ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Potactasol 1 mg powder for concentrate for solution for infusion
Each vial contains 1 mg topotecan (as hydrochloride).
After reconstitution, 1 ml concentrate contains 1 mg topotecan.
Excipient with known effect
Each vial contains 0.52 mg (0.0225 mmol) sodium.

Potactasol 4 mg powder for concentrate for solution for infusion
Each vial contains 4 mg topotecan (as hydrochloride).
After reconstitution, 1 ml concentrate contains 1 mg topotecan.
Excipient with known effect
Each vial contains 2.07 mg (0.09 mmol) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

Yellow lyophilisate.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Topotecan in combination with cisplatin is indicated for patients with carcinoma of the cervix recurrent after radiotherapy and for patients with Stage IVB disease. Patients with prior exposure to cisplatin require a sustained treatment free interval to justify treatment with the combination (see section 5.1).

4.2 Posology and method of administration

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

Posology

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

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

Ovarian and small cell lung carcinoma

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

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

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

If dose reduction is chosen for patients who experience severe neutropenia (neutrophil count < 0.5 x 10^9/l) for seven days or more, or severe neutropenia associated with fever or infection, or who have had treatment delayed due to neutropenia, the dose should be reduced by 0.25 mg/m^2/day to 1.25 mg/m^2/day (or subsequently down to 1.0 mg/m^2/day if necessary).

Doses should be similarly reduced if the platelet count falls below 25 x 10^9/l. In clinical studies, topotecan was discontinued if the dose had been reduced to 1.0 mg/m^2/day and a further dose reduction was required to manage adverse effects.

Cervical carcinoma

Initial dose
The recommended dose of topotecan is 0.75 mg/m^2/day administered as a 30-minute intravenous infusion on days 1, 2 and 3. Cisplatin is administered as an intravenous infusion on day 1 at a dose of 50 mg/m^2/day and following the topotecan dose. This treatment schedule is repeated every 21 days for six courses or until progressive disease.

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

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

If dose reduction is chosen for patients who experience severe neutropenia (neutrophil count < 0.5 x 10^9/l) for seven days or more, or severe neutropenia associated with fever or infection or who have had treatment delayed due to neutropenia, the dose should be reduced by 20 % to 0.60 mg/m^2/day for subsequent courses (or subsequently down to 0.45 mg/m^2/day if necessary).

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

Special populations

Patients with renal impairment
Monotherapy (ovarian and small cell lung carcinoma)
There is insufficient experience with the use of topotecan in patients with severely impaired renal function (creatinine clearance <20 ml/min). Use of topotecan in this group of patients is not recommended (see section 4.4).

Limited data indicate that the dose should be reduced in patients with moderate renal impairment. The recommended monotherapy dose of topotecan in patients with ovarian or small cell lung carcinoma and a creatinine clearance between 20 and 39 ml/min is 0.75 mg/m^2/day for five consecutive days.

Combination therapy (cervical carcinoma)
In clinical studies with topotecan in combination with cisplatin for the treatment of cervical cancer, therapy was only initiated in patients with serum creatinine less than or equal to 1.5 mg/dl. If, during topotecan/cisplatin combination therapy serum creatinine exceeds 1.5 mg/dl, it is recommended that the full prescribing information be consulted for any advice on cisplatin dose reduction/continuation. If cisplatin is discontinued, there are insufficient data regarding continuing monotherapy with topotecan in patients with cervical cancer.

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

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

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

Method of administration

Potactasol is for intravenous infusion after reconstitution and dilution. It must be reconstituted and further diluted before use (see section 6.6).

Precautions to be taken before handling or administering the medicinal product
Reconstitution and dilution of the medicinal product must be performed by trained personnel. The preparation should be performed in a designated area under aseptic conditions.
Adequate protective disposable gloves, goggles, gown and mask should be worn. Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes. In the event of contact with the eyes, irrigate with large amounts of water. Then seek medical evaluation by a physician. In case of skin contact, thoroughly wash the affected area with large amount of water. Always wash hands after removing gloves. See section 6.6.

Pregnant staff should not handle the cytotoxic preparation.

4.3 Contraindications

- Severe hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Breast-feeding (see section 4.6)
- Severe bone marrow depression prior to starting first course, as evidenced by baseline neutrophils < 1.5 x 10^9/l and/or a platelet count of < 100 x 10^9/l.

4.4 Special warnings and precautions for use

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

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

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

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

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

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

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

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

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

When combining topotecan with other chemotherapy agents, reduction of the doses of each medicinal product may be required to improve tolerability. However, when combining with platinum agents, there is a distinct sequence-dependent interaction depending on whether the platinum agent is given on day 1 or 5 of the topotecan dosing. If either cisplatin or carboplatin is given on day 1 of the topotecan dosing, a lower dose of each agent must be given to improve tolerability compared to the dose of each agent which can be given if the platinum agent is given on day 5 of the topotecan dosing.

When topotecan (0.75 mg/m^2/day for 5 consecutive days) and cisplatin (60 mg/m^2/day on day 1) were administered in 13 patients with ovarian cancer, a slight increase in AUC (12 %, n = 9) and C_{max} (23 %, n = 11) was noted on day 5. This increase is considered unlikely to be of clinical relevance.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

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

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

Pregnancy

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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

The integrated safety data for topotecan monotherapy are presented below.

Adverse reactions are listed below, by system organ class and absolute frequency (all reported events). Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (cannot be estimated from the available data).

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

Infections and infestations	
Very common:	infection
Common:	sepsis[1]
Blood and lymphatic system disorders	
Very common:	febrile neutropenia
	neutropenia (see Gastrointestinal disorders below)
	thrombocytopenia
	anaemia
	leucopenia
Common:	pancytopenia
Not known:	severe bleeding (associated with thrombocytopenia)
Immune system disorders	
Common:	hypersensitivity reaction including rash
Rare:	anaphylactic reaction
	angioedema
	urticaria
Metabolism and nutrition disorders	
Very common:	anorexia (which may be severe)
Respiratory, thoracic and mediastinal disorders	
Rare:	interstitial lung disease (some cases have been fatal)
Gastrointestinal disorders	
Very common:	nausea, vomiting and diarrhoea (all of which may be severe)
	constipation
	abdominal pain[2]
	mucositis
Not known:	gastrointestinal perforation
Hepatobiliary disorders	
Common:	hyperbilirubinaemia
Skin and subcutaneous tissue disorders	
Very common:	alopecia
Common:	pruritus
General disorders and administration site conditions	
Very common:	pyrexia
	asthenia
	fatigue
Common:	malaise
Very rare:	extravasation[3]
Not known:	mucosal inflammation

[1] Fatalities due to sepsis have been reported in patients treated with topotecan (see section 4.4)
[2] Neutropenic colitis, including fatal neutropenic colitis, has been reported to occur as a complication of topotecan-induced neutropenia (see section 4.4).
[3] Reactions have been mild and have not generally required specific therapy.

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

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

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

of patients (6 % of courses). Median time to onset of severe neutropenia was nine days and the median duration was seven days. Severe neutropenia lasted beyond seven days in 11 % of courses overall. Among all patients treated in clinical studies (including both those with severe neutropenia and those who did not develop severe neutropenia), 11 % (4 % of courses) developed fever and 26 % (9 % of courses) developed infection. In addition, 5 % of all patients treated (1 % of courses) developed sepsis (see section 4.4).

Thrombocytopenia: Severe (platelets < 25 x 10^9/l) in 25 % of patients (8 % of courses); moderate (platelets between 25.0 and 50.0 x 10^9/l) in 25 % of patients (15 % of courses). Median time to onset of severe thrombocytopenia was day 15 and the median duration was five days. Platelet transfusions were given in 4 % of courses. Reports of significant sequelae associated with thrombocytopenia including fatalities due to tumour bleeds have been infrequent.

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

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

Mild abdominal pain was reported in 4 % of patients.

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

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

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

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

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

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Clinical efficacy and safety

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 2. Study results Study GOG-0179

ITT population		
	Cisplatin 50 mg/m^2 on day 1, every 21 days	**Cisplatin 50 mg/m^2 on day 1, + Topotecan 0,75 mg/m^2 on days 1–3, every 21 days**
Survival (months)	**(n = 146)**	**(n = 147)**
Median (95 % CI)	6.5 (5.8, 8.8)	9.4 (7.9, 11.9)
Hazard ratio (95 % CI)	0.76 (0.59, 0.98)	
Log rank p-value	0.033	
Patients without prior cisplatin chemoradiotherapy		
	Cisplatin	**Topotecan/Cisplatin**

Survival (months)	(n = 46)	(n = 44)
Median (95 % CI)	8.8 (6.4, 11.5)	15.7 (11.9, 17.7)
Hazard ratio (95 % CI)	0.51 (0.31, 0.82)	
Patients with prior cisplatin chemoradiotherapy		
	Cisplatin	**Topotecan/Cisplatin**
Survival (months)	**(n = 72)**	**(n = 69)**
Median (95 % CI)	5.9 (4.7, 8.8)	7.9 (5.5, 10.9)
Hazard ratio (95 % CI)	0.85 (0.59, 1.21)	

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

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

In an open-label study involving children (n = 108, age range: infant to 16 years) with recurrent or progressive solid tumours, topotecan was administered at a starting dose of 2.0 mg/m^2 given as a 30 minute infusion for 5 days repeated every 3 weeks for up to one year depending on response to therapy. Tumour types included were Ewing's sarcoma/primitive neuroectodermal tumour, neuroblastoma, osteoblastoma, and rhabdomyosarcoma. Anti-tumour activity was demonstrated primarily in patients with neuroblastoma. Toxicities of topotecan in paediatric patients with recurrent and refractory solid tumours were similar to those historically seen in adult patients. In this study, forty-six (43 %) patients received G-CSF over 192 (42.1 %) courses; sixty-five (60 %) received transfusions of packed red blood cells and fifty (46 %) of platelets over 139 and 159 courses (30.5 % and 34.9 %), respectively. Based on the dose-limiting toxicity of myelosuppression, the maximum tolerated dose (MTD) was established at 2.0 mg/m^2/day with G-CSF and 1.4 mg/m^2/day without G-CSF in a pharmacokinetic study in paediatric patients with refractory solid tumours (see section 5.2).

5.2 Pharmacokinetic properties

Distribution

Following intravenous administration of topotecan at doses of 0.5 to 1.5 mg/m^2 as a 30 minute infusion daily for five days, topotecan demonstrated a high plasma clearance of 62 l/h (SD 22), corresponding to approximately 2/3 of liver blood flow. Topotecan also had a high volume of distribution, about 132 l, (SD 57), and a relatively short half-life of 2-3 hours. Comparison of pharmacokinetic parameters did not suggest any change in pharmacokinetics over the 5 days of dosing. Area under the curve increased approximately in proportion to the increase in dose. There is little or no accumulation of topotecan with repeated daily dosing and there is no evidence of a change in the pharmacokinetics after multiple doses. Preclinical studies indicate plasma protein binding of topotecan is low (35 %) and distribution between blood cells and plasma was fairly homogeneous.

Biotransformation

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

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

topotecan lactone. An O-glucuronidation metabolite of topotecan and N-desmethyl topotecan has been identified in the urine.

Elimination

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

In vitro data using human liver microsomes indicate the formation of small amounts of N-demethylated topotecan. In vitro, topotecan did not inhibit human P450 enzymes CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A or CYP4A nor did it inhibit the human cytosolic enzymes dihydropyrimidine or xanthine oxidase.

When given in combination with cisplatin (cisplatin day 1, topotecan days 1 to 5), the clearance of topotecan was reduced on day 5 compared to day 1 (19.1 l/h/m^2 compared to 21.3 l/h/m^2 [n = 9]) (see section 4.5).

Special populations

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

Renal impairment
Plasma clearance in patients with renal impairment (creatinine clearance 41-60 ml/min.) decreased to about 67 % compared with control patients. Volume of distribution was slightly decreased and thus half-life only increased by 14 %. In patients with moderate renal impairment topotecan plasma clearance was reduced to 34 % of the value in control patients. Mean half-life increased from 1.9 hours to 4.9 hours.

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

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

5.3 Preclinical safety data

Resulting from its mechanism of action, topotecan is genotoxic to mammalian cells (mouse lymphoma cells and human lymphocytes) *in vitro* and mouse bone marrow cells *in vivo*. Topotecan was also shown to cause embryo-foetal lethality when given to rats and rabbits.

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

The carcinogenic potential of topotecan has not been studied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

Vials
4 years.

Reconstituted and diluted solution
Chemical and physical stability of the concentrate has been demonstrated for 24 hours at 25 ± 2°C in normal light conditions, and for 24 hours at 2°C to 8°C when protected from light.

Chemical and physical stability of the solution obtained **after dilution** of the concentrate in sodium chloride 9 mg/ml (0.9 %) solution for injection or 50 mg/ml (5 %) glucose solution for infusion has been demonstrated for 4 hours at 25 ± 2°C, in normal lighting conditions. The concentrates tested were stored at 25 ± 2°C for 12 hours and 24 hours respectively after reconstitution, and then diluted.

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°C to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

Potactasol 1 mg powder for concentrate for solution for infusion
Type I colourless glass vial (5 ml) with grey bromobutylic stopper and aluminium seal with plastic flip-off cap containing 1 mg topotecan.

Potactasol 4 mg powder for concentrate for solution for infusion
Type I colourless glass vial (8 ml), with grey bromobutylic stopper and aluminium seal with plastic flip-off cap containing 4 mg topotecan.

Vials may or may not be sheathed in a protective sleeve.

Potactasol is available in cartons containing 1 vial.

6.6 Special precautions for disposal and other handling

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

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

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

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

7. MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.
Dalshraun 1
220 Hafnarfjörður
Iceland

8. MARKETING AUTHORISATION NUMBER(S)

Potactasol 1 mg powder for concentrate for solution for infusion
EU/1/10/660/001

Potactasol 4 mg powder for concentrate for solution for infusion
EU/1/10/660/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6 January 2011
Date of latest renewal: 5 October 2015

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. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

S.C. Sindan-Pharma S.R.L.
11 Ion Mihalache Blvd.
011171 Bucharest
Romania

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer Carton

1. NAME OF THE MEDICINAL PRODUCT

Potactasol 1 mg powder for concentrate for solution for infusion
topotecan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 1 mg topotecan (as hydrochloride).
After reconstitution, 1 ml concentrate contains 1 mg topotecan.

3. LIST OF EXCIPIENTS

Contains mannitol (E421), tartaric acid (E334), hydrochloric acid (E507) and sodium hydroxide. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion.
1 x 1 mg vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use as infusion, after reconstitution and dilution.

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, special handling instructions (see package leaflet).
Cytotoxic

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.
220 Hafnarfjörður
Iceland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/660/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

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

Potactasol 1 mg powder for concentrate for solution for infusion
topotecan
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mg

6. OTHER

Cytotoxic

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer Carton

1. NAME OF THE MEDICINAL PRODUCT

Potactasol 4 mg powder for concentrate for solution for infusion
topotecan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 4 mg topotecan (as hydrochloride).
After reconstitution, 1 ml concentrate contains 1 mg topotecan.

3. LIST OF EXCIPIENTS

Contains mannitol (E421), tartaric acid (E334), hydrochloric acid (E507) and sodium hydroxide. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion.
1 x 4 mg vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use as infusion, after reconstitution and dilution.

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, special handling instructions (see package leaflet).
Cytotoxic

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.
220 Hafnarfjörður
Iceland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/660/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial

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

Potactasol 4 mg powder for concentrate for solution for infusion
topotecan
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

4 mg

6. OTHER

Cytotoxic

B. PACKAGE LEAFLET

Package leaflet: Information for the user

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

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

What is in this leaflet

1. What Potactasol is and what it is used for

Potactasol contains the active substance topotecan which helps to kill tumour cells.

Potactasol is used to treat:
- ovarian cancer or small cell lung cancer that has come back after chemotherapy
- advanced cervical cancer if surgery or radiotherapy is not possible. In this case Potactasol treatment is combined with medicines containing cisplatin.

2. What you need to know before you use Potactasol

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

Tell you doctor if you think any of these could apply to you.

Warnings and precautions
Talk to your doctor before using Potactasol:
- if you have any kidney problems. Your dose of Potactasol may need to be adjusted. Potactasol is not recommended in case of severe kidney impairment;
- if you have liver problems. Potactasol is not recommended in case of severe liver impairment;
- if you suffer from lung inflammation with signs such as cough, fever and difficulties in breathing, see also section 4 “Possible side effects”.

Potactasol may cause a decrease in the number of blood clotting cells (platelets). This can lead to severe bleeding from relatively small injuries such as a small cut. Rarely, it can lead to more severe bleeding (haemorrhage). Talk to your doctor for advice on how to minimize the risk of bleeding.

The incidence of side effects is more frequent in patients who are in poor general health. The doctor will evaluate your general health during the treatment and you should tell him/her in case you have fever, infection or are in some ways feeling unwell.

Use in children and adolescents
The experience in children and adolescents is limited and treatment is therefore not recommended.

Other medicines and Potactasol
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
Potactasol should not be used in pregnant women, unless clearly necessary. If you are or think you might be pregnant, tell your doctor immediately.

Effective contraception methods should be used to avoid becoming pregnant or fathering a child while on treatment with Potactasol. Ask your doctor for advice.

Patients who are concerned about their fertility should ask their doctor for counselling on fertility and family planning options prior to starting treatment.

You must not breast-feed while on treatment with Potactasol.

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

Potactasol contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially 'sodium-free'.

3. How to use Potactasol

Your dose of Potactasol will depend on:
- the disease being treated,
- your body surface area (m^2),
- the results of blood tests carried out before and during treatment,
- how well you tolerate treatment.

Adults
Ovarian cancer and small cell lung cancer
The usual dose is 1.5 mg per m^2 of body surface area once daily for 5 days. This treatment cycle will normally be repeated every three weeks.

Cervical cancer
The usual dose is 0.75 mg per m^2 of body surface area once daily for 3 days. This treatment cycle will normally be repeated every three weeks.
For cervical cancer, it will be used together with another anticancer medicines containing cisplatin. For more information about cisplatin, please refer to the corresponding package leaflet.

Patients with impaired kidney function
Your doctor might need to reduce your dose based on your kidney function.

How Potactasol is prepared
Topotecan is supplied as a powder for concentrate for solution for infusion. The powder must be dissolved, and the resulting concentrate further diluted before administration.

How Potactasol is given
A doctor or nurse will give you the reconstituted and diluted Potactasol solution as an infusion (drip), usually into your arm, over about 30 minutes.

If you are given too much Potactasol

As this medicine is being given by your doctor or nurse, it is unlikely that you will be given too much. In the unlikely event of an overdose, your doctor will monitor you for side effects. Tell your doctor or nurse if you have any concerns about the amount of medicine that you receive.

4. Possible side effects

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

Serious side effects
You must tell your doctor **immediately** if you experience any of the following serious side effects. They may require hospitalisation and could even be life-threatening.

- **Infections** (very common; may affect more than 1 in 10 people), with signs such as:
  - fever
  - serious decline of your general condition
  - local symptoms, such as sore throat or burning sensation when urinating
  - severe stomach pain, fever and possibly diarrhoea (rarely with blood) can be signs of bowel inflammation (neutropenic colitis)

Potactasol may reduce your ability to fight infections.

- **Lung inflammation** (rare; may affect up to 1 in 1,000 people), with signs such as:
  - difficulty breathing
  - cough
  - fever

The risk of developing this severe condition (interstitial lung disease) is higher if you currently have lung problems, or if you have received previous radiation treatment or medicines that affected your lungs, see also section 2 “Warnings and precautions”. This condition can be fatal.

- **Severe allergic (anaphylactic) reactions** (rare; may affect up to 1 in 1,000 people), with signs such as:
  - swelling of the face, lips, tongue or throat, difficulty breathing, low blood pressure, dizziness and itchy rash.

Other side effects with Potactasol include:

Very common side effects (may affect more than 1 in 10 people)
- Feeling generally weak and tired, which can be symptoms of a decrease in the number of red blood cells (anaemia). In some cases you may need a blood transfusion.
- Decrese in number of circulating white blood cells (leucotyes) in the blood. Abnormal low number of neutrophil granulocytes (a type of white blood cell) in the blood, with or without fever.
- Unusual bruising or bleeding, sometimes severe, caused by a decrease in the number of blood clotting cells (platelets).
- Weight loss and loss of appetite (anorexia); tiredness; weakness.
- Feeling sick (nausea), vomiting; diarrhoea; stomach pain; constipation.
- Inflammation of the lining of the mouth and digestive tract.
- Fever.
- Hair loss.

Common side effects (may affect up to 1 in 10 people)
- Allergic (hypersensitivity) reactions (including rash).
- Abnormal high level of bilirubin, a waste product produced by the liver during breakdown of red blood cells. Symptoms may include yellow skin (jaundice).
- Decrease in the number of all blood cells (pancytopenia).
- Feeling unwell.
- Serious blood infection, which can be fatal.

- Itching (pruritus).

Rare side effects (may affect up to 1 in 1,000 people)
- Swelling caused by fluid build-up (angioedema) e.g. around the eyes and lips as well as hands, feet and throat. If severe it may cause breathing difficulties.
- Itchy rash (or hives).

Very rare side effects (may affect up to 1 in 10,000 people)
- 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.

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

If you are being treated for cervical cancer, you may get side effects from the other medicine (cisplatin) that you will be given along with Potactasol.

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

5. How to store Potactasol

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

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

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

Storage after reconstitution and dilution
Chemical and physical stability of the concentrate has been demonstrated for 24 hours at 25 ± 2°C, in normal light conditions and 24 hours at 2°C to 8°C, protected from light.

The physico-chemical stability of the medicinal product solution obtained after dilution in solutions for infusion (NaCl 0.9 % and Glucose 5 %) has been demonstrated for 4 hours at room temperature, in normal lighting conditions, on samples reconstituted and stored for 12 hours and respectively 24 hours at 25°C ± 2°C and then diluted.

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°C to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

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

6. Contents of the pack and other information

What Potactasol contains
- The active substance is topotecan. Each vial contains 1 mg or 4 mg topotecan (as hydrochloride). After reconstitution 1 ml concentrate contains 1 mg topotecan.
- The other ingredients are: mannitol (E421), tartaric acid (E334), hydrochloric acid (E507) and sodium hydroxide (see section 2).

What Potactasol looks like and contents of the pack
Potactasol is supplied in type I colourless glass vials with grey bromobutylic stopper and aluminium seals with plastic flip-off caps. Vials may or may not be sheathed in a protective sleeve. Vials contain either 1 mg or 4 mg of topotecan.

Each pack contains one vial.

Marketing Authorisation Holder
Actavis Group PTC ehf.
Dalshraun 1
220 Hafnarfjörður
Iceland

Manufacturer
S.C. Sindan-Pharma S.R.L.
11 Ion Mihalache Blvd
Bucharest
Romania

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

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This leaflet was last revised in {MM/YYYY}.

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

The following information is intended for healthcare professionals only:

Potactasol

INSTRUCTIONS ON USE

Reconstitution and dilution prior to administration

Before infusion, Potactasol powder for concentrate for solution for infusion must be reconstituted with an appropriate volume of water for injections, as follows:

- Potactasol 1 mg with 1.1 ml water for injections (as it contains 10 % overage of fill)
- Potactasol 4 mg with 4 ml water for injections

Reconstitution will result in a concentrate containing 1 mg topotecan per ml.
This concentrate (1 mg/ml) must be diluted prior to administration.

The volume of reconstituted concentrate corresponding to the calculated individual dose should be further diluted with either sodium chloride 9 mg/ml (0.9 %) or 5 % w/v glucose, to give a final concentration of between 25 and 50 microgram per ml in the solution for infusion, for example:

	Volume for 25 microgram/ml solution	**Volume for 50 microgram/ml solution**
1 ml of 1 mg/ml topotecan solution	Add 39 ml to give 40 ml	Add 19 ml to give 20 ml
4 ml of 1 mg/ml topotecan solution	Add 156 ml to give 160 ml	Add 76 ml to give 80 ml

Storage after reconstitution and dilution
Chemical and physical stability of the concentrate has been demonstrated for 24 hours at 25 ± 2°C in normal light conditions, and for 24 hours at 2°C to 8°C when protected from light.

Chemical and physical stability of the solution obtained **after dilution** of the concentrate in sodium chloride 9 mg/ml (0.9 %) solution for injection or 50 mg/ml (5 %) glucose solution for infusion has been demonstrated for 4 hours at 25 ± 2°C, in normal lighting conditions .The concentrates tested were reconstituted and stored at 25 ± 2°C for 12 hours and 24 hours respectively after reconstitution, and then diluted.

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