reduce the dose by 0,4 mg/m^2/day to 1,9 mg/m^2/day (or subsequently down to 1,5 mg/m^2/day if necessary)

  Doses should be similarly reduced if the platelet count falls below 25 x 10^9/ℓ.

  In clinical trials, HYCAMTIN hard capsules were discontinued if the dose had to be reduced below 1,5 mg/m^2.

or

- be given G-CSF prophylactically in subsequent courses to maintain dose intensity starting from day six of the course (the day after completion of the HYCAMTIN administration). If neutropenia is not adequately managed with G-CSF administration, doses should be reduced.

Instructions for Use/Handling:

HYCAMTIN capsules must not be opened or crushed. If the capsules are punctured or leaking, you should immediately wash your hands thoroughly with soap and water. If you get it in your eyes, wash them immediately with gently flowing water for at least 15 minutes. Consult your doctor/healthcare provider after eye contact or if you experience a skin reaction.

Special Populations:

Children:

Due to limited data on efficacy and safety in the paediatric population, no recommendation for treatment of children with HYCAMTIN can be given.

Elderly:

No overall differences in effectiveness were observed between patients over 65 years and younger adult patients. However it has been reported that patients older than 65 years old receiving oral HYCAMTIN experienced an increase in drug related diarrhoea compared to those younger than 65 years of age (see WARNINGS and SIDE EFFECTS AND SPECIAL PRECAUTIONS).

Renal impairment:

Dosing recommendations for patients receiving oral HYCAMTIN with a creatinine clearance less than 60 ml/min have not been established.

Hepatic impairment: Pharmacokinetics of HYCAMTIN hard capsules have not been specifically studied in patients with impaired hepatic function.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (greater than or equal to 1/10), common (greater than or equal to 1/100 and less than 1/10), uncommon (greater than or equal to 1/1 000 and less than 1/100), rare (greater than or equal to 1/10 000 and less than 1/1 000) and very rare (less than 1/10 000) including isolated reports, not known (cannot be estimated from the available data). Very common, common and uncommon events were generally determined from clinical trial data.

Infections and Infestations

Very common: infections

Common: sepsis (see WARNINGS)

Blood and lymphatic system disorders

Very common: anaemia, febrile neutropenia, leucopenia (see *Gastrointestinal disorders*), neutropenia, thrombocytopenia

Common: pancytopenia

Unknown: severe bleeding (associated with thrombocytopenia)

Immune system disorders

Common: hypersensitivity, including rash

Metabolism and nutrition disorders

Very common: anorexia (which may be severe)

Gastrointestinal disorders

Very common: diarrhoea# (see WARNINGS), nausea and vomiting (all of which may be severe), abdominal pain*, constipation and stomatitis.

*with oral HYCAMTIN the overall incidence of medicine-related diarrhoea was 22 %, including 4 % with Grade 3 and 0,4 % with Grade 4. Medicine-related diarrhoea was more frequent in patients greater than or equal to 65 years of age (28 %) compared to those less than 65 years of age (19 %). After i.v. HYCAMTIN, medicine related diarrhoea in patients greater than 65 years of age was 10 %.

* Neutropenic colitis, including fatal neutropenic colitis, has been reported to occur as a complication of HYCAMTIN-induced neutropenia (see WARNINGS).

Hepatobiliary disorders

Common: hyperbilirubinaemia

Skin and subcutaneous disorders

Very common: alopecia

General disorders and administrative site conditions

Very common: asthenia, fatigue, pyrexia

Common: malaise

Special Precautions:

Effects on Ability to Drive and Use Machines: Caution should be observed when driving or operating machinery if fatigue and asthenia persist.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms and Signs:

The primary complications of overdosage are anticipated to be bone marrow suppression and stomatitis.

Treatment:

There is no known antidote for HYCAMTIN overdosage.

IDENTIFICATION:

HYCAMTIN 0,25 mg: Opaque white to yellowish white hard gelatin capsules, imprinted with HYCAMTIN 0.25 mg

HYCAMTIN 1 mg: Opaque pink hard gelatin capsules, imprinted with HYCAMTIN 1 mg

PRESENTATION:

HYCAMTIN capsules are supplied in a white, opaque, PVC/PCTFE/aluminium, child resistant ('peel-push' layer) blister strip of 10 capsules.

STORAGE INSTRUCTIONS:

Store in a refrigerator (2 °C to 8 °C). Do not freeze.

Keep blister cards in the outer carton in order to protect from light.

Keep out of reach of children.

REGISTRATION NUMBERS:

HYCAMTIN 0,25 mg: 42/26/0739

HYCAMTIN 1 mg: 42/26/0740

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

Sandoz SA (Pty) Ltd[1]

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[1] Company Reg. No.: 1990/001979/07