NOVARTIS

# HYCAMTIN™

## Topotecan hydrochloride

## Description and Composition Topotecan hydrochloride

### Pharmaceutical form

### Powder for i.v. infusion:

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

Powder for solution for infusion, 4 mg.

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

## Indications

HYCAMTIN is indicated for the treatment of:

- metastatic carcinoma of the ovary after failure of initial or subsequent 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 III study) or at least 90 days (in the Phase II studies) after chemotherapy (*See Clinical Studies Section*).

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 (*See Clinical Studies Section*).

For efficacy data see Clinical Studies.

## Dosage regimen and administration

HYCAMTIN must be reconstituted and further diluted before use (*see Pharmaceutical information – 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 and a platelet count of more than or equal to 100 x $10^9$/L and a hemoglobin level of more than or equal to 9g/dL.

## Dosage regimen

### Populations – Adults

***Powder for i.v. Infusion - 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 tumour progression, a minimum of 4 courses is recommended because tumour 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 three small cell lung cancer trials was 5.6-6.4 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 9g/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 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$^2$.

***Powder for i.v. Infusion - 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 hemoglobin level is more than or equal to 9g/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 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.

**Combination therapy**

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

**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 dosage adjustment appears to be needed in the elderly, other than adjustments related to renal function.

**Renal Impairment**
**Monotherapy – Powder for i.v infusion**

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 – Powder for i.v infusion**
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**

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 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 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 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 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, dyspnoea 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 Interactions*).

**Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity of topotecan.** Neutropenia is not cumulative over time. The following data on myelosuppression with topotecan is based on the combined experience of 879 patients with metastatic ovarian cancer or small cell lung cancer.

**Neutropenia:** Grade 4 neutropenia (<500 cells/$mm^3$) was most common during course 1 of treatment (60% of patients) and occurred in 39% of all courses, with a median duration of 7 days. The nadir neutrophil count occurred at a median of 12 days. Therapy-related sepsis or febrile neutropenia occurred in 23% of patients and sepsis was fatal in 1%.

**Thrombocytopenia:** Grade 4 thrombocytopenia (<25,000/$mm^3$) occurred in 27% of patients and in 9% of courses, with a median duration of 5 days and platelet nadir at a median of 15 days. Platelet transfusions were given to 15% of patients in 4% of courses.

**Anaemia:** Grade 3/4 anaemia (<8 g/dL) occurred in 37% of patients and in 14% of courses. Median nadir was at day 15. Transfusions were needed in 52% of patients in 22% of courses.

In ovarian cancer, the overall treatment-related death rate was 1%. In the comparative study in small cell lung cancer, however, the treatment-related death rates were 5% for HYCAMTIN and 4% for CAV.

**Monitoring of Bone Marrow Function:** HYCAMTIN should only be administered in patients with adequate bone marrow reserves, including baseline neutrophil count of at least 1,500 cells/$mm^3$ and platelet count at least 100,000/$mm^3$. Frequent monitoring of peripheral blood cell counts should be instituted during treatment with HYCAMTIN. Patients should not be treated with subsequent courses of HYCAMTIN until neutrophils recover to >1,000 cells/$mm^3$, platelets recover to >100,000 cells/$mm^3$ and hemoglobin levels recover to 9.0 g/dL (with transfusion if necessary). Severe myelotoxicity has been reported when HYCAMTIN is used in combination with cisplatin (s*ee Drug Interactions*).

## Interactions

Concomitant administration of G-CSF can prolong the duration of neutropenia, so if G-CSF is to be used, it should not be initiated until day 6 of the course of therapy, 24 hours after completion of treatment with HYCAMTIN.

Myelosuppression was more severe when HYCAMTIN was given in combination with cisplatin in Phase I studies. In a reported study on concomitant administration of cisplatin 50 mg/$m^2$ and HYCAMTIN at a dose of 1.25 mg/$m^2$/day x 5 days, one of three patients had severe neutropenia for 12 days and a second patient died with neutropenic sepsis.

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 Dosage regimen and administration*).

When topotecan (0.75 mg/$m^2$/day for 5 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 3 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 Clinical Pharmacology - 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 (*see Clinical Pharmacology - Pharmacokinetics*).

## Pregnancy, lactation, females and males of reproductive potential

### Pregnancy

**Risk summary**
HYCAMTIN is contra-indicated during pregnancy *(see 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 Contraindications).*

It is not known whether this drug is present in human milk; however, topotecan is transferred 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 transferred 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

Female 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 Non-clinical Safety Data).* However, as with other cytotoxic medicinal products, topotecan is genotoxic and effects on fertility, including male fertility, cannot be excluded.

### Effects on Ability to Drive and Use Machines

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

## Adverse drug reactions

### Tabulated summary of adverse drug reactions from clinical trials

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.

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 1/1000 and less than 1/100), rare (greater than or equal to 1/10,000 and less than 1/1000) and very rare (less than 1/10,000) including isolated reports, not known (cannot be estimated from the available data).

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.

**Infections and infestations**

| | |
|---|---|
| Very common | Infection |
| Common | Sepsis (*see Warnings and precautions*) |

**Blood and lymphatic system disorders**

| | |
|---|---|
| Very Common | Anaemia, febrile neutropenia, leucopenia, neutropenia, (*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[#](*see Warnings and precautions*), nausea and vomiting (all of which may be severe), abdominal pain*, constipation and stomatitis |

[#]With oral topotecan the overall incidence of drug-related diarrhoea was 22%, including 4% with Grade 3 and 0.4% with Grade 4. With oral topotecan, drug-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. topotecan, drug-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 topotecan-induced neutropenia (*see Warnings and precautions*)

**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[#] (i.v. formulation only) |

[#]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.

**Blood and lymphatic system disorders**

Severe bleeding (associated with thrombocytopenia) *(see Warnings and precautions)*

**Immune system disorders**

Anaphylactic reaction

**Gastrointestinal disorders**

Gastrointestinal perforation

**General disorders and administration site conditions**

Mucosal inflammation

In the HYCAMTIN plus cisplatin versus cisplatin comparative trial in cervical cancer patients, the most common dose-limiting toxicity was myelosuppression. Table 1 shows the hematologic adverse events and Table 2 shows the non-hematologic adverse events in cervical cancer patients.

**Table 1. Hematologic Adverse Events in Cervical Cancer Patients Treated with HYCAMTIN Plus Cisplatin or Cisplatin Monotherapy***

| Hematologic Adverse Event | HYCAMTIN Plus Cisplatin (n = 140) | Cisplatin (n = 144) |
|---|---|---|
| Anemia | | |
| All grades (Hgb <12 g/dL) | 131 (94%) | 130 (90%) |
| Grade 3 (Hgb <8-6.5 g/dL) | 47 (34%) | 28 (19%) |
| Grade 4 (Hgb <6.5 g/dL) | 9 (6%) | 5 (3%) |
| Leukopenia | | |
| All grades (<3,800 cells/$mm^3$) | 128 (91%) | 43 (30%) |
| Grade 3 (<2,000-1,000 cells/$mm^3$) | 58 (41%) | 1 (1%) |
| Grade 4 (<1,000 cells/$mm^3$) | 35 (25%) | 0 (0%) |
| Neutropenia | | |
| All grades (<2,000 cells/$mm^3$) | 125 (89%) | 28 (19%) |
| Grade 3 (<1,000-500 cells/$mm^3$) | 36 (26%) | 1 (1%) |
| Grade 4 (<500 cells/$mm^3$) | 67 (48%) | 1 (1%) |
| Thrombocytopenia | | |
| All grades (<130,000 cells/$mm^3$) | 104 (74%) | 21 (15%) |
| Grade 3 (<50,000-10,000 cells/$mm^3$) | 36 (26%) | 5 (3%) |
| Grade 4 (<10,000 cells/$mm^3$) | 10 (7%) | 0 (0%) |

* Includes patients who were eligible and treated.

**Table 2. Non-hematologic Adverse Events Experienced by ≥5% of Cervical Cancer Patients Treated with HYCAMTIN Plus Cisplatin or Cisplatin Monotherapy***

| | HYCAMTIN Plus Cisplatin n = 140 | | | Cisplatin n = 144 | | |
|---|---|---|---|---|---|---|
| **Adverse Event** | **All Grades†** | **Grade 3** | **Grade 4** | **All Grades†** | **Grade 3** | **Grade 4** |
| **General disorders and administrative site conditions** | | | | | | |
| Constitutional‡ | 96 (69%) | 11 (8%) | 0 | 89 (62%) | 17 (12%) | 0 |
| Pain§ | 82 (59%) | 28 (20%) | 3 (2%) | 72 (50%) | 18 (13%) | 5 (3%) |
| **Gastrointestinal disorders** | | | | | | |
| Vomiting | 56 (40%) | 20 (14%) | 2 (1%) | 53 (37%) | 13 (9%) | 0 |
| Nausea | 77 (55%) | 18 (13%) | 2 (1%) | 79 (55%) | 13 (9%) | 0 |
| Stomatitis-pharyngitis | 8 (6%) | 1 (<1%) | 0 | 0 | 0 | 0 |
| Other | 88 (63%) | 16 (11%) | 4 (3%) | 80 (56%) | 12 (8%) | 3 (2%) |
| **Dermatology** | 67 (48%) | 1 (<1%) | 0 | 29 (20%) | 0 | 0 |
| **Metabolic-Laboratory** | 55 (39%) | 13 (9%) | 7 (5%) | 44 (31%) | 14 (10%) | 1 (<1%) |
| **Genitourinary** | 51 (36%) | 9 (6%) | 9 (6%) | 49 (34%) | 7 (5%) | 7 (5%) |
| **Nervous system disorders** | | | | | | |
| Neuropathy | 4 (3%) | 1 (<1%) | 0 | 3 (2%) | 1 (<1%) | 0 |
| Other | 49 (35%) | 3 (2%) | 1 (<1%) | 43 (30%) | 7 (5%) | 2 (1%) |
| **Infection-febrile neutropenia** | 39 (28%) | 21 (15%) | 5 (4%) | 26 (18%) | 11 (8%) | 0 |
| **Cardiovascular** | 35 (25%) | 7 (5%) | 6 (4%) | 22 (15%) | 8 (6%) | 3 (2%) |
| **Hepatic** | 34 (24%) | 5 (4%) | 2 (1%) | 23 (16%) | 2 (1%) | 0 |
| **Pulmonary** | 24 (17%) | 4 (3%) | 0 | 23 (16%) | 5 (3%) | 3 (2%) |
| **Vascular disorders** | | | | | | |
| Hemorrhage | 21 (15%) | 8 (6%) | 1 (<1%) | 20 (14%) | 3 (2%) | 1 (<1%) |
| Coagulation | 8 (6%) | 4 (3%) | 3 (2%) | 10 (7%) | 7 (5%) | 0 |
| **Musculoskeletal** | 19 (14%) | 3 (2%) | 0 | 7 (5%) | 1 (<1%) | 1 (<1%) |
| **Allergy-Immunology** | 8 (6%) | 2 (1%) | 1 (<1%) | 4 (3%) | 0 | 1 (<1%) |
| **Endocrine** | 8 (6%) | 0 | 0 | 4 (3%) | 2 (1%) | 0 |
| **Sexual reproduction function** | 7 (5%) | 0 | 0 | 10 (7%) | 1 (<1%) | 0 |
| **Ocular-visual** | 7 (5%) | 0 | 0 | 7 (5%) | 1 (<1%) | 0 |

Data were collected using NCI Common Toxicity Criteria, v. 2.0.

* Includes patients who were eligible and treated.

† Grades 1 through 4 only. There were 3 patients who experienced grade 5 deaths with investigator-designated attribution. One was a grade 5 hemorrhage in which the drug-related thrombocytopenia aggravated the event. A second patient experienced bowel obstruction, cardiac arrest, pleural effusion and respiratory failure which were not treatment related but probably aggravated by treatment. A third patient experienced a pulmonary embolism and adult respiratory distress syndrome, the latter was indirectly treatment-related.

‡ Constitutional includes fatigue (lethargy, malaise, asthenia), fever (in the absence of neutropenia), rigors, chills, sweating, and weight gain or loss.

§ Pain includes abdominal pain or cramping, arthralgia, bone pain, chest pain (non-cardiac and non-pleuritic), dysmenorrhea, dyspareunia, earache, headache, hepatic pain, myalgia, neuropathic pain, pain due to radiation, pelvic pain, pleuritic pain, rectal or perirectal pain, and tumor pain.

Table 3 shows the grade 3/4 hematologic and major non-hematologic adverse events in the topotecan/paclitaxel comparator trial in ovarian cancer.

**Table 3. Comparative Toxicity Profiles for Ovarian Cancer Patients Randomized to Receive Hycamtin or Paclitaxel**

| Adverse Event | Hycamtin | | Paclitaxel | |
|---|---|---|---|---|
| | Pts | Courses | Pts | Courses |
| | n=112 | n=597 | n=114 | n=589 |
| **Haematologic Grade 3/4** | % | % | % | % |
| Grade 4 Neutropenia (<500 cells/mL) | 80 | 36 | 21 | 9 |
| Grade 3/4 Anemia (Hgb < 8 g/dL) | 41 | 16 | 6 | 2 |
| Grade 4 Thrombocytopenia (<25,000 plts/mL) | 27 | 10 | 3 | <1 |
| Fever/Grade 4 Neutropenia | 23 | 6 | 4 | 1 |
| Documented Sepsis | 5 | 1 | 2 | <1 |
| Death related to Sepsis | 2 | NA | 0 | NA |
| **Non-haematologic Grade 3/4** | | | | |
| Gastrointestinal | | | | |
| Abdominal Pain | 5 | 1 | 4 | 1 |
| Constipation | 5 | 1 | 0 | 0 |
| Diarrhoea | 6 | 2 | 1 | <1 |
| Intestinal Obstruction | 5 | 1 | 4 | 1 |
| Nausea | 10 | 3 | 2 | <1 |
| Stomatitis | 1 | <1 | 1 | <1 |
| Vomiting | 10 | 2 | 3 | <1 |
| Constitutional | | | | |
| Anorexia | 4 | 1 | 0 | 0 |
| Dyspnoea | 6 | 2 | 5 | 1 |
| Fatigue | 7 | 2 | 6 | 2 |
| Malaise | 2 | <1 | 2 | <1 |
| Neuromuscular | | | | |
| Arthralgia | 1 | <1 | 3 | <1 |
| Asthenia | 5 | 2 | 3 | 1 |

| | | | | |
|---|---|---|---|---|
| Chest Pain | 2 | <1 | 1 | <1 |
| Headache | 1 | <1 | 2 | 1 |
| Myalgia | 0 | 0 | 3 | 2 |
| Pain* | 5 | 1 | 7 | 2 |
| Skin/Appendages | | | | |
| Rash** | 0 | 0 | 1 | <1 |
| Liver/Biliary | | | | |
| Increased Hepatic Enzymes† | 1 | <1 | 1 | <1 |

* Pain includes body pain, skeletal pain and back pain.

** Rash also includes pruritus, rash erythematous, urticaria, dermatitis, bullous eruption and rash maculopapular.

† Increased hepatic enzymes includes increased SGOT/AST, increased SGPT/ALT and increased hepatic enzymes.

Premedications were not routinely used in patients randomized to HYCAMTIN, while patients receiving paclitaxel received routine pretreatment with corticosteroids, diphenhydramine, and histamine receptor type 2 blockers.

Table 4 shows the grade 3/4 haematologic and major non-haematologic adverse events in the topotecan/CAV comparator trial in small cell lung cancer.

**Table 4. Comparative Toxicity Profiles for Small Cell Lung Cancer Patients Randomized to Receive Hycamtin (topotecan hydrochloride) or CAV**

| **Adverse Event** | **Hycamtin** | | **CAV** | |
|---|---|---|---|---|
| | **Pts** | **Courses** | **Pts** | **Courses** |
| | **n=107** | **n=446** | **n=104** | **n=359** |
| **Haematologic Grade 3/4** | **%** | **%** | **%** | **%** |
| Grade 4 Neutropenia (<500 cells/mL) | 70 | 38 | 72 | 51 |
| Grade 3/4 Anemia (Hgb <8 g/dL) | 42 | 18 | 20 | 7 |
| Grade 4 Thrombocytopenia (<25,000 plts/mL) | 29 | 10 | 5 | 1 |
| Fever/Grade 4 Neutropenia | 28 | 9 | 26 | 13 |
| Documented Sepsis | 5 | 1 | 5 | 1 |
| Death related to Sepsis | 3 | NA | 1 | NA |
| **Non-haematologic Grade 3/4** | | | | |
| Gastrointestinal | | | | |
| Abdominal Pain | 6 | 1 | 4 | 2 |
| Constipation | 1 | <1 | 0 | 0 |
| Diarrhoea | 1 | <1 | 0 | 0 |
| Nausea | 8 | 2 | 6 | 2 |
| Stomatitis | 2 | <1 | 1 | <1 |
| Vomiting | 3 | <1 | 3 | 1 |
| Constitutional | | | | |
| Anorexia | 3 | 1 | 4 | 2 |
| Dyspnoea | 9 | 5 | 14 | 7 |
| Fatigue | 6 | 4 | 10 | 3 |
| Neuromuscular | | | | |
| Asthenia | 9 | 4 | 7 | 2 |

| | | | | |
|---|---|---|---|---|
| Headache | 0 | 0 | 2 | <1 |
| Pain* | 5 | 2 | 7 | 4 |
| Respiratory System | | | | |
| Coughing | 2 | 1 | 0 | 0 |
| Pneumonia | 8 | 2 | 6 | 2 |
| Skin/Appendages | | | | |
| Rash** | 1 | <1 | 1 | <1 |
| Liver/Biliary | | | | |
| Increased Hepatic Enzymes† | 1 | <1 | 0 | 0 |

* Pain includes body pain, skeletal pain and back pain.

** Rash also includes pruritus, rash erythematous, urticaria, dermatitis, bullous eruption and rash maculopapular.

† Increased hepatic enzymes includes increased SGOT/AST, increased SGPT/ALT and increased hepatic enzymes.

Premedications were not routinely used in patients randomized to HYCAMTIN, while patients receiving CAV received routine pretreatment with corticosteroids, diphenhydramine, and histamine receptor type 2 blockers.

# 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 Adverse drug reactions*). In addition, elevated hepatic enzymes and mucositis have been reported following overdose.

## Treatment

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

One patient on a single-dose regimen of 17.5 mg/m$^2$ given on day 1 of a 21-day cycle had received a single dose of 35 mg/m$^2$. This patient experienced severe neutropenia (nadir of
320/mm$^3$) 14 days later but recovered without incident.

The LD10 in mice receiving single intravenous infusions of HYCAMTIN was 75 mg/m$^2$ (CI 95%: 47 to 97).

# Clinical Pharmacology

## Pharmacotherapeutic group, ATC

Antineoplastic agents, L01XX17

## Pharamcodynamics (PD)
## Mechanism of action (MOA)

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 stabilizing 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.

*Paediatrics*

Topotecan was also evaluated in the paediatric population; however, only limited data on efficacy and safety are available.

In an open-label trial involving children (n = 108, age range: infant to 16 years) with recurrent or progressive solid tumours, topotecan was administered at a starting dose of
2.0 mg/m$^2$ given as a 30-minute infusion for 5 days repeated every 3 weeks for up to one year depending on response to therapy. Tumour types included were Ewing's Sarcoma/primitive neuroectodermal tumour, neuroblastoma, osteoblastoma, and rhabdomyosarcoma. Antitumour activity was demonstrated primarily in patients with neuroblastoma. Toxicities of topotecan in paediatric patients with recurrent and refractory solid tumours were similar to those historically seen in adult patients. In this study, forty- six (43%) patients received G-CSF over 192 (42.1%) courses; sixty-five (60%) received transfusions of Packed Red Blood Cells and fifty (46%) of platelets over 139 and 159 courses (30.5% and 34.9%) respectively. Based on the dose-limiting toxicity of
myelosuppression, the maximum tolerated dose (MTD) was established at 2.0 mg/m$^2$/day with G-CSF and 1.4 mg/m$^2$/day without G-CSF in a pharmacokinetic study in paediatric patients with refractory solid tumours (*see Pharmacokinetic Properties*).

## Pharmacokinetics (PK)

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 either formulation of topotecan with repeated daily dosing, and there is no evidence of a change in the pharmacokinetics with multiple dosing.

Following intravenous 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 plasma clearance of
62 L/h (SD 22), corresponding to approximately 2/3 of liver blood flow. Topotecan also had a high volume of distribution, about 132 L, (SD 57) and a relatively short half-life of
2-3 hours. Comparison of pharmacokinetic parameters did not suggest any change in pharmacokinetics over the 5 days of dosing.The binding of topotecan to plasma proteins was low (35%) and distribution between blood cells and plasma was fairly homogeneous.

In a population study, a number of factors including age, weight and ascites had no significant effect on clearance of total topotecan (active and inactive form).

The elimination of topotecan has only been partly investigated in man. A major route of clearance of topotecan was by hydrolysis of the lactone ring to form the ring-opened carboxylate.

Metabolism accounts for <10% of the elimination of topotecan. A N-desmethyl metabolite, which was shown to have similar or less activity than the parent in a cell-based assay, was found in urine, plasma and faeces. The mean metabolite:parent AUC ratio was less than 10% for both total topotecan and topotecan lactone. An O-glucuronidation metabolite of topotecan and N-desmethyl topotecan has been identified in the urine.

Overall recovery of medicinal product-related material following five daily doses of topotecan was 71 to 76% of the administered IV dose. Approximately 51% was excreted as total topotecan and 3% was excreted as N-desmethyl topotecan in the urine. Faecal elimination of total topotecan accounted for 18 % while faecal elimination of N-desmethyl topotecan was 1.7%. Overall, the N-desmethyl metabolite contributed a mean of less than 7% (range 4-9 %) of the total medicinal product 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 2.0%.

*In vitro* data using human liver microsomes indicate the formation of small amounts of N-demethylated topotecan. In man, as in animal species, a significant proportion of the dose (generally 20-60 %) was excreted in the urine as topotecan or the open ring form *In vitro,* topotecan did not inhibit human P450 enzymes CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A, or CYP4A nor did it inhibit the human cytosolic enzymes dihydropyrimidine or xanthine oxidase.

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/$m^2$ [n=9]) (*see Interactions*).

Plasma clearance in patients with hepatic impairment (serum bilirubin between 1.5 and 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. Plasma clearance of total topotecan (active and inactive form) in patients with hepatic impairment only decreased by about 10% compared with the control group of patients.

Plasma clearance in patients with renal impairment (creatinine clearance 40-60 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. Mean half-life increased from 1.9 hours
to 4.9 hours.

*Paediatrics*

The pharmacokinetics of topotecan given as a 30-minute infusion for 5 days were evaluated in two studies. One study included a dose range of 1.4 mg/m$^2$ to 2.4 mg/m$^2$ in children (aged 2 up to 12 years, n = 18), adolescents (aged 12 up to 16 years, n = 9), and young adults (aged 16 to 21 years, n = 9) with refractory solid tumours. The second study included a dose range of 2.0 mg/m$^2$ to 5.2 mg/m$^2$ in children (n = 8), adolescents (n = 3), and young adults (n = 3) with leukaemia. In these studies, there were no apparent differences in the pharmacokinetics of topotecan among children, adolescents and young adult patients with solid tumours or leukaemia, but data are too limited to draw definite conclusions.

**Preclinical safety data**

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*. Topotecan was also shown to cause embryo-foetal lethality when given to rats and rabbits.

The carcinogenic potential of topotecan has not been studied.

## Clinical Studies

### Ovarian Cancer

HYCAMTIN (topotecan hydrochloride) was studied in two clinical trials of 223 patients given topotecan with metastatic ovarian carcinoma. All patients had disease that had recurred on, or was unresponsive to, a platinum-containing regimen. Patients in these two studies received an initial dose of 1.5 mg/m$^2$ given by intravenous infusion over 30 minutes for 5 consecutive days, starting on day 1 of a 21-day course.

One study was a randomized trial of 112 patients treated with HYCAMTIN (1.5 mg/m$^2$/day x 5 days starting on day 1 of a 21-day course) and 114 patients treated with paclitaxel (175 mg/m$^2$ over 3 hours on day 1 of a 21-day course). All patients had recurrent ovarian cancer after a platinum-containing regimen or had not responded to at least one prior platinum-containing regimen. Patients who did not respond to the study therapy, or who progressed, could be given the alternative treatment.

Response rates, response duration and time to progression are shown in Table 5.

**Table 5. Efficacy of Hycamtin (topotecan hydrochloride) vs. Paclitaxel in Ovarian Cancer**

| **Parameter** | **Hycamtin (n=112)** | **Paclitaxel (n=114)** |
|---|---|---|
| Complete Response Rate | 5% | 3% |
| Partial Response Rate | 16% | 11% |
| Overall Response Rate | 21% | 14% |
| 95% Confidence Interval | 13 to 28% | 8 to 20% |
| (p-value) | (0.20) | |
| **Response Duration (weeks)** | **n=23** | **n=16** |
| Median | 25.9 | 21.6 |
| 95% Confidence Interval hazard-ratio | 22.1 to 32.9 | 16.0 to 34.0 |
| (**Hycamtin**:paclitaxel) | 0.78 | |
| (p-value) | (0.48) | |
| **Time to Progression (weeks)** | | |
| Median | 18.9 | 14.7 |
| 95% Confidence Interval hazard-ratio | 12.1 to 23.6 | 11.9 to 18.3 |

| | | |
|---|---|---|
| (**Hycamtin**:paclitaxel) | 0.76 | |
| (p-value) | (0.07) | |
| **Survival (weeks)** | | |
| Median | 63.0 | 53.0 |
| 95% Confidence Interval hazard-ratio | 46.6 to 71.9 | 42.3 to 68.7 |
| (**Hycamtin**:paclitaxel) | 0.97 | |
| (p-value) | (0.87) | |

The calculation for duration of response was based on the interval between first response and time to progression.

The median time to response was 7.6 weeks (range 3.1 to 21.7) with HYCAMTIN compared to 6.0 weeks (range 2.4 to 18.1) with paclitaxel. Consequently, the efficacy of HYCAMTIN may not be achieved if patients are withdrawn from treatment prematurely.

In the crossover phase, 8 of 61 (13%) patients who received HYCAMTIN after paclitaxel had a partial response and 5 of 49 (10%) patients who received paclitaxel after HYCAMTIN had a response (two complete responses).

HYCAMTIN was active in ovarian cancer patients who had developed resistance to platinum-containing therapy, defined as tumor progression while on, or tumor relapse within 6 months after completion of, a platinum-containing regimen. One complete and six partial responses were seen in 60 patients, for a response rate of 12%. In the same study, there were no complete responders and four partial responders on the paclitaxel arm, for a response rate of 7%.

HYCAMTIN was also studied in an open-label, non-comparative trial in 111 patients with recurrent ovarian cancer after treatment with a platinum-containing regimen, or who had not responded to one prior platinum-containing regimen. The response rate was 14% (95% CI=7% to 20%). The median duration of response was 22 weeks (range 4.6 to 41.9 weeks). The time to progression was 11.3 weeks (range 0.7 to 72.1 weeks). The median survival was 67.9 weeks (range 1.4 to 112.9 weeks).

**Small Cell Lung Cancer**

HYCAMTIN (topotecan hydrochloride) was studied in 426 patients with recurrent or progressive small cell lung cancer in one randomized, comparative study and in three single arm studies.

**Randomized Comparative Study**

In a randomized, comparative, Phase 3 trial, 107 patients were treated with HYCAMTIN (1.5 mg/m$^2$/day x 5 days starting on day 1 of a 21-day course) and 104 patients were treated with CAV (1000 mg/m$^2$ cyclophosphamide, 45 mg/m$^2$ doxorubicin, 2 mg vincristine administered sequentially on day 1 of a 21-day course). All patients were considered sensitive to first-line chemotherapy (responders who then subsequently progressed ≥60 days after completion of first-line therapy). A total of 77% of patients treated with HYCAMTIN and 79% of patients treated with CAV received platinum/etoposide with or without other agents as first-line chemotherapy.

Response rates, response duration, time to progression, and survival are shown in Table 6.

**Table 6. Efficacy of Hycamtin (topotecan hydrochloride) vs CAV (cyclophosphamide-doxorubicin-vincristine) in Small Cell Lung Cancer Patients Sensitive to First-Line Chemotherapy**

| **Parameter** | **Hycamtin (n=107)** | **CAV (n=104)** |
|---|---|---|
| Complete Response Rate | 0% | 1% |
| Partial Response Rate | 24% | 17% |
| Overall Response Rate | 24% | 18% |
| Difference in Overall Response Rates | 6% | |
| 95% Confidence Interval of the Difference | (-6% to 18%) | |
| **Response Duration (weeks)** | **n=26** | **n=19** |
| Median | 14.4 | 15.3 |
| 95% Confidence Interval hazard-ratio | 13.1 to 18.0 | 13.1 to 23.1 |
| (**Hycamtin***:*CAV) | 1.42 (0.73 to 2.76) | |
| (p-value) | (0.30) | |
| **Time to Progression (weeks)** | | |
| Median | 13.3 | 12.3 |
| 95% Confidence Interval hazard-ratio | 11.4 to 16.4 | 11.0 to 14.1 |
| (**Hycamtin:**CAV) | 0.92 (0.69 to 1.22) | |
| (p-value) | (0.55) | |
| **Survival (weeks)** | | |
| Median | 25.0 | 24.7 |
| 95% Confidence Interval hazard-ratio | 20.6 to 29.6 | 21.7 to 30.3 |
| (**Hycamtin:**CAV) | 1.04 (0.78 to 1.39) | |
| (p-value) | (0.80) | |

The calculation for duration of response was based on the interval between first response and time to progression.

The time to response was similar in both arms: HYCAMTIN median of 6 weeks (range 2.4 to 15.7) versus CAV median 6 weeks (range 5.1 to 18.1).

Changes on a disease-related symptom scale in patients who received HYCAMTIN or who received CAV are presented in Table 7. It should be noted that not all patients had all symptoms nor did all patients respond to all questions. Each symptom was rated on a four category scale with an improvement defined as a change in one category from baseline sustained over two courses. Limitations in interpretation of the rating scale and responses preclude formal statistical analysis.

**Table 7. Percentage of Patients with Symptom Improvement*: Hycamtin versus CAV in Patients with Small Cell Lung Cancer**

| **Symptom** | **Hycamtin (n=107)** | | **CAV (n=104)** | |
|---|---|---|---|---|
| | **n**** | **(%)** | **N**** | **(%)** |
| Shortness of Breath | 68 | (28) | 61 | (7) |
| Interference with Daily Activity | 67 | (27) | 63 | (11) |
| Fatigue | 70 | (23) | 65 | (9) |
| Hoarseness | 40 | (33) | 38 | (13) |

| | | | | |
|---|---|---|---|---|
| Cough | 69 | (25) | 61 | (15) |
| Insomnia | 57 | (33) | 53 | (19) |
| Anorexia | 56 | (32) | 57 | (16) |
| Chest Pain | 44 | (25) | 41 | (17) |
| Haemoptysis | 15 | (27) | 12 | (33) |

* Defined as improvement sustained over at least two courses compared to baseline.
** Number of patients with baseline and at least one post-baseline assessment.

**Single Arm Studies**

HYCAMTIN (topotecan hydrochloride) was also studied in three open-label, non-comparative trials in a total of 319 patients with recurrent or progressive small cell lung cancer after treatment with first-line chemotherapy. In all three studies, patients were stratified as either sensitive (responders who then subsequently progressed ≥90 days after completion of first-line therapy) or refractory (no response to first-line chemotherapy or who responded to first-line therapy and then progressed within 90 days of completing first-line therapy). Response rates ranged from 11% to 31% for sensitive patients and 2% to 7% for refractory patients. Median time to progression and median survival were similar in all three studies and the comparative study.

**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. 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 randomisation, prior to cycles 2 and 5 of treatment and nine 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 HrQoL outcomes.

**Study Results Study GOG-0179**

| **ITT population** | | |
|---|---|---|
| | **Cisplatin 50mg/m$^2$ d.l q21d.** | **Cisplatin 50mg/m$^2$ d.l + Topotecan 0.75mg/ m$^2$ dx$^3$** |

| | | q21d |
|---|---|---|
| **Survival (months)** | **(n=146)** | **(n=147)** |
| Median (95% CI) | 6.5 (5.8 - 8.8) | 9.4 (7.9 - 11.9) |
| Hazard Ratio (95% CI) | 0.76 (0.59, 0.98) | |
| Log-rank p-value | 0.033 | |
| | | |
| **Patients without Prior Cisplatin Chemoradiotherapy** | | |
| | **Cisplatin** | **Topotecan/Cisplatin** |
| **Survival (months)** | **(n=46)** | **(n=44)** |
| Median (95% CI) | 8.8 (6.4 – 11.5) | 15.7 (11.9 – 17.7) |
| Hazard Ratio (95% CI) | 0.51 (0.31, 0.82) | |
| | | |
| **Patients with Prior Cisplatin Chemoradiotherapy** | | |
| | **Cisplatin** | **Topotecan/Cisplatin** |
| **Survival (months)** | **(n=72)** | **(n=69)** |
| Median (95% CI) | 5.9 (4.7 - 8.8) | 7.9 (5.5 – 10.9) |
| Hazard Ratio (95% CI) | 0.85 (0.59, 1.21) | |

# 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 toxicity

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.

# Pharmaceutical information

## List of Excipients

Powder for i.v.

Infusion: Tartaric acid

(Ph Eur)
Mannitol (Ph Eur)
Hydrochloric acid (Ph Eur)
Sodium hydroxide (Ph
Eur)

## Incompatibilities

**Not applicable.**

## Shelf Life

The expiry date is indicated on the packaging.

## Storage

### Vials

Store at temperatures up to 30$^{o}$C.

### Reconstituted solutions

It is recommended that the product is used immediately after reconstitution or stored in a refrigerator (2 to 8$^{o}$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.

## Nature and Contents of Container

Topotecan 4 mg is supplied in 17 mL type I flint glass vials, together with 20 mm grey butyl rubber stoppers and 20 mm aluminium seals with plastic flip-off caps.

Topotecan 4 mg is available in cartons containing 1 vial and 5 vials.

## Pharmaceutical information- 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 4 mg vials must be reconstituted with 4 mL Sterile Water for Injection. The reconstituted solutions provide 1 mg per mL of topotecan. 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.

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**Novartis Pharma AG, Basel, Switzerland**