ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Topotecan Eagle 3 mg/1 ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of concentrate for solution for infusion contains 3 mg topotecan (as hydrochloride).

Each 1 ml single dose vial contains 3 mg of topotecan.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear light yellow to orange solution, pH ≤ 1.2.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Topotecan monotherapy is indicated for the treatment of 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

Posology

When 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).

Small Cell Lung Carcinoma

Initial dose
The recommended dose of topotecan is 1.5 mg/m^2 body surface area/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 medications (e.g. G-CSF) or to dose reduce 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 trials, topotecan was discontinued if the dose had been reduced to 1.0 mg/m^2 and a further dose reduction was required to manage adverse effects.

Cervical Carcinoma

Initial dose
The recommended dose of topotecan is 0.75 mg/m^2/day administered as 30 minute intravenous infusion daily on days 1, 2 and 3. Cisplatin is administered as an intravenous infusion on day 1 at a dose of 50 mg/m^2/day and following the 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 more than or equal to 1.5 x 10^9/l, the platelet count is more than or equal to 100 x 10^9/l, and the haemoglobin level is more than or equal to 9 g/dl (after transfusion if necessary).

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

If dose reduction is chosen for patients who experience severe neutropenia (neutrophil count less than 0.5 x 10^9/l) for 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.

Dosage in renally impaired patients
Monotherapy (Small cell lung carcinoma)
Insufficient data are available to make a recommendation for patients with a creatinine clearance < 20 ml/min. Limited data indicate that the dose should be reduced in patients with moderate renal impairment. The recommended monotherapy dose of topotecan in patients with 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.

Paediatric population
The experience in children is limited, therefore no recommendation for treatment of paediatric patients with topotecan can be given (see sections 5.1 and 5.2).

Method of administration

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

The concentration of topotecan in the 1 ml vial is higher (3 mg/ml) than with other topotecan products. It is important that Topotecan Eagle is further diluted before use (see section 6.6).

Concentration must be noticed or life-threatening overdose may occur.

Topotecan Eagle contains a higher dose concentration (3 mg/ml) than other topotecan products for intravenous infusion (usually 1 mg/ml). Topotecan Eagle must be diluted to a final concentration between 25 µg/ml and 50 µg/ml (see section 6.6 for dilution instructions).

4.3 Contraindications

Topotecan is contraindicated in patients who
- have a history of severe hypersensitivity to the active substance or to any of the excipients
- are breast feeding (see section 4.6)
- already have 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

Topotecan Eagle requires appropriate dilution before use. The concentration of topotecan in Topotecan Eagle differs from other topotecan products (see section 6.6 for further instructions on dilution).

Concentration must be noticed or life-threatening overdose may occur.

Topotecan Eagle contains a higher dose concentration (3 mg/ml) than other topotecan products for intravenous infusion (usually 1 mg/ml). Topotecan Eagle must be diluted to a final concentration between 25 µg/ml and 50 µg/ml (see section 6.6 for dilution instructions).

Haematological toxicity is dose-related and full blood count including platelets should be monitored 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 trials 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 topotecan, e.g. in case patients at increased risk of tumour bleeds are considered for therapy.

As 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 performance status 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. Topotecan is not recommended to be used in these patient groups.

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 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.

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 an intravenous population study, 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).

In combining topotecan with other chemotherapy agents, reduction of the doses of each medicinal product may be required to improve tolerability. However, in combining with platinum agents, there is a distinct sequence-dependent interaction depending on whether the platinum agent is given on day 1 or 5 of the topotecan dosing. If either cisplatin or carboplatin is given on day 1 of the topotecan dosing, 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 five 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

Contraception in males and females
As with all cytotoxic chemotherapy, effective contraceptive methods must be advised when either partner is treated with topotecan.

Women of childbearing potential
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.

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.

Breastfeeding
Topotecan is contra-indicated 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 on 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 trials 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 adverse event profile for topotecan when given in combination with cisplatin in the cervical cancer clinical trials 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 not attributable to topotecan. The prescribing information for cisplatin should be consulted for a full list of adverse events associated 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), including isolated reports and not known (cannot be estimated from the available data).

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

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)

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[1], mucositis
Neutropenic colitis, including fatal neutropenic colitis, has been reported to occur as a complication of topotecan-induced neutropenia (see section 4.4)

Skin and subcutaneous tissue disorders
Very common: alopecia
Common: pruritus

Metabolism and nutrition disorders
Very common: anorexia (which may be severe)

Infections and infestations
Very common: infection
Common: sepsis[2]

[2] Fatalities due to sepsis have been reported in patients treated with topotecan (see section 4.4)

General disorders and administration site conditions
Very common: pyrexia, asthenia, fatigue
Common: malaise
Very rare: extravasation[3]
[3] Extravasation has been reported very rarely. Reactions have been mild and have not generally required specific therapy.

Immune system disorders
Common: hypersensitivity reaction including rash
Rare: anaphylactic reaction, angioedema, urticaria

Hepato-biliary disorders
Common: hyperbilirubinaemia

The incidence of 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 was seen in 55 % of the patients and 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 trials (including both those with severe neutropenia and those who did not develop severe neutropenia), 11 % (4 % of courses) developed fever and 26 % (9 % of courses) developed infection. In addition, 5 % of all patients treated (1 % of courses) developed sepsis (see section 4.4).

Thrombocytopenia: Severe (platelets less than 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 %), and diarrhoea (18 %), constipation (9 %) and mucositis (14 %). Severe (grade 3 or 4) nausea, vomiting, diarrhoea and mucositis incidence was 4, 3, 2 and 1 % respectively.

Mild abdominal pain was also reported amongst 4 % of patients.

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

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

Other severe events occurring in patients 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 trials, rash was reported in 4 % of patients and pruritus in 1.5 % of patients.

4.9 Overdose

There is no known antidote for topotecan overdose. The primary complications of overdose are anticipated to be bone marrow suppression and mucositis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XX17.

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.

Relapsed SCLC

A phase III trial (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 + BSC, 90 days for BSC) and for whom retreatment with intravenous chemotherapy was not considered appropriate. Oral topotecan plus BSC group had a statistically significant improvement in overall survival compared with the BSC alone group (Log-rank p = 0.0104). The unadjusted hazard ratio for oral topotecan plus BSC group relative to BSC alone group was 0.63 (95 % CI: 0.45, 0.90). The median survival for patients treated with topotecan + BSC was 25.9 weeks (95 % C.I. 18.3, 31.6) compared to 13.9 weeks (95 % C.I. 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 + BSC.

One Phase 2 study (Study 065) and one Phase 3 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)	14.0 (11.3, 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 trial which compared intravenous topotecan to cyclophosphamide, Adriamycin (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 of 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 %. The 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 trial conducted by the Gynaecological Oncology Group (GOG 0179), topotecan plus cisplatin (n = 147) was compared with cisplatin alone (n = 146) for the treatment of 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 50mg/m^2 d.1 q21 d.	**Cisplatin 50mg/m^2 d.1 + Topotecan 0.75mg/m^2 dx3 q21**
Survival (months)	**(n = 146)**	**(n = 147)**
Median (95 % C.I.)	6.5 (5.8, 8.8)	9.4 (7.9, 11.9)
Hazard ratio (95 % C.I.)	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 % C.I.)	8.8 (6.4, 11.5)	15.7 (11.9, 17.7)
Hazard ratio (95 % C.I.)	0.51 (0.31, 0.82)	
Patients with prior Cisplatin chemoradiotherapy		
	Cisplatin	**Topotecan/Cisplatin**
Survival (months)	**(n = 72)**	**(n = 69)**
Median (95 % C.I)	5.9 (4.7, 8.8)	7.9 (5.5, 10.9)
Hazard ratio (95 % C.I.)	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 % C.I.: 2.6, 6.1) versus 4.5 months (95 % C.I.: 2.9, 9.6) for the cisplatin arm with an hazard ratio of 1.15 (0.59, 2.23). In those (n = 102) with recurrence after 180 days, the median survival in the topotecan plus cisplatin arm was 9.9 months (95 % C.I.: 7, 12.6) versus 6.3 months (95 % C.I.: 4.9, 9.5) for the cisplatin arm with an 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 trial involving children (n = 108, age range: infant to 16 years) with recurrent or progressive solid tumours, topotecan was administered at a starting dose of 2.0 mg/m^2 given as a 30-minute infusion for 5 days repeated every 3 weeks for up to one year depending on response to therapy. Tumour types included were Ewing's Sarcoma/primitive neuroectodermal tumour, neuroblastoma, osteosarcoma, and rhabdomyosarcoma. Antitumour activity was demonstrated primarily in patients with neuroblastoma. Toxicities of topotecan in paediatric patients with recurrent and refractory solid tumours were similar to those historically seen in adult patients. In this study, forty-six (43 %) patients received G-CSF over 192 (42.1 %) courses; sixty-five (60 %) received transfusions of Packed Red Blood Cells and fifty (46 %) of platelets over 139 and 159 courses (30.5 % and 34.9 %) respectively. Based on the dose-limiting toxicity of myelosuppression, the maximum tolerated dose (MTD) was established at 2.0 mg/m^2/day with G-CSF and 1.4 mg/m^2/day without G-CSF in a pharmacokinetic study in paediatric patients with refractory solid tumours (see section 5.2).

5.2 Pharmacokinetic properties

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 PK after multiple doses. Preclinical studies indicate plasma protein binding of topotecan is low (35 %) and distribution between blood cells and plasma was fairly homogeneous.

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

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

In vitro data using human liver microsomes indicate the formation of small amounts of N-demethylated topotecan. In 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).

Plasma clearance in patients with hepatic impairment (serum bilirubin between 1.5 and 10 mg/dl) decreased to about 67 % when compared with a control group of patients. Topotecan half-life was increased by about 30 % but no clear change in volume of distribution was observed. Plasma clearance of total topotecan (active and inactive form) in patients with hepatic impairment only decreased by about 10 % compared with the control group of patients.

Plasma clearance in patients with renal impairment (creatinine clearance 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.

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

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

Hydrochloric acid (E507) (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Vial before opening
18 months.

Diluted solution
From a microbiological point of view, the solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 20°C - 25°C and ambient lighting conditions.

6.4 Special precautions for storage

Do not store above 25°C.

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

For storage conditions of once-opened and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

1 ml concentrate in type 1 clear glass vial, together with grey butyl rubber stopper and aluminium seal with blue polypropylene flip-off cap, and with yellow vial ring collar.
Each pack contains 1 vial.

6.6 Special precautions for disposal and other handling

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

- Personnel should be trained to dilute the medicinal product.
- Pregnant staff should be excluded from working with this medicinal product.
- Personnel handling this medicinal product during dilution should wear protective clothing including mask, goggles and gloves.

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

Instructions for dilution

Concentration must be noticed or life-threatening overdose may occur.

Topotecan Eagle concentrate is clear yellow to orange in colour and contains 3 mg/ml of topotecan which is a higher concentration than found in other topotecan products for intravenous infusion.

The user is requested to report any medication errors.

The following dosing tables should be used as reference:

Instructions for Preparation for Intravenous Administration for Small Cell Lung Cancer

Body surface area (m^2)	For recommended dose '1.5 mg/m^2'		For reduced dose '1.25 mg/m^2'		For reduced dose '1.0 mg/m^2'	
	Volume of solution required (ml)	Total dose (mg)	Volume of solution required (ml)	Total dose (mg)	Volume of solution required (ml)	Total dose (mg)
1	0.50	1.50	0.42	1.26	0.33	0.99
1.1	0.55	1.65	0.46	1.38	0.37	1.11
1.2	0.60	1.80	0.50	1.50	0.40	1.20
1.3	0.65	1.95	0.54	1.62	0.43	1.29
1.4	0.70	2.10	0.58	1.74	0.47	1.41
1.5	0.75	2.25	0.63	1.89	0.50	1.50
1.6	0.80	2.40	0.67	2.01	0.53	1.59
1.7	0.85	2.55	0.71	2.13	0.57	1.71
1.8	0.90	2.70	0.75	2.25	0.60	1.80
1.9	0.95	2.85	0.79	2.37	0.63	1.89
2	1.00	3.00	0.83	2.49	0.67	2.01
2.1	1.05	3.15	0.88	2.64	0.70	2.10
2.2	1.10	3.30	0.92	2.76	0.73	2.19
2.3	1.15	3.45	0.96	2.88	0.77	2.31
2.4	1.20	3.60	1.00	3.00	0.80	2.40
2.5	1.25	3.75	1.04	3.12	0.83	2.49

Instructions for Preparation for Intravenous Administration for Cervical Cancer

Body surface area (m^2)	For recommended dose '0.75 mg/m^2'		For reduced dose '0.60 mg/m^2'		For reduced dose '0.45 mg/m^2'	
	Volume of solution required (ml)	Total dose (mg)	Volume of solution required (ml)	Total dose (mg)	Volume of solution required (ml)	Total dose (mg)
1	0.25	0.75	0.20	0.60	0.15	0.45
1.1	0.28	0.84	0.22	0.66	0.17	0.51
1.2	0.30	0.90	0.24	0.72	0.18	0.54
1.3	0.33	0.99	0.26	0.78	0.20	0.60
1.4	0.35	1.05	0.28	0.84	0.21	0.63
1.5	0.38	1.14	0.30	0.90	0.23	0.69
1.6	0.40	1.20	0.32	0.96	0.24	0.72
1.7	0.43	1.29	0.34	1.02	0.26	0.78
1.8	0.45	1.35	0.36	1.08	0.27	0.81
1.9	0.48	1.44	0.38	1.14	0.29	0.87
2	0.50	1.50	0.40	1.20	0.30	0.90
2.1	0.53	1.59	0.42	1.26	0.32	0.96
2.2	0.55	1.65	0.44	1.32	0.33	0.99
2.3	0.58	1.74	0.46	1.38	0.35	1.05
2.4	0.60	1.80	0.48	1.44	0.36	1.08
2.5	0.63	1.89	0.50	1.50	0.38	1.14

Further dilution of Topotecan Eagle is required with either sodium chloride 9 mg/ml (0.9 % w/v) solution for injection or glucose 50 mg/ml (5 % w/v) solution for injection in order to reach a final topotecan concentration of between 25 µg/ml and 50 µg/ml in the solution for infusion to the patient. Dilution should be performed under strict aseptic conditions (e.g. an LAF bench).

Disposal

Topotecan Eagle 3 mg/1 ml is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eagle Laboratories Limited
The Clock House
Station Approach
Marlow, Bucks, SL7 1NT
United Kingdom
Tel: +1 (201) 326-5324
Fax: +1 (201) 391-2430

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/744/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:
22/12/2011

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Topotecan Eagle 15 mg/5 ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of concentrate for solution for infusion contains 3 mg topotecan (as hydrochloride).

Each 5 ml multi dose vial contains 15 mg of topotecan.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear light yellow to orange solution, pH ≤ 1.2.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Topotecan monotherapy is indicated for the treatment of 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

Posology

When 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).

Small Cell Lung Carcinoma

Initial dose
The recommended dose of topotecan is 1.5 mg/m^2 body surface area/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 dose reduce 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 trials, topotecan was discontinued if the dose had been reduced to 1.0 mg/m^2 and a further dose reduction was required to manage adverse effects.

Cervical Carcinoma

Initial dose
The recommended dose of topotecan is 0.75 mg/m^2/day administered as 30 minute intravenous infusion daily on days 1, 2 and 3. Cisplatin is administered as an intravenous infusion on day 1 at a dose of 50 mg/m^2/day and following the 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 more than or equal to 1.5 x 10^9/l, the platelet count is more than or equal to 100 x 10^9/l, and the haemoglobin level is more than or equal to 9 g/dl (after transfusion if necessary).

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

If dose reduction is chosen for patients who experience severe neutropenia (neutrophil count less than 0.5 x 10^9/l) for 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.

Dosage in renally impaired patients
Monotherapy (Small cell lung carcinoma)
Insufficient data are available to make a recommendation for patients with a creatinine clearance < 20 ml/min. Limited data indicate that the dose should be reduced in patients with moderate renal impairment. The recommended monotherapy dose of topotecan in patients with 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.

Paediatric population
The experience in children is limited, therefore no recommendation for treatment of paediatric patients with topotecan can be given (see sections 5.1 and 5.2).

Method of administration

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

The concentration of topotecan in the 5 ml vial is higher (3 mg/ml) than with other topotecan products. It is important that Topotecan Eagle is further diluted before use (see section 6.6).

Concentration must be noticed or life-threatening overdose may occur.

Topotecan Eagle contains a higher dose concentration (3 mg/ml) than other topotecan products for intravenous infusion (usually 1 mg/ml). Topotecan Eagle must be diluted to a final concentration between 25 µg/ml and 50 µg/ml (see section 6.6 for dilution instructions).

4.3 Contraindications

Topotecan is contraindicated in patients who
- have a history of severe hypersensitivity to the active substance or to any of the excipients
- are breast feeding (see section 4.6)
- already have 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

Topotecan Eagle requires appropriate dilution before use. The concentration of topotecan in Topotecan Eagle differs from other topotecan products (see section 6.6 for further instructions on dilution).

Concentration must be noticed or life-threatening overdose may occur.

Topotecan Eagle contains a higher dose concentration (3 mg/ml) than other topotecan products for intravenous infusion (usually 1 mg/ml). Topotecan Eagle must be diluted to a final concentration between 25 µg/ml and 50 µg/ml (see section 6.6 for dilution instructions).

Haematological toxicity is dose-related and full blood count including platelets should be monitored 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 trials 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 topotecan, e.g. in case patients at increased risk of tumour bleeds are considered for therapy.

As 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 performance status 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. Topotecan is not recommended to be used in these patient groups.

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 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.

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 an intravenous population study, 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).

In combining topotecan with other chemotherapy agents, reduction of the doses of each medicinal product may be required to improve tolerability. However, in combining with platinum agents, there is a distinct sequence-dependent interaction depending on whether the platinum agent is given on day 1 or 5 of the topotecan dosing. If either cisplatin or carboplatin is given on day 1 of the topotecan dosing, 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 five 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

Contraception in males and females
As with all cytotoxic chemotherapy, effective contraceptive methods must be advised when either partner is treated with topotecan.

Women of childbearing potential
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.

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.

Breastfeeding
Topotecan is contra-indicated 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 on 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 trials 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 adverse event profile for topotecan when given in combination with cisplatin in the cervical cancer clinical trials 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 not attributable to topotecan. The prescribing information for cisplatin should be consulted for a full list of adverse events associated 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), including isolated reports and not known (cannot be estimated from the available data).

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

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)

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[1], mucositis
Neutropenic colitis, including fatal neutropenic colitis, has been reported to occur as a complication of topotecan-induced neutropenia (see section 4.4)

Skin and subcutaneous tissue disorders
Very common: alopecia
Common: pruritus

Metabolism and nutrition disorders
Very common: anorexia (which may be severe)

Infections and infestations
Very common: infection
Common: sepsis[2]

[2] Fatalities due to sepsis have been reported in patients treated with topotecan (see section 4.4)

General disorders and administration site conditions
Very common: pyrexia, asthenia, fatigue
Common: malaise
Very rare: extravasation[3]
[3] Extravasation has been reported very rarely. Reactions have been mild and have not generally required specific therapy.

Immune system disorders
Common: hypersensitivity reaction including rash
Rare: anaphylactic reaction, angioedema, urticaria

Hepato-biliary disorders
Common: hyperbilirubinaemia

The incidence of 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 was seen in 55 % of the patients and 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 trials (including both those with severe neutropenia and those who did not develop severe neutropenia), 11 % (4 % of courses) developed fever and 26 % (9 % of courses) developed infection. In addition, 5 % of all patients treated (1 % of courses) developed sepsis (see section 4.4).

Thrombocytopenia: Severe (platelets less than 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 %), and diarrhoea (18 %), constipation (9 %) and mucositis (14 %). Severe (grade 3 or 4) nausea, vomiting, diarrhoea and mucositis incidence was 4, 3, 2 and 1 % respectively.

Mild abdominal pain was also reported amongst 4 % of patients.

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

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

Other severe events occurring in patients 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 trials, rash was reported in 4 % of patients and pruritus in 1.5 % of patients.

4.9 Overdose

There is no known antidote for topotecan overdose. The primary complications of overdose are anticipated to be bone marrow suppression and mucositis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XX17.

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.

Relapsed SCLC

A phase III trial (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 + BSC, 90 days for BSC) and for whom retreatment with intravenous chemotherapy was not considered appropriate. Oral topotecan plus BSC group had a statistically significant improvement in overall survival compared with the BSC alone group (Log-rank p = 0.0104). The unadjusted hazard ratio for oral topotecan plus BSC group relative to BSC alone group was 0.63 (95 % CI: 0.45, 0.90). The median survival for patients treated with topotecan + BSC was 25.9 weeks (95 % C.I. 18.3, 31.6) compared to 13.9 weeks (95 % C.I. 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 + BSC.

One Phase 2 study (Study 065) and one Phase 3 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)	14.0 (11.3, 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 trial which compared intravenous topotecan to cyclophosphamide, Adriamycin (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 of 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 %. The 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 trial conducted by the Gynaecological Oncology Group (GOG 0179), topotecan plus cisplatin (n = 147) was compared with cisplatin alone (n = 146) for the treatment of 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 50mg/m^2 d.1 q21 d.	**Cisplatin 50mg/m^2 d.1 + Topotecan 0.75mg/m^2 dx3 q21**
Survival (months)	**(n = 146)**	**(n = 147)**
Median (95 % C.I.)	6.5 (5.8, 8.8)	9.4 (7.9, 11.9)
Hazard ratio (95 % C.I.)	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 % C.I.)	8.8 (6.4, 11.5)	15.7 (11.9, 17.7)
Hazard ratio (95 % C.I.)	0.51 (0.31, 0.82)	
Patients with prior Cisplatin chemoradiotherapy		
	Cisplatin	**Topotecan/Cisplatin**
Survival (months)	**(n = 72)**	**(n = 69)**
Median (95 % C.I)	5.9 (4.7, 8.8)	7.9 (5.5, 10.9)
Hazard ratio (95 % C.I.)	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 % C.I.: 2.6, 6.1) versus 4.5 months (95 % C.I.: 2.9, 9.6) for the cisplatin arm with an hazard ratio of 1.15 (0.59, 2.23). In those (n = 102) with recurrence after 180 days, the median survival in the topotecan plus cisplatin arm was 9.9 months (95 % C.I.: 7, 12.6) versus 6.3 months (95 % C.I.: 4.9, 9.5) for the cisplatin arm with an 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 trial involving children (n = 108, age range: infant to 16 years) with recurrent or progressive solid tumours, topotecan was administered at a starting dose of 2.0 mg/m^2 given as a 30-minute infusion for 5 days repeated every 3 weeks for up to one year depending on response to therapy. Tumour types included were Ewing's Sarcoma/primitive neuroectodermal tumour, neuroblastoma, osteosarcoma, and rhabdomyosarcoma. Antitumour activity was demonstrated primarily in patients with neuroblastoma. Toxicities of topotecan in paediatric patients with recurrent and refractory solid tumours were similar to those historically seen in adult patients. In this study, forty-six (43 %) patients received G-CSF over 192 (42.1 %) courses; sixty-five (60 %) received transfusions of Packed Red Blood Cells and fifty (46 %) of platelets over 139 and 159 courses (30.5 % and 34.9 %) respectively. Based on the dose-limiting toxicity of myelosuppression, the maximum tolerated dose (MTD) was established at 2.0 mg/m^2/day with G-CSF and 1.4 mg/m^2/day without G-CSF in a pharmacokinetic study in paediatric patients with refractory solid tumours (see section 5.2).

5.2 Pharmacokinetic properties

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 PK after multiple doses. Preclinical studies indicate plasma protein binding of topotecan is low (35 %) and distribution between blood cells and plasma was fairly homogeneous.

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

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

In vitro data using human liver microsomes indicate the formation of small amounts of N-demethylated topotecan. In 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).

Plasma clearance in patients with hepatic impairment (serum bilirubin between 1.5 and 10 mg/dl) decreased to about 67 % when compared with a control group of patients. Topotecan half-life was increased by about 30 % but no clear change in volume of distribution was observed. Plasma clearance of total topotecan (active and inactive form) in patients with hepatic impairment only decreased by about 10 % compared with the control group of patients.

Plasma clearance in patients with renal impairment (creatinine clearance 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.

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

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

Hydrochloric acid (E507) (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Vial before opening
3 years.

Vial after first opening
Chemical and physical in-use stability has been demonstrated for 14 days at 20°C - 25°C when stored in the outer carton to protect from light.
From a microbiological point of view, once opened, the product may be stored for a maximum of 14 days at 20°C - 25°C. Other in-use storage times and conditions are the responsibility of the user.

Diluted solution
From a microbiological point of view, the solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 20°C - 25°C and ambient lighting conditions.

6.4 Special precautions for storage

Do not store above 25°C.

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

For storage conditions of once-opened and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

5 ml concentrate in type 1 clear glass vial, together with grey butyl rubber stopper and aluminium seal with yellow polypropylene flip-off cap, and with yellow vial ring collar.
Each pack contains 1 vial.

6.6 Special precautions for disposal and other handling

General precautions

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

- Personnel should be trained to dilute the medicinal product.
- Pregnant staff should be excluded from working with this medicinal product.
- Personnel handling this medicinal product during dilution should wear protective clothing including mask, goggles and gloves.
- All items for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high-temperature incineration. Liquid waste may be flushed with large amounts of water.
- Accidental contact with the skin or eyes should be treated immediately with copious amounts of water.

Instructions for dilution

Concentration must be noticed or life-threatening overdose may occur.

Topotecan Eagle concentrate is clear yellow to orange in colour and contains 3 mg/ml of topotecan, which is a higher concentration than found in other topotecan products for intravenous infusion.

The user is requested to report any medication errors.

The following dosing tables should be used as reference:

Instructions for Preparation for Intravenous Administration for Small Cell Lung Cancer

Body surface area (m^2)	For recommended dose '1.5 mg/m^2'		For reduced dose '1.25 mg/m^2'		For reduced dose '1.0 mg/m^2'	
	Volume of solution required (ml)	Total dose (mg)	Volume of solution required (ml)	Total dose (mg)	Volume of solution required (ml)	Total dose (mg)
1	0.50	1.50	0.42	1.26	0.33	0.99
1.1	0.55	1.65	0.46	1.38	0.37	1.11
1.2	0.60	1.80	0.50	1.50	0.40	1.20
1.3	0.65	1.95	0.54	1.62	0.43	1.29
1.4	0.70	2.10	0.58	1.74	0.47	1.41
1.5	0.75	2.25	0.63	1.89	0.50	1.50
1.6	0.80	2.40	0.67	2.01	0.53	1.59
1.7	0.85	2.55	0.71	2.13	0.57	1.71
1.8	0.90	2.70	0.75	2.25	0.60	1.80
1.9	0.95	2.85	0.79	2.37	0.63	1.89
2	1.00	3.00	0.83	2.49	0.67	2.01
2.1	1.05	3.15	0.88	2.64	0.70	2.10
2.2	1.10	3.30	0.92	2.76	0.73	2.19
2.3	1.15	3.45	0.96	2.88	0.77	2.31
2.4	1.20	3.60	1.00	3.00	0.80	2.40
2.5	1.25	3.75	1.04	3.12	0.83	2.49

Instructions for Preparation for Intravenous Administration for Cervical Cancer

Body surface area (m^2)	For recommended dose '0.75 mg/m^2'		For reduced dose '0.60 mg/m^2'		For reduced dose '0.45 mg/m^2'	
	Volume of solution required (ml)	Total dose (mg)	Volume of solution required (ml)	Total dose (mg)	Volume of solution required (ml)	Total dose (mg)
1	0.25	0.75	0.20	0.60	0.15	0.45
1.1	0.28	0.84	0.22	0.66	0.17	0.51
1.2	0.30	0.90	0.24	0.72	0.18	0.54
1.3	0.33	0.99	0.26	0.78	0.20	0.60
1.4	0.35	1.05	0.28	0.84	0.21	0.63
1.5	0.38	1.14	0.30	0.90	0.23	0.69
1.6	0.40	1.20	0.32	0.96	0.24	0.72
1.7	0.43	1.29	0.34	1.02	0.26	0.78
1.8	0.45	1.35	0.36	1.08	0.27	0.81
1.9	0.48	1.44	0.38	1.14	0.29	0.87
2	0.50	1.50	0.40	1.20	0.30	0.90
2.1	0.53	1.59	0.42	1.26	0.32	0.96
2.2	0.55	1.65	0.44	1.32	0.33	0.99
2.3	0.58	1.74	0.46	1.38	0.35	1.05
2.4	0.60	1.80	0.48	1.44	0.36	1.08
2.5	0.63	1.89	0.50	1.50	0.38	1.14

Further dilution of Topotecan Eagle is required with either sodium chloride 9 mg/ml (0.9 % w/v) solution for injection or glucose 50 mg/ml (5 % w/v) solution for injection in order to reach a final topotecan concentration of between 25 µg/ml and 50 µg/ml in the solution for infusion to the patient. Dilution should be performed under strict aseptic conditions (e.g. an LAF bench).

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

7. MARKETING AUTHORISATION HOLDER

Eagle Laboratories Limited
The Clock House
Station Approach
Marlow, Bucks, SL7 1NT
United Kingdom
Tel: +1 (201) 326-5324
Fax: +1 (201) 391-2430

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/744/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:
22/12/2011

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

MAWDSLEY-BROOKS & COMPANY LIMITED
Unit 22, Quest Park
Wheatley Hall Road
Doncaster, DN2 4LT
United Kingdom

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

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan
The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

PSURs
The PSUR cycle for the medicinal product should follow a half-yearly cycle until otherwise agreed by the CHMP.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Prior to launch of the product in each Member State, the Marketing Authorisation Holder shall agree the content and format of a Safety Information Communication with the national competent authority, including the need and the timing of any follow-up Safety Communication Information, as well as the distribution list of such information.

The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals who are expected to use and/or prescribe Topotecan Eagle are provided with a Safety Information Communication.

The Safety Information Communication should contain the following:

- The risk of medication error due to the higher concentration than the dilution concentration of the originator, with potentially life-threatening consequences.
- Reference to the vial collar as visual reminder of this difference and the instruction that it must not be removed at any time.
- The anticipated effects of overdose (e.g. bone marrow suppression).
- An encouragement of reporting of actual medication errors and any safety events that might be a consequence of a medication error.
- A form to report medication errors.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 1 ml vial

1. NAME OF THE MEDICINAL PRODUCT

Topotecan Eagle 3 mg/1 ml concentrate for solution for infusion
topotecan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of concentrate for solution for infusion contains 3 mg topotecan (as hydrochloride).
Each vial contains 3 mg topotecan (as hydrochloride) in 1 ml concentrate.

3. LIST OF EXCIPIENTS

Hydrochloric acid (E507)
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use. Must be diluted 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

CYTOTOXIC
Read the package leaflet before use.

Notice concentration or life-threatening overdose may occur.

8. EXPIRY DATE

EXP

Read the leaflet for the shelf life of the diluted product.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25ºC.
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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eagle Laboratories Limited
The Clock House
Station Approach
Marlow, Bucks, SL7 1NT
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/744/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL 1 ml

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

Topotecan Eagle 3 mg/1 ml concentrate for solution for infusion
Topotecan
IV

2. METHOD OF ADMINISTRATION

To be diluted before use.
Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

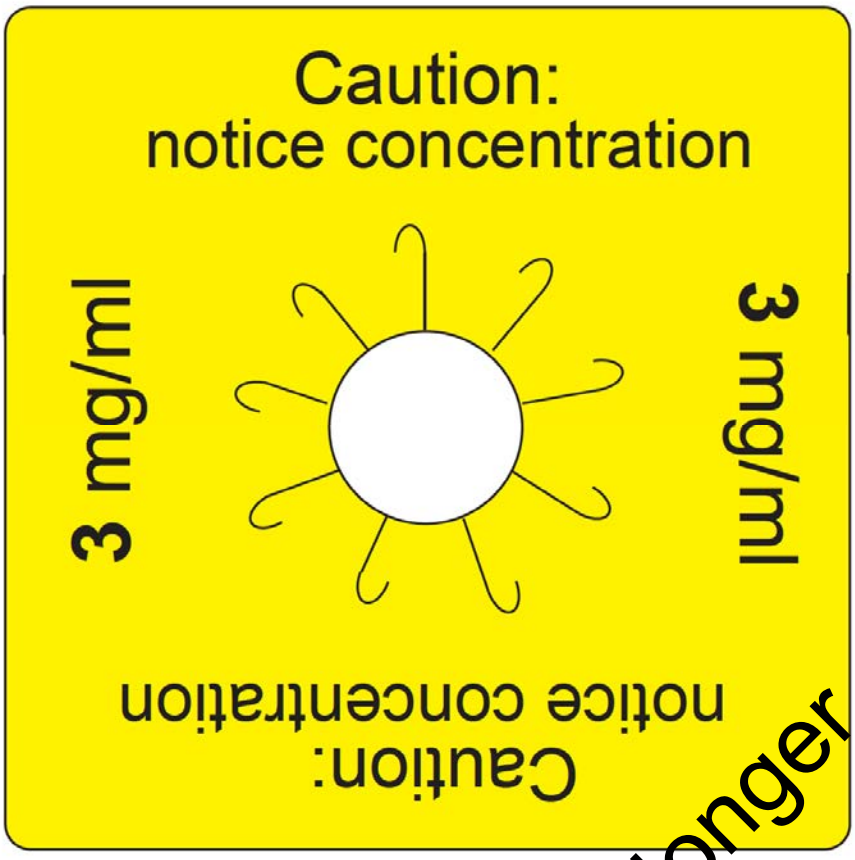
5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

Cytotoxic

Notice concentration or life-threatening overdose may occur.



PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON 5 ml multidose vial

1. NAME OF THE MEDICINAL PRODUCT

Topotecan Eagle 15 mg/5 ml concentrate for solution for infusion
topotecan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml of concentrate for solution for infusion contains 3 mg topotecan (as hydrochloride).
Each vial contains 15 mg topotecan (as hydrochloride) in 5 ml concentrate.

3. LIST OF EXCIPIENTS

Hydrochloric acid (E507)
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
(3 mg/ml)
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use. Must be diluted 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

CYTOTOXIC
Read the package leaflet before use.

Notice concentration or life-threatening overdose may occur.

8. EXPIRY DATE

EXP

Multidose vial: once opened, store for a maximum of 14 days at 20°C-25°C.
Opened on: DD/MM/YY

Read the leaflet for the shelf life of the diluted product.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25ºC.
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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eagle Laboratories Limited
The Clock House
Station Approach
Marlow, Buck, SL7 1NT
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/744/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL 5 ml

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

Topotecan Eagle 15 mg/5 ml concentrate for solution for infusion
Topotecan
IV

2. METHOD OF ADMINISTRATION

To be diluted before use.
Read the package leaflet before use.

3. EXPIRY DATE

EXP

Multidose vial: once opened, store for a maximum of 14 days at 20°-25°C.
Opened on: DD/MM/YY

4. BATCH NUMBER

Batch

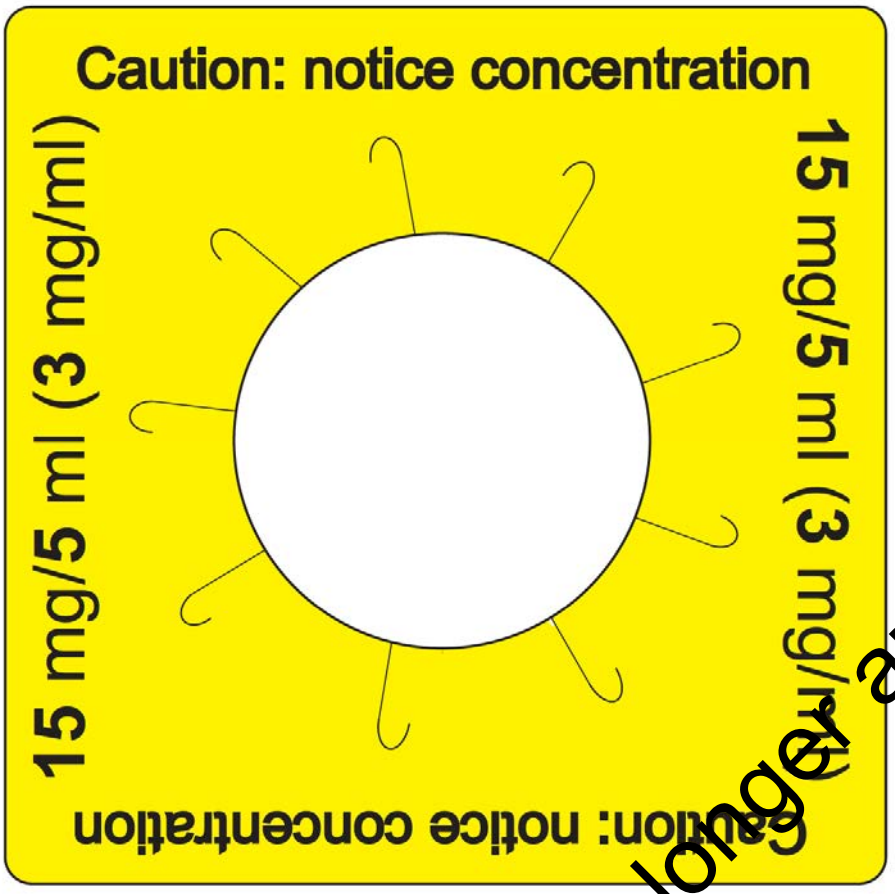
5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml
3 mg/ml

6. OTHER

Cytotoxic

Notice concentration or life-threatening overdose may occur.



B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Topotecan Eagle 3 mg/1 ml concentrate for solution for infusion
topotecan

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

In this leaflet:

1. WHAT TOPOTECAN EAGLE IS AND WHAT IT IS USED FOR

The name of your medicine is Topotecan Eagle 3 mg/1 ml concentrate for solution for infusion (called Topotecan Eagle in this leaflet).

Topotecan Eagle helps to kill tumour cells. It is a type of chemotherapy.

Topotecan Eagle is used to treat:
- small cell lung cancer that has come back after chemotherapy
- advanced cervical cancer when surgery or radiotherapy are not possible. In this case, it is used with another medicine called cisplatin.

2. BEFORE YOU ARE GIVEN TOPOTECAN EAGLE

You should not receive Topotecan Eagle:
- if you are allergic (hypersensitive) to topotecan or to any of the other ingredients of this medicine listed in Section 6
- if you are breast-feeding. You should stop breast-feeding before starting treatment with Topotecan Eagle
- if your blood cell count is too low. Your doctor will check this.

Do not use Topotecan Eagle if any of the above apply to you. If you are not sure, talk to your doctor or nurse before using this medicine.

Take special care with Topotecan Eagle
Check with your doctor or nurse before using your medicine:
- if you have any kidney problems. Your dose of Topotecan Eagle may need to be adjusted. This medicine is not recommended if you have severe kidney problems;
- if you have liver problems. Your dose of Topotecan Eagle may need to be adjusted. This medicine is not recommended if you have severe liver problems;
- if you have lung problems, or if you have had lung problems before from using other medicines or radiation. This is because you are more likely to get severe lung problems (interstitial lung disease) when using Topotecan Eagle;

- if you have unusual bruising or bleeding;
- if you are feeling very ill.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before using Topotecan Eagle.

Using other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal medicines. This is because Topotecan Eagle can affect the way some other medicines work. Also some other medicines can affect the way Topotecan Eagle works.

Pregnancy and breast-feeding
- Topotecan Eagle should not be used during pregnancy, unless clearly necessary. If you are pregnant or think you might be pregnant, tell your doctor immediately.
- Women who could get pregnant should use contraception to stop them getting pregnant during treatment.
- Men having Topotecan Eagle who wish to father a child should ask their doctor for family planning advice.
- Do not breast-feed while using Topotecan Eagle.

Driving and using machines
Topotecan Eagle can make you feel tired or weak. If this happens, do not drive or use any tools or machines.

3. HOW TO USE TOPOTECAN EAGLE

How much you will be given
Your dose of Topotecan Eagle will depend on:
- the disease being treated
- the size of your body (measured in 'square meters' or 'm^2')
- the results of blood tests before and during treatment
- how well your body responds to the medicine.

Small cell lung cancer
- The usual dose is 1.5 mg of the medicine for each square meter of your body.
- It is given once each day for 5 days.
- This treatment cycle will normally be repeated every 3 weeks.

Cervical cancer
- The usual dose is 0.75 mg of the medicine for each square meter of your body.
- It is given once each day for 3 days.
- This treatment cycle will normally be repeated every 3 weeks.

For cervical cancer Topotecan Eagle will be used with another medicine called cisplatin. For more information about cisplatin, please read its Package Leaflet.

The experience of using Topotecan Eagle in children is limited. This means that treatment is not recommended.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

How Topotecan Eagle is prepared
Topotecan Eagle is supplied as a concentrate for solution for infusion. The concentration of topotecan is higher (3 mg/ml) than with other topotecan products. The concentrate must be diluted before administration.

How Topotecan Eagle is given
Topotecan Eagle is normally given by a doctor or nurse:
- as a drip (infusion) for about 30 minutes
- usually into your arm.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Topotecan Eagle can cause side effects, although not everybody gets them.

How likely these side effects may happen, is as follows:
- very common affects more than 1 user in 10
- common affects 1 to 10 users in 100
- uncommon affects 1 to 10 users in 1,000
- rare affects 1 to 10 users in 10,000
- very rare affects less than 1 user in 10,000
- not known frequency cannot be estimated from the available data.

Serious side effects
Tell your doctor immediately if you notice any of the following serious side effects. You may need urgent medical treatment:

- **Infections** (very common) – because Topotecan Eagle may reduce your ability to fight infections. The signs include:
  - fever
  - sudden decline of your general health
  - sore throat or burning sensation when passing water
  - severe stomach pain, fever and possibly diarrhoea (rarely with blood in it) - these can be signs of bowel inflammation (neutropenic colitis).
- **Lung inflammation** (rare), with signs such as:
  - difficulty in breathing
  - cough
  - fever.

You are more likely to get severe lung problems (interstitial lung disease) if you already have lung problems or have had lung problems before from using other medicines or radiation.

Other side effects may include:
Very common
- feeling generally weak and tired. These may be signs of a drop in the number of your red blood cells (anaemia). In some cases you may need a blood transfusion.
- unusual bruising or bleeding, sometimes severe. This is caused by a drop in the number of blood clotting cells (platelets).
- abnormally low white blood cell count (neutropenia) which may be accompanied with fever and signs of infection (febrile neutropenia)
- weight loss and loss of appetite, feeling tired or weak
- feeling or being sick, diarrhoea, stomach pain, constipation
- inflammation and ulcers of the mouth, throat, tongue or gums (mucositis)
- high body temperature (fever)
- infections
- hair loss.

Common
- mild allergic reactions (including rash)
- yellow skin (jaundice) caused by liver problems
- itching (pruritus)

- severe infection (sepsis)
- feeling unwell (malaise).

Rare
- severe allergic (anaphylactic) reactions causing swelling of the lips, face or neck leading to severe difficulty in breathing, skin rash or hives, anaphylactic shock (a severe reduction in blood pressure, paleness, agitation, weak pulse, decreased consciousness)
- sudden swelling of the skin and mucosa (e.g. throat or tongue) caused by fluid build up (angioedema)
- itchy rash (or hives).

Very rare
- Mild pain and inflammation at the site of injection due to accidental administration of the medicinal product into the surrounding tissue (extravasation) e.g. by leakage.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

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 Topotecan Eagle.

5. HOW TO STORE TOPOTECAN EAGLE

Keep out of the sight and reach of children.

Do not use Topotecan Eagle after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.

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

Diluted solution
From a microbiological point of view, 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 and would normally not be longer than 24 hours at 20°C - 25°C and ambient lighting conditions.

Do not use Topotecan Eagle if you notice any visible particles or if the solution is unclear.

Medicines should not be disposed of via wastewater or household waste. Your doctor should dispose of medicines that are no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Topotecan Eagle contains
- The active substance is topotecan.
- One ml of concentrate for solution for infusion contains 3 mg topotecan (as hydrochloride). Each 1 ml single dose vial contains 3 mg of topotecan.
- The other ingredients are: hydrochloric acid (E507) (for pH adjustment) and water for injections.

What Topotecan Eagle looks like and contents of the pack
- Topotecan Eagle is a clear yellow to orange liquid in a colourless glass vial with a butyl rubber stopper, aluminium seal and blue snap-cap and with yellow vial ring collar.

- Topotecan Eagle is supplied in cartons containing 1 vial.

Marketing Authorisation Holder
Eagle Laboratories Limited
The Clock House
Station Approach
Marlow, Bucks, SL7 1NT
United Kingdom

Manufacturer
MAWDSLEY-BROOKS & COMPANY LIMITED
Unit 22, Quest Park
Wheatley Hall Road
Doncaster, DN2 4LT
United Kingdom

This leaflet was last approved in

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 medical or healthcare professionals only:

Instructions on how to dilute, store and dispose of Topotecan Eagle

General precautions
The concentration of topotecan in Topotecan Eagle differs from other topotecan products and care should be taken to ensure appropriate dilution occurs to achieve the intended dose, which should be checked prior to administration to the patient.

The normal procedures for proper handling and disposal of anticancer medicinal products should be adopted:
- Staff should be trained to dilute the medicinal product.
- Pregnant staff should be excluded from working with this medicinal product.
- Staff handling this medicinal product during dilution should wear protective clothing including mask, goggles and gloves.
- All items for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high-temperature incineration.
- Liquid waste may be flushed with large amounts of water.
- Accidental contact with the skin or eyes should be treated immediately with copious amounts of water.

Instructions for dilution

Concentration must be noticed or life-threatening overdose may occur.

Topotecan Eagle concentrate is clear yellow to orange in colour and contains 3 mg/ml of topotecan, which is a higher concentration than found in other topotecan products for intravenous infusion.

The user is requested to report any medication errors.

The following dosing tables should be used as reference:

Instructions for Preparation for Intravenous Administration for Small Cell Lung Cancer

Body surface area (m^2)	For recommended dose '1.5 mg/m^2'		For reduced dose '1.25 mg/m^2'		For reduced dose '1.0 mg/m^2'	
	Volume of solution required (ml)	Total dose (mg)	Volume of solution required (ml)	Total dose (mg)	Volume of solution required (ml)	Total dose (mg)
1	0.50	1.50	0.42	1.26	0.33	0.99
1.1	0.55	1.65	0.46	1.38	0.37	1.11
1.2	0.60	1.80	0.50	1.50	0.40	1.20
1.3	0.65	1.95	0.54	1.62	0.43	1.29
1.4	0.70	2.10	0.58	1.74	0.47	1.41
1.5	0.75	2.25	0.63	1.89	0.50	1.50
1.6	0.80	2.40	0.67	2.01	0.53	1.59
1.7	0.85	2.55	0.71	2.13	0.57	1.71
1.8	0.90	2.70	0.75	2.25	0.60	1.80
1.9	0.95	2.85	0.79	2.37	0.63	1.89
2	1.00	3.00	0.83	2.49	0.67	2.01
2.1	1.05	3.15	0.88	2.64	0.70	2.10
2.2	1.10	3.30	0.92	2.76	0.73	2.19
2.3	1.15	3.45	0.96	2.88	0.77	2.31
2.4	1.20	3.60	1.00	3.00	0.80	2.40
2.5	1.25	3.75	1.04	3.12	0.83	2.49

Instructions for Preparation for Intravenous Administration for Cervical Cancer

Body surface area (m^2)	For recommended dose '0.75 mg/m^2'		For reduced dose '0.60 mg/m^2'		For reduced dose '0.45 mg/m^2'	
	Volume of solution required (ml)	Total dose (mg)	Volume of solution required (ml)	Total dose (mg)	Volume of solution required (ml)	Total dose (mg)
1	0.25	0.75	0.20	0.60	0.15	0.45
1.1	0.28	0.84	0.22	0.66	0.17	0.51
1.2	0.30	0.90	0.24	0.72	0.18	0.54
1.3	0.33	0.99	0.26	0.78	0.20	0.60
1.4	0.35	1.05	0.28	0.84	0.21	0.63
1.5	0.38	1.14	0.30	0.90	0.23	0.69
1.6	0.40	1.20	0.32	0.96	0.24	0.72
1.7	0.43	1.29	0.34	1.02	0.26	0.78
1.8	0.45	1.35	0.36	1.08	0.27	0.81
1.9	0.48	1.44	0.38	1.14	0.29	0.87
2	0.50	1.50	0.40	1.20	0.30	0.90
2.1	0.53	1.59	0.42	1.26	0.32	0.96
2.2	0.55	1.65	0.44	1.32	0.33	0.99
2.3	0.58	1.74	0.46	1.38	0.35	1.05
2.4	0.60	1.80	0.48	1.44	0.36	1.08
2.5	0.63	1.89	0.50	1.50	0.38	1.14

Further dilution of Topotecan Eagle is required with either sodium chloride 9 mg/ml (0.9 % w/v) solution for injection or glucose 50 mg/ml (5 % w/v) solution for injection in order to reach a final topotecan concentration of between 25 µg/ml and 50 µg/ml in the solution for infusion to the patient. Dilution should be performed under strict aseptic conditions (e.g. an LAF bench).

Storage of the diluted solution
From a microbiological point of view, the solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 20°C - 25°C and ambient lighting conditions.

Disposal
Topotecan Eagle 1mg/1 ml is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Topotecan Eagle 15 mg/5 ml concentrate for solution for infusion
topotecan

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

In this leaflet:

1. WHAT TOPOTECAN EAGLE IS AND WHAT IT IS USED FOR

The name of your medicine is Topotecan Eagle 15 mg/5 ml concentrate for solution for infusion (called Topotecan Eagle in this leaflet).

Topotecan Eagle helps to kill tumour cells. It is a type of chemotherapy.

Topotecan Eagle is used to treat:
- small cell lung cancer that has come back after chemotherapy
- advanced cervical cancer when surgery or radiotherapy are not possible. In this case, it is used with another medicine called cisplatin.

2. BEFORE YOU ARE GIVEN TOPOTECAN EAGLE

You should not receive Topotecan Eagle:
- if you are allergic (hypersensitive) to topotecan or to any of the other ingredients of this medicine listed in Section 6
- if you are breast-feeding. You should stop breast-feeding before starting treatment with Topotecan Eagle
- if your blood cell count is too low. Your doctor will check this.

Do not use Topotecan Eagle if any of the above apply to you. If you are not sure, talk to your doctor or nurse before using this medicine.

Take special care with Topotecan Eagle
Check with your doctor or nurse before using your medicine:
- if you have any kidney problems. Your dose of Topotecan Eagle may need to be adjusted. This medicine is not recommended if you have severe kidney problems;
- if you have liver problems. Your dose of Topotecan Eagle may need to be adjusted. This medicine is not recommended if you have severe liver problems;
- if you have lung problems, or if you have had lung problems before from using other medicines or radiation. This is because you are more likely to get severe lung problems (interstitial lung disease) when using Topotecan Eagle;

- if you have unusual bruising or bleeding;
- if you are feeling very ill.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before using Topotecan Eagle.

Using other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal medicines. This is because Topotecan Eagle can affect the way some other medicines work. Also some other medicines can affect the way Topotecan Eagle works.

Pregnancy and breast-feeding
- Topotecan Eagle should not be used during pregnancy, unless clearly necessary. If you are pregnant or think you might be pregnant, tell your doctor immediately.
- Women who could get pregnant should use contraception to stop them getting pregnant during treatment.
- Men having Topotecan Eagle who wish to father a child should ask their doctor for family planning advice.
- Do not breast-feed while using Topotecan Eagle.

Driving and using machines
Topotecan Eagle can make you feel tired or weak. If this happens, do not drive or use any tools or machines.

3. HOW TO USE TOPOTECAN EAGLE

How much you will be given
Your dose of Topotecan Eagle will depend on:
- the disease being treated
- the size of your body (measured in 'square meters' or 'm^2')
- the results of blood tests before and during treatment
- how well your body responds to the medicine.

Small cell lung cancer
- The usual dose is 1.5 mg of the medicine for each square meter of your body.
- It is given once each day for 5 days.
- This treatment cycle will normally be repeated every 3 weeks.

Cervical cancer
- The usual dose is 0.75 mg of the medicine for each square meter of your body.
- It is given once each day for 3 days.
- This treatment cycle will normally be repeated every 3 weeks.

For cervical cancer Topotecan Eagle will be used with another medicine called cisplatin. For more information about cisplatin, please read its Package Leaflet.

The experience of using Topotecan Eagle in children is limited. This means that treatment is not recommended.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

How Topotecan Eagle is prepared
Topotecan Eagle is supplied as a concentrate for solution for infusion. The concentration of topotecan is higher (3 mg/ml) than with other topotecan products. The concentrate must be diluted before administration.

How Topotecan Eagle is given
Topotecan Eagle is normally given by a doctor or nurse:
- as a drip (infusion) for about 30 minutes
- usually into your arm.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Topotecan Eagle can cause side effects, although not everybody gets them.

How likely these side effects may happen, is as follows:
- very common affects more than 1 user in 10
- common affects 1 to 10 users in 100
- uncommon affects 1 to 10 users in 1,000
- rare affects 1 to 10 users in 10,000
- very rare affects less than 1 user in 10,000
- not known frequency cannot be estimated from the available data.

Serious side effects
Tell your doctor immediately if you notice any of the following serious side effects. You may need urgent medical treatment:

- **Infections** (very common) – because Topotecan Eagle may reduce your ability to fight infections. The signs include:
- fever
- sudden decline of your general health
- sore throat or burning sensation when passing water
- severe stomach pain, fever and possibly diarrhoea (rarely with blood in it) - these can be signs of bowel inflammation (neutropenic colitis).

- **Lung inflammation** (rare), with signs such as:
- difficulty in breathing
- cough
- fever.

You are more likely to get severe lung problems (interstitial lung disease) if you already have lung problems or have had lung problems before from using other medicines or radiation.

Other side effects may include:
Very common
- feeling generally weak and tired. These may be signs of a drop in the number of your red blood cells (anaemia). In some cases you may need a blood transfusion.
- unusual bruising or bleeding, sometimes severe. This is caused by a drop in the number of blood clotting cells (platelets).
- abnormally low white blood cell count (neutropenia) which may be accompanied with fever and signs of infection (febrile neutropenia)
- weight loss and loss of appetite, feeling tired or weak
- feeling or being sick, diarrhoea, stomach pain, constipation
- inflammation and ulcers of the mouth, throat, tongue or gums (mucositis)
- high body temperature (fever)
- infections
- hair loss.

Common
- mild allergic reactions (including rash)
- yellow skin (jaundice) caused by liver problems
- itching (pruritus)

- severe infection (sepsis)
- feeling unwell (malaise).

Rare
- severe allergic (anaphylactic) reactions causing swelling of the lips, face or neck leading to severe difficulty in breathing, skin rash or hives, anaphylactic shock (a severe reduction in blood pressure, paleness, agitation, weak pulse, decreased consciousness)
- sudden swelling of the skin and mucosa (e.g. throat or tongue) caused by fluid build up (angioedema)
- itchy rash (or hives).

Very rare
- Mild pain and inflammation at the site of injection due to accidental administration of the medicinal product into the surrounding tissue (extravasation) e.g. by leakage.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

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 Topotecan Eagle.

5. HOW TO STORE TOPOTECAN EAGLE

Keep out of the sight and reach of children.

Do not use Topotecan Eagle after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.

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

Vials after first opening
Chemical and physical in-use stability has been demonstrated for 14 days at 20°C - 25°C when stored in the outer carton to protect from light.
From a microbiological point of view, once opened, the product may be stored for a maximum of 14 days at 20°C - 25°C. Other in-use storage times and conditions are the responsibility of the user.

Diluted solution
From a microbiological point of view, 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 and would normally not be longer than 24 hours at 20°C - 25°C and ambient lighting conditions.

Do not use Topotecan Eagle if you notice any visible particles or if the solution is unclear.

Medicines should not be disposed of via wastewater or household waste. Your doctor should dispose of medicines that are no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Topotecan Eagle contains
- The active substance is topotecan.
- One ml of concentrate for solution for infusion contains 3 mg topotecan (as hydrochloride). Each 5 ml multi dose vial contains 15 mg of topotecan.

- The other ingredients are: hydrochloric acid (E507) (for pH adjustment) and water for injections.

What Topotecan Eagle looks like and contents of the pack
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- Topotecan Eagle is supplied in cartons containing 1 vial.

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1.2	0.60	1.80	0.50	1.50	0.40	1.20
1.3	0.65	1.95	0.54	1.62	0.43	1.29
1.4	0.70	2.10	0.58	1.74	0.47	1.40
1.5	0.75	2.25	0.63	1.89	0.50	1.50
1.6	0.80	2.40	0.67	2.01	0.53	1.59
1.7	0.85	2.55	0.71	2.13	0.57	1.71
1.8	0.90	2.70	0.75	2.25	0.60	1.80
1.9	0.95	2.85	0.79	2.37	0.63	1.89
2	1.00	3.00	0.83	2.49	0.67	2.01
2.1	1.05	3.15	0.88	2.64	0.70	2.10
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2.4	1.20	3.60	1.00	3.00	0.80	2.40
2.5	1.25	3.75	1.04	3.12	0.83	2.49

Instructions for Preparation for Intravenous Administration for Cervical Cancer

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1.1	0.28	0.84	0.22	0.66	0.17	0.51
1.2	0.30	0.90	0.24	0.72	0.18	0.54
1.3	0.33	0.99	0.26	0.78	0.20	0.60
1.4	0.35	1.05	0.28	0.84	0.21	0.63
1.5	0.38	1.14	0.30	0.90	0.23	0.69
1.6	0.40	1.20	0.32	0.96	0.24	0.72
1.7	0.43	1.29	0.34	1.02	0.26	0.78
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2.3	0.58	1.74	0.46	1.38	0.35	1.05
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Further dilution of Topotecan Eagle is required with either sodium chloride 9 mg/ml (0.9 % w/v) solution for injection or glucose 50 mg/ml (5 % w/v) solution for injection in order to reach a final topotecan concentration of between 25 µg/ml and 50 µg/ml in the solution for infusion to the patient. Dilution should be performed under strict aseptic conditions (e.g. an LAF bench).

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Vials after first opening
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Disposal
Any unused product or waste material should be disposed of in accordance with local requirements.