SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Treosulfan Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Vials containing 1 g or 5 g treosulfan.

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 progressive disease 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's 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 Injection 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

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.

Cardiac toxicity

It cannot be totally ruled out that one case of cardiomyopathy was related to treosulfan.

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 (see section 4.2).

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 and breast-feeding

No data are available on the use of treosulfan in pregnant women and it is unknown whether treosulfan is able to penetrate into breast milk.

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 and up to 6 months after treatment.

Fertility

No data are available

4.7 Effects on ability to drive and use machines

No data 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	*Common:*

infestations	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:* Myelosuppression (leukocytopenia, thrombocytopenia, anaemia) *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
Hepatobiliary disorders:	*Very rare:* Hepatic enzyme increased, blood bilirubin increased
Skin and subcutaneous tissue disorders	*Very common:* Alopecia (usually mild), bronze skin pigmentation *Very rare:* Scleroderma, triggering of psoriasis, erythema, urticaria
Renal and urinary disorders	*Very rare:* Haemorrhagic cystitis
General disorders and administration site	*Very rare:* Flu-like complaints, local painful

conditions	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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

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 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. Treosulfan does not bind to plasma proteins.

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

The mean (± SD) terminal half-life ($t_{1/2ß}$) of intravenously administered treosulfan (8 g/m²) is 1.94 ± 0.99 hours, with cumulative renal elimination of unchanged treosulfan of about 25 % (range 5-49 %).

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

Reconstituted/diluted solutions
The prepared solutions 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

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

100 ml colourless infusion glass vial (glass type I or II) with butyl rubber stopper and cap of aluminium completed with labels with integrated hanger.

100 ml colourless injection glass vial (glass type III) with butyl rubber stopper and cap of aluminium completed with labels with integrated hanger.

Each vial contains 1 g or 5 g treosulfan.

The vials are packed in boxes of 5.

6.6 Special precautions for disposal

Treosulfan Injection 1 g or 5 g is used for intravenous infusion after being dissolved in 20 or 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.

Instructions for reconstitution of Treosulfan Injection

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

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Theaterstr. 6

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8 MARKETING AUTHORISATION NUMBER(S)

11587/0002

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