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 the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.

White opaque capsules.

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

Treosulfan 400-600 mg/m²/day orally; day 1 - 28; four weeks rest, repeat day 57.

Duration of treatment

Treatment should be continued until disease progression. In the case of occurrence of non-tolerable adverse events, the treatment must be stopped.

Dose modification

A treatment cycle should not be started if the white blood cell count is less than 3,500/µl or the thrombocyte count less than 100,000/µl. A repeat blood count should be made after a week's interval, when treatment may be restarted if haematological parameters are satisfactory.

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 daily dose must be reduced by one capsule (250 mg).

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 daily dose in the following course of treatment may be increased by one capsule (250 mg).

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 Capsules are not recommended for use in children.

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 stomatitis

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

Risk of cystitis

Due to possible development of a haemorrhagic cystitis, patients are advised to drink more fluids during the course of treatment.

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.

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 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 adverse drug reactions 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 (incl 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 *Uncommon:* Stomatitis
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 conditions	*Very rare:* Flu-like complaints

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 efficacy and safety of orally administered treosulfan (1 g daily for 28 days; every 8 weeks) was shown in a phase II study that included 47 patients with advanced ovarian cancer. 18 patients (38 %) achieved a complete remission, 14 (30 %) a partial remission for an overall response rate of 68 %. Main toxicities were myelosuppression, skin pigmentation, and nausea.

Paediatric population

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

5.2 Pharmacokinetic properties

Absorption

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

Distribution

After absorption 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 orally administered treosulfan (1.5-2.0 g/d for 5-8 days) is 1.93 ± 0.59 hours, with cumulative renal elimination of unchanged treosulfan of about 15 % (range 6-16 %).

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

Capsule content:	maize starch, hydroxypropyl methylcellulose, magnesium stearate
Capsule shell:	titanium dioxide E171, gelatine

6.2 Incompatibilities

Not applicable.

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 Content of Container

Amber glass bottles of 100 capsules.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

medac

Gesellschaft für klinische Spezialpräparate mbH

Theaterstr. 6

22880 Wedel

Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 11587/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of latest renewal: 11/07/2008

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02/12/2016