

SUMMARY OF THE PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Hydroxycarbamide medac 500 mg capsule, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule contains 500 mg hydroxycarbamide.

For a full list of excipients, see section 6.1.

Excipients: One capsule contains 25 mg lactose monohydrate.

3 PHARMACEUTICAL FORM

Capsule, hard

White capsules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of patients with chronic myeloid leukaemia (CML) in the chronic or accelerated phase of the disease.

Treatment of patients with essential thrombocythemia or polycythemia vera with a high risk for thromboembolic complications.

4.2 Posology and method of administration

Therapy should only be conducted by a physician experienced in oncology or haematology. Doses are based on real or ideal bodyweight of the patient, whichever is the less.

In CML hydroxycarbamide is usually given at an initial dose of 40 mg/kg daily dependent on the white cell count. The dose is reduced by 50 % (20 mg/kg daily) when the white cell count is dropped below $20 \times 10^9/l$. The dose is then adjusted individually to keep the white cell count at $5 - 10 \times 10^9/l$. Hydroxycarbamide dose should be reduced if white cell counts fall below $5 \times 10^9/l$ and increased if white cell counts $> 10 \times 10^9/l$ are observed.

If white cell count falls below $2.5 \times 10^9/l$, or the platelet count below $100 \times 10^9/l$, therapy should be interrupted until the counts rise significantly towards normal.

An adequate trial period for determining the antineoplastic effect of Hydroxycarbamide medac is six weeks. Therapy should be interrupted indefinitely, if there is a significant progress of the disease. If there is a significant clinical response therapy may be continued indefinitely.

In essential thrombocythemia hydroxycarbamide is usually given at starting doses of 15 mg/kg/day with dose adjustment to maintain a platelet count below $600 \times 10^9/l$ without lowering the white blood cell count below $4 \times 10^9/l$.

In polycythemia vera hydroxycarbamide should be started at a dosage of 15 – 20 mg/kg/day. Hydroxycarbamide dose should be adjusted individually to maintain the hematocrit below 45 % and platelet count below $400 \times 10^9/l$. In most patients this can be achieved with hydroxycarbamide given continuously at average daily doses of 500 to 1000 mg.

If hematocrit and platelet count can be sufficiently controlled therapy should be continued indefinitely.

Children:

Because of the rarity of these conditions in children, dosage regimens have not been established.

Elderly:

Elderly patients may be more sensitive to the effects of hydroxycarbamide, and may require a lower dosage regimen.

Dosage in conditions of impaired renal and/or liver function:

There are no data available. Dose recommendation cannot be given to patients with impaired renal and/or liver function (see section 4.4).

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

4.3 Contraindications

Hydroxycarbamide medac is contraindicated in severe bone marrow depression, leucocytopenia ($< 2.5 \times 10^9$ leukocytes/l), thrombocytopenia ($< 100 \times 10^9$ platelets/l) or severe anaemia.

Hydroxycarbamide medac is contraindicated in patients with hypersensitivity to hydroxycarbamide or to any of the excipients. Therapy should be discontinued if hypersensitivity to Hydroxycarbamide medac occurs.

4.4 Special warnings and precautions for use

Hydroxycarbamide can cause bone marrow depression with leucopenia as first and most often occurring sign of this depression. Thrombocytopenia and anaemia occur less frequently and are rare without preceding leucopenia. Complete blood counts including determination of haemoglobin level, total leukocyte differentiation counts, and platelet counts should be performed regularly also after the individual optimal dose has been established. The control interval should be individualised, but is normally once a week. If white cell count falls below

$2.5 \times 10^9/l$, or the platelet count below $100 \times 10^9/l$, therapy should be interrupted until the counts rise significantly towards normal. (See section 4.2).

In case of anaemia before or during ongoing treatment red blood cells may be replaced when needed. Megaloblastic erythropoiesis, which is self limiting, is often seen early in the course of hydroxycarbamide therapy. The morphologic change resembles pernicious anaemia, but is not related to vitamin B₁₂ or folic acid deficiency.

During therapy with Hydroxycarbamide medac frequent monitoring of blood counts should be conducted as well as monitoring of hepatic and renal function. In patients with impaired renal and/or liver function the experience is limited. Therefore special care should be taken in the treatment of these patients, especially at the beginning of therapy.

Patients should be instructed to drink abundantly.

In patients receiving long-term treatment with hydroxycarbamide for myeloproliferative disorders, such as polycythemia vera and thrombocythemia, secondary leukemia may develop. To what extent this relates to the underlying disease or to treatment with hydroxycarbamide is presently unknown.

The monitoring of skin changes is advisable during hydroxycarbamide treatment as in single cases squamous cell carcinoma of the skin was reported.

Hydroxycarbamide can induce painful leg ulcers which are usually difficult to treat and require cessation of therapy. Discontinuation of hydroxycarbamide usually leads to slow resolution of the ulcers over some weeks.

Hydroxycarbamide should be administered with caution to patients who receive concomitant or have received previous therapy with other antineoplastic drugs or irradiation, since adverse reactions can occur more frequently and more severe than those reported with the use of hydroxycarbamide, other antineoplastic drugs or irradiation alone. These effects primarily include bone marrow depression, gastric irritation, and mucositis.

An exacerbation of erythema caused by previous or simultaneous irradiation may occur.

The combination of hydroxycarbamide and nucleoside reverse transcriptase inhibitors (NRTI) may enhance the risk of side effects of NRTI, see also section 4.5, Interaction with other medicinal products and other forms of interaction.

Hydroxycarbamide may be genotoxic. Therefore, men under therapy are advised to use safe contraceptive measures during and for at least 3 months after therapy. They should be informed about the possibility of sperm conservation before the start of therapy.

Hydroxycarbamide medac should not be administered to patients who are pregnant or to mothers who are breast feeding, unless the benefits outweigh the possible hazards (see section 4.6).

Hydroxycarbamide medac should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

Hydroxycarbamide should be administered with caution to patients who receive concomitant or have received previous therapy with other antineoplastic drugs or irradiation, since adverse reactions can occur more frequently and more severe than those reported with the use of hydroxycarbamide, other antineoplastic drugs or irradiation alone. These effects primarily include bone marrow depression, gastric irritation, and mucositis.

An exacerbation of erythema caused by previous or simultaneous irradiation may occur.

In-vitro studies have demonstrated hydroxycarbamide's ability to enhance the cytotoxicity of both ara-C and the fluoropyrimidines. Whether this interaction leads clinically to a co-operative toxicity or to the necessity of adjusting the doses is unclear.

Hydroxycarbamide may enhance the antiretroviral activity of nucleoside reverse transcriptase inhibitors like didanosine and stavudine. Hydroxycarbamide inhibits HIV DNA synthesis and HIV replication by decreasing the amount of intracellular deoxynucleotides. Hydroxycarbamide may also enhance the potential side effects of nucleoside reverse transcriptase inhibitors such as pancreatitis and peripheral neuropathy.

4.6 Pregnancy and lactation

Pregnancy

Hydroxycarbamide may be a potent mutagenic agent. Animal experiments with hydroxycarbamide indicated an increased incidence of congenital defects (see 5.3 Preclinical safety data). Hydroxycarbamide should not be administered to patients who are pregnant unless the benefits outweigh the possible hazards. Women of child-bearing potential have to take contraceptive precautions before the start of and during treatment with hydroxycarbamide.

If pregnancy still occurs during treatment the possibility of genetic consultation should be used. Hydroxycarbamide crosses the placenta.

Lactation

As hydroxycarbamide passes into breast-milk, breast-feeding has to be interrupted before the start of treatment.

Fertility

Hydroxycarbamide may be genotoxic, therefore, if a patient intends to become pregnant after a therapy with hydroxycarbamide a genetic consultation is recommended.

Men under therapy are advised to use safe contraceptive measures during and for at least 3 months after therapy. They should be informed about the possibility of sperm conservation before the start of therapy.

4.7 Effects on ability to drive and use machines

Ability to react may be impaired during treatment with Hydroxycarbamide medac. This should be borne in mind when heightened attention is required, e.g. for driving and using machines.

4.8 Undesirable effects

Bone marrow depression is the dose limiting toxicity. Gastrointestinal side effects are common but require rarely dose reduction or cessation of treatment.

Adverse event frequencies have been categorised as follows:

Very common ($\geq 1/10$)

Common ($\geq 1/100, < 1/10$)

Uncommon ($\geq 1/1,000, < 1/100$)

Rare ($\geq 1/10,000, < 1/1,000$)

Very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

<u>Blood and lymphatic system disorders:</u>	<u>Common:</u> Bone marrow depression, leucopenia, megaloblastosis <u>Uncommon:</u> Thrombocytopenia, anaemia
<u>Nervous system disorders:</u>	<u>Rare:</u> Neurological disturbances including headache, dizziness, disorientation, convulsion
<u>Respiratory, thoracic and mediastinal disorders:</u>	<u>Rare:</u> Acute pulmonary reactions consisting of diffuse pulmonary infiltrates, fever and dyspnoea, allergic alveolitis.
<u>Gastrointestinal disorders:</u>	<u>Common:</u> Diarrhoea, constipation <u>Uncommon:</u> Nausea, vomiting, stomatitis
<u>Renal and urinary disorders:</u>	<u>Uncommon:</u> Transient renal tubular dysfunction accompanied by increased blood uric acid, increased blood urea and increased blood creatinine <u>Rare:</u> Dysuria

	<p><u>Very rare:</u> Renal impairment</p>
<p><u>Skin and subcutaneous tissue disorders:</u></p>	<p><u>Uncommon:</u> Maculopapular rash, facial erythema, acral erythema</p> <p><u>Rare:</u> Alopecia</p> <p><u>Very rare:</u> Dermatomyositis-like skin changes, skin hyperpigmentation, skin atrophy, nail pigmentation, nail atrophy, skin ulcers (especially leg ulcers), pruritus, actinic keratosis, skin cancer (squamous cell cancer, basal cell carcinoma), violet papules, desquamation.</p>
<p><u>Metabolism and nutrition disorders:</u></p>	<p><u>Uncommon:</u> Anorexia</p> <p><u>Rare:</u> Tumour lysis syndrome</p>
<p><u>General disorders and administration site conditions:</u></p>	<p><u>Uncommon:</u> Drug fever, chills, malaise</p>
<p><u>Immune system disorders:</u></p>	<p><u>Rare:</u> Hypersensitivity reaction</p>
<p><u>Hepatobiliary disorders:</u></p>	<p><u>Uncommon:</u> Hepatic enzyme increased, blood bilirubin increased</p>
<p><u>Psychiatric disorders:</u></p>	<p><u>Rare:</u> Hallucinations</p>

Blood and lymphatic system disorders:

In the therapy with hydroxycarbamide megaloblastosis may occur which does not respond to treatment with folic acid or B₁₂.

The bone-marrow suppression subsides, however, when therapy is discontinued.

Hydroxycarbamide can reduce plasma iron clearance and iron utilisation by erythrocytes. However, it does not appear to alter the red blood cell survival time.

Gastrointestinal disorders:

Severe gastric distress (nausea, emesis, anorexia) resulting from combined hydroxycarbamide and irradiation therapy may usually be controlled by temporarily discontinuing hydroxycarbamide administration.

Skin and subcutaneous tissue disorders:

Hydroxycarbamide may aggravate the inflammation of mucous membranes secondary to irradiation. It can cause a recall of erythema and hyperpigmentation in previously irradiated tissues.

Erythema, atrophy of skin and nails, desquamation, violet papules, alopecia, dermatomyositis-like skin changes, actinic keratosis, skin cancer (squamous cell cancer, basal cell carcinoma), cutaneous ulcers (especially leg ulcers), pruritus and hyperpigmentation of skin and nails have been observed in isolated cases partly after years of long-term daily maintenance therapy with hydroxycarbamide.

Nervous system disorders:

High doses may cause moderate drowsiness.

Neoplasms benign, malignant and unspecified (incl cysts and polyps):

In patients receiving long-term treatment with hydroxycarbamide for myeloproliferative disorders, such as polycythemia vera and thrombocythemia, secondary leukemia may develop. To what extent this relates to the underlying disease or to treatment with hydroxycarbamide is presently unknown.

4.9 Overdose

Acute mucocutaneous symptoms have been observed in patients receiving hydroxycarbamide dosages several times the recommended dose. Soreness, violet erythema, oedema on palms and soles followed by scaling of hands and feet, severe generalised hyperpigmentation of the skin, and stomatitis have also been observed.

Immediate treatment consists of gastric lavage, followed by supportive care and monitoring of the haematopoietic system.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents

ATC-code: L01XX05

The exact mechanism of action of hydroxycarbamide is unknown. The most important effect of hydroxycarbamide appears to be blocking of the ribonucleotide reductase system resulting in inhibition of DNA synthesis. Cellular resistance is usually caused by increased ribonucleotide reductase levels as a result of gene amplification.

5.2 Pharmacokinetic properties

The pharmacokinetic information is limited. Hydroxycarbamide is well absorbed and the oral bioavailability is complete. After oral administration maximum plasma concentrations are reached within 0.5 to 2 hours. Hydroxycarbamide is eliminated partly via renal excretion. The contribution of this route of elimination to the total elimination of hydroxycarbamide is unclear since the fractions of the given dose recovered in urine ranged from 9 to 95 %. Metabolism of hydroxycarbamide has not been thoroughly studied in humans. Hydroxycarbamide crosses the blood-brain barrier.

5.3 Preclinical safety data

Repeated dose toxicity

Bone marrow damages, lymphoid atrophy in the spleen and degenerative changes in the epithelium of the small and large intestines are toxic effects which have been observed in animal studies. The potential risk for similar effects in humans must be considered.

Reproduction toxicity

Teratogenicity of hydroxycarbamide was demonstrated in many species, including rat, mouse and rabbit. The large variety of teratogenic effects was ranging from death of a large proportion of embryos to limb deformities, neural defects and even behavioural effects.

Additionally, hydroxycarbamide affected spermatogenesis and sperm motility of mice after repeated administration.

Genotoxicity

Hydroxycarbamide showed genotoxic properties in conventional testing systems.

Carcinogenicity

The preclinical information on the carcinogenic potential of hydroxycarbamide is meagre. A 12 months study on mice where the occurrence of lung tumours was studied did not show any carcinogenic potential in hydroxycarbamide.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:	calcium citrate, disodium citrate, magnesium stearate, lactose monohydrate
Capsule shell:	titanium dioxide (E 171), gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

4 years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and content of container

The capsules are packed in blisters made of Al/PVDC and PVC/PVDC opacified with titanium dioxide.

Available pack sizes: 50 and 100 capsules.

6.6 Special precautions for disposal and other handling

Procedures for proper handling and disposal of anticancer drugs should be considered.

7 MARKETING AUTHORISATION HOLDER

medac
Gesellschaft für klinische Spezialpräparate mbH
Fehlandtstraße 3
20354 Hamburg
Germany

8 MARKETING AUTHORISATION NUMBER

PL 11587/0019

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09/10/2008

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09/10/2008