NOVARTIS

For the use of only Registered Medical Practitioners or a Hospital or a Laboratory.

Topotecan Hydrochloride for Injection

HYCAMTIN®

Antineoplastic agents.

DESCRIPTION AND COMPOSITION

Pharmaceutical form

A sterile, lyophilized powder in single-dose vials for intravenous (i.v.) infusion following reconstitution and further dilution.

Powder for solution for infusion, 1 mg and 4 mg.

Each 1 mg vial contains 1 mg topotecan as topotecan hydrochloride, with a 10% overage of fill.

Each 4 mg vial contains 4 mg topotecan as topotecan hydrochloride.

Certain dosage strengths may not be available in all countries.

Active Moiety

Topotecan hydrochloride.

Excipients

Tartaric acid (Ph Eur), Mannitol (Ph Eur), Hydrochloric acid (Ph Eur), Sodium hydroxide (Ph Eur).

INDICATIONS

HYCAMTIN is indicated for the treatment of:

- Metastatic ovarian cancer after failure of first line chemotherapy.
- Small cell lung cancer sensitive disease after failure of first-line chemotherapy. In clinical studies submitted to support approval, sensitive disease was defined as disease responding to chemotherapy but subsequently progressing at least 60 days (in the Phase 3 study) or at least 90 days (in the Phase 2 studies) after chemotherapy.
- *HYCAMTIN* in combination with cisplatin is indicated for the treatment of patients with histologically confirmed Stage IV-B, recurrent, or persistent carcinoma of the cervix, which is not amenable to curative treatment with surgery and/or radiation therapy.

For efficacy data see Clinical Studies.

DOSAGE REGIMEN AND ADMINISTRATION

Hycamtin must be reconstituted and further diluted before use (see section INSTRUCTIONS FOR USE AND HANDLING).

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 hemoglobin level of more than or equal to 9 g/dL (after transfusion if necessary).

Populations - Adults and Elderly

Ovarian and small cell lung carcinoma Initial dose

The recommended dose of Hycamtin is 1.5 mg/m^2 by intravenous infusion over 30 minutes daily for 5 consecutive days, starting on day 1 of a 21-day course. In the absence of tumor progression, a minimum of 4 courses is recommended because tumor response may be delayed. The median time to response in three ovarian clinical trials was 7.6 to 11.7 weeks and median time to response in four small cell lung cancer trials was 6.1 weeks.

Subsequent doses

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 hemoglobin level is more than or equal to 9 g/dL (after transfusion if necessary).

Standard oncology practice for the management of neutropenia is either to administer Hycamtin with other medications (e.g. G-CSF) or to reduce the dose to maintain neutrophil counts.

If dose reduction is chosen for patients who experience severe neutropenia (neutrophil count less than or equal to 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, the dose should be reduced by 0.25 mg/m^2/day to 1.25 mg/m^2/day (or subsequently down to 1.0 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, topotecan powder for i.v. infusion was discontinued if the dose had to be reduced below 1.0 mg/m^2.

Cervical Cancer

Initial dose

The recommended dose of Hycamtin is 0.75 mg/m^2 administered as a 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 and following the Hycamtin dose. This treatment schedule is repeated every 21 days for 6 courses or until disease progression.

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 9 g/dL (after transfusion if necessary).

Standard oncology practice for the management of neutropenia is either to administer Hycamtin with other medications (e.g. G-CSF) or to reduce the dose to maintain neutrophil counts.

If dose reduction is chosen for patients who experience severe neutropenia (neutrophil count less than 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, the dose should be reduced by 20% to 0.60 mg/m^2 for subsequent courses (or subsequently down to 0.45 mg/m^2/day).

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

Dosage in Combination

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

Special Populations

Pediatric patients (below 18 years)

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

Geriatric patients (65 years or above)

No dosage adjustment appears to be needed in the elderly, other than adjustments related to renal function.

Renal impairment

Monotherapy

No dosage adjustment appears to be required for treating patients with mild renal impairment (creatinine clearance 40 to 60 mL/min.). Dosage adjustment to 0.75 mg/m^2 is recommended for patients with a creatinine clearance of 20 to 39 mL/min. Insufficient data are available in patients with severe renal impairment to provide a dosage recommendation. Advice on dosing of Hycamtin for patients with moderate renal impairment (20 to 39 mL/min) is based on studies involving patients with advanced cancer.

Combination therapy

It is recommended that Hycamtin in combination with cisplatin for the treatment of cervical cancer only be 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 topotecan in patients with cervical cancer.

Hepatic impairment

Monotherapy

No dosage adjustment appears to be required for treating patients with impaired hepatic function (serum bilirubin in the range 1.5 to 10 mg/dL).

CONTRAINDICATIONS

Hycamtin is contra-indicated in patients who

- have a history of severe hypersensitivity reactions to topotecan and/or its excipients
- are pregnant or breast-feeding (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL)
- 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 100 x 10^9/L.

WARNINGS AND PRECAUTIONS

Hycamtin should be initiated under the direction of a physician experienced in the use of cytotoxic agents.

Hematological toxicity is dose-related and full blood count including platelets should be monitored regularly (see section DOSAGE REGIMEN AND ADMINISTRATION).

As with other cytotoxic drugs, Hycamtin can cause severe myelosuppression. Myelosuppression leading to sepsis and fatalities due to sepsis have been reported in patients treated with Hycamtin (see section ADVERSE DRUG REACTIONS).

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.

Hycamtin has been associated with reports of interstitial lung disease (ILD), some of which have been fatal (see section ADVERSE DRUG REACTIONS). Underlying risk factors include history of ILD, pulmonary fibrosis, lung cancer, thoracic exposure to radiation and use of pneumotoxic drugs and/or colony stimulating factors. Patients should be monitored for pulmonary symptoms indicative of ILD (e.g. cough, fever, dyspnea and/or hypoxia), and Hycamtin should be discontinued if a new diagnosis of ILD is confirmed.

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

Driving and using machines

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

ADVERSE DRUG REACTIONS

In the intravenous topotecan studies for treatment of ovarian cancer, prolonged use (more than six courses) of topotecan was not associated with an increase in the rate of haematologic toxicity.

The following frequencies are estimated at the standard recommended doses of topotecan according to indication and formulation.

Further information regarding incidence and grade of toxicity is presented in the Clinical Studies section.
Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1 Percentage of patients with adverse drug reactions in clinical trials

Infections and infestations	
Very Common	Infection
Common	Sepsis (see section WARNINGS AND PRECAUTIONS)
Blood and lymphatic system disorders	
Very Common	Anaemia, febrile neutropenia, leucopenia, neutropenia [2](see Gastrointestinal disorders), thrombocytopenia
Common	Pancytopenia
Immune system disorders	
Common	Hypersensitivity, including rash
Metabolism and nutrition disorders	
Very Common	Anorexia (which may be severe)
Respiratory, thoracic and mediastinal disorders	
Rare	Interstitial lung disease
Gastrointestinal disorders	
Very Common	Diarrhoea[1] (see section WARNINGS AND PRECAUTIONS), nausea and vomiting (all of which may be severe), abdominal pain[2], constipation and stomatitis.
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[3] (i.v. formulation only)

[1]With oral topotecan the overall incidence of drug-related diarrhea was 22%, including 4% with Grade 3 and 0.4% with Grade 4. With oral topotecan, drug-related diarrhea 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. topotecan, drug-related diarrhea in patients greater than 65 years of age was 10%.

[2]Neutropenic colitis, including fatal neutropenic colitis, has been reported to occur as a complication of topotecan-induced neutropenia (see section WARNINGS AND PRECAUTIONS).

[3]Reactions associated with extravasation have been mild and have not generally required specific therapy.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Hycamtin via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency, which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 1 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Blood and lymphatic system disorders

Severe bleeding (associated with thrombocytopenia) (see section WARNINGS AND PRECAUTIONS)

Immune system disorders

Anaphylactic reaction

Gastrointestinal disorders

Gastrointestinal perforation

General disorders and administration site conditions

Mucosal inflammation

Gastrointestinal disorders

Gastrointestinal perforation

General disorders and administration site conditions

Mucosal inflammation

INTERACTIONS

As with other myelosuppressive cytotoxic agents, greater myelosuppression is likely to be seen 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 topotecan dosing. If the platinum agent 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 (see section DOSAGE REGIMEN AND ADMINISTRATION).

When topotecan (0.75 mg/m^2/day for five consecutive days) and cisplatin (60 mg/m^2/day on Day 1) were administered intravenously 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 C_{max}, on Day 5 were 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 three consecutive days) and cisplatin (50 mg/m^2/day on Day 1) in patients with cervical cancer.

Topotecan does not inhibit human cytochrome P450 enzymes (see section PHARMACOKINETICS). 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 intravenously administered topotecan.

Topotecan is a substrate for both ABCG2 (BCRP) and ABCB1 (P-glycoprotein). Inhibitors of ABCB1 and ABCG2 (e.g. 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, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

Hycamtin is contraindicated during pregnancy (see section CONTRAINDICATIONS).

Based on animal data, Hycamtin can cause fetal harm when administered to a pregnant woman. Topotecan caused embryotoxicity, fetotoxicity, and teratogenicity when administered in rats and rabbits at doses lower than the clinical dose [see Animal data].

Animal data

As with other cytotoxic agents, topotecan was also shown to cause embryo-fetal toxicity when given to rats (0.59 mg/m^2/day) and rabbits (1.25 mg/m^2/day) at doses less than the clinical i.v. dose in humans (1.5 mg/m^2/day). A dose of 0.59 mg/m^2 was teratogenic in rats (predominantly effects of the eye, brain, skull and vertebrae).

Lactation

Risk summary

Hycamtin is contra-indicated during breast-feeding (see section CONTRAINDICATION).

It is not known whether this drug is present in human milk; however, topotecan is transfered into rat milk at high concentrations [see Animal data]. Because of the potential for serious adverse reactions in nursing infants with topotecan, nursing mothers should be advised to discontinue breastfeeding during treatment with Hycamtin.

Animal Data

Following intravenous administration of topotecan to lactating rats at a dose of 4.72 mg/m^2 (about twice the clinical dose on a mg/m^2 basis), topotecan was transfered into milk at concentrations up to 48-fold higher than those in plasma . The concentration in milk declined to 2-fold higher than that in plasma at 72 h.

Females and males of reproductive potential

Females of reproductive potential should be advised to avoid becoming pregnant during therapy with Hycamtin and to inform the treating physician immediately should this occur.

Pregnancy testing

Pregnancy status should be verified for females of reproductive potential prior to starting treatment with Hycamtin.

Contraception

Females:

As with all cytotoxic drugs, females of reproductive potential should use effective contraception (methods that result in less than 1 % pregnancy rates) during treatment with Hycamtin

Males:

Because of genotoxic potential, male patients should use condoms during sexual intercourse while taking Hycamtin and for at least 3 months after stopping treatment with Hycamtin.

Infertility

No effects on male or female fertility have been observed in reproductive toxicity studies in rats (see section NON-CLINICAL SAFETY DATA). However, as with other cytotoxic medicinal products, topotecan is genotoxic and effects on fertility, including male fertility, cannot be excluded.

OVERDOSAGE

Symptoms and Signs

Overdoses (up to 10 fold of the prescribed dose) have been reported in patients being treated with intravenous topotecan. The primary complication of overdosage is bone marrow suppression. The observed signs and symptoms for overdose are consistent with the known adverse reactions associated with topotecan (see section ADVERSE DRUG REACTIONS). In addition, elevated hepatic enzymes and mucositis have been reported following overdose.

Treatment

There is no known antidote for topotecan overdosage. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Mechanism of Action

The anti-tumor 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. The cellular sequelae of inhibition of topoisomerase-I by topotecan is the induction of protein-associated DNA single-strand breaks.

Pharmacokinetics

Absorption

Not applicable for i.v.

Distribution

Topotecan has a high volume of distribution of about 132 L, approximately three times total body water, and a relatively short half-life of two to three hours. Comparison of pharmacokinetic parameters did not suggest any change in pharmacokinetics over the five days of dosing.

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

Plasma clearance and volume of distribution were found to be slightly higher in males than females. However, differences were found to be similar in magnitude to differences in body surface area.

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. A 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

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

Following i.v. administration of topotecan at doses of 0.5 to 1.5 mg/m^2 as a 30 minute infusion daily for five days, topotecan demonstrated a high clearance (64 L/h), approximately 2/3 of liver blood flow.

Overall recovery of drug-related material following five daily doses of topotecan was 71 to 76% (i.v.) of the administered dose. Approximately 51% was excreted as total topotecan and 2.5% was excreted as N-desmethyl topotecan in the urine. Faecal elimination of total topotecan accounted for 18% of the administered dose while faecal elimination of N-desmethyl topotecan was approximately 1.5%. Overall, the N-desmethyl metabolite contributed a mean of less than 7% (range 4 to 9%) of the total drug-related material accounted for in the urine and faeces. The topotecan-O-glucuronide and N-desmethyl topotecan-O-glucuronide in the urine were less than or equal to 2% of the dose.

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/m^2 compared to 21.3 L/h/m^2) (see section INTERACTIONS). In population studies, the co-administration of granisetron, ondansetron, morphine or corticosteroids did not appear to have a significant effect on the pharmacokinetics of topotecan.

Special Patient Populations

In a population study with i.v. topotecan, a number of factors including age, weight and ascites had no significant effect on clearance (see section INTERACTIONS).

Pediatric patients (below 18 years)

The pharmacokinetics of topotecan in paediatrics was studied in paediatrics who had either received a 24 hour continuous infusion of between 2 and 7.5 mg/m^2 or a 72 hour continuous infusion of between 0.75 and 1.95 mg/m^2/day. In both studies the clearance was similar to that found in adults using the same dosing regimens.

Renal impairment

Plasma clearance of i.v. topotecan in patients with renal impairment (creatinine clearance 40 to 60 ml/min.) decreased to about 67% compared with control patients. Volume of distribution was slightly decreased and thus half-life only increased by 14%. In patients with moderate renal impairment (creatinine clearance 20 to 39 ml/min) topotecan plasma clearance was reduced to 34% of the value in control patients. Volume of distribution also decreased by about 25% which resulted in an increase in mean half-life from 1.9 hours to 4.9 hours.

Hepatic impairment

Plasma clearance of topotecan lactone after i.v. administration in patients with hepatic impairment (serum bilirubin in the range 1.5 to 10 mg/dL) decreased to about 67% when compared with a control group of patients. Topotecan half-life was increased by about 30% but no clear change in volume of distribution was observed. Total topotecan plasma clearance in patients with hepatic impairment only decreased by about 10% compared with the control group of patients.

CLINICAL STUDIES
Small Cell Lung Carcinoma

In a comparative study (SK&F 104864/090) of i.v. topotecan and the treatment regimen CAV (cyclophosphamide, doxorubicin, vincristine) in relapsed small cell lung carcinoma which was sensitive to first line therapy, there was a numerically superior response rate with topotecan 22%

(95% CI; 15, 30) versus CAV 15% (95% CI; 8, 22). All radiological responses were independently verified. "Sensitivity" was defined as 3 months treatment-free interval; to facilitate recruitment this was amended to 60 days treatment-free interval. The median duration of response (14 weeks for topotecan and 15 weeks for CAV), time to progression (topotecan 13 weeks versus CAV 12 weeks) and survival time (topotecan 25 weeks versus CAV 22 weeks) were similar for both treatments. Using the Patient Symptom Assessment in Lung Cancer Scale, patients treated with topotecan reported greater symptom relief improvement) over CAV for the following symptoms: dyspnea, cough, chest pain, loss of appetite, interference with sleep, hoarseness, fatigue and interference with daily activities, with significant results for dyspnea, hoarseness, fatigue and interference with daily activities.

Hemoptysis was alleviated to a greater (but not statistically significant) extent in patients treated with CAV. The time to worsening of the following symptoms was numerically greater (i.e. delayed worsening) for topotecan treated patients than for CAV: dyspnea, loss of appetite, interference with sleep, cough, interference with daily activity, hoarseness and fatigue, with significant results for dyspnea and loss of appetite. Time to worsening for chest pain was similar for i.v. topotecan and CAV treatments, and for hemoptysis numerically greater for CAV (30th May 1997 cut-off).

Efficacy data for study SKF104864/090 was updated based on a second clinical cut-off of the 20th March 1998. Qualitatively the efficacy data remained unchanged with only minor numerical updates for response rate, topotecan 24.3% versus CAV 18.3% and median survival, topotecan 25 weeks versus CAV 24.77 weeks.

Ovarian carcinoma

In a comparative study (SK&F 104864/039) of i.v. topotecan (n=112) and i.v. paclitaxel (n=114) in relapsed ovarian carcinoma, there was a numerically superior response rate with topotecan 20.5% (95% CI; 13.1 to 28.0) versus paclitaxel 14% (95% CI; 7.7 to 20.4). The difference between treatments was 6.5% (95% CI -3.3, 16.3). All radiological responses were independently verified. The median duration of response (25.9 weeks for topotecan and 21.6 weeks for paclitaxel), median time to progression (topotecan 18.9 weeks (95% CI 12.1, 23.6) versus paclitaxel 14.7 weeks (95% CI 11.9, 18.3) and median survival (topotecan 63.0 weeks (95% CI 46.6, 71.9) versus paclitaxel 53 weeks (95% CI 42.3, 68.7).

Note: All data denote values for ITT analysis population.

Cervical carcinoma

In a randomized, 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-free 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 one 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 health-related quality of life (HrQoL) was assessed using the Functional Assessment of Cancer Therapy-Cervix Cancer, Brief Pain Inventory as well as the UNISCALE. HrQoL assessments were made prior to randomization, prior to cycles 2 and 5 of treatment and nine months post-randomisation. Compared to cisplatin alone, the increased hematological toxicity seen with the combination of topotecan and cisplatin did not significantly reduce the patient HrQoL outcomes.

Integrated safety data

Safety data is presented on an integrated data set of 631 patients with relapsed lung cancer and 523 patients with relapsed ovarian cancer administered 5583 courses of topotecan (see section ADVERSE DRUG REACTIONS).

Hematological

Neutropenia: Severe (neutrophil count less than 0.5 x 10^9/L) during course 1 was seen in 55% of the patients and with duration greater than or equal to 7 days in 21% and overall in 76% of patients (39% of courses). In association with severe neutropenia, fever or infection occurred in 11% of patients during course 1 and overall in 18% of patients (5% of courses). Median time to onset of severe neutropenia was nine days and the median duration was seven days. Severe neutropenia lasted beyond seven days in 11% of courses overall. Among all patients treated in clinical trials (including both those with severe neutropenia and those who did not develop severe neutropenia), 11% (4% of courses) developed fever and 26% (9% of courses) developed infection. In addition, 5% of all patients treated (1% of courses) developed sepsis.

Thrombocytopenia: Severe (platelets less than 25 x 10^9/L (as defined by v1 of CTC criteria)) in 25% of patients (8% of courses); moderate (platelets between 25.0 and 50.0 x 10^9/L) in 25 % of patients (15% of courses). Median time to onset of severe thrombocytopenia was Day 15 and the median duration was 5 days. Platelet transfusions were given in 4% of courses. Reports of significant sequelae associated with thrombocytopenia including fatalities due to tumor bleeds have been infrequent.

Anemia: Moderate to severe (Hb less than 8.0 g/dl) in 37% of patients (14% of courses). Red cell transfusions were given in 52% of patients (21% of courses).

Non-hematological

Frequently reported non-hematological effects were gastrointestinal such as nausea (52%), vomiting (32%), and diarrhea (19%), constipation (9%) and stomatitis (15%). Severe (grade 3 or 4) nausea, vomiting, diarrhea and stomatitis incidence was 4, 3, 2 and 1% respectively. Mild

abdominal pain was also reported amongst 4% of patients.

Fatigue was observed in approximately 25% and asthenia in 16% of patients whilst receiving topotecan. Severe (grade 3 or 4) fatigue and asthenia incidence was 3% and 3% respectively.

Total or pronounced alopecia was observed in 30% of patients and partial alopecia in 15% of patients.

Other events occurring in patients that were recorded as related or possibly related to topotecan treatment were anorexia (13%), malaise (4%) and hyperbilirubinemia (1%).

Hypersensitivity reactions including rash, urticaria, angioedema and anaphylactic reactions have been reported rarely. In clinical trials, rash was reported in 4% of patients and pruritus in 1.5% of patients.

NON-CLINICAL SAFETY DATA

Carcinogenicity and mutagenicity

The carcinogenic potential of topotecan has not been studied. In common with a number of other cytotoxic agents, and resulting from its mechanism of action, topotecan is genotoxic to mammalian cells (mouse lymphoma cells and human lymphocytes) *in vitro* and mouse bone marrow cells *in vivo*.

Reproductive toxicology

In reproductive toxicity studies with topotecan in rats, there was no effect on male or female fertility; however, in females rats super-ovulation and slightly increased pre-implantation loss were observed (see section FEMALES AND MALES OF REPRODUCTIVE POTENTIAL FOR REPRODUCTIVE TOXICITY).

INCOMPATIBILITIES

None known.

STORAGE

See folding box.

Shelf-Life

The expiry date is indicated on the packaging.

Three years at temperatures up to 30°C. The vial must be protected from light and retained in its carton.

Reconstituted solutions

It is recommended that the product is used immediately after reconstitution or stored in a refrigerator (2 to 8°C) and discarded after 24 hours, as the product contains no antibacterial preservative.

Diluted solutions

It is recommended that diluted solutions are infused within 24 hours.

Hycamtin should not be used after the date marked “EXPIRY” on the pack.

Hycamtin must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

Precautions: Hycamtin is a cytotoxic anti-cancer drug. As with other potentially toxic compounds, Hycamtin should be prepared under a vertical laminar flow hood while wearing gloves and protective clothing. If Hycamtin solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If Hycamtin contacts mucous membranes, flush thoroughly with water.

Hycamtin must be reconstituted and further diluted before use.

Hycamtin 1 mg vials must be reconstituted with 1.1 mL Sterile Water for Injection. Hycamtin 4 mg vials must be reconstituted with 4 mL Sterile Water for Injection. The reconstituted solutions provide 1 mg per mL of Hycamtin. Further dilution of the appropriate volume of the reconstituted solution with either 0.9% Sodium Chloride BP i.v. Infusion or 5% Dextrose BP i.v. Infusion is required to achieve a final concentration of between 25 and 50 micrograms/mL.

The normal procedures for proper handling and disposal of anti-cancer drugs should be adopted, including:

- Personnel should be trained to reconstitute the drug.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling this drug 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.

Manufacturer:

See folding box.

A product of Novartis Pharma AG, Basel, Switzerland

Further information is available from:

Novartis Healthcare Private Limited

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