Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Treosulfan Powder for Solution for Injection or Infusion 5 g

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 5 g of treosulfan, intended for reconstitution with 100 ml water for injection resulting in a 50 mg/ml solution.

3 PHARMACEUTICAL FORM

Powder for solution for injection/infusion.

A white crystalline odourless powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treosulfan is indicated for the palliative treatment of epithelial ovarian cancer.

4.2 Posology and method of administration

Posology
The dosage of treosulfan as monotherapy is 8 g/m² in patients who have not undergone previous chemotherapy. The dose should be reduced to 6 g/m² or less in patients with risk factors such as pre-treatment with myelosuppressive agents or radiotherapy and reduced performance status.

The therapy should be repeated every three to four weeks.

In combination with cisplatin, treosulfan should be dosed at 5 g/m², with cycles repeated every 3 − 4 weeks.

Duration of treatment
In general, 6 courses of treatment with treosulfan are given.
In the case of a progressive clinical picture and/or occurrence of non-tolerable adverse events, the treatment must be stopped.

Dose modification
If, following administration of treosulfan, the white cell count falls below 1,000/µl and/or the platelet count falls below 25,000/µl, the following dose must be reduced by 1 g/m².

Treatment should not be given if the white blood cell count is less than 3,500/µl or the thrombocyte count less than 100,000/µl after three weeks.

A repeat blood count should be made after a week interval, when treatment may be restarted if haematological parameters are satisfactory. If the values after this are still unchanged, the treosulfan dose must be reduced to 6 g/m² in case of monotherapy and to 3 g/m² in combination with cisplatin.

If during treatment the white cell count does not fall below 3,500/µl and/or the platelet count does not fall below 100,000/µl, the dose in the following course of treatment may be increased by 1 g/m².

Elderly patients and patients with renal impairment
Treosulfan is renally excreted. Blood counts should be carefully monitored in elderly and renally impaired patients and the dose adjusted accordingly.

Paediatric population
Treosulfan is not recommended for use in children.

Method of administration
Treosulfan should be administered by intravenous infusion over 15 to 30 minutes.

Precautions to be taken before handling or administering the medicinal product
For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance.

Severe and lasting bone marrow depression.

4.4 Special warnings and precautions for use

This product should only be used under specialist oncologist direction, with facilities for appropriate clinical and laboratory surveillance.

Risk of infections
The risk of infections (mycotic, viral, bacterial) is increased.

Haematological effects and monitoring of blood count
The dose-limiting side effect of treosulfan is myelosuppression, which is usually reversible. It is manifested by a reduction in leukocytes and platelets and a decrease in haemoglobin. The leukocytes and platelets usually reach their baseline level after 28 days.
As the inhibition of bone marrow function is cumulative, the blood count should be monitored at shorter intervals starting with the third course of treatment. This is especially important if treosulfan is combined with other forms of therapy that suppress bone marrow function such as radiotherapy.

Risk of malignancy
During long-term therapy with oral treosulfan doses eight patients (1.4% of 553 patients) developed an acute non-lymphocytic leukaemia. The risk was depending on the cumulative dose of treosulfan. Single cases of myeloma, myeloproliferative disorder and myelodysplastic syndrome have additionally been reported.

Pulmonary toxicity
If allergic alveolitis or pulmonary fibrosis develop treosulfan should be permanently discontinued.

Risk of cystitis
Due to the possible development of a haemorrhagic cystitis, patients are advised to drink more fluids for up to 24 hours after intravenous infusion.

Renal impairment
As treosulfan is excreted renally, blood counts should be carefully monitored in patients with renal impairment and the dose adjusted accordingly.

Use with live vaccines
Cytostatic therapy may increase the risk of generalised infection after immunisation using live vaccines. Therefore live vaccines should not be used in patients receiving treosulfan.

Extravasation
During infusion, care must be taken to use a flawless technique, since painful inflammatory reactions may occur as a result of extravasation of treosulfan solution into surrounding tissue.

4.5 Interaction with other medicinal products and other forms of interaction

In one patient the effect of ibuprofen/chloroquine was reduced with concomitant administration of treosulfan.

4.6 Fertility, pregnancy and lactation

Pregnancy
This product should not be used during pregnancy or in nursing mothers unless considered absolutely essential by the physician.

Women of childbearing potential have to use effective contraception during treatment.

Fertility
No data available.

4.7 Effects on ability to drive and use machines

No details are known about the effect of treosulfan on the ability to drive and use machines. In case of nausea and vomiting the ability to drive or operate machines may be influenced.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported undesirable effects are myelosuppression and gastrointestinal complaints. They are usually mild and resolve after therapy with treosulfan.
Bone marrow suppression is the dose-limiting side effect of treosulfan.

Tabulated list of adverse reactions

Frequency:
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), not known (cannot be estimated from the available data)

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

Organ class	**Frequency**
Infections and infestations	*Common:* Infections (mycotic, viral, bacterial) *Very rare:* Sepsis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	*Uncommon* Treatment related secondary malignancies (acute non-lymphocytic leukaemia, myelodysplastic syndrome, myeloma, myeloproliferative disorder)
Blood and lymphatic system disorders	*Very common:* Myelosupression (leukocytopenia, thrombocytopenia, anaemia) *Very rare:* Pancytopenia

Immune system disorders	*Rare:* Allergic reactions
Endocrine disorders	*Very rare:* Addison's disease
Metabolism and nutrition disorders	*Very rare:* Hypoglycaemia
Nervous system disorders	*Very rare:* Paraesthesia
Cardiac disorders	*Very rare:* Cardiomyopathy
Respiratory, thoracic and mediastinal disorders	*Very rare:* Pulmonary fibrosis, alveolitis, pneumonia,
Gastrointestinal disorders	*Very common:* Vomiting, nausea, gastrointestinal discomfort
Hepatobiliary disorders	*Very rare:* Icterus; increased liver function parameters
Skin and subcutaneous tissue disorders	*Very common:* Alopecia, bronze skin pigmentation *Very rare:* Scleroderma, triggering of psoriasis, erythema, urticaria
Renal and urinary disorders	*Very rare:* Haemorrhagic cystitis
General disorders and administration site conditions	*Very rare:* Flu-like complaints, local painful inflammatory reactions (in case of extravasation)

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

There is no experience of acute overdose with treosulfan, but it is expected that adverse effects like nausea, vomiting and gastritis may occur. Prolonged or excessive therapeutic doses may result in bone marrow depression which has occasionally been irreversible. The medicinal product should be withdrawn and a blood transfusion as well as general supportive measures given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, alkylating agents, alkyl sulfonates
ATC code: L 01 AB 02

Mechanism of action
Treosulfan is a bifunctional alkylating agent which has been shown to possess antineoplastic activity in the animal tumour screen and in clinical trials. The activity of treosulfan is due to the formation of epoxide compounds *in vivo*.

Treosulfan is converted *in vitro* under physiological conditions (pH 7.4; 37 °C) non-enzymatically via a monoepoxide to the diepoxide (diepoxybutane) with a half-life of 2.2 hours.

The epoxides formed react with nucleophilic centres of the DNA and are responsible via secondary biological mechanisms for the antineoplastic effect. It is important that *in vivo* the monoepoxide first formed can already alkylate a nucleophilic centre of the DNA. This fixes the compound to this centre by chemical reaction before the second epoxide ring is formed.

Pharmacodynamic effects
Treosulfan has a broad antineoplastic and antileukaemic activity. Antineoplastic activity was demonstrated against transplanted mouse and rat lymphomas/leukaemias, sarcomas and hepatomas, human tumour xenografts, human tumour biopsies and cell lines. Treosulfan is effective *in vivo* when administered intraperitoneally, intravenously as well as orally.

Clinical efficacy and safety
The clinical efficacy of treosulfan in combination with cisplatin in patients with ovarian cancer was demonstrated in a large randomised clinical trial. A total of 519 patients were randomised to receive cisplatin (70 mg/m²) combined with either treosulfan (5 g/m²; PT regimen) or cyclophosphamide (1 g/m²; PC regimen). Both regimens were given at 4−weekly intervals. After a median follow up of 5 years, 366 patients (PC: 179; PT: 187) could be evaluated for efficacy and 290 patients (PC: 135; PT: 155) for safety. Median time to progression (the primary endpoint) was longer with the combination cisplatin/treosulfan (20.6 versus 15.1 months); however, this difference was not statistically significant (P = 0.3). No differences in response rates could be detected between both treatment regimens. Overall survival did not differ between treatment arms (29.4 versus 33.5 months; P = 0.8). In the PC arm, significant more hair loss was observed (P = 0.0001), in the PT-arm more leukocytopenia (P = 0.01). Quality of life was better for patients treated with the treosulfan-containing regimen.

The efficacy of intravenous administration of treosulfan monotherapy (5 − 7 g/m²; every 4 weeks) was demonstrated in a phase II study in 88 pre-treated patients (80 evaluable for efficacy) with advanced ovarian cancer. There were 2 complete and 13 partial responses, giving an objective response rate of 19 %. Among responding patients, median survival time was 41 months. Thirty-four percent of the patients had stable disease with median survival of 18 months.

In 48 women with progressive disease within 12 months after primary therapy, a response rate of 19 % and stable disease in 31 % could be achieved. Toxic side effects were rare and moderate in intensity. Life-threatening myelosuppression, emesis resistant to therapy, and alopecia were not observed.

Paediatric population
The efficacy and safety of treosulfan in paediatric tumour patients has not been established.

5.2 Pharmacokinetic properties

Absorption
Oral absorption of treosulfan is excellent with the bioavailability approaching 100 %.

Distribution
After intravenous administration treosulfan is rapidly distributed in the body.

Biotransformation
Under physiological conditions (pH 7.4, temperature 37 °C), treosulfan is converted spontaneously (non-enzymatically) from the pharmacologically inactive treosulfan into an active monoepoxide intermediate and finally to L−diepoxibutane. At concentrations up to 100 µM, treosulfan had no unequivocal effect on either CYP1A2, 2C9, 2C19, 2D6, or 3A4 activities *in vitro*.

Elimination
Elimination follows a first order kinetics with a half-life of 1 − 2 hours. Approximately 20 – 40 % of the substance is excreted unchanged with the urine within 24 hours, nearly 90 % of which within the first 6 hours after administration.

5.3 Preclinical safety data

Acute toxicity
In mice the oral LD_{50} is 3,360 mg treosulfan/kg body weight and the intravenous LD_{50} > 2,500 mg treosulfan/kg body weight.

In rats the oral LD_{50} is 2,575 mg treosulfan/kg body weight and the intraperitoneal LD_{50} > 2,860 mg treosulfan/kg body weight.

Subacute toxicity
In monkeys receiving a subacute dose (56 − 111 mg/kg/day) the haematopoietic system was damaged. At higher doses (222 – 445 mg/kg/day) diarrhoea, anorexia and marked weight loss were also noted.

Chronic toxicity
Administration of treosulfan to rats for seven months led to a reduction in spermiogenesis in males and cycle disturbances in females. All other organs were unchanged.

Tumorigenic and mutagenic potential
In long-term therapy with oral treosulfan doses an acute non-lymphatic leukaemia was observed in 1.4 % of the patients.

Treosulfan, like other cytostatic agents with alkylating properties, has a mutagenic potential. Therefore, patients of childbearing potential have to use effective contraception during treatment.

Reproductive toxicity
Treosulfan has not been tested for reproductive toxicity in animal experiments. However, during chronic toxicity testing in rats, a delayed spermiogenesis and the absence of corpora lutea and follicles was determined.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Medicinal product as packaged for sale
5 years.

The medicinal product should not be used after the expiry date.

Reconstituted solution in the original vial
The prepared solution should be used immediately.

Do not store the reconstituted or the diluted product in a refrigerator (2 – 8 °C) as this might cause precipitation. Solutions showing any sign of precipitation should not be used.

6.4 Special precautions for storage

Do not store above 25 °C.

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

6.5 Nature and contents of container

Type III clear glass infusion bottle (100 ml) with butyl rubber stopper and cap of aluminium completed with labels with integrated hanger.

The vials are packed in boxes of 5.

6.6 Special precautions for disposal and other handling

Treosulfan Injection 5 g is used for intravenous infusion after being dissolved in 100 ml of water for injection.
The reconstituted solution is a clear, colourless solution.
Inspect visually prior to use. Only clear solutions without particles should be used.
Any reconstituted solution that shows evidence of precipitation should not be used and should be destroyed with regard to legal requirements for disposal of hazardous waste (see below).

For single use only, discard any unused contents.

As with all cytotoxic substances, appropriate precautions should be taken when handling treosulfan.

Guidelines for the safe handling of antineoplastic agents

1. Trained personnel should reconstitute the medicinal product.
2. This should be performed in a designated area.
3. Adequate protective gloves, masks and clothing should be worn.
4. Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes. In case the solution comes in contact with the skin or the eyes, the affected area should be washed with copious amounts of water or normal saline. A bland cream may be used to treat the transient stinging of the skin. Medical advice should be sought if the eyes are affected.
5. Cytotoxic preparations should not be handled by staff who may be pregnant.
6. Adequate care and precautions should be taken in the disposal of items (syringes, needles, etc.) used to reconstitute cytotoxic agents.
7. The work surface should be covered with disposable plastic-backed absorbent paper.
8. Use Luer-lock fittings on all syringes and sets. Large bore needles are recommended to minimise pressure and the possible formation of aerosols. The latter may also be reduced by the use of a venting needle.
9. In the event of spillage, trained personnel wearing appropriate personal protective equipment as outlined above should mop the spilled material with a spill kit or sponge kept in the area for that purpose. Rinse the area with copious amounts of water. Put all solutions and sponges into a designated suitable high risk waste disposal bag and then seal it.

Instructions for reconstitution of Treosulfan Powder for solution for infusion or injection 5 g
To avoid solubility problems during reconstitution the following aspects should be regarded.

1. The solvent, water for injection, is warmed to 25 – 30 °C (not higher!) by using a water bath.
2. The treosulfan is carefully removed from the inner surface of the infusion bottle by shaking. This procedure is very important, because moistening of powder that sticks to the surface results in caking. In case caking occurs the bottle has to be shaken long and vigorously.
3. One side of the double sided cannula is put into the rubber stopper of the water bottle. The treosulfan bottle is then put on the other end of the cannula with the bottom on top. The whole construction is converted and the water let run into the lower bottle while the bottle is shaken gently.

Following these instructions, the whole reconstitution procedure should take no longer than 2 minutes.

7 MARKETING AUTHORISATION HOLDER

Medac
Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

8 MARKETING AUTHORISATION NUMBER

PA0623/001/002

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