ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Topotecan Hospira 4 mg/4 ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of concentrate for solution for infusion contains 1 mg topotecan (as hydrochloride).
Each 4 ml vial of concentrate contains 4 mg topotecan (as hydrochloride).

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

A clear yellow to yellow-green solution.

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

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).

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 $\geq 1.5 \times 10^9$/l, a platelet count of $\geq 100 \times 10^9$/l and a haemoglobin level of $\geq$ 9g/dl (after transfusion if necessary).

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

<u>Small Cell Lung Carcinoma</u>

Initial dose
The recommended dose of topotecan is 1.5 mg/m^2 body surface area/day, administered by intravenous infusion over 30 minutes for 5 consecutive days, with a 3 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 $\geq 1 \times 10^9$/l, the platelet count is $\geq 100 \times 10^9$/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 $< 0.5 \times 10^9$/l) for 7 days or more, or severe neutropenia associated with fever or infection, or who have had treatment delayed due to neutropenia, the dose should be reduced by 0.25 mg/m^2/day to 1.25 mg/m^2/day (or subsequently down to 1.0 mg/m^2/day if necessary).

Doses should be similarly reduced if the platelet count falls below 25×10^9/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 6 courses or until progressive disease.

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

Standard oncology practice for the management of neutropenia is either to administer 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 0.5×10^9/l) for 7 days or more, or severe neutropenia associated with fever or infection or who have had treatment delayed due to neutropenia, the dose should be reduced by 20% to 0.60 mg/m^2/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 25×10^9/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 5 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 132 μmol/l. If, during topotecan/cisplatin combination therapy serum creatinine exceeds 132 μmol/l, 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).

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

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, 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 drugs and/or colony stimulating factors. Patients should be monitored for pulmonary symptoms indicative of interstitial lung disease (e.g. cough, fever, dyspnoea and/or hypoxia), and topotecan should be discontinued if a new diagnosis of ILD is confirmed.

Topotecan and topotecan in combination with cisplatin are commonly associated with clinically relevant thrombocytopenia. This should be taken into account, 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 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 a population study, the coadministration 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 5 consecutive days) and cisplatin (60 mg/m^2/day on Day 1) were administered in 13 patients with ovarian cancer, a slight increase in AUC (12%, n=9) and C_{max} (23%, n=11) was noted on day 5. This increase is considered unlikely to be of clinical relevance.

4.6 Pregnancy and lactation

As with all cytotoxic chemotherapy, effective contraceptive methods must be advised when either partner is treated with topotecan.

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 child bearing potential should be advised to avoid becoming pregnant during therapy with topotecan. 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.

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.

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 of 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 were 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.

Infections and infestations	*Very common:* infection *Common:* sepsis
Blood and lymphatic system disorders	*Very common:* febrile neutropenia, neutropenia (see gastrointestinal disorders), thrombocytopenia, anaemia, leucopenia
Immune system disorders	*Common:* hypersensitivity reaction including rash *Rare:* anaphylactic reaction, angioedema, urticaria
Metabolism and nutrition disorders	*Very common:* anorexia (which may be severe)
Respiratory, thoracic and mediastinal disorders	*Rare*: interstitial lung disease
Gastrointestinal disorders	*Very common:* nausea, vomiting and diarrhoea (all of which may be severe), constipation, abdominal pain* and mucositis *Neutropenic colitis, including fatal neutropenic colitis, has been reported to occur as a complication of topotecan-induced neutropenia (see section 4.4).
Hepato-biliary disorders	*Common:* hyperbilirubinaemia
Skin and subcutaneous tissue disorders	*Very common:* alopecia *Common:* pruritus
General disorders and administration site conditions	*Very common:* pyrexia, asthenia, fatigue. *Common:* malaise *Very rare:* extravasation[†] [†]Extravasation has been reported very rarely. Reactions have been mild and have not generally required specific therapy.

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 ≥7 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 9 days and the median duration was 7 days. Severe neutropenia lasted beyond 7 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 5 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 (15 %). 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 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 i.v 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 0.64 (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 topotecan or intravenous topotecan

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

N = total number of patients treated.
CI = Confidence interval.

In another randomised phase III trial which compared IV 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).

Study results Study GOG-0179

ITT population		
	Cisplatin 50 mg/m^2 d. 1 q2l d.	**Cisplatin 50 mg/m^2 d. 1 + Topotecan 0.75 mg/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, osteoblastoma, and rhabdomyosarcoma. Antitumour activity was demonstrated primarily in patients with neuroblastoma. Toxicities of topotecan in paediatric patients with recurrent and refractory solid tumours were similar to those historically seen in adult patients. In this study, forty-six (43%) patients received G-CSF over 192 (42.1%) courses; sixty-five (60%) received transfusions of Packed Red Blood Cells and fifty (46%) of platelets over 139 and 159 courses (30.5% and 34.9%) respectively. Based on the dose-limiting toxicity of myelosuppression, the maximum tolerated dose (MTD) was established at 2.0 mg/m^{2}day with G-CSF and 1.4 mg/m^2/day without G-CSF in a pharmacokinetic study in paediatric patients with refractory solid tumours (see 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 IV dose. Approximately 51% was excreted as total topotecan and 3 % was excreted as N-desmethyl topotecan in the urine. Faecal elimination of total topotecan accounted for 18 % while faecal elimination of N-desmethyl topotecan was 1.7 %. Overall, the N-desmethyl metabolite contributed a mean of less than 7% (range 4-9 %) of the total medicinal product related material accounted for in the urine and faeces. The topotecan-O-glucuronide and N-desmethyl topotecan-O-glucuronide in the urine were less than 2.0 %.

In vitro data using human liver microsomes indicate the formation of small amounts of Ndemethylated 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

Tartaric acid (E334)
Hydrochloric acid (E507) (for pH adjustment)
Sodium hydroxide (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

Unopened vial
18 months.

After first opening
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C under normal light conditions and at 2-8°C when protected from light. 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 2 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Topotecan Hospira 4 mg/4 ml is supplied in Type I clear glass vials, each sealed with a chlorobutyl rubber stopper, aluminium seal and plastic flip-off closure.

Each vial contains 4 ml of concentrate.

Topotecan Hospira is available in pack sizes of 1 vial and 5 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Topotecan Hospira is provided as a sterile concentrate containing 4 mg topotecan in 4 ml solution (1 mg/ml).

Parenteral products should be visually inspected for particulate matter and discolouration prior to administration. Topotecan Hospira is a yellow/yellow green solution. If visible particles are observed, the product should not be administered.

Further dilution with either sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection is required, to obtain a final concentration of between 25 and 50 micrograms/ml prior to administration to the patient.

The normal procedures for proper handling and disposal of anticancer medicinal products should be adopted, namely:
− Personnel should be trained to prepare and administer the medicinal product.
− Pregnant staff should be excluded from working with this medicinal product.
− Personnel handling this medicinal product 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. If there is lasting irritation, a doctor should be consulted.
- Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Hospira UK Limited
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Hospira UK Limited
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW
United Kingdom

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

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

Not applicable

- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of Pharmacovigilance, as presented in version 5.3 (dated 17 November 2009) in Module 1.8.1 of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

PSUR

The PSUR submission schedule should follow the PSUR schedule for the reference product.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Topotecan Hospira 4 mg/4 ml concentrate for solution for infusion
topotecan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of sterile concentrate contains 1 mg topotecan (as hydrochloride).
Each 4 ml vial contains 4 mg topotecan (as hydrochloride).

3. LIST OF EXCIPIENTS

Also contains: tartaric acid (E334), water for injections, and hydrochloric acid (E507) or sodium hydroxide (for pH adjustment).

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
4 mg/4 ml
1 vial
5 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use.
Dilute before use.
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:
Use immediately after opening.

9. SPECIAL STORAGE CONDITIONS

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

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

WARNING: This is a cytotoxic agent. Special handling and disposal instructions apply (see package leaflet).

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hospira UK Limited
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

BN:

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 LABEL

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

Topotecan Hospira 4 mg/4 ml sterile concentrate
Intravenous use

2. METHOD OF ADMINISTRATION

Dilute before use.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

BN:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

4 mg/ 4ml

6. OTHER

Hospira UK Limited

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Topotecan Hospira 4 mg/4 ml concentrate for solution for infusion
topotecan

Read all of this leaflet carefully before you are given this medicine.
• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor.
• If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

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

Topotecan Hospira is an anti-cancer medicine, which will be given to you through a drip, as an infusion into a vein.

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

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

2. BEFORE YOU ARE GIVEN TOPOTECAN HOSPIRA

You should not receive Topotecan Hospira:
• if you are allergic (hypersensitive) to topotecan or any of the other ingredients of Topotecan Hospira
• if you are breast-feeding
• if your blood cell counts are too low. Your doctor will tell if this applies to you based on the results of your last blood test.

If you think any of these things may apply to you, please tell your doctor.

Take special care with Topotecan Hospira
Your doctor needs to know before you are given this medicine if:
• you have a problem with your kidneys
• you have a problem with your liver
If either of these applies to you, your doctor will need to know before treatment begins, as he or she may need to adjust your dose
• you are pregnant or plan to become pregnant
• you plan to father a child
If either of these applies to you, your doctor will need to know before treatment begins, as topotecan may harm a baby which is conceived before, during or soon after treatment. You should therefore use an effective method of contraception. Ask your doctor for further advice.

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. It is also important that you check with your doctor before you start taking any other medicines or herbal products while you are treated with Topotecan Hospira**.**

Using Topotecan Hospira with food and drink
Alcohol: There is no known interaction between topotecan and alcohol; however, you should check with your doctor whether drinking alcohol is advisable for you.

Pregnancy and breast-feeding
Topotecan is not recommended for use by pregnant women**.** Topotecan may harm a baby which is conceived before, during or soon after treatment. You should tell your doctor if you are pregnant before your treatment starts.

An effective method of contraception should be used during treatment, to avoid becoming pregnant or fathering a child. Do not try to become pregnant or father a child until a doctor advises you that it is safe to do so. You can ask your doctor for family planning advice. If a baby is conceived/you fall pregnant during treatment, you should tell their doctor immediately.

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

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

3. HOW TOPOTECAN HOSPIRA IS GIVEN

The dose of topotecan you receive is calculated by your doctor, based on:
• your body size (your surface area, measured in square metres (m^2))
• the results of your blood tests (these will be carried out before your treatment starts)
• the disease you are being treated for

The usual dose
Your doctor will calculate what dose you need to be given, based on your own circumstances. Typical doses are given below.

• **For small cell lung cancer:** 1.5 milligrams per m^2 of body surface area per day.
• **For cervical cancer:** 0.75 milligrams per m^2 of body surface area per day. When treating cervical cancer, topotecan will be given to you with another medicine, called cisplatin. Your doctor will advise you about the correct dose of cisplatin.

How topotecan is given
Topotecan Hospira is a concentrated solution which will be diluted before use. A doctor or nurse will give you your dose of topotecan as an infusion (a drip). It is usually given into a vein in your arm, over a period of about 30 minutes.

Duration of treatment
Your treatment may vary and will depend on the results of your regular blood tests. Typical courses of treatment are given below.

• **For small cell lung cancer:** treatment will usually be given once a day for 5 days.
• **For cervical cancer:** treatment will usually be given once a day for 3 days.

This course of treatment will normally be repeated every three weeks, for all types of cancer. Your doctor will decide when to stop your treatment.

If you are concerned about your dose or the duration of your treatment, talk to your doctor.

4. POSSIBLE SIDE EFFECTS

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

The frequency of possible side effects listed below is defined using the following convention:

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

The following very common side effects may be serious. Tell your doctor immediately if you notice any of these symptoms, as hospitalisation may be necessary.

• **Signs of infection.** Topotecan may reduce the number of white blood cells in your body and make you more likely to get an infection. This can be life threatening. A blood test will be taken to check for a reduction in the amount of your white blood cells. Signs of infection should be monitored and include:

- fever
- serious deterioration in your general condition/health
- local symptoms, such as a sore throat or urinary problems (for example, a burning sensation when urinating, which may be a sign of a urinary tract infection)

• **Severe stomach pain, fever and possibly diarrhoea (rarely with blood).**
Occasionally, these symptoms can be a sign of bowel inflammation (*colitis*)

The following rare side effects may be serious. Tell your doctor immediately if you notice any of the symptoms.

• **Lung inflammation (interstitial lung disease).** You are most at risk of this side effect if you have an existing lung disease, if you have had radiation treatment on your lungs, or have previously taken medicines that caused lung damage. Signs of lung inflammation include:

- difficulty in breathing
- cough
- fever

Very common side effects

The following side effects are very common. Tell a doctor if any of these become troublesome.
• Feeling generally weak and tired (temporary *anaemia*). In some cases you may need a blood transfusion
• Unusual bruising or bleeding, caused by a decrease in the number of clotting cells in the blood. This can lead to severe bleeding from relatively minor injuries such as a small cut. Rarely, it can lead to more severe bleeding (*haemorrhage*). Talk to your doctor for advice on how to minimise the risk of bleeding
• Weight loss and loss of appetite (*anorexia*), tiredness, weakness, feeling unwell
• Feeling sick *(nausea*), being sick (*vomiting*), diarrhoea, stomach pain, constipation

• Inflammation and ulcers of the mouth, tongue, or gums
• High body temperature (*fever*)
• Hair loss

Common side effects

The following side effects are common. Tell a doctor if any of these become troublesome.
• Allergic or hypersensitivity reactions (including rash)
• Yellow skin (jaundice)
• Itching sensation
• Muscle pain

Rare side effects

The following side effects are rare. Tell a doctor if any of these become troublesome.
• Severe allergic or anaphylactic reactions
• Swelling caused by fluid build up *(*angioedema*)*
• Mild pain and inflammation at the site of injection
• Itchy rash (or hives)

Note for patients treated for cervical cancer: If you are being treated for cervical cancer, you will usually receive another medicine called cisplatin, alongside your topotecan treatment. You may also get side effects from the cisplatin medication. These side effects will be described in the cisplatin patient information leaflet.

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

5. HOW TO STORE TOPOTECAN HOSPIRA

Keep out of the reach and sight of children.

Do not use Topotecan Hospira after the expiry date stated on the vial and carton after EXP.

Store in a refrigerator (2°C-8°C). Do not freeze.

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

This medicine is for single use only. After opening, the product should be used immediately. If not used immediately, Topotecan Hospira can be used for up to 24 hours when stored in the fridge (protected from light) or at room temperature (in normal daylight conditions).

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

6. FURTHER INFORMATION

What Topotecan Hospira contains
The active substance in Topotecan Hospira is topotecan (as hydrochloride). 1 ml of concentrate for solution for infusion contains 1 mg topotecan (as hydrochloride). Each 4 ml vial of concentrate contains 4 mg topotecan (as hydrochloride).

The other ingredients are: tartaric acid (E334), water for injections and hydrochloric acid (E507) or sodium hydroxide (to adjust the pH of the solution).

What Topotecan Hospira looks like and the contents of the pack
Topotecan Hospira is a clear, yellow or yellow-green concentrate for solution for infusion, supplied in clear glass vials, each containing 4 ml concentrate. Topotecan Hospira is available in two pack sizes, containing either 1 vial or 5 vials. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Hospira UK Limited
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW
United Kingdom

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

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This leaflet was last approved in

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

The following information is intended for medical or health care professionals only.

Storage, Use, Handling & Disposal of Topotecan Hospira

Storage
Unopened vial: Store in a refrigerator (2°C-8°C). Do not freeze. Keep the vial in the outer carton in order to protect from light.

Use
Refer to the SPC for full details.

Topotecan Hospira 4 mg/4 ml concentrate for solution for infusion requires dilution to a final concentration of 25-50 micrograms/ml, prior to administration to the patient. The approved diluents for the concentrate are sodium chloride 9 mg/ml (0.9%) solution for injection and glucose 50 mg/ml (5%) solution for injection. Use the aseptic technique during any further dilution of the solution for infusion.

Parenteral products should be visually inspected for particulate matter and discolouration prior to administration. Topotecan Hospira is a yellow/yellow green solution. If visible particles are observed, the product should not be administered.

Prior to administration of the first course of topotecan, patients must have a baseline neutrophil count of $\geq 1.5 \times 10^9$/l, a platelet count of $\geq 100 \times 10^9$/l and a haemoglobin level of $\geq$ 9g/dl (after transfusion if necessary). Neutropenia and thrombocytopenia should be managed. For further details, refer to the SPC.

Dosage: Small Cell Lung Carcinoma
Initial dose: 1.5 mg/ m^2 body surface area/day, administered by intravenous infusion over 30 minutes for 5 consecutive days, with a 3 week interval between the start of each course.

Subsequent doses: Topotecan should not be re-administered unless the neutrophil count is $\geq$ 1 x 109/l, the platelet count is $\geq 100 \times 10^9$/l, and the haemoglobin level is $\geq$ 9 g/dl (after transfusion if necessary).

Dosage: Cervical Carcinoma
Initial dose: 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 6 courses or until progressive disease.

Subsequent doses: Topotecan should not be re-administered unless the neutrophil count is more than or equal to 1.5×10^9/l, the platelet count is more than or equal to 100×10^9/l, and the haemoglobin level is more than or equal to 9g/dl (after transfusion if necessary).

Dosage: Renally impaired patients
Limited data indicate that the dose should be reduced in patients with moderate renal impairment. Please refer to the SPC for further details.

Dosage: Paediatric population
Limited data available. Use not recommended.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C under normal light conditions and at 2-8°C when protected from light. 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 2 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Handling and disposal
The normal procedures for proper handling and disposal of anti-tumour medicinal products should be adopted:
• Staff should be adequately trained in the preparation, administration and disposal of cytotoxics
• Pregnant staff should be excluded from working with this medicinal product.
• Staff handling this medicinal product should wear adequate protective clothing including mask, goggles and gloves.

• All items for used in the preparation, administration, and cleaning of the medicinal product, 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. If there is lasting irritation, a doctor should be consulted.
• Any unused product or waste material should be disposed of in accordance with local requirements.