SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Treosulfan Capsules 250 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsules each containing 250 mg treosulfan as active substance.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

White opaque capsules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of all types of ovarian cancer, either supplementary to surgery or palliatively. Some uncontrolled studies have suggested activity in a wider range of neoplasms.

Because of a lack of cross-resistance reported between Treosulfan and other cytotoxic agents Treosulfan may be useful in any neoplasm refractive to conventional therapy.

Treosulfan has been used in combination regimens in conjunction with vincristine, methotrexate, 5-FU and procarbazine.

4.2 Posology and method of administration

The following dosage regimens have been indicated. All regimens indicate that a total dose of 21-28 g of treosulfan should be given in the initial 8 weeks of treatment.

Regimen A: 1 g daily, given in four divided doses for four weeks, followed by four weeks off therapy.

Regimen B: 1 g daily, given in four divided doses for two weeks, followed by two weeks off therapy.

Regimen C: 1.5 g daily, given in three divided doses for one week only, followed by three weeks off therapy. If no evidence of haematological toxicity at this dose in Regimen C, increase to 2 g daily in four divided doses for one week for the second and subsequent courses.

These cycles should be repeated with the dose being adjusted if necessary, as outlined below, according to the effect on the peripheral blood counts. The capsules should be swallowed whole and not allowed to disintegrate within the mouth.

Dose modification (all regimens):

For excessive haematological toxicity (white blood cell count less than 3.000/microlitre or thrombocyte count less than 100.000/microlitre, a repeat blood count should be made after 1-2 weeks interval and treatment restarted if haematological parameters are satisfactory, reducing dose as follows:

Regimen A: 1 g daily x 28 to 0.75 g daily x 28 (and to 0.5 g daily x 28 if necessary).

Regimen B: 1 g daily x 14 to 0.75 g daily x 14 (and to 0.5 g daily x 14 if necessary).

Regimen C: 2 g daily x 7 to 1.5 g daily x 7 (and to 1 g daily x 7 if necessary).

Present evidence, whilst not definitive, suggests that Regimens B and C are less myelosuppressive than Regimen A, whilst retaining maximum cytotoxic efficacy.

Dosage in the elderly

Treosulfan is renally excreted. Blood counts should be carefully monitored in the elderly and the dosage adjusted accordingly.

Children

Treosulfan Capsules are not recommended for use in children.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

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 a 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.

Because 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 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 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 stomatitis

Stomatitis may occur if the patients chew the capsule. Therefore the capsules should be swallowed whole.

Risk of cystitis

Because of the possible development of a haemorrhagic cystitis patients are advised to drink more fluids during the course of medication.

Use with live vaccines

Cytostatic therapy may increase the risk of generalized infection after immunization using live vaccines. Therefore live vaccines should not be used in patients receiving treosulfan.

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 Pregnancy and lactation

Warning: This product should not normally be administered to patients who are pregnant or to mothers who are breast-feeding.

Woman of childbearing age should take adequate contraceptive precautions.

4.7 Effects on ability to drive and use machines

Because of nausea and vomiting the ability to drive or operate machines may be influenced.

4.8 Undesirable effects

The most commonly reported adverse drug reactions are myelosuppression and gastrointestinal complaints. They are usually mild and resolve after therapy with treosulfan.

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.

Frequency	
Very common ≥1/10	*Blood and lymphatic system disorders* Leucocytopenia, thrombocytopenia, anaemia, myelosuppression *Gastrointestinal disorders* Vomiting, nausea *Skin and subcutaneous tissue disorders* Alopecia (usually mild), bronze skin pigmentation
Uncommon (≥1/1,000 to <1/100	*Neoplasms benign, malignant and unspecified (incl cysts and polyps)* Treatment related secondary malignancies (acute non-lymphocytic leukaemia, myeloma, myeloproliferative disorder, myelodysplastic syndrome)
Not known	*Immune system disorders* Allergic reactions *Blood and lymphatic system disorders* Pancytopenia

The following undesirable effects have also been reported:

Addison's disease, hypoglycaemia, paraesthesia, cardiomyopathy, stomatitis, alveolitis, pneumonia, pulmonary fibrosis, urticaria, erythema, scleroderma, triggering of psoriasis, haemorrhagic cystitis, flu-like complaints.

4.9 Overdose

Although there is no experience of acute overdosage with treosulfan, nausea, vomiting and gastritis may occur. Prolonged or excessive therapeutic doses may result in bone marrow depression which has occasionally been irreversible. The drug should be withdrawn, a blood transfusion given and general supportive measures given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Treosulfan is a bifunctional alkylating agent which has been shown to possess antineoplastic activity in the animal tumor 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.

5.2 Pharmacokinetic properties

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

5.3 Preclinical safety data

Acute toxicity

In mice the oral LD_{50} is 3360 mg treosulfan/kg body weight and the intravenous LD_{50} >2500 mg treosulfan/kg body weight.

In rats the oral LD_{50} is 2575 mg treosulfan/kg body weight and the intraperitoneal LD_{50} > 2860 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.

Tumorogenic 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 child-bearing age should practice contraception while receiving treosulfan.

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

Capsule content: maize starch, hydroxypropyl methylcellulose, magnesium stearate

Capsule shell: titanium dioxide E171, gelatine

6.2 Incompatibilities

None known.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Amber glass bottles of 100 capsules.

6.6 Special precautions for disposal and other handling

The capsules should be swallowed whole and not allowed to disintegrate within the mouth.

7 MARKETING AUTHORISATION HOLDER

medac

Gesellschaft für klinische Spezialpräparate mbH

Fehlandtstraße 3 · D-20354 Hamburg

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8 MARKETING AUTHORISATION NUMBER(S)

11587/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/01/1992

10 DATE OF REVISION OF THE TEXT

24/06/2008

Full information is available on request from

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