190 mm

480 mm

10000000042897

HYCAMTIN™

Intravenous Injection

topotecan hydrochloride

WARNING

HYCAMTIN (topotecan hydrochloride) for Injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Therapy with **HYCAMTIN** should not be given to patients with baseline neutrophil counts of less than 1500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection and death, frequent peripheral blood cell counts should be performed on all patients receiving **HYCAMTIN**.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 4 mg vial contains 4 mg topotecan as topotecan hydrochloride. (see *excipients*)

PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
Topotecan is a white powder

INDICATIONS AND USAGE

HYCAMTIN monotherapy is indicated for the treatment of:

- Metastatic carcinoma of the ovary after failure of first-line or subsequent therapy.
- Relapsed small cell lung cancer sensitive disease after failure of first-line chemotherapy.

HYCAMTIN in combination with cisplatin is indicated for the treatment of:

- Patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IVB disease. Patients with prior exposure to cisplatin require a sustained treatment-free interval to justify treatment with the combination.

CONTRAINDICATIONS

HYCAMTIN is contraindicated in patients who have a history of hypersensitivity reactions to topotecan or to any of its ingredients. **HYCAMTIN** should not be used in patients who are pregnant or breast-feeding, or those with 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.

PRECAUTIONS

Topotecan should be administered under the direction of a physician experienced in the use of cytotoxic agents.
Haematological toxicity is dose-related and full blood count including platelets should be monitored regularly.
In common with other cytotoxic drugs, severe myelosuppression leading to sepsis and and fatalities due to sepsis have been reported in patients treated with topotecan.
Topotecan-induced neutropenia can cause neutropenic colitis. Fatalities due to neutropenic colitis have been reported in clinical trials with topotecan. 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 topotecan is administered in combination with other cytotoxic agents (see *Interactions*).

INTERACTIONS

As with other myelosuppressive cytotoxic agents, greater myelosuppression is likely to be seen when topotecan is used in combination with other cytotoxic agents (e.g. paclitaxel or etoposide) thereby necessitating dose reduction. However, in combining with platinum agents, there is a distinct sequence-dependent interaction depending on whether the platinum agent is given on day 1 or 5 of the topotecan dosing. If either cisplatin or carboplatin is given on day 1 of the topotecan dosing, lower doses of each agent must be given compared to the doses which can be given if the platinum agent is given on day 5 of the topotecan dosing.
Examples of doses and schedules which have been tested in phase I/II studies in first-line patients include:

1. cisplatin day 1: 50 mg/m^2 with topotecan 0.75 mg/m^2 days 1 to 5
2. cisplatin day 5: 50 mg/m^2 with topotecan 1.25 mg/m^2 days 1 to 5
3. carboplatin day 1: AUC 5 (Calvert formula); topotecan 0.5 mg/m^2 days 1 to 5
4. carboplatin day 5: AUC 5 (isotope creatinine clearance); topotecan 1.0 mg/m^2 days 1 to 5.

HYCAMTIN When given in combination with cisplatin (cisplatin day 1, topotecan days 1 to 5), the clearance of topotecan was reduced on day 5 compared to day 1 (19.1 L/h/m2 compared to 21.3 L/h/m^2).
Topotecan does not inhibit human cytochrome P450 enzymes. In population studies, the co-administration (in separate lines or by separate routes) of granisetron, ondansetron, morphine or corticosteroids did not appear to have a significant effect on the pharmacokinetics of topotecan.
When topotecan (0.75 mg/m^2/day for 5 consecutive days) and cisplatin (60 mg/m^2/day on Day 1) were administered in 13 patients with ovarian cancer, mean topotecan plasma clearance on Day 5 was slightly reduced compared to values on Day 1. As a result, systemic exposure of total topotecan, as measured by AUC and Cmax, on Day 5 was increased by 12% (95% CI; 2%, 24%) and 23% (95% CI; -7%, 63%), respectively. No pharmacokinetic data are available following topotecan (0.75 mg/m^2/day for 3 consecutive days) and cisplatin (50 mg/m^2/day on Day 1) in patients with cervical cancer.
Topotecan is a substrate for both ABCG2 (BCRP) and ABCB1 (P-glycoprotein). Inhibitors of ABCB1 and ABCG2 (eg. elacridar) administered with oral topotecan increased topotecan exposure. The effect of elacridar on the pharmacokinetics of intravenous topotecan was much less than the effect on oral topotecan.

PREGNANCY

Topotecan has been shown to be both embryotoxic and foetotoxic in preclinical studies. As with other cytotoxic drugs, topotecan may cause foetal harm when administered to pregnant women and therefore is contraindicated during pregnancy. Women should be advised to avoid becoming pregnant during therapy with topotecan and to inform the treating physician immediately should this occur.

LACTATION

Topotecan is contraindicated during breast-feeding. It is not known whether the drug is excreted in human breast milk. Breast-feeding should be discontinued when women are receiving **HYCAMTIN** (see *Contraindications*).

ABILITY TO PERFORM TASKS THAT REQUIRE JUDGEMENT, MOTOR OR COGNITIVE SKILLS

Caution should be observed when driving or operating machinery if fatigue and asthenia persist.

ADVERSE REACTIONS

Clinical Trial Data

Prolonged use is not associated with an increase in the rate of toxicity as observed in an analysis of 2991 courses from 523 patients with relapsed ovarian cancer who have received up to 33 consecutive courses. For patients who received prolonged treatment there was no increase in the incidence of toxicity when the first six courses of treatment are compared with subsequent courses.
No evidence of significant cardiotoxicity, neurotoxicity or major organ toxicity has been observed with topotecan.
Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<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.
Topotecan clinical trials usually did not include a placebo arm, therefore background rates were not taken into account when assigning frequency categories and all reports of these adverse events have been used.
The following frequencies are estimated at the standard recommended doses of topotecan according to indication and formulation.

Infections and infestations
Very Common: Infection
Common: sepsis (see *Warnings and Precautions*)

Blood and lymphatic system disorders
Very Common: Anaemia, febrile neutropenia, leucopenia, neutropenia, thrombocytopenia
Common: Pancytopenia
Not known: 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, nausea and vomiting (all of which may be severe), abdominal pain*, constipation and stomatitis.
*Neutropenic colitis, including fatal neutropenic colitis, has been reported to occur as a complication of topotecan-induced neutropenia.

Hepatobiliary disorders
Common: Hyperbilirubinaemia

Skin and subcutaneous disorders
Very Common: Alopecia

General disorders and administrative site conditions
Very Common: Asthenia, fatigue, pyrexia
Common: Malaise
Very Rare: Extravasation
Reactions associated with extravasation have been mild and have not generally required specific therapy.

OVERDOSAGE

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

Treatment
There is no known antidote for topotecan overdosage.

DOSAGE AND ADMINISTRATION

The use of **HYCAMTIN** should be confined to units specialised in the administration of cytotoxic chemotherapy and should only be administered under the supervision of a physician experienced in the use of chemotherapy.
When used in combination with cisplatin, the full prescribing information for cisplatin should be consulted.
Prior to administration of the first course of **HYCAMTIN**, patients must have a baseline neutrophil count of ≥1.5 x 10^9/l, and a platelet count of ≥100 x 10^9/l. **HYCAMTIN** must be reconstituted and further diluted before use.

Ovarian and Small Cell Lung Carcinoma

Initial dose: The recommended dose of **HYCAMTIN** is 1.5 mg/m^2 body surface area/day administered by intravenous infusion over 30 minutes daily for 5 consecutive days with a 3 week interval between the start of each course. If well-tolerated, treatment may continue until disease progression.
Subsequent doses: HYCAMTIN should not be re-administered unless the neutrophil count is ≥1 x 10^9/l, the platelet count is ≥100 x 10^9/l, and the haemoglobin level is ≥9g/dl (after transfusion if necessary).
Patients who experience severe neutropenia (neutrophil count <0.5 x 10^9/l) for 7 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 be given a reduced dose i.e. 1.25 mg/m^2/day (or subsequently down to 1.0 mg/m^2/day if necessary) or be given G-CSF prophylactically in subsequent courses to maintain dose intensity, starting from day 6 of the course (the day after completion of **HYCAMTIN** administration). If neutropenia is not adequately managed with G-CSF administration, doses should be reduced.
Doses should be similarly reduced if the platelet count falls below 25 x 10^9/l. In clinical trials, **HYCAMTIN** was discontinued if the dose had been reduced to 1.0 mg/m^2 and a further dose reduction was required to manage adverse effects.

Cervical Carcinoma

Initial dose: The recommended dose of **HYCAMTIN** is 0.75 mg/m^2/day administered as 30 minute intravenous infusion daily on days 1, 2 and 3. Cisplatin is administered as an intravenous infusion on day 1 at a dose of 50 mg/m^2/day and following the **HYCAMTIN** dose. This treatment schedule is repeated every 21 days for 6 courses or until progressive disease.
Subsequent doses: HYCAMTIN should not be re-administered unless the neutrophil count is more than or equal to 1.5 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 9g/dl (after transfusion if necessary).
Patients who experience febrile neutropenia (neutrophil count less than 1 x 10^9/l with a temperature of 38ºC or above) are recommended to have the dose of **HYCAMTIN** reduced by 20% to 0.60 mg/m^2/day for subsequent courses.
As an alternative to dose reduction, in the event of febrile neutropenia, patients are recommended to be given G-CSF following the subsequent course (before resorting to dose reduction) starting from day 4 of the course (at least 24 hours after completion of **HYCAMTIN** administration).
If febrile neutropenia occurs despite the use of G-CSF, it is recommended that the dose of **HYCAMTIN** be reduced a further 20% to 0.45 mg/m^2/day for subsequent courses.
Patients whose platelet count falls below 10 x 10^9/l are recommended to have the dose of **HYCAMTIN** reduced by 20% to 0.60 mg/m^2/day.

Dosage in renally-impaired patients

Monotherapy (Ovarian and Small cell lung carcinoma): Insufficient data are available to make a recommendation for patients with a creatinine clearance < 20 ml/min. Limited data indicate that the dose should be reduced in patients with moderate renal impairment. The recommended monotherapy dose of **HYCAMTIN** in patients with ovarian or small cell lung cancer and a creatinine clearance between 20 and 39 ml/min is 0.75 mg/m^2 /day for 5 consecutive days.
Combination therapy (Cervical carcinoma): In clinical studies with **HYCAMTIN** in combination with cisplatin for the treatment of cervical cancer, therapy was only initiated in patients with serum creatinine less than or equal to 1.5 mg/dL. If, during **HYCAMTIN** /cisplatin combination therapy serum creatinine exceeds 1.5 mg/dL, it is recommended that the full prescribing information be consulted for any advice on cisplatin dose reduction/continuation.
If cisplatin is discontinued, there are insufficient data regarding continuing monotherapy with **HYCAMTIN** in patients with cervical cancer.

Children

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

Clinical Studies

Cervical carcinoma

In a randomised, comparative phase III trial conducted by the Gynaecological Oncology Group (GOG 0179), topotecan plus cisplatin (n=147) was compared with cisplatin alone (n=146) for the treatment of confirmed Stage IV-B, recurrent or persistent carcinoma of the cervix where curative treatment with surgery and/or radiation was not considered appropriate. No patient had received primary chemotherapy with cisplatin or any other cytotoxic agent. The overall response rate in the topotecan plus cisplatin group of 24% was significantly higher (p=0.0073) than the 12% achieved in the cisplatin alone group. The complete response rate in the topotecan plus cisplatin and cisplatin alone arms were 10% and 3% respectively. This was associated with a longer progression survival of 4.6 (range 3.5 to 5.7) months versus 2.9 (range 2.6 to 3.5) months (p=0.026) and a longer overall survival of 9.4 (range 7.9 to 11.9) months compared to 6.5 (range 5.8 to 8.8) months (p=0.033) in the topotecan plus cisplatin arm compared to the cisplatin alone arm. The 1 year survival rate in the topotecan plus cisplatin group was 40.4% (95% CI; 32.3, 48.5) compared to 28% (95% CI; 20.6, 35.4) in the cisplatin alone group. Two year survival was 11.9 % (95% CI; 5.5, 18.3) and 7.1% (95% CI; 2.0, 12.2) for the two patient populations respectively. The secondary endpoint of Quality of Life (QoL) was assessed using the Functional Assessment of Cancer Therapy-Cervix Cancer, Brief Pain Inventory as well as the UNISCALE. QoL readings were taken prior to randomisation, prior to cycles 2 and 5 of treatment and 9 months post-randomisation. Compared to cisplatin alone, the increased haematological toxicity seen with the combination of topotecan and cisplatin did not significantly reduce the patient Quality of Life outcomes.

SHELF-LIFE

Vials:
As indicated on the outer packaging.
Reconstituted and diluted solutions
The product should be used immediately after reconstitution as it contains no antibacterial preservative. If reconstitution and dilution is performed under strict aseptic conditions (e.g. an LAF bench) the product should be used (infusion completed) within 12 hours at room temperature or 24 hours if stored at 2-8°C after the first puncture of the vial.

HOW SUPPLIED

Hycamtin (topotecan hydrochloride) for injection is supplied in 4 mg (free base) single-dose vials in package of 1 vial and 5 vials.

STORAGE:

Store in dry place below 30°C.
Keep the vial in the outer carton in order to protect from light.

List of excipients
Tartaric acid (E334)
Mannitol (E421)
Hydrochloric acid (E507)
Sodium hydroxide

HANDLING AND DISPOSAL:

HYCAMTIN 4 mg vials must be reconstituted with 4 ml water for injections. The reconstituted solution is pale yellow in colour and provides 1 mg per ml of topotecan. Further dilution of the appropriate volume of the reconstituted solution with either 0.9 % w/v sodium chloride intravenous infusion or 5 % w/v glucose intravenous infusion is required to a final concentration of between 25 and 50 microgram/ml.
Procedures for proper handling and disposal of anticancer drugs should be used. Personnel should be trained to reconstitute the medicinal product.
Pregnant staff should be excluded from working with this medicinal product.
Personnel handling this medicinal product during reconstitution should wear protective clothing including mask, goggles and gloves.
All items for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high-temperature incineration. Liquid waste may be flushed with large amounts of water.
Accidental contact with the skin or eyes should be treated immediately with copious amounts of water.

Manufactured by: GlaxoSmithKline Manufacturing S.p.A., Parma, Italy
HYCAMTIN is a trademark of the GlaxoSmithKline group of companies

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THIS IS A MEDICAMENT
Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children.

Council of Arab Health Ministers,
Union of Arab Pharmacists.

GlaxoSmithKline

180 mm Measuring Bar

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