SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hydroxyurea medac 500 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule contains 500 mg hydroxycarbamide.

Excipient with known effect

This medicine contains 25 mg lactose monohydrate per capsule.
This medicine contains less than 1 mmol sodium (23 mg) per capsule.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule
White, gelatin capsules, filled with an off-white powder.

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 thrombocythaemia or polycythaemia vera with a high risk for thromboembolic complications.

4.2 Posology and method of administration

Posology

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 has dropped below 20 x 10^9/l. The dose is then adjusted individually to keep the white cell count at 5 – 10 x 10^9/l. The hydroxycarbamide dose should be reduced if white cell counts fall below 5 x 10^9/l, and increased if white cell counts > 10 x 10^9/l are observed.
If the white cell count falls below 2.5 x 10^9/l, or the platelet count below 100 x 10^9/l, therapy should be interrupted until the counts rise significantly towards normal.

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

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

In polycythaemia vera, hydroxycarbamide should be started at a dose of 15 – 20 mg/kg/day. The hydroxycarbamide dose should be adjusted individually to maintain the haematocrit below 45 % and platelet count below 400 x 10^9/l. In most patients this can be achieved with hydroxycarbamide given continuously at average daily doses of 500 to 1,000 mg.

If haematocrit and platelet count can be sufficiently controlled therapy may be continued indefinitely.

Paediatric population
The safety and efficacy of in children and adolescents under the age of 18 years have not yet been established.

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

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

Method of administration

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Therapy should be discontinued if hypersensitivity to Hydroxyurea medac occurs.
- Severe bone marrow depression, leukocytopenia (< 2.5 x 10^9 leukocytes/l), thrombocytopenia (< 100 x 10^9 platelets/l) or severe anaemia.

4.4 Special warnings and precautions for use

Hydroxycarbamide can cause bone marrow depression with leukopenia as the first and most commonly occurring sign. Thrombocytopenia and anaemia occur less frequently and are rare without preceding leukopenia. 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 the white cell count falls below 2.5 x 10^9/l, or the platelet count below 100 x 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 B_{12} or folic acid deficiency. Cases of haemolytic anaemia in patients treated with hydroxycarbamide for myeloproliferative diseases have been reported. Patients who develop severe anaemia should have laboratory tests evaluated for haemolysis. If diagnosis of haemolytic anaemia is established, hydroxycarbamide should be discontinued.

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

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

Skin cancer has been reported in patients receiving long-term hydroxycarbamide. Patients should be advised to protect skin from sun exposure. In addition, patients should conduct self-inspection of the skin during the treatment and after discontinuation of the therapy with hydroxycarbamide and be screened for secondary malignancies during routine follow-up visits.

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.

Cutaneous vasculitic toxicities including vasculitic ulcerations and gangrene have occurred in patients with myeloproliferative disorders during therapy with hydroxycarbamide. The risk of vasculitic toxicities is increased in patients who receive prior or concomitant interferon therapy. Due to potentially severe clinical outcomes for the cutaneous vasculitic ulcers reported in patients with myeloproliferative disease, hydroxycarbamide should be discontinued if cutaneous vasculitic ulcerations develop and treatment with alternative cytoreductive medicinal products should be initiated as indicated.

Interstitial lung disease including pulmonary fibrosis, lung infiltration, pneumonitis, and alveolitis/allergic alveolitis have been reported in patients treated for myeloproliferative neoplasm and may be associated with fatal outcome. Patient developing pyrexia, cough, dyspnoea or other respiratory symptoms should be closely monitored, investigated and treated. Promptly discontinue of hydroxyurea and treatment with corticosteroids appears to be associated with resolution of the pulmonary events (see section 4.8)

The possibility of an increase in serum uric acid, resulting in the development of gout or, at worst, uric acid nephropathy, should be borne in mind in patients treated with hydroxycarbamide, especially when used with other cytotoxic agents. It is therefore important to monitor uric acid levels regularly. Patients should be instructed to drink abundantly.

Interference with laboratory tests

A published study has shown increases of laboratory values of urea, uric acid (5 – 9 %) and lactic acid (6 – 11 %) measured by in vitro enzymatic assays, in the presence of hydroxycarbamide (0.1 – 1 mM), indicating an analytical interference. The clinical relevance of these results is unknown.
The combination of hydroxycarbamide and nucleoside reverse transcriptase inhibitors (NRTI) may enhance the risk of side effects of NRTI, see also section 4.5.

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.

Hydroxyurea 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).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Vaccinations

Concomitant use of Hydroxyurea medac with a live virus vaccine may potentiate the replication of the vaccine virus and/or may increase some of the adverse reactions of the vaccine virus because normal defence mechanisms may be suppressed by hydroxycarbamide. Vaccination with a live vaccine in a

patient taking Hydroxyurea medac may result in severe infection. The patient's antibody response to vaccines may be decreased. The use of live vaccines should be avoided during treatment and for at least six months after treatment has finished and individual specialist advice has been sought (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Hydroxycarbamide should be given with caution to patients with previous or concomitant radiotherapy or cytotoxic therapy. In these cases the patients have an increased risk to develop bone marrow depression, gastric irritation and mucositis (more severe, higher frequency). Furthermore, 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 fluoropyrimidines.

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. Patients treated with hydroxycarbamide in combination with didanosine, stavudine, and indinavir in study ACTG 5025 showed a median decline in CD4 cells of approximately 100/mm^3. Hydroxycarbamide may also enhance potential side effects of nucleoside reverse transcriptase inhibitors such as hepatotoxicity, pancreatitis and peripheral neuropathy (see section 4.8).

Vaccinations

There is an increased risk of severe or fatal infections with the concomitant use of live vaccines. Live vaccines are not recommended in immunosuppressed patients (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Hydroxycarbamide may be a potent mutagenic agent. Animal studies with hydroxycarbamide indicated an increased incidence of congenital defects (see section 5.3). Hydroxyurea medac should not be used during pregnancy unless the clinical condition of the woman requires treatment with hydroxycarbamide. Women of childbearing potential have to use effective contraception before the start of and during treatment with hydroxycarbamide.
If pregnancy still occurs during treatment the possibility of genetic consultation should be offered.
Hydroxycarbamide crosses the placenta.

Breast-feeding

Hydroxyurea medac is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from hydroxycarbamide, a decision should be made whether to discontinue nursing or to discontinue Hydroxyurea medac, taking into account the importance of the drug to the mother.

Fertility

Hydroxycarbamide may be genotoxic, therefore, genetic consultation is recommended if a patient intends to become pregnant after therapy with hydroxycarbamide.
Men under therapy are advised to use effective contraception during and for at least 3 months after therapy. They should be informed about the possibility of sperm conservation before the start of therapy. Fertility in males might be affected by treatment. Reversible oligo- and azoospermia are very commonly observed.

4.7 Effects on ability to drive and use machines

The ability to react may be impaired during treatment with Hydroxyurea 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 rarely require dose reduction or cessation of treatment.

The frequencies of adverse events are categorised using the following convention: 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).

Infections and Infestations	**Rare** Gangrene
Neoplasms Benign and Malignant(including cysts and polyps)	**Common** Skin Cancer (squamous cell cancer, basal cell carcinoma)
Blood and lymphatic system disorders	**Very common** Bone marrow depression, CD4 lymphocytes decreased, leukocytopenia, anaemia,thrombocytopenia **Common** Megaloblastosis **Not known** Haemolytic anaemia
Immune system disorders	**Rare** Hypersensitivity reaction
Metabolism and nutrition disorders	**Very common** Anorexia **Rare** Tumour lysis syndrome **Not known** Hyperkalaemia
Psychiatric disorders	**Common** Hallucinations, disorientation
Nervous system disorders	**Common** Peripheral neuropathy[1], somnolence, neurological disturbances including headache, dizziness and convulsion
Respiratory, thoracic and mediastinal disorders	**Common** Pulmonary fibrosis, pulmonary oedema, acute pulmonary reactions consisting of diffuse pulmonary infiltrates, fever and dyspnoea

	Not known Interstitial lung disease, pneumonitis, alveolitis, allergic alveolitis, cough

Gastrointestinal disorders	**Very common** Pancreatitis[1], nausea, vomiting, diarrhoea, constipation, stomatitis, mucositis, stomach discomfort, dyspepsia, abdominal pain, melaena
Hepatobiliary disorders	**Common** Hepatotoxicity[1], hepatic enzyme increased, cholestasis, hepatitis **Uncommon** Blood bilirubin increased
Skin and subcutaneous tissue disorders	**Very common** Skin ulcers (especially leg ulcers), cutaneous vasculitis, pruritus, violet papules, dermatomyositis-like skin changes, alopecia, maculopapular rash, skin exfoliation, skin atrophy, erythema (e.g. facial erythema, acral erythema), skin hyperpigmentation, nail disorder (e.g. nail pigmentation, nail atrophy) **Uncommon** Actinic keratosis **Very rare** Systemic and cutaneous lupus erythematosus **Not known** Dry skin
Renal and urinary disorders	**Very common** Dysuria, transient renal tubular dysfunction accompanied by increased blood uric acid, increased blood urea and increased blood creatinine **Very rare** Renal impairment
Reproductive system and breast disorders	**Very common** Azoospermia, oligospermia
General disorders and administration site conditions	**Very common** Drug fever, asthenia, chills, malaise
[1]Fatal and non-fatal pancreatitis and hepatotoxicity and severe peripheral neuropathy have been reported in HIV-infected patients who received hydroxycarbamide in combination with antiretroviral agents, in particular didanosine plus stavudine.	

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

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

Blood and lymphatic system disorders

During hydroxycarbamide therapy megaloblastosis may occur which does not respond to treatment with folic acid or B_{12}.
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.

Immune system disorders

Hypersensitive reactions: High fever (>39°C) requiring hospitalisation in some cases has been reported concurrently with gastrointestinal, pulmonary, musculoskeletal, hepatobiliary, dermatological or cardiovascular manifestations. Onset typically occurred within 6 weeks of initiation and resolved promptly after discontinuation of hydroxycarbamide. Upon readministration fever re-occurred within 24 hours.

Metabolism and nutrition disorders

Cases of hyponatraemia have been observed during post-marketing surveillance.

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, skin exfoliation, violet papules, alopecia, dermatomyositis-like skin changes, actinic keratosis, cutaneous ulcers (especially leg ulcers), cutaneous vasculitis, pruritus, hyperpigmentation of skin and nails, and dry skin have been observed partly after years of long-term daily maintenance therapy with hydroxycarbamide.

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

In addition, you may report by sending an e-mail message to: safety@tzamal-medical.co.il

4.9 Overdose

Acute mucocutaneous symptoms have been observed in patients receiving hydroxycarbamide doses 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

Mechanism of action

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

Absorption

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.

Distribution

Hydroxycarbamide crosses the blood-brain barrier.

Biotransformation

The metabolism of hydroxycarbamide has not been thoroughly studied in humans.

Elimination

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 %.

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.

Reproductive 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-month-study in mice in which the occurrence of lung tumours was studied did not show any carcinogenic potential of hydroxycarbamide.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content: disodium citrate, lactose monohydrate, calcium citrate, magnesium stearate.
Capsule shell: gelatin, titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and content of container

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

Available pack sizes: 100 capsules.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Tzamal Bio-Pharma Ltd., 20 Hamagshimim st., Petah-Tikva.

8. MANUFACTURER

medac, GmbH, Theaterstr. 6, 22880 Wedel Germany.

9. MARKETING AUTHORISATION NUMBER(S)

168-84-35373-00

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