ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

HYCAMTIN 1 mg powder for concentrate for solution for infusion
HYCAMTIN 4 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

HYCAMTIN 1 mg powder for concentrate for solution for infusion

Each vial contains 1 mg topotecan (as hydrochloride).

The total content of active substance in the vial provides 1 mg per ml of active substance when reconstituted as recommended.

HYCAMTIN 4 mg powder for concentrate for solution for infusion

Each vial contains 4 mg topotecan (as hydrochloride).

The total content of active substance in the vial provides 1 mg per ml of active substance when reconstituted as recommended.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

Light yellow to greenish powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Topotecan monotherapy is indicated for the treatment of:
- patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy.
- patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate (see section 5.1).

Topotecan in combination with cisplatin is indicated for 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 (see section 5.1).

4.2 Posology and method of administration

The use of topotecan should be confined to units specialised in the administration of cytotoxic chemotherapy. Topotecan should only be administered under the supervision of a physician experienced in the use of chemotherapy (see section 6.6).

Posology

When topotecan is used in combination with cisplatin, the full prescribing information for cisplatin should be consulted.

Prior to administration of the first course of topotecan, patients must have a baseline neutrophil count of ≥1.5 x 10^9/l, a platelet count of ≥100 x 10^9/l and a haemoglobin level of ≥9 g/dl (after transfusion if necessary).

Ovarian and small cell lung carcinoma
Initial dose
The recommended dose of topotecan is 1.5 mg/m^2 body surface area per day administered by intravenous infusion over 30 minutes daily for five consecutive days with a three-week interval between the start of each course. If well tolerated, treatment may continue until disease progression (see sections 4.8 and 5.1).

Subsequent doses
Topotecan 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 ≥9 g/dl (after transfusion if necessary).

Standard oncology practice for the management of neutropenia is either to administer topotecan with other medicinal products (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 <0.5 x 10^9/l) for seven days or more or severe neutropenia associated with fever or infection, or who have had treatment delayed due to neutropenia, 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 studies, topotecan was discontinued if the dose had been reduced to 1.0 mg/m^2/day and a further dose reduction was required to manage adverse effects.

Cervical carcinoma
Initial dose
The recommended dose of topotecan is 0.75 mg/m^2/day administered as a 30-minute intravenous infusion 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 topotecan dose. This treatment schedule is repeated every 21 days for six courses or until progressive disease.

Subsequent doses
Topotecan should not be re-administered unless the neutrophil count is ≥1.5 x 10^9/l, the platelet count is ≥100 x 10^9/l, and the haemoglobin level is ≥9 g/dl (after transfusion if necessary).

Standard oncology practice for the management of neutropenia is either to administer topotecan with other medicinal products (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 <0.5 x 10^9/l) for seven days or more or severe neutropenia associated with fever or infection, or who have had treatment delayed due to neutropenia, the dose should be reduced by 20% to 0.60 mg/m^2/day for subsequent courses (or subsequently down to 0.45 mg/m^2/day if necessary).

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

Special populations
Patients with renal impairment
Monotherapy (ovarian and small cell lung carcinoma):
There is insufficient experience with the use of topotecan in patients with severely impaired renal function (creatinine clearance <20 ml/min). Use of topotecan in this group of patients is not recommended (see section 4.4).
Limited data indicate that the dose should be reduced in patients with moderate renal impairment. The recommended monotherapy dose of topotecan in patients with ovarian or small cell lung carcinoma and a creatinine clearance between 20 and 39 ml/min is 0.75 mg/m^2/day for five consecutive days.

Combination therapy (cervical carcinoma):
In clinical studies with topotecan 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 topotecan/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.

Patients with hepatic impairment
A small number of hepatically impaired patients (serum bilirubin between 1.5 and 10 mg/dl) were given intravenous topotecan at 1.5 mg/m^2/day for five days every three weeks. A reduction in topotecan clearance was observed. However, there are insufficient data available to make a dose recommendation for this patient group (see section 4.4).

There is insufficient experience with the use of topotecan in patients with severely impaired hepatic function (serum bilirubin ≥10 mg/dl) due to cirrhosis. Topotecan is not recommended to be used in this patient group (see section 4.4).

Paediatric population
Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

Topotecan must be reconstituted and further diluted before use (see section 6.6).

4.3 Contraindications

- Severe hypersensitivity to the active substance or to any of the excipients.
- Breast-feeding (see section 4.6).
- Severe bone marrow depression prior to starting first course, as evidenced by baseline neutrophils <1.5 x 10^9/l and/or a platelet count of <100 x 10^9/l.

4.4 Special warnings and precautions for use

Haematological toxicity is dose-related and full blood count including platelets should be determined regularly (see section 4.2).

As with other cytotoxic medicinal products, topotecan can cause severe myelosuppression. Myelosuppression leading to sepsis and fatalities due to sepsis have been reported in patients treated with topotecan (see section 4.8).

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

Topotecan has been associated with reports of interstitial lung disease (ILD), some of which have been fatal (see section 4.8). Underlying risk factors include history of ILD, pulmonary fibrosis, lung cancer, thoracic exposure to radiation and use of pneumotoxic substances and/or colony stimulating factors. Patients should be monitored for pulmonary symptoms indicative of ILD (e.g. cough, fever, dyspnoea and/or hypoxia), and topotecan should be discontinued if a new diagnosis of ILD is confirmed.

Topotecan monotherapy and topotecan in combination with cisplatin are commonly associated with clinically relevant thrombocytopenia. This should be taken into account when prescribing HYCAMTIN, e.g. if patients at increased risk of tumour bleeds are considered for therapy.

As would be expected, patients with poor performance status (PS >1) have a lower response rate and an increased incidence of complications such as fever, infection and sepsis (see section 4.8). Accurate assessment of performance status at the time therapy is given is important, to ensure that patients have not deteriorated to PS 3.

There is insufficient experience of the use of topotecan in patients with severely impaired renal function (creatinine clearance <20 ml/min) or severely impaired hepatic function (serum bilirubin ≥10 mg/dl) due to cirrhosis. Use of topotecan in these patient groups is not recommended (see section 4.2).

A small number of hepatically impaired patients (serum bilirubin between 1.5 and 10 mg/dl) were given intravenous topotecan at 1.5 mg/m^2/day for five days every three weeks. A reduction in topotecan clearance was observed. However, there are insufficient data available to make a dose recommendation for this patient group (see section 4.2).

Hycamtin contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium free". However, if a solution of common salt (0.9% w/v sodium chloride solution) is used for the dilution of Hycamtin prior to administration then the dose of sodium received would be higher.

4.5 Interaction with other medicinal products and other forms of interaction

No *in vivo* human pharmacokinetic interaction studies have been performed.

Topotecan does not inhibit human P450 enzymes (see section 5.2). In a population study using the intravenous route, the co-administration of granisetron, ondansetron, morphine or corticosteroids did not appear to have a significant effect on the pharmacokinetics of total topotecan (active and inactive form).

When combining topotecan with other chemotherapy agents, reduction of the doses of each medicinal product may be required to improve tolerability. However, when 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, a lower dose of each agent must be given to improve tolerability compared to the dose of each agent which can be given if the platinum agent is given on day 5 of the topotecan dosing.

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, a slight increase in AUC (12%, n = 9) and C_{max} (23%, n = 11) was noted on day 5. This increase is considered unlikely to be of clinical relevance.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Topotecan has been shown to cause embryo-foetal lethality and malformations in preclinical studies (see section 5.3). As with other cytotoxic medicinal products, topotecan may cause foetal harm and therefore women of childbearing potential should be advised to avoid becoming pregnant during therapy with topotecan.

As with all cytotoxic chemotherapy, patients being treated with topotecan must be advised that they or their partner must use an effective method of contraception.

Women of childbearing potential should use effective contraceptive measures while being treated with topotecan and for 6 months following completion of treatment.
Men are recommended to use effective contraceptive measures and to not father a child while receiving topotecan and for 3 months following completion of treatment.

Pregnancy

If topotecan is used during pregnancy, or if the patient becomes pregnant during therapy with topotecan, the patient must be warned of the potential hazards to the foetus.

Breast-feeding

Topotecan is contraindicated during breast-feeding (see section 4.3). Although it is not known whether topotecan is excreted in human breast milk, breast-feeding should be discontinued at the start of therapy.

Fertility

No effects on male or female fertility have been observed in reproductive toxicity studies in rats (see section 5.3). However, as with other cytotoxic medicinal products, topotecan is genotoxic and effects on fertility, including male fertility, cannot be excluded.

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed. However, caution should be observed when driving or operating machines if fatigue and asthenia persist.

4.8 Undesirable effects

In dose-finding studies involving 523 patients with relapsed ovarian cancer and 631 patients with relapsed small cell lung cancer, the dose-limiting toxicity of topotecan monotherapy was found to be haematological. Toxicity was predictable and reversible. There were no signs of cumulative haematological or non-haematological toxicity.

The safety profile of topotecan when given in combination with cisplatin in the cervical cancer clinical studies is consistent with that seen with topotecan monotherapy. The overall haematological toxicity is lower in patients treated with topotecan in combination with cisplatin compared to topotecan monotherapy, but higher than with cisplatin alone.

Additional adverse events were seen when topotecan was given in combination with cisplatin; however, these events were seen with cisplatin monotherapy and were not attributable to topotecan. The prescribing information for cisplatin should be consulted for a full list of adverse events associated with cisplatin use.

The integrated safety data for topotecan monotherapy are presented below.

Adverse reactions are listed below, by system organ class and absolute frequency (all reported events). Frequencies are defined as: 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) and not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations	
Very common	Infection
Common	Sepsis[1]
Blood and lymphatic system disorders	
Very common	Febrile neutropenia, neutropenia (see “Gastrointestinal disorders”), thrombocytopenia, anaemia, leucopenia
Common	Pancytopenia
Not known	Severe bleeding (associated with thrombocytopenia)

Immune system disorders	
Common	Hypersensitivity reaction including rash
Rare	Anaphylactic reaction, angioedema, urticaria
Metabolism and nutrition disorders	
Very common	Anorexia (which may be severe)
Respiratory, thoracic and mediastinal disorders	
Rare	Interstitial lung disease (some cases have been fatal)
Gastrointestinal disorders	
Very common	Nausea, vomiting and diarrhoea (all of which may be severe), constipation, abdominal pain[2], mucositis
Not known	Gastrointestinal perforation
Hepatobiliary disorders	
Common	Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	
Very common	Alopecia
Common	Pruritus
General disorders and administration site conditions	
Very common	Pyrexia, asthenia, fatigue
Common	Malaise
Very rare	Extravasation[3]
Not known	Mucosal inflammation
[1] Fatalities due to sepsis have been reported in patients treated with topotecan (see section 4.4). [2] Neutropenic colitis, including fatal neutropenic colitis, has been reported to occur as a complication of topotecan-induced neutropenia (see section 4.4). [3] Reactions have been mild and have not generally required specific therapy.	

The adverse events listed above have the potential to occur with a higher frequency in patients who have a poor performance status (see section 4.4).

The frequencies associated with the haematological and non-haematological adverse events listed below represent the adverse event reports considered to be related/possibly related to topotecan therapy.

Haematological

Neutropenia
Severe (neutrophil count <0.5 x 10^9/l) during course 1 in 55% of patients, with duration ≥ seven days in 20%, and overall in 77% of patients (39% of courses). In association with severe neutropenia, fever or infection occurred in 16% of patients during course 1 and overall in 23% of patients (6% 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 studies (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 (see section 4.4).

Thrombocytopenia
Severe (platelets <25 x 10^9/l) 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 five days. Platelet transfusions were given in 4% of courses. Reports of significant sequelae associated with thrombocytopenia, including fatalities due to tumour bleeds, have been infrequent.

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

Non-haematological

Frequently reported non-haematological effects were gastrointestinal, such as nausea (52%), vomiting (32%), diarrhoea (18%), constipation (9%) and mucositis (14%). The incidence of severe (Grade 3 or 4) nausea, vomiting, diarrhoea and mucositis was 4, 3, 2 and 1%, respectively.

Mild abdominal pain was reported in 4% of patients.

Fatigue was observed in approximately 25% and asthenia in 16% of patients receiving topotecan. Severe (Grade 3 or 4) fatigue and asthenia both occurred with an incidence of 3%.

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

Other severe events that were recorded as related or possibly related to topotecan treatment were anorexia (12%), malaise (3%) and hyperbilirubinaemia (1%).

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdoses have been reported in patients being treated with intravenous topotecan (up to 10 fold of the recommended dose) and topotecan capsules (up to 5 fold of the recommended dose). The signs and symptoms observed following overdose were consistent with the known undesirable events associated with topotecan (see section 4.8). The primary complications of overdose are bone marrow suppression and mucositis. In addition, elevated hepatic enzymes have been reported with intravenous topotecan overdose.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, plant alkaloids and other natural products, ATC code: L01CE01.

Mechanism of action

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

Clinical efficacy and safety

Relapsed ovarian cancer
In a comparative study of topotecan and paclitaxel in patients previously treated for ovarian carcinoma with platinum-based chemotherapy (n = 112 and 114, respectively), the response rate (95% CI) was 20.5% (13%, 28%) versus 14% (8%, 20%) and median time to progression 19 weeks versus 15 weeks (hazard ratio 0.7 [0.6, 1.0]), for topotecan and paclitaxel, respectively. Median overall survival was 62 weeks for topotecan versus 53 weeks for paclitaxel (hazard ratio 0.9 [0.6, 1.3]).

The response rate in the whole ovarian carcinoma programme (n = 392, all previously treated with cisplatin or cisplatin and paclitaxel) was 16%. The median time to response in clinical studies was 7.6-11.6 weeks. In patients refractory to or relapsing within 3 months after cisplatin therapy (n = 186), the response rate was 10%.

These data should be evaluated in the context of the overall safety profile of the medicinal product, in particular of the significant haematological toxicity (see section 4.8).

A supplementary retrospective analysis was conducted on data from 523 patients with relapsed ovarian cancer. Overall, 87 complete and partial responses were observed, with 13 of these occurring during cycles 5 and 6 and 3 occurring thereafter. Of the patients who received more than 6 cycles of therapy, 91% completed the study as planned or were treated until disease progression, with only 3% withdrawn for adverse events.

Relapsed SCLC
A Phase III study (Study 478) compared oral topotecan plus best supportive care (BSC) (n = 71) with BSC alone (n = 70) in patients who had relapsed following first-line therapy (median time to progression [TTP] from first-line therapy: 84 days for oral topotecan plus BSC, 90 days for BSC alone) and for whom re-treatment with intravenous chemotherapy was not considered appropriate. In the oral topotecan plus BSC group there was a statistically significant improvement in overall survival compared with the BSC alone group (Log-rank p = 0.0104). The unadjusted hazard ratio for the oral topotecan plus BSC group relative to the BSC alone group was 0.64 (95% CI: 0.45, 0.90). Median survival in patients treated with oral topotecan plus BSC was 25.9 weeks (95% CI: 18.3, 31.6) compared to 13.9 weeks (95% CI: 11.1, 18.6) for patients receiving BSC alone (p = 0.0104).

Patient self-reports of symptoms using an unblinded assessment showed a consistent trend for symptom benefit for oral topotecan plus BSC.

One Phase II study (Study 065) and one Phase III study (Study 396) were conducted to evaluate the efficacy of oral topotecan versus intravenous topotecan in patients who had relapsed ≥90 days after completion of one prior regimen of chemotherapy (see Table 1). Oral and intravenous topotecan were associated with similar symptom palliation in patients with relapsed sensitive SCLC in patient self-reports on an unblinded symptom scale assessment in each of these two studies.

Table 1 Summary of survival, response rate, and time to progression in SCLC patients

treated with oral or intravenous topotecan

	Study 065		Study 396	
	Oral topotecan	**Intravenous topotecan**	**Oral topotecan**	**Intravenous topotecan**
	(N = 52)	**(N = 54)**	**(N = 153)**	**(N = 151)**
Median survival (weeks) (95% CI)	32.3 (26.3, 40.9)	25.1 (21.1, 33.0)	33.0 (29.1, 42.4)	35.0 (31.0, 37.1)
Hazard ratio (95% CI)	0.88 (0.59, 1.31)		0.88 (0.7, 1.11)	
Response rate (%) (95% CI)	23.1 (11.6, 34.5)	14.8 (5.3, 24.3)	18.3 (12.2, 24.4)	21.9 (15.3, 28.5)
Difference in response rate (95% CI)	8.3 (-6.6, 23.1)		-3.6 (-12.6, 5.5)	
Median time to progression (weeks) (95% CI)	14.9 (8.3, 21.3)	13.1 (11.6, 18.3)	11.9 (9.7, 14.1)	14.6 (13.3, 18.9)
Hazard ratio (95% CI)	0.90 (0.60, 1.35)		1.21 (0.96, 1.53)	

N = total number of patients treated
CI = confidence interval

In another randomised Phase III study which compared intravenous (IV) topotecan to cyclophosphamide, doxorubicin and vincristine (CAV) in patients with relapsed, sensitive SCLC, the overall response rate was 24.3% for topotecan compared to 18.3% for the CAV group. Median time to progression was similar in the two groups (13.3 weeks and 12.3 weeks, respectively). Median survivals for the two groups were 25.0 and 24.7 weeks, respectively. The hazard ratio for survival with IV topotecan relative to CAV was 1.04 (95% CI: 0.78, 1.40).

The response rate to topotecan in the combined small cell lung cancer programme (n = 480) for patients with relapsed disease sensitive to first-line therapy was 20.2%. Median survival was 30.3 weeks (95% CI: 27.6, 33.4).

In a population of patients with refractory SCLC (those not responding to first-line therapy), the response rate to topotecan was 4.0%.

Cervical carcinoma
In a randomised, comparative Phase III study conducted by the Gynecologic Oncology Group (GOG 0179), topotecan plus cisplatin (n = 147) was compared with cisplatin alone (n = 146) for the treatment of histologically confirmed persistent, recurrent or Stage IVB carcinoma of the cervix where curative treatment with surgery and/or radiation was not considered appropriate. Topotecan plus cisplatin had a statistically significant benefit in overall survival relative to cisplatin monotherapy after adjusting for interim analyses (Log-rank p = 0.033).

Table 2 Study results Study GOG-0179

ITT population		
	Cisplatin 50 mg/m^2 on day 1, every 21 days	**Cisplatin 50 mg/m^2 on day 1 + Topotecan 0.75 mg/m^2 on days 1-3, every 21 days**
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)	

In patients (n = 39) with recurrence within 180 days after chemoradiotherapy with cisplatin, the median survival in the topotecan plus cisplatin arm was 4.6 months (95% CI: 2.6, 6.1) versus 4.5 months (95% CI: 2.9, 9.6) for the cisplatin arm, with a hazard ratio of 1.15 (0.59, 2.23). In those patients (n = 102) with recurrence after 180 days, median survival in the topotecan plus cisplatin arm was 9.9 months (95% CI: 7, 12.6) versus 6.3 months (95% CI: 4.9, 9.5) for the cisplatin arm, with a hazard ratio of 0.75 (0.49, 1.16).

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

In an open-label study 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. Anti-tumour 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 section 5.2).

5.2 Pharmacokinetic properties

Distribution

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. Area under the curve increased approximately in proportion to the increase in dose. There is little or no accumulation of topotecan with repeated daily dosing and there is no evidence of a change in the pharmacokinetics after multiple doses. Preclinical studies indicate plasma protein binding of topotecan is low (35%) and distribution between blood cells and plasma was fairly homogeneous.

Biotransformation

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. An 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 <10% for both total topotecan and topotecan lactone. An O-glucuronidation metabolite of topotecan and N-desmethyl topotecan has been identified in the urine.

Elimination

Overall recovery of topotecan-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 topotecan-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 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 section 4.5).

Special populations

Hepatic impairment
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.

Renal impairment
Plasma clearance in patients with renal impairment (creatinine clearance 41-60 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 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.

Age/weight
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).

Paediatric population
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 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 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.

5.3 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.

In reproductive toxicity studies with topotecan in rats there was no effect on male or female fertility; however, in females super-ovulation and slightly increased pre-implantation loss were observed.

The carcinogenic potential of topotecan has not been studied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tartaric acid (E334)
Mannitol (E421)
Hydrochloric acid (E507)
Sodium hydroxide

6.2 Incompatibilities

None known.

6.3 Shelf life

Vials
3 years.

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 ^{0}C after the first puncture of the vial.

6.4 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

HYCAMTIN 1 mg powder for concentrate for solution for infusion

Type I flint glass vial with grey butyl rubber stopper and aluminium seal with plastic flip-off cap

containing 1 mg of topotecan.

HYCAMTIN 1 mg is available in packs containing 1 vial and 5 vials.

HYCAMTIN 4 mg powder for concentrate for solution for infusion

Type I flint glass vial, with grey butyl rubber stopper and aluminium seal with plastic flip-off cap containing 4 mg of topotecan.

HYCAMTIN 4 mg is available in packs containing 1 vial and 5 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

HYCAMTIN 1 mg powder for concentrate for solution for infusion

The contents of HYCAMTIN 1 mg vials must be reconstituted with 1.1 ml water for injections. Since the vial contains a 10% overage, the clear, reconstituted solution is yellow to yellow-green in colour and provides 1 mg of topotecan per ml. Further dilution of the appropriate volume of the reconstituted solution with either sodium chloride 9 mg/ml (0.9%) or 5% w/v glucose is required to give a final concentration of between 25 and 50 microgram/ml.

HYCAMTIN 4 mg powder for concentrate for solution for infusion

The contents of HYCAMTIN 4 mg vials must be reconstituted with 4 ml water for injections. The clear, reconstituted solution is yellow to yellow-green in colour and provides 1 mg of topotecan per ml. Further dilution of the appropriate volume of the reconstituted solution with either sodium chloride 9 mg/ml (0.9%) or 5% w/v glucose is required to a final concentration of between 25 and 50 microgram/ml.

The normal procedures for proper handling and disposal of anticancer medicinal products should be adopted, namely:

- 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.
- Accidental contact with the skin or eyes should be treated immediately with copious amounts of water.
- All items for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high-temperature incineration.

7. MARKETING AUTHORISATION HOLDER

Sandoz Pharmaceuticals d.d.
Verovškova ulica 57
1000 Ljubljana
Slovenia

8. MARKETING AUTHORISATION NUMBERS

HYCAMTIN 1 mg powder for concentrate for solution for infusion

EU/1/96/027/004
EU/1/96/027/005

HYCAMTIN 4 mg powder for concentrate for solution for infusion

EU/1/96/027/001
EU/1/96/027/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 November 1996
Date of latest renewal: 20 November 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

HYCAMTIN 0.25 mg hard capsules
HYCAMTIN 1 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

HYCAMTIN 0.25 mg hard capsules

Each capsule contains 0.25 mg of topotecan (as hydrochloride).

HYCAMTIN 1 mg hard capsules

Each capsule contains 1 mg of topotecan (as hydrochloride).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

HYCAMTIN 0.25 mg hard capsules

The capsules are opaque, white to yellowish white and imprinted with “HYCAMTIN” and “0.25 mg”.

HYCAMTIN 1 mg hard capsules

The capsules are opaque, pink and imprinted with “HYCAMTIN” and “1 mg”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HYCAMTIN capsules are indicated as monotherapy for the treatment of adult patients with relapsed small cell lung cancer (SCLC) for whom re-treatment with the first-line regimen is not considered appropriate (see section 5.1).

4.2 Posology and method of administration

HYCAMTIN capsules should only be prescribed and therapy supervised by a physician experienced in the use of chemotherapeutic agents.

Posology

Prior to administration of the first course of topotecan, patients must have a baseline neutrophil count of $\geq 1.5 \times 10^9$/l, a platelet count of $\geq 100 \times 10^9$/l and a haemoglobin level of ≥9 g/dl (after transfusion if necessary).

Initial dose
The recommended dose of HYCAMTIN capsules is 2.3 mg/m^2 body surface area per day administered for five consecutive days with a three-week interval between the start of each course. If well tolerated, treatment may continue until disease progression (see sections 4.8 and 5.1).

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

Hycamtin capsules may be taken with or without food (see section 5.2).

Subsequent doses
Topotecan 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 ≥9 g/dl (after transfusion if necessary).

Standard oncology practice for the management of neutropenia is either to administer topotecan with other medicinal products (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 <0.5 x 10^9/l) for seven days or more or severe neutropenia associated with fever or infection, or who have had treatment delayed due to neutropenia, the dose should be reduced by 0.4 mg/m^2/day to 1.9 mg/m^2/day (or subsequently down to 1.5 mg/m^2/day if necessary).

Doses should be similarly reduced if the platelet count falls below 25 x 10^9/l. In clinical studies, topotecan was discontinued if the dose needed to be reduced below 1.5 mg/m^2/day.

For patients who experience Grade 3 or 4 diarrhoea, the dose should be reduced by 0.4 mg/m^2/day for subsequent courses (see section 4.4). Patients with Grade 2 diarrhoea may need to follow the same dose modification guidelines.

Proactive management of diarrhoea with anti-diarrhoeal agents is important. Severe cases of diarrhoea may require administration of oral or intravenous electrolytes and fluids, and interruption of topotecan therapy (see sections 4.4 and 4.8).

Special populations
Patients with renal impairment
The recommended monotherapy dose of oral topotecan in patients with small cell lung carcinoma with creatinine clearance between 30 and 49 ml/min is 1.9 mg/m^2/day for five consecutive days. If well tolerated, the dose may be increased to 2.3 mg/m^2/day in subsequent cycles (see section 5.2).

Limited data in Korean patients with creatinine clearance less than 50 ml/min suggest a further lowering of dose may be required (see section 5.2).

Insufficient data are available to make a recommendation for patients with a creatinine clearance <30 ml/min.

Patients with hepatic impairment
Pharmacokinetics of HYCAMTIN capsules have not been specifically studied in patients with impaired hepatic function. There are insufficient data available with HYCAMTIN capsules to make a dose recommendation for this patient group (see section 4.4).

Paediatric population
Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

Elderly
No overall differences in effectiveness were observed between patients aged over 65 years and younger adult patients. However in the two studies in which both oral and intravenous topotecan were administered, patients over 65 years old receiving oral topotecan experienced an increase in drug-related diarrhoea compared to those younger than 65 years of age (see section 4.4 and 4.8).

4.3 Contraindications

- Severe hypersensitivity to the active substance or to any of the excipients.
- Breast-feeding (see section 4.6).
- Severe bone marrow depression prior to starting first course, as evidenced by baseline

neutrophils <1.5 x 10^9/l and/or a platelet count of <100 x 10^9/l.

4.4 Special warnings and precautions for use

Haematological toxicity is dose-related and full blood count including platelets should be determined regularly (see section 4.2).

As with other cytotoxic medicinal products, topotecan can cause severe myelosuppression. Myelosuppression leading to sepsis and fatalities due to sepsis have been reported in patients treated with topotecan (see section 4.8).

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

Topotecan has been associated with reports of interstitial lung disease (ILD), some of which have been fatal (see section 4.8). Underlying risk factors include history of ILD, pulmonary fibrosis, lung cancer, thoracic exposure to radiation and use of pneumotoxic substances and/or colony stimulating factors. Patients should be monitored for pulmonary symptoms indicative of ILD (e.g. cough, fever, dyspnoea and/or hypoxia), and topotecan should be discontinued if a new diagnosis of ILD is confirmed.

Topotecan monotherapy and topotecan in combination with cisplatin are commonly associated with clinically relevant thrombocytopenia. This should be taken into account when prescribing HYCAMTIN, e.g. if patients at increased risk of tumour bleeds are considered for therapy.

As would be expected, patients with poor performance status (PS >1) have a lower response rate and an increased incidence of complications such as fever, infection and sepsis (see section 4.8). Accurate assessment of performance status at the time therapy is given is important, to ensure that patients have not deteriorated to PS 3.

Topotecan is partly eliminated via renal excretion and renal impairment might lead to increased exposure to topotecan. Dosing recommendations for patients receiving oral topotecan with creatinine clearance less than 30 ml/min have not been established. Use of topotecan in these patients is not recommended (see section 4.2).

A small number of hepatically impaired patients (serum bilirubin between 1.5 and 10 mg/dl) were given intravenous topotecan at 1.5 mg/m^2/day for five days every three weeks. A reduction in topotecan clearance was observed. However, there are insufficient data available to make a dose recommendation for this patient group. There is insufficient experience of the use of topotecan in patients with severely impaired hepatic function (serum bilirubin ≥10 mg/dl). Use of topotecan in these patients is not recommended (see section 4.2).

Diarrhoea, including severe diarrhoea requiring hospitalisation, has been reported during treatment with oral topotecan. Diarrhoea related to oral topotecan can occur at the same time as drug-related neutropenia and its sequelae. Communication with patients prior to drug administration regarding these side effects and proactive management of early and all signs and symptoms of diarrhoea is important. Cancer treatment-induced diarrhoea (CTID) is associated with significant morbidity and may be life-threatening. Should diarrhoea occur during treatment with oral topotecan, physicians are advised to aggressively manage diarrhoea. Clinical guidelines describing the aggressive management of CTID include specific recommendations on patient communication and awareness, recognition of early warning signs, use of anti-diarrhoeals and antibiotics, changes in fluid intake and diet, and need for hospitalisation (see sections 4.2 and 4.8).

Intravenous topotecan should be considered in the following clinical situations: uncontrolled emesis, swallowing disorders, uncontrolled diarrhoea, clinical conditions and medication that may alter gastrointestinal motility and drug absorption.

4.5 Interaction with other medicinal products and other forms of interaction

No *in vivo* human pharmacokinetic interaction studies have been performed.

Topotecan does not inhibit human P450 enzymes (see section 5.2). In a population study using the intravenous route, the co-administration of granisetron, ondansetron, morphine or corticosteroids did not appear to have a significant effect on the pharmacokinetics of total topotecan (active and inactive form).

Topotecan is a substrate for both ABCB1 (P-glycoprotein) and ABCG2 (BCRP). Inhibitors of ABCB1 and ABCG2 administered with oral topotecan have been shown to increase topotecan exposure.

Cyclosporin A (an inhibitor of ABCB1, ABCC1 [MRP-1], and CYP3A4) administered with oral topotecan increased topotecan AUC to approximately 2-2.5-fold of control.

Patients should be carefully monitored for adverse reactions when oral topotecan is administered with a substance known to inhibit ABCB1 or ABCG2 (see section 5.2).

When combining topotecan with other chemotherapy agents, reduction of the doses of each medicinal product may be required to improve tolerability. However, when 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, a lower dose of each agent must be given to improve tolerability compared to the dose of each agent which can be given if the platinum agent is given on day 5 of the topotecan dosing. Currently there is only limited experience in combining oral topotecan with other chemotherapy agents.

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Topotecan has been shown to cause embryo-foetal lethality and malformations in preclinical studies (see section 5.3). As with other cytotoxic medicinal products, topotecan may cause foetal harm and therefore women of childbearing potential should be advised to avoid becoming pregnant during therapy with topotecan.

As with all cytotoxic chemotherapy, patients being treated with topotecan must be advised that they or their partner must use an effective method of contraception.

Women of childbearing potential should use effective contraceptive measures while being treated with topotecan and for 6 months following completion of treatment.
Men are recommended to use effective contraceptive measures and to not father a child while receiving topotecan and for 3 months following completion of treatment.

Pregnancy

If topotecan is used during pregnancy, or if the patient becomes pregnant during therapy with topotecan, the patient must be warned of the potential hazards to the foetus.

Breast-feeding

Topotecan is contraindicated during breast-feeding (see section 4.3). Although it is not known whether topotecan is excreted in human breast milk, breast-feeding should be discontinued at the start of therapy.

Fertility

No effects on male or female fertility have been observed in reproductive toxicity studies in rats (see section 5.3). However, as with other cytotoxic medicinal products, topotecan is genotoxic and effects on fertility, including male fertility, cannot be excluded.

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed. However, caution should be observed when driving or operating machines if fatigue and asthenia persist.

4.8 Undesirable effects

In clinical studies involving patients with relapsed small cell lung cancer, the dose-limiting toxicity of oral topotecan monotherapy was found to be haematological. Toxicity was predictable and reversible. There were no signs of cumulative haematological or non-haematological toxicity.

The frequencies associated with the haematological and non-haematological adverse events presented are for adverse events considered to be related/possibly related to oral topotecan therapy.

Adverse reactions are listed below, by system organ class and absolute frequency (all reported events). Frequencies are defined as: 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) and not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations	
Very common	Infection
Common	Sepsis[1]
Blood and lymphatic system disorders	
Very common	Febrile neutropenia, neutropenia (see "Gastrointestinal disorders"), thrombocytopenia, anaemia, leucopenia
Common	Pancytopenia
Not known	Severe bleeding (associated with thrombocytopenia)
Immune system disorders	
Common	Hypersensitivity reaction including rash
Rare	Anaphylactic reaction, angioedema, urticaria
Metabolism and nutrition disorders	
Very common	Anorexia (which may be severe)
Respiratory, thoracic and mediastinal disorders	
Rare	Interstitial lung disease (some cases have been fatal)
Gastrointestinal disorders	
Very common	Nausea, vomiting and diarrhoea (all of which may be severe), which may lead to dehydration (see sections 4.2 and 4.4)
Common	Abdominal pain[2], constipation, mucositis, dyspepsia
Not known	Gastrointestinal perforation
Hepatobiliary disorders	
Common	Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	
Very common	Alopecia
Common	Pruritus
General disorders and administration site conditions	
Very common	Fatigue
Common	Asthenia, pyrexia, malaise

Not known	Mucosal inflammation
[1] Fatalities due to sepsis have been reported in patients treated with topotecan (see section 4.4). [2] Neutropenic colitis, including fatal neutropenic colitis, has been reported to occur as a complication of topotecan-induced neutropenia (see section 4.4)	

The adverse events listed above have the potential to occur with a higher frequency in patients who have a poor performance status (see section 4.4).

Safety data are presented based on an integrated data set of 682 patients with relapsed lung cancer administered 2,536 courses of oral topotecan monotherapy (275 patients with relapsed SCLC and 407 with relapsed non-SCLC).

Haematological

Neutropenia
Severe neutropenia (Grade 4 - neutrophil count <0.5 x 10^9/l) occurred in 32% of patients in 13% of courses. Median time to onset of severe neutropenia was day 12 with a median duration of 7 days. In 34% of courses with severe neutropenia, the duration was >7 days. In course 1 the incidence was 20%, by course 4 the incidence was 8%. Infection, sepsis and febrile neutropenia occurred in 17%, 2%, and 4% of patients, respectively. Death due to sepsis occurred in 1% of patients. Pancytopenia has been reported. Growth factors were administered to 19% of patients in 8% of courses.

Thrombocytopenia
Severe thrombocytopenia (Grade 4 - platelets <10 x 10^9/l) occurred in 6% of patients in 2% of courses. Median time to onset of severe thrombocytopenia was day 15 with a median duration of 2.5 days. In 18% of courses with severe thrombocytopenia the duration was >7 days. Moderate thrombocytopenia (Grade 3 - platelets between 10.0 and 50.0 x 10^9/l) occurred in 29% of patients in 14% of courses. Platelet transfusions were given to 10% of patients in 4% of courses. Reports of significant sequelae associated with thrombocytopenia including fatalities due to tumour bleeds have been infrequent.

Anaemia
Moderate to severe anaemia (Grade 3 and 4 – Hb ≤8.0 g/dl) occurred in 25% of patients (12% of courses). Median time to onset of moderate to severe anaemia was day 12 with a median duration of 7 days. In 46% of courses with moderate to severe anaemia, the duration was >7 days. Red blood cell transfusions were given in 30% of patients (13% of courses). Erythropoietin was administered to 10% of patients in 8% of courses.

Non-haematological

The most frequently reported non-haematological effects were nausea (37%), diarrhoea (29%), fatigue (26%), vomiting (24%), alopecia (21%) and anorexia (18%). All cases were irrespective of associated causality. For severe cases (CTC Grade 3/4) reported as related/possibly related to topotecan administration the incidence was diarrhoea 5% (see section 4.4), fatigue 4%, vomiting 3%, nausea 3% and anorexia 2%.

The overall incidence of drug-related diarrhoea was 22%, including 4% with Grade 3 and 0.4% with Grade 4. Drug-related diarrhoea was more frequent in patients ≥65 years of age (28%) compared to those less than 65 years of age (19%).

Complete alopecia related/possibly related to topotecan administration was observed in 9% of patients and partial alopecia related/possibly related to topotecan administration in 11% of patients.

Therapeutic interventions associated with non-haematological effects included anti-emetic agents, given to 47% of patients in 38% of courses and anti-diarrhoeal agents, given to 15% of patients in 6% of courses. A 5-HT3 antagonist was administered to 30% of patients in 24% of courses. Loperamide was administered to 13% of patients in 5% of courses. The median time to onset of Grade 2 or worse diarrhoea was 9 days.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdoses have been reported in patients being treated with topotecan capsules (up to 5 fold of the recommended dose) and intravenous topotecan (up to 10 fold of the recommended dose). The signs and symptoms observed following overdose were consistent with the known undesirable events associated with topotecan (see section 4.8). The primary complications of overdose are bone marrow suppression and mucositis. In addition, elevated hepatic enzymes have been reported with intravenous topotecan overdose.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, plant alkaloids and other natural products, ATC code: L01CE01.

Mechanism of action

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

Clinical efficacy and safety

Relapsed SCLC
A Phase III study (Study 478) compared oral topotecan plus best supportive care (BSC) (n = 71) with BSC alone (n = 70) in patients who had relapsed following first-line therapy (median time to progression [TTP] from first-line therapy: 84 days for oral topotecan plus BSC, 90 days for BSC alone) and for whom re-treatment with intravenous chemotherapy was not considered appropriate. In the oral topotecan plus BSC group there was a statistically significant improvement in overall survival compared with the BSC alone group (Log-rank p = 0.0104). The unadjusted hazard ratio for the oral topotecan plus BSC group relative to the BSC alone group was 0.64 (95% CI: 0.45, 0.90). Median survival in patients treated with oral topotecan plus BSC was 25.9 weeks (95% CI: 18.3, 31.6) compared to 13.9 weeks (95% CI: 11.1, 18.6) for patients receiving BSC alone (p = 0.0104).

Patient self-reports of symptoms using an unblinded assessment showed a consistent trend for symptom benefit for oral topotecan plus BSC.

One Phase II study (Study 065) and one Phase III study (Study 396) were conducted to evaluate the efficacy of oral topotecan versus intravenous topotecan in patients who had relapsed ≥90 days after completion of one prior regimen of chemotherapy (see Table 1). Oral and intravenous topotecan were associated with similar symptom palliation in patients with relapsed sensitive SCLC in patient self-

reports on an unblinded symptom scale assessment in each of these two studies.

Table 1 Summary of survival, response rate, and time to progression in SCLC patients treated with oral or intravenous topotecan

	Study 065		Study 396	
	Oral topotecan	**Intravenous topotecan**	**Oral topotecan**	**Intravenous topotecan**
	(N = 52)	**(N = 54)**	**(N = 153)**	**(N = 151)**
Median survival (weeks) (95% CI)	32.3 (26.3, 40.9)	25.1 (21.1, 33.0)	33.0 (29.1, 42.4)	35.0 (31.0, 37.1)
Hazard ratio (95% CI)	0.88 (0.59, 1.31)		0.88 (0.7, 1.11)	
Response rate (%) (95% CI)	23.1 (11.6, 34.5)	14.8 (5.3, 24.3)	18.3 (12.2, 24.4)	21.9 (15.3, 28.5)
Difference in response rate (95% CI)	8.3 (-6.6, 23.1)		-3.6 (-12.6, 5.5)	
Median time to progression (weeks) (95% CI)	14.9 (8.3, 21.3)	13.1 (11.6, 18.3)	11.9 (9.7, 14.1)	14.6 (13.3, 18.9)
Hazard ratio (95% CI)	0.90 (0.60, 1.35)		1.21 (0.96, 1.53)	

N = total number of patients treated
CI = confidence interval

Paediatric population
The safety and effectiveness of oral topotecan in paediatric patients have not been established.

5.2 Pharmacokinetic properties

Distribution

The pharmacokinetics of topotecan after oral administration have been evaluated in cancer patients following doses of 1.2 to 3.1 mg/m^2/day and 4 mg/m^2/day administered daily for 5 days. The bioavailability of oral topotecan (total and lactone) in humans is approximately 40%. Plasma concentrations of total topotecan (i.e. lactone and carboxylate forms) and topotecan lactone (active moiety) peak at approximately 2.0 hours and 1.5 hours, respectively, and decline bi-exponentially with mean terminal half-life of approximately 3.0 to 6.0 hours. Total exposure (AUC) increases approximately proportionally with dose. There is little or no accumulation of topotecan with repeated daily dosing and there is no evidence of a change in pharmacokinetics after multiple doses. Preclinical studies indicate plasma protein binding of topotecan is low (35%) and distribution between blood cells and plasma was fairly homogeneous.

Biotransformation

A major route of clearance of topotecan is by hydrolysis of the lactone ring to form the ring-opened carboxylate. Other than hydrolysis, topotecan is cleared predominantly renally, with a minor component metabolised to the N-desmethyl metabolite (SB-209780) identified in plasma, urine and faeces.

Elimination

Overall recovery of topotecan-related material following five daily doses of topotecan was 49 to 72% (mean 57%) of the administered oral dose. Approximately 20% was excreted as total topotecan and 2% was excreted as N-desmethyl topotecan in the urine. Faecal elimination of total topotecan accounted for 33% while faecal elimination of N-desmethyl topotecan was 1.5%. Overall, the N-desmethyl metabolite contributed a mean of less than 6% (range 4-8%) of the total topotecan-related material accounted for in the urine and faeces. O-glucuronides of both topotecan and N-desmethyl

topotecan have been identified in the urine. The mean metabolite: parent plasma AUC ratio was less than 10% for both total topotecan and topotecan lactone.

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.

Following co-administration of the ABCB1 (P-gp) and ABCG2 (BCRP) inhibitor, elacridar (GF120918) at 100 to 1000 mg with oral topotecan, the $AUC_{0-\infty}$ of topotecan lactone and total topotecan increased approximately 2.5-fold (see section 4.5 for guidance).

Administration of oral cyclosporine A (15 mg/kg), an inhibitor of transporters ABCB1 (P-gp) and ABCC1 (MRP-1) as well as the metabolising enzyme CYP3A4, within 4 hours of oral topotecan increased the dose normalised AUC0-24h of topotecan lactone and total topotecan approximately 2.0- and 2.5-fold, respectively (see section 4.5).

The extent of exposure was similar following a high-fat meal and in the fasted state, while t_{max} was delayed from 1.5 to 3 hours (topotecan lactone) and from 3 to 4 hours (total topotecan).

Special populations

Hepatic impairment
The pharmacokinetics of oral topotecan have not been studied in patients with hepatic impairment (see section 4.2 and 4.4).

Renal impairment
Results of a cross-study analysis suggest that the exposure to topotecan lactone, the active moiety following topotecan administration, increases with decreased renal function. Geometric mean topotecan lactone dose-normalised $AUC_{(0-\infty)}$ values were 9.4, 11.1 and 12.0 ng*h/ml in subjects with creatinine clearance values of more than 80 ml/min, 50 to 80 ml/min and 30 to 49 ml/min, respectively. In this analysis, creatinine clearance was calculated using the Cockcroft-Gault method. Similar results were obtained if glomerular filtration rate (ml/min) was estimated using the MDRD formula corrected for body weight. Patients with creatinine clearance >60 ml/min have been included in efficacy/safety studies of topotecan. Therefore, use of the normal starting dose in patients with a mild decrease in renal function is considered established (see section 4.2).

Korean patients with renal impairment had generally higher exposure than non-Asian patients with the same degree of renal impairment. The clinical significance of this finding is unclear. Geometric mean topotecan lactone dose-normalised $AUC_{(0-\infty)}$ values for Korean patients were 7.9, 12.9 and 19.7 ng*h/ml in subjects with creatinine clearance values of more than 80 ml/min, 50 to 80 ml/min and 30 to 49 ml/min, respectively (see section 4.2 and 4.4). There are no data from Asian patients with renal impairment other than Koreans.

Gender
A cross-study analysis in 217 patients with advanced solid tumours indicated that gender did not affect the pharmacokinetics of HYCAMTIN capsules to a clinically relevant extent.

5.3 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.

In reproductive toxicity studies with topotecan in rats there was no effect on male or female fertility; however, in females super-ovulation and slightly increased pre-implantation loss were observed.

The carcinogenic potential of topotecan has not been studied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

HYCAMTIN 0.25 mg hard capsules

Capsule contents
Hydrogenated vegetable oil
Glyceryl monostearate

Capsule shell
Gelatin
Titanium dioxide (E171)

Sealing band
Gelatin

Black ink
Black iron oxide (E172)
Shellac
Anhydrous ethanol – see leaflet for further information
Propylene glycol
Isopropyl alcohol
Butanol
Concentrated ammonia solution
Potassium hydroxide

HYCAMTIN 1 mg hard capsules

Capsule contents
Hydrogenated vegetable oil
Glyceryl monostearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Red iron oxide (E172)

Sealing band
Gelatin

Black ink
Black iron oxide (E172)
Shellac
Anhydrous ethanol – see leaflet for further information
Propylene glycol
Isopropyl alcohol
Butanol
Concentrated ammonia solution
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2ºC - 8ºC).

Do not freeze.

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

6.5 Nature and contents of container

White polyvinyl chloride / polychlorotrifluoroethylene blister sealed with aluminium / Polyethylenterephtalate (PET) / paper foil lidding. The blisters are sealed with a peel-push child resistant opening feature.

Each blister contains 10 capsules.

6.6 Special precautions for disposal and other handling

HYCAMTIN capsules should not be opened or crushed.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sandoz Pharmaceuticals d.d.
Verovškova ulica 57
1000 Ljubljana
Slovenia

8. MARKETING AUTHORISATION NUMBERS

HYCAMTIN 0.25 mg hard capsules

EU/1/96/027/006

HYCAMTIN 1 mg hard capsules

EU/1/96/027/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 November 1996
Date of latest renewal: 20 November 2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Powder for concentrate for solution for infusion
Novartis Farmacéutica S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

GlaxoSmithKline Manufacturing S.p.A.
Strada Provinciale Asolana 90
43056 San Polo di Torrile
Parma
Italy

Salutas Pharma GmbH
Otto-von-Guericke-Allee 1
39179 Barleben
Germany

Hard capsules
Novartis Farmacéutica S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

GlaxoSmithKline Manufacturing S.p.A.
Strada Provinciale Asolana 90
43056 San Polo di Torrile
Parma
Italy

Salutas Pharma GmbH
Otto-von-Guericke-Allee 1,
39179 Barleben,
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

HYCAMTIN 1 mg powder for concentrate for solution for infusion
topotecan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

The total content of active substance in the vial provides 1 mg per ml of active substance when reconstituted as recommended (see Package Leaflet).

3. LIST OF EXCIPIENTS

Also contains: tartaric acid (E334), mannitol (E421), hydrochloric acid (E507), sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion

1 x 1 mg
5 x 1 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Reconstitute before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

WARNING: Cytotoxic agents, special handling instructions (see Package Leaflet).

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz Pharmaceuticals d.d.
Verovškova ulica 57
1000 Ljubljana
Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/027/005	1 x 1 mg vial
EU/1/96/027/004	5 x 1 mg vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16 INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

HYCAMTIN 1 mg powder for concentrate for solution for infusion
topotecan
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mg vial

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

HYCAMTIN 4 mg powder for concentrate for solution for infusion
topotecan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

The total content of active substance in the vial provides 1 mg per ml of active substance when reconstituted as recommended (see Package Leaflet).

3. LIST OF EXCIPIENTS

Also contains: tartaric acid (E334), mannitol (E421), hydrochloric acid (E507), sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion

1 x 4 mg
5 x 4 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Reconstitute before use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

WARNING: Cytotoxic agents, special handling instructions (see Package Leaflet).

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz Pharmaceuticals d.d.
Verovškova ulica 57
1000 Ljubljana
Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/027/003	1 x 4 mg vial
EU/1/96/027/001	5 x 4 mg vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

HYCAMTIN 4 mg powder for concentrate for solution for infusion
topotecan
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

4 mg vial

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

HYCAMTIN 0.25 mg hard capsules
topotecan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains topotecan hydrochloride equivalent to 0.25 mg of topotecan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules

10 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

HYCAMTIN capsules should not be broken or crushed.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the blister in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

WARNING: Cytotoxic agent, special handling instructions (see Package Leaflet).

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz Pharmaceuticals d.d.
Verovškova ulica 57
1000 Ljubljana
Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/027/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16 INFORMATION IN BRAILLE

hycamtin 0.25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS BLISTERS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

HYCAMTIN 0.25 mg hard capsules
topotecan

2. NAME OF MARKETING AUTHORISATION HOLDER

Sandoz Pharmaceuticals d.d.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

HYCAMTIN 1 mg hard capsules
topotecan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains topotecan hydrochloride equivalent to 1 mg of topotecan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsules

10 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

HYCAMTIN capsules should not be broken or crushed.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the blister in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

WARNING: Cytotoxic agent, special handling instructions (see Package Leaflet).

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz Pharmaceuticals d.d.
Verovškova ulica 57
1000 Ljubljana
Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/027/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

hycamtin 1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

HYCAMTIN 1 mg hard capsules
topotecan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sandoz Pharmaceuticals d.d.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Hycamtin 1 mg powder for concentrate for solution for infusion
Hycamtin 4 mg powder for concentrate for solution for infusion
topotecan

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Hycamtin is and what it is used for

Hycamtin helps to destroy tumours. A doctor or a nurse will give you the medicine as an infusion into a vein in hospital.

Hycamtin is used to treat:
- **ovarian cancer or small cell lung cancer** that has come back after chemotherapy.
- **advanced cervical cancer** if surgery or radiotherapy treatment is not possible. When treating cervical cancer, Hycamtin is combined with another medicine called cisplatin.

Your doctor will decide with you whether Hycamtin therapy is better than further treatment with your initial chemotherapy.

2. What you need to know before you are given Hycamtin

You should not receive Hycamtin
- if you are allergic to topotecan or any of the other ingredients of this medicine (listed in section 6).
- if you are breast-feeding.
- if your blood cell counts are too low. Your doctor will tell you whether this is the case, based on the results of your last blood test.

Tell your doctor if any of these applies to you.

Warnings and precautions
Before you are given this medicine your doctor needs to know:
- if you have any kidney or liver problems. Your dose of Hycamtin may need to be adjusted.
- if you are pregnant or plan to become pregnant. See section “Pregnancy and breast-feeding” below.
- if you plan to father a child. See section “Pregnancy and breast-feeding” below.

Tell your doctor if any of these applies to you.

Other medicines and Hycamtin
Tell your doctor if you are taking, have recently taken, or might take any other medicines, including any herbal products or medicines obtained without a prescription.

Remember to tell your doctor if you start to take any other medicines while you are on Hycamtin.

Pregnancy and breast-feeding
Hycamtin is not recommended for pregnant women. It may harm a baby conceived before, during or soon after treatment. You should use effective contraceptive measures while being treated with Hycamtin and for 6 months following completion of treatment. Ask your doctor for advice. Do not try to become pregnant until a doctor advises you it is safe to do so.

Men are recommended to use effective contraceptive measures and to not father a child while receiving Hycamtin and for 3 months following completion of treatment. Male patients who wish to father a child should ask their doctor for family planning advice or treatment. If your partner becomes pregnant during your treatment, tell your doctor immediately.

Do not breast-feed if you are being treated with Hycamtin. Do not restart breast-feeding until the doctor tells you it is safe to do so.

Driving and using machines
Hycamtin can make people feel tired. If you feel tired or weak, do not drive or use machines.

Hycamtin contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium free". If your doctor uses a solution of common salt to dilute Hycamtin, the dose of sodium received would be larger.

3. How Hycamtin is used

The dose of Hycamtin you are given will be worked out by your doctor, based on:
- your body size (surface area measured in square metres)
- the results of blood tests carried out before treatment
- the disease being treated.

The usual dose
- **Ovarian and small cell lung cancer:** 1.5 mg per square metre of body surface area per day. You will have treatment once a day for 5 days. This pattern of treatment will normally be repeated every 3 weeks.
- **Cervical cancer:** 0.75 mg per square metre of body surface area per day. You will have treatment once a day for 3 days. This pattern of treatment will normally be repeated every 3 weeks.
  When treating cervical cancer, Hycamtin is combined with another medicine, called cisplatin. Your doctor will determine the correct dose of cisplatin.

The treatment may vary, depending on the results of your regular blood tests.

How Hycamtin is given
A doctor or nurse will administer Hycamtin as an infusion into your arm lasting about 30 minutes.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects: tell your doctor
These **very common** side effects may affect **more than 1 in 10 people** treated with Hycamtin:

- **Signs of infections:** Hycamtin may reduce the number of white blood cells and lower your resistance to infection. This can even be life threatening. Signs include:
  - fever
  - serious deterioration of your general condition
  - local symptoms such as sore throat or urinary problems (for example, a burning sensation when urinating, which may be a urinary infection).
- Occasionally severe stomach pain, fever and possibly diarrhoea (rarely with blood) can be signs of bowel inflammation (*colitis*).

This **rare** side effect may affect **up to 1 in 1,000 people** treated with Hycamtin:

- **Lung inflammation** (*interstitial lung disease*): You are most at risk if you have existing lung disease, have had radiation treatment to your lungs, or have previously taken medicines that caused lung damage. Signs include:
  - difficulty breathing
  - cough
  - fever.

Tell your doctor immediately if you get any symptoms of these conditions, as hospitalisation may be necessary.

Very common side effects
These may affect **more than 1 in 10 people** treated with Hycamtin:

- Feeling generally weak and tired (temporary *anaemia*). In some cases you may need a blood transfusion.
- Unusual bruising or bleeding, caused by a decrease in the number of clotting cells in the blood. This can lead to severe bleeding from relatively small injuries such as a small cut. Rarely, it can lead to more severe bleeding (*haemorrhage*). Talk to your doctor for advice on how to minimise the risk of bleeding.
- Weight loss and loss of appetite (*anorexia*); tiredness; weakness.
- Feeling sick (nausea), being sick (vomiting); diarrhoea; stomach pain; constipation.
- Inflammation and ulcers of the mouth tongue or gums.
- High body temperature (fever).
- Hair loss.

Common side effects
These may affect **up to 1 in 10 people** treated with Hycamtin:

- Allergic or *hypersensitivity* reactions (including rash).
- Yellow skin.
- Feeling unwell.
- Itching sensation.

Rare side effects
These may affect **up to 1 in 1,000 people** treated with Hycamtin:

- Severe allergic or *anaphylactic* reactions.
- Swelling caused by fluid build-up (*angioedema*).
- Mild pain and inflammation at the site of injection.
- Itchy rash (or *hives*).

Side effects with frequency not known
The frequency of some side effects is not known (events from spontaneous reports and the frequency

cannot be estimated from the available data):
- Severe stomach pain, nausea, vomiting of blood, black or bloody stools (possible symptoms of gastrointestinal perforation).
- Mouth sores, difficulty swallowing, abdominal pain, nausea, vomiting, diarrhoea, bloody stools (possible signs and symptoms of inflammation of the inner lining of the mouth, stomach and/or gut [mucosal inflammation]).

If you are being treated for cervical cancer, you may get side effects from the other medicine (cisplatin) that you will be given along with Hycamtin. Those effects are described in the cisplatin patient leaflet.

Reporting of side effects
If you get any side effects, talk to your **doctor or pharmacist**. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Hycamtin

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton.

Keep the vial in the outer carton in order to protect from light.

This medicine is for single use only. After opening, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. If reconstitution and dilution are performed under strict aseptic conditions (e.g. an LAF bench) the product should be used (infusion completed) within 24 hours if stored at 2ºC – 8ºC after the first puncture of the vial.

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

6. Contents of the pack and other information

What Hycamtin contains
- **The active substance is** topotecan. Each vial contains 1 mg or 4 mg of topotecan (as hydrochloride).
- **The other ingredients are:** tartaric acid (E334), mannitol (E421), hydrochloric acid (E507) and sodium hydroxide.

What Hycamtin looks like and contents of the pack
Hycamtin comes as a powder for concentrate for solution for intravenous infusion.
It is available in packs containing either 1 or 5 glass vials; each vial contains 1 mg or 4 mg of topotecan.
The powder needs to be reconstituted and diluted before infusion.
The powder in the vial provides 1 mg per ml of active substance when reconstituted as recommended.

Marketing Authorisation Holder
Sandoz Pharmaceuticals d.d.
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Manufacturer
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Parma
Italy

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Otto-von-Guericke-Allee 1
39179 Barleben
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

The following information is intended for healthcare professionals only:

Instructions on how to reconstitute, store and dispose of Hycamtin

Reconstitution
Hycamtin 1 mg powder for concentrate for solution for infusion should be reconstituted with 1.1 ml of water for injections to provide 1 mg per ml of topotecan.
Hycamtin 4 mg powder for concentrate for solution for infusion should be reconstituted with 4 ml of water for injections to provide 1 mg per ml of topotecan.

Further dilution is required. The appropriate volume of the reconstituted solution should be diluted with **either** 0.9 % w/v sodium chloride intravenous infusion **or** 5 % w/v glucose intravenous infusion, to a final concentration of between 25 and 50 microgram per ml.

Storage of the prepared solution
The product should be used immediately after it is prepared for infusion. If reconstitution is performed under strict aseptic conditions Hycamtin infusion may be completed within 12 hours at room temperature (or 24 hours if stored at 2-8^{o}C).

Handling and disposal
The normal procedures for proper handling and disposal of anti-tumour medicinal products should be adopted:

- Staff should be trained to reconstitute the medicinal product.
- Pregnant staff should be excluded from working with this medicinal product.
- Staff 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.
- Accidental contact with the skin or eyes should be treated immediately with copious amounts of water.

Package leaflet: Information for the user

Hycamtin 0.25 mg hard capsules
Hycamtin 1 mg hard capsules
topotecan

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms seem to be the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Hycamtin is and what it is used for

Hycamtin helps to destroy tumours.

Hycamtin is used to treat small cell lung cancer that has come back after chemotherapy.

Your doctor will decide with you whether Hycamtin therapy is better than further treatment with your initial chemotherapy.

2. What you need to know before you take Hycamtin

Do not take Hycamtin
- if you are allergic to topotecan or any of the other ingredients of this medicine (listed in section 6).
- if you are breast-feeding.
- if your blood cell counts are too low. Your doctor will tell you whether this is the case, based on the results of your last blood test.

Tell your doctor if any of these applies to you.

Warnings and precautions
Before you are given this medicine your doctor needs to know:
- if you have any kidney or liver problems. Your dose of Hycamtin may need to be adjusted.
- if you are pregnant or plan to become pregnant. See section “Pregnancy and breast-feeding” below.
- if you plan to father a child. See section “Pregnancy and breast-feeding” below.

Tell your doctor if any of these applies to you.

Other medicines and Hycamtin
Tell your doctor if you are taking, have recently taken, or might take any other medicines, including any herbal products or medicines obtained without a prescription.

There may be a higher than usual chance of you getting side effects if you are also being treated with cyclosporin A. You will be monitored closely if you are taking both these medicines.

Remember to tell your doctor if you start to take any other medicines while you are on Hycamtin.

Pregnancy and breast-feeding
Hycamtin is not recommended for pregnant women. It may harm a baby conceived before, during or soon after treatment. You should use effective contraceptive measures while being treated with Hycamtin and for 6 months following completion of treatment. Ask your doctor for advice. Do not try to become pregnant until a doctor advises you it is safe to do so.

Men are recommended to use effective contraceptive measures and to not father a child while receiving Hycamtin and for 3 months following completion of treatment. Male patients who wish to father a child should ask their doctor for family planning advice or treatment. If your partner becomes pregnant during your treatment, tell your doctor immediately.

Do not breast-feed if you are being treated with Hycamtin. Do not restart breast-feeding until the doctor tells you it is safe to do so.

Driving and using machines
Hycamtin can make people feel tired. If you feel tired or weak, do not drive or use machines.

Hycamtin contains ethanol
This medicine contains small amounts of ethanol (alcohol).

3. How to take Hycamtin

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

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

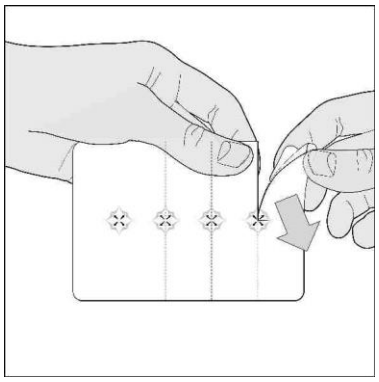
The dose (and number of capsules) of Hycamtin you are given will be worked out by your doctor, based on:
- your body size (surface area measured in square metres)
- the results of blood tests carried out before treatment

The prescribed number of capsules should be swallowed whole, once a day for 5 days.

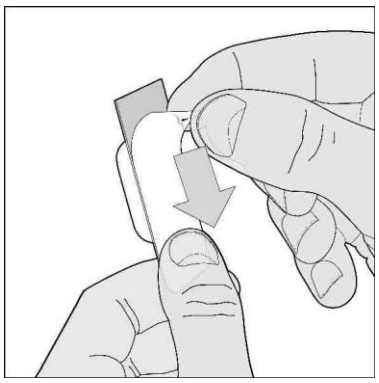
Hycamtin capsules must not be opened or crushed. If the capsules are punctured or leaking, you should immediately wash your hands thoroughly with soap and water. If you get the capsule contents in your eyes, wash them immediately with gently flowing water for at least 15 minutes. Consult your doctor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

Taking out a capsule
These capsules come in special packaging to prevent children removing them.

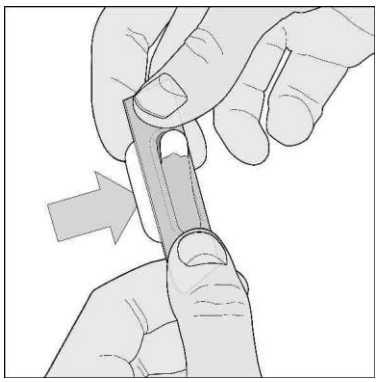
1. **Separate one capsule:** tear along the perforated lines to separate one capsule "pocket" from the strip.



2. **Peel back the outer layer:** starting at the coloured corner, lift and peel over the pocket.



3. **Push out the capsule:** gently push one end of the capsule through the foil layer.



If you take more Hycamtin than you should
Contact a doctor or pharmacist immediately for advice if you have taken too many capsules or if a child has accidentally taken the medicine.

If you forget to take Hycamtin
Do not take a double dose to make up for a forgotten dose. Just take the next dose at the scheduled time.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects: tell your doctor
These **very common** side effects may affect **more than 1 in 10 people** treated with Hycamtin:

- **Signs of infections:** Hycamtin may reduce the number of white blood cells and lower your resistance to infection. This can even be life threatening. Signs include:
  - fever
  - serious deterioration of your general condition
  - local symptoms such as sore throat or urinary problems (for example, a burning sensation when urinating, which may be a urinary infection).
- **Diarrhoea.** This can be serious. If you have more than 3 episodes of diarrhoea per day you should contact your doctor immediately.
- Occasionally severe stomach pain, fever and possibly diarrhoea (rarely with blood) can be signs of bowel inflammation (*colitis*).

This **rare** side effect may affect **up to 1 in 1,000 people** treated with Hycamtin).

- **Lung inflammation** (interstitial lung disease): You are most at risk if you have existing lung disease, had radiation treatment to your lungs, or have previously taken medicines that caused lung damage. Signs include:
  - difficulty in breathing
  - cough
  - fever

Tell your doctor immediately if you get any symptoms of these conditions, as hospitalisation may be necessary.

Very common side effects
These may affect **more than 1 in 10 people** treated with Hycamtin:

- Feeling generally weak and tired (temporary *anaemia*). In some cases you may need a blood transfusion.
- Unusual bruising or bleeding, caused by a decrease in the number of clotting cells in the blood. This can lead to severe bleeding from relatively small injuries such as a small cut. Rarely, it can lead to more severe bleeding (*haemorrhage*). Talk to your doctor for advice on how to minimise the risk of bleeding.
- Weight loss and loss of appetite (*anorexia*); tiredness; weakness.
- Feeling sick (nausea), being sick (vomiting).
- Hair loss.

Common side effects
These may affect **up to 1 in 10 people** treated with Hycamtin:

- Allergic or *hypersensitivity* reactions (including rash).
- Inflammation and ulcers of the mouth, tongue or gums.
- High body temperature (fever).
- Stomach pain, constipation, indigestion.
- Feeling unwell.
- Itching sensation.

Uncommon side effects
These may affect **up to 1 in 100 people** treated with Hycamtin:

- Yellow skin.

Rare side effects
These may affect **up to 1 in 1,000 people** treated with Hycamtin:

- Severe allergic or *anaphylactic* reactions.

- Swelling caused by fluid build up (*angioedema*).
- Itchy rash (or *hives*).

Side effects with frequency not known
The frequency of some side effects is not known (events from spontaneous reports and the frequency cannot be estimated from the available data):
- Severe stomach pain, nausea, vomiting of blood, black or bloody stools (possible symptoms of gastrointestinal perforation).
- Mouth sores, difficulty swallowing, abdominal pain, nausea, vomiting, diarrhoea, bloody stools (possible signs and symptoms of inflammation of the inner lining of the mouth, stomach and/or gut [mucosal inflammation]).

Reporting of side effects
If you get any side effects, talk to your **doctor or pharmacist.** This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Hycamtin

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton.

Store in a refrigerator (2ºC - 8ºC).

Do not freeze.

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

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Hycamtin contains
- **The active substance is** topotecan. Each capsule contains 0.25 mg or 1 mg of topotecan (as hydrochloride).
- **The other ingredients are:** hydrogenated vegetable oil, glyceryl monostearate, gelatin, titanium dioxide (E171), and for 1 mg capsules only, red iron oxide (E172). The capsules are printed with black ink that contains black iron oxide (E172), shellac, anhydrous ethanol, propylene glycol, isopropyl alcohol, butanol, concentrated ammonia solution and potassium hydroxide.

What Hycamtin looks like and contents of the pack
Hycamtin 0.25 mg capsules are white to yellowish white and imprinted with “Hycamtin” and “0.25 mg”.

Hycamtin 1 mg capsules are pink and imprinted with “Hycamtin” and “1 mg”.

Hycamtin 0.25 mg and 1 mg capsules are available in packs containing 10 capsules.

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This leaflet was last revised in

Other sources of information
Detailed information on this medicine product is available on the European Medicines Agency web site: http://www.ema.europa.eu/.