Zolasol (Powder for concentrate for solution for infusion)
Each vial contains 4 mg topotecan (as hydrochloride)
Application no.: 56/26/0642

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE
ZOLASOL 4 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains 4 mg topotecan (as hydrochloride).
The total content of active ingredient in the vial provides 1 mg per ml of topotecan when reconstituted as recommended.
Contains sugar (mannitol 48,0 mg per vial).
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Powder for concentrate for solution for infusion.
Light yellow to greenish, freeze-dried powder in a colourless vial.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
ZOLASOL is indicated for the treatment of patients with metastatic carcinoma of the ovary after failure of first-line or subsequent therapy.
ZOLASOL is indicated for palliative treatment of small cell lung carcinoma as second-line chemotherapeutic agent in patients who have relapsed after an initial response to treatment with first-line chemotherapy agents.
ZOLASOL in combination with cisplatin is indicated for the treatment of patients with histologically confirmed Stage IV-B, recurrent, or persistent carcinoma of the cervix, which is not amenable to curative treatment with surgery and/or radiation therapy.

4.2 Posology and method of administration
ZOLASOL should be administered under the direction of a medical practitioner experienced in the use of cytotoxic medicines (see section 6.6). Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

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

Ovarian and small cell lung carcinoma
Initial dose:
The recommended dose of ZOLASOL is 1.5 mg/m^2 per day administered by intravenous infusion over 30 minutes daily for 5 consecutive days with a 3 week interval between the start of each course. A minimum of 4 courses is recommended unless patient progresses since median time to response in clinical trials was 8 - 11,7 weeks in ovarian cancer and 6,1 weeks in small cell lung cancer.
Subsequent doses:
ZOLASOL should not be re-administered unless the neutrophil count is ≥ 1 x 10^9/l, and the haemoglobin level is ≥ 9 g/dl (after transfusion if necessary).
If dose reduction is chosen for patients who experience severe neutropenia (neutrophil count ≤ 0.5 x 10^9/l) 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/day0

Doses should be similarly reduced if the platelet count falls below 25 x 10^9/l. In clinical trials, topotecan was discontinued if the dose had been reduced to 1,0 mg/m^2 and a further dose reduction was required to manage adverse effects.
Dosage in combination:
Dose adjustment may be necessary if ZOLASOL is administered in combination with other cytotoxic medicines.

Cervical cancer
Initial dose:
The recommended dose of ZOLASOL is 0.75 mg/m^2 administered as a 30 minute intravenous infusion daily on days 1, 2 and 3. Cisplatin is administered as an intravenous infusion on day 1 at a dose of 50 mg/m^2 following the ZOLASOL dose. This treatment schedule is repeated every 21 days for 6 courses or until progressive disease.
Subsequent doses:
ZOLASOL 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).
Patients who experience severe neutropenia (neutrophil count less than 0.5 x 10^9/l for seven days or more, or severe neutropenia associated with fever or infection or who have had treatment delayed due to neutropenia should have the dose of ZOLASOL reduced by 20 % to 0.60 mg/m^2/day down for subsequent courses (or subsequently down 0,45 mg/m^2/day).
Doses of ZOLASOL should be similarly reduced if the platelet count falls below 25 x 10^9/day.

Special populations
Patients with renal impairment
Monotherapy:
The recommended dose in patients with creatinine clearance between 20 and 39 ml/min is 0,75 mg/m^2/day. No dosage adjustment is required in patients with a creatinine clearance ≥ 40 ml/min. Insufficient data is available to make a recommendation for patients with a creatinine clearance < 20 ml/min. Advice on dosing of ZOLASOL for patients with moderate renal impairment (20 to 39 ml/min) is based on studies involving patients with advanced ovarian and small cell lung cancer.
Combination therapy:
It is recommended that ZOLASOL in combination with cisplatin for the treatment of cervical cancer only be initiated in patients with serum creatinine less than or equal to 1,5 mg/dl. If, during ZOLASOL/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 ZOLASOL in patients with cervical cancer.

Patients with hepatic impairment
No dosage adjustment is required in patients with hepatic impairment (serum bilirubin ≥ 1.5 to ≤ 10 mg/dl). Hepatically impaired patients were able to tolerate 1.5 mg/m^2 for five days every three weeks although a small reduction in topotecan clearance was observed.

Paediatric population
Use in children is not recommended as only limited data are available.

Method of administration
For intravenous use.
ZOLASOL must be reconstituted and further diluted before use (see section 6.6).

4.3 Contraindications
• History of severe hypersensitivity reactions to topotecan or any of the excipients listed in 6.1.
• Pregnancy or breastfeeding (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).
ZOLASOL 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, as contained in ZOLASOL. In patients presenting with fever, neutropenia and a compatible pattern of abdominal pain, the possibility of neutropenic colitis should be considered.
Topotecan, as in ZOLASOL, 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 medicines and/or colony stimulating factors. Patients should be monitored for pulmonary symptoms indicative of ILD (e.g., cough, fever, dyspnoea and/or hypoxia), and ZOLASOL should be discontinued if a new diagnosis of ILD is confirmed.
It is recommended that ZOLASOL is not used as a single medicine therapy in first-line patients.
ZOLASOL monotherapy and in combination with cisplatin are commonly associated with clinically relevant thrombocytopenia. This should be taken into account when prescribing ZOLASOL, 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 ZOLASOL 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 ZOLASOL in these patient groups is not recommended (see section 4.2).
ZOLASOL contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium free”. However, if 0.9 % sodium chloride BP intravenous infusion is used for the dilution of ZOLASOL prior to administration then the dose of sodium received would be higher.

4.5 Interaction with other medicines 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). It has been reported in population studies using the intravenous route, that 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).
There is an increased risk of myelosuppression when ZOLASOL is used in combination with other cytotoxic medicines, (e.g. paclitaxel or etoposide) thereby necessitating dose reduction.
When combining ZOLASOL with other chemotherapy agents, reduction of the doses of each medicine 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 ZOLASOL dosing. If either cisplatin or carboplatin is given on day 1 of ZOLASOL dosing, a lower dose of each medicine must be given to improve tolerability compared to the dose of each medicine which can be given if the platinum agent is given on day 5 of ZOLASOL dosing.
It has been reported when topotecan (0.75 mg/m^2/day for 5 consecutive days) and cisplatin (60 mg/m^2/day on 1 day) were administered in 13 patients with ovarian cancer, a slight increase in AUC (12 %) and Cmax (23%) was noted on day 5. This increase is considered unlikely to be of clinical relevance.

.6 Fertility, pregnancy and lactation
Women of child-bearing potential / Contraception in males and females
ZOLASOL may cause foetal harm and therefore women of childbearing potential should be advised to avoid becoming pregnant during therapy with ZOLASOL.
Patients being treated with ZOLASOL must be advised that they or their partner must use an effective method of contraception.

Pregnancy
Topotecan has been shown to cause embryo-foetal lethality and malformations in preclinical studies. ZOLASOL may cause foetal harm when administered to pregnant women and therefore is contraindicated during pregnancy (see section 4.3).

Breastfeeding
ZOLASOL is contraindicated during breastfeeding (see section 4.3). Although it is not known whether topotecan is excreted in human breast milk, it is recommended that breastfeeding be discontinued when receiving ZOLASOL.
Fertility
No effects on male or female fertility have been observed in reproductive toxicity studies in rats. However, ZOLASOL is genotoxic and effects on fertility, including male fertility, cannot be excluded.

4.7 Effects on ability to drive and use machines
Caution should be exercised when driving or operating machines if fatigue and asthenia persist.

4.8 Undesirable effects
Summary of the safety profile
It has been reported in dose-finding studies, that the dose-limiting toxicity was found to be haematological. Toxicity was predictable and reversible. No evidence of cumulative haematological or non-haematological toxicity was seen in patients.
In patients with small cell lung or ovarian carcinoma, the onset of neutropenia and thrombocytopenia was generally within 2 weeks of treatment and in the majority of cases lasted no more than 7 days. In 11 % of courses severe neutropenia lasted more than 7 days.
The most frequently reported treatment-related or possibly related non-haematological effects were gastrointestinal such as nausea, vomiting and diarrhoea, constipation, and mucositis. These were usually mild at the recommended dose level.
No evidence of significant cardiotoxicity, neurotoxicity or major organ toxicity was observed with topotecan.
The safety profile of ZOLASOL when given in combination with cisplatin in cervical cancer is consistent with that seen with ZOLASOL monotherapy. The overall haematological toxicity is lower in patients treated with ZOLASOL in combination with cisplatin compared to ZOLASOL monotherapy, but higher than with cisplatin alone.
Additional adverse events were reported when topotecan was given in combination with cisplatin; however, these events were seen with cisplatin monotherapy and were not attributable to ZOLASOL. The prescribing information for cisplatin should be consulted for a full list of adverse events associated with cisplatin use.
Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Frequency not known
Infections and infestations	Infection, sepsis 1		
Blood and lymphatic system disorders	Febrile neutropenia, neutropenia (see "Gastrointestinal disorders"), thrombocytopenia, anaemia, leukopenia, pancytopenia		Severe bleeding (associated with thrombocytopenia)
Immune system disorders	Hypersensitivity reaction including rash	Anaphylactic reaction, angioedema, urticaria	
Metabolism and nutrition disorders	Anorexia (which may be severe)		
Respiratory, thoracic, and mediastinal disorders		Interstitial lung disease (some cases have been fatal)	
Gastrointestinal disorders	Nausea, vomiting and diarrhoea (all of which may be severe), constipation, abdominal pain[2], mucositis		Gastrointestinal perforation
Hepato-biliary disorders	Hyperbilirubinaemia		
Skin and subcutaneous tissue disorders	Alopecia, pruritus		
General disorders and administration site conditions	Pyrexia, asthenia, fatigue, malaise	Extravasation[3]	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 in the table above have the potential to occur with a higher frequency in patients who have a poor performance status (see section 4.4).
Description of selected adverse reactions
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 such as ZOLASOL.

Haematological
Neutropenia:
Severe (neutrophil count < 0.5 x 10^9/l) during course 1 in 55 % of patients, with duration ≥ seven days in 20 %, and overall, in 77 % of patients (39 % of courses). In association with severe neutropenia, fever or infection occurred in 16 % of patients during course 1 and overall, in 23 % of patients (6 % of courses). Median time to onset of severe neutropenia was nine days and the median duration was seven days. Severe neutropenia lasted beyond seven days in 11 % of courses overall. Among all patients treated in clinical studies (including both those with severe neutropenia and those who did not develop severe neutropenia), 11 % (4 % of courses) developed fever and 26 % (9 % of courses) developed infection. In addition, 5 % of all patients treated (1 % of courses) developed sepsis (see section 4.4).
Thrombocytopenia:
Severe (platelets < 25 x 10^9/l) in 25 % of patients (8 % of courses); moderate (platelets between 25.0 and 50.0 x 10^9/l) in 25 % of patients (15 % of courses). Median time to onset of severe thrombocytopenia was day 15 and the median duration was five days. Platelet transfusions were given in 4 % of courses. Reports of significant sequelae associated with thrombocytopenia, including fatalities due to tumour bleeds, have been infrequent.
Anaemia:
Moderate to severe (Hb ≤ 8,0 g/dl) in 37 % of patients (14 % of courses). Red cell transfusions were given in

52 % of patients (21 % of courses).

Non-haematological
Frequently reported non-haematological effects were gastrointestinal, such as nausea (52 %), vomiting (32 %), diarrhoea (18 %), constipation (9 %) and mucositis (14 %). The incidence of severe (Grade 3 or 4) nausea, vomiting, diarrhoea, and mucositis was 4, 3, 2 and 1 %, respectively.
Mild abdominal pain was reported in 4 % of patients.
Fatigue was observed in approximately 25 % and asthenia in 16 % of patients receiving topotecan. Severe (Grade 3 or 4) fatigue and asthenia both occurred with an incidence of 3 %.
Total or pronounced alopecia was observed in 30 % of patients and partial alopecia in 15 % of patients.
Other severe events that were recorded as related or possibly related to topotecan treatment were anorexia (12 %), malaise (3 %) and hyperbilirubinaemia (1 %).
Hypersensitivity reactions including rash, urticaria, angioedema and anaphylactic reactions have been reported less frequently. 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Category and class: A.26 Cytostatic agents.
Pharmacotherapeutic group: antineoplastic agents, 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.
The cytotoxicity of topotecan is thought to be due to double strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topotecan, topoisomerase-I and DNA. Mammalian cells cannot efficiently repair these double strand breaks.
The dose-limiting toxicity of topotecan is leukopenia. White blood cell count decreases with increasing topotecan dose or topotecan AUC. When topotecan is administered at a dose of 1,5 mg/m^2/day for 5 days, an 80 % to 90 % decrease in white blood cell count at nadir is typically observed after the first cycle of therapy.

5.2 Pharmacokinetic properties
Distribution
The pharmacokinetics of topotecan have been evaluated in cancer patients following doses of 0.5 to 1.5 mg/m^2 administered as a 30 minute infusion. Topotecan exhibits multi-exponential pharmacokinetics with a terminal half-life of 2 to 3 hours. Total exposure (AUC) is approximately dose-proportional. Binding of topotecan to plasma proteins is about 35 %.

Biotransformation
A major route of inactivation of topotecan is a reversible pH-dependent ring opening to the inactive carboxylate form.
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 2,5 % 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 approximately 1.5 %. 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 approximately≤ 2.0 % of the dose.
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^2compared to 21.3 l/h/m^2)(see section 4.5).

Special populations
Gender:
The overall mean topotecan plasma clearance in male patients was approximately 24 % higher than in female patients, largely reflecting difference in body size.
Elderly:
Topotecan pharmacokinetics have not been specifically studied in an elderly population, but population pharmacokinetic analysis in female patients did not identify age as a significant factor. Decreased renal clearance, common in elderly, is a more important determinant of topotecan clearance.
Renal impairment:
In patients with mild renal impairment (creatinine clearance of 40 to 60 ml/min), topotecan plasma clearance was decreased to about 67 % of the value in patients with normal renal function. In patients with moderate renal impairment (Cl$_c$ of 20 to 39 ml/min), topotecan plasma clearance was reduced to about 34 % of the value in control patients, with an increase in half-life. Mean half-life, estimated in three renally impaired patients was about 5,0 hours. Dosage adjustment is recommended for these patients (see section 4.2).
Hepatic impairment:
Plasma clearance in patients with hepatic impairment (serum bilirubin levels between 1.7 and 15.0 mg/dl) was decreased to about 67 % of the value in patients without hepatic impairment. Topotecan half-life increased slightly from 2.0 hours to 2.5 hours, but these hepatically impaired patients tolerated the usual recommended topotecan dosage regimen (see section 4.2).
Medicine interactions:
Pharmacokinetic studies of the interaction of topotecan with concomitantly administered medications have not been formally investigated. *In vitro* inhibition studies using marker substrates known to be metabolised by human P450 CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A, or CYP4A or dihydropyrimidine dehydrogenase indicate that the activity of these enzymes were not altered by topotecan. Enzyme inhibition by topotecan has not been evaluated *in vivo*.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not known.
ZOLASOL must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials:
3 years.
Reconstituted and diluted solutions:
Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C. From a microbiological point of view, ZOLASOL should be used immediately; it contains no preservative. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2-8°C when reconstituted and diluted under validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 30 °C.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after reconstitution and dilution of ZOLASOL, see section 6.3.

6.5 Nature and contents of container

20 ml colourless Type I glass vial, closed with a 22 mm chlorobutyl rubber stopper and sealed with a red aluminium cap.
Pack size of 1 vial per outer carton.

6.6 Special precautions for disposal and other handling

ZOLASOL 4 mg vials must be reconstituted with 4 ml sterile water for injection. The clear, reconstituted solution is light yellow to greenish in colour and provides 1 mg of topotecan per ml. Further dilution of the appropriate volume of the reconstituted solution with either 0,9 % sodium chloride BP intravenous infusion or 5 % dextrose BP intravenous infusion is required to a final concentration of between 25 and 50 µg/ml.
The normal procedures for proper handling and disposal of anticancer medicines should be adopted, namely:
• Personnel should be trained to reconstitute ZOLASOL.
• Pregnant staff should be excluded from working with ZOLASOL.
• Personnel handling ZOLASOL during reconstitution should wear protective clothing including mask, goggles, and gloves.
• All items for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high-temperature incineration. Liquid waste may be flushed with large amounts of water.
• Accidental contact with the skin or eyes should be treated immediately with copious amounts of water.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ando Pharma (Pty) Ltd.
73 Keurboom Crescent
Plattekloof
Cape Town

8. REGISTRATION NUMBER(S)

56/26/0642

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 February 2023

10. DATE OF REVISION OF THE TEXT

To be allocated.