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 or infusion.

A white crystalline powder.

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

3 - 8 g/m^2 i.v. every 1-3 weeks depending on blood count and concurrent chemotherapy. Single injections of up to 8 g/m^2 have been given with no serious adverse effects. Doses up to 1.5 g/m^2 have been given intraperitoneally. Doses up to 3 g/m^2 treosulfan may be given as a bolus injection. Larger doses should be administered as an i.v. infusion at a rate of 3 g/m^2 every 5-10 minutes (8 g/m^2 as a 30 minutes infusion).

Treatment should not be given if the white blood cell count is less than 3.000/microlitre or the thrombocyte count less than 100.000/microlitre. A repeat blood count should be made after a weeks interval, when treatment may be restarted if haematological parameters are satisfactory. Lower doses of treosulfan should be used if other cytotoxic drugs or radiotherapy are being given concurrently. Treatment is initiated as soon as possible after diagnosis.

Care should be taken in administration of the injection to avoid extravasation into tissues since this will cause local pain and tissue damage. If extravasation occurs, the injection should be discontinued immediately and any remaining portion of the dose should be introduced into another vein.

Dosage in the elderly

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

Children

Treosulfan Injection is not recommended for use in children.

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 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 cystitis

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

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.

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 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, alveolitis, pneumonia, pulmonary fibrosis, urticaria, erythema, scleroderma, triggering of psoriasis, haemorrhagic cystitis, flu-like complaints, local painful inflammatory reactions (in case of extravasation).

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

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 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

None.

6.2 Incompatibilities

No incompatibilities are as yet known.

6.3 Shelf life

5 years when stored at room temperature.

The drug product should not be used after the expiration date.

Once brought into solution the injection should be used immediately.

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 and other handling

Route of administration

Treosulfan Injection 1 g or 5 g is used for intravenous infusion after being dissolved in 20 or 100 mL of water for injection.

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 drug.
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 drug accidentally coming into contact with the eyes.
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 drugs.
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 not longer than 2 minutes.

7 MARKETING AUTHORISATION HOLDER

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Full information is available on request from

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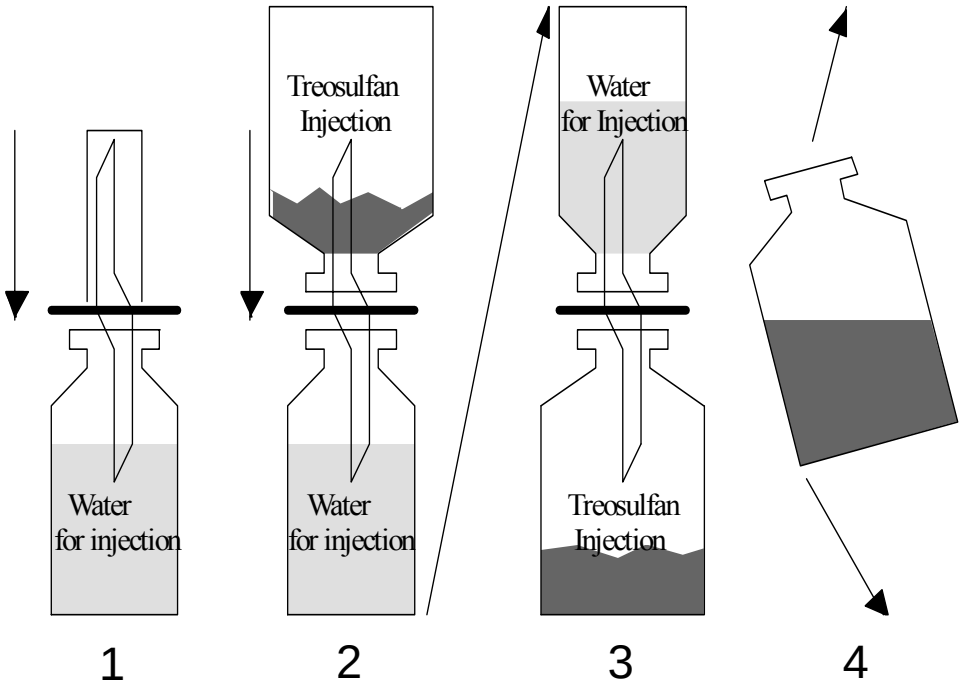
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