Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Treosulfan Capsules 250 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg treosulfan.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Capsules, hard.

White opaque capsules containing a white odourless crystalline powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the management of cancer, including those resistant to conventional therapy. The drug may be used as first line therapy in ovarian cancer, either as one single agent, in conjunction with surgery or as part of a combination regimen. Treosulfan has been shown to be active in lung cancer (both small cell and non-small cell), Hodgkin's disease, chronic myeloid leukaemia, adenocarcinoma and solid tumours.

4.2 Posology and method of adminstration

The following dosage regimens have been indicated. All regimens indicate that a total dose of 21-28g 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: 1g daily x 28 to 0.75g daily x 28 (and to 0.5g daily x 28 if necessary).
Regimen B: 1g daily x 14 to 0.75g daily x 14 (and to 0.5g daily x 14 if necessary).
Regimen C: 2g daily x 7 to 1.5g daily x 7 (and to 1g 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
Not recommended.

4.3 Contraindications

Severe and lasting bone marrow depression.

4.4 Special warnings and special precautions for use

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

4.5 Interaction with other medicinal products and other forms of interaction

If radiotherapy is used concomitantly the initial doses of drug should be reduced by up to 50%. Concomitant use of other cytotoxic drugs will also require reduction in dosage.

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

4.6 Pregnancy and lactation

Warning: This product should no be used during pregnancy or in nursing mothers unless considered absolutely essential by the physician.

Women 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, alopecia and gastrointestinal complaints. They are usually mild and resolve after therapy with Treosulfan.

Frequency

Very common >1/10
Blood and the lymphatic system disorders
Leucocytopenia, thrombocytopenia, anaemia, myelosuppression

Gastrointestinal disorders
Gastrointestinal discomfort, nausea, vomiting

Skin and subcutaneous tissue disorders
Alopecia, bronze skin pigmentation

Uncommon <1/100
Gastrointestinal disorders
Stomatitis

Very rare <1/10,000
Blood and the lymphatic system disorders
Acute non-lymphocytic leukaemia, including isolated myelodysplastic syndrome reports.

Endocrine disorders
Addison's disease, hypoglycaemia

Nervous system disorders
Paraesthesia

Cardiac disorders
Cardiomyopathy

Respiratory disorders
Alveolitis, pneumonia, pulmonary fibrosis

Skin and subcutaneous tissue disorders
Urticaria, erythema, scleroderma, triggering of psoriasis

Renal and urinary disorders
Haemorrhagic cystitis

General disorders
Flu-like complaints

Blood and the lymphatic system disorders
Anemia, leucocytopenia, thrombopenia occur very commonly. In most cases it is mild and reversible within 28 days. This myelosuppression can be cumulative during therapy and aggravated if combination with radiation or other antineoplastic substances is performed. Therefore, blood count should be controlled in shorter intervals from 3rd cycle on.

In isolated cases of long-term therapy with treosulfan development of acute non-lymphocytic leukaemia and myelodysplastic syndrome were reported.

Endocrine disorders
In isolated cases Addison's disease, hypoglycaemia were observed.

Nervous system disorders
In isolated cases paraesthesia was observed.

Cardiac disorders
In one case cardiomyopathy was reported.

Respiratory, thoracic and mediastinal disorders
Single cases of allergic alveolitis, pneumonia and pulmonary fibrosis were reported.

Gastrointestinal disorders
Gastrointestinal discomfort, especially nausea and vomiting, is observed very commonly.
Frequency of gastrointestinal complaints can be reduced with concomitant uptake of food or milk.
Stomatitis is observed uncommonly, especially if the patient chews the capsule. The patient should be advised to swallow the capsule as a whole.

Skin and subcutaneous tissue disorders
Mild alopecia and bronze skin pigmentation are observed very commonly. Other skin changes, which were reported in isolated cases: urticaria, erythema, scleroderma, triggering of psoriasis.

Renal and urinary disorders
In isolated cases haemorrhagic cystitis was observed. Therefore, patients are advised to drink abundantly for 24 hours after therapy with treosulfan.

General disorders and administration site conditions
In isolated cases 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

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.

5.2 Pharmacokinetic properties

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

After intravenous administration treosulfan is rapidly distributed in the body.

Elimination follows a 1st order kinetics with a half-life of 1.6 h. Approximately 30% of the substance are 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 3360mg treosulfan/kg body weight and the intravenous LD_{50} >2500mg treosulfan/kg body weight.

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

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

Chronic toxicity
Administration of treosulfan in 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 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
Hypromellose
Magnesium stearate

Capsule shell
Titanium dioxide (E171)
Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Amber glass bottles of 100 capsules with black closures of urea formaldehyde and coated with polyvinylidene chloride.

6.6 Instructions for use and handling

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Medac
Gesellschaft für klinische Spezialpräparate
Fehlandtstraβe 3
D-20354 Hamburg
Germany

8 MARKETING AUTHORISATION NUMBER

PA 623/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 24th March 2002

10 DATE OF REVISION OF THE TEXT

May 2004