SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Hydroxycarbamide 500 mg capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule, hard contains 500 mg hydroxycarbamide.

Excipient(s) with known effect:

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

White capsule body with yellow cap

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hydroxycarbamide is indicated for:
- 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 of thromboembolic complications.
- prevention of recurrent painful vaso-occlusive crises, recurrent acute chest syndrome and chronic severe anemia in patients with body weight of 33 kg and more with Sickle Cell Disease (see section 5.1).

4.2 Posology and method of administration

Treatment must only be administered by a doctor experienced in oncology or haematology. The doses are based on the patient's actual or ideal bodyweight, whichever is the less.

Posology

Sickle Cell Disease

The posology should be based on the patient's body weight (b.w.).

The starting dose of hydroxycarbamide is 15 mg/kg b.w. and the usual dose is between 15 and 30 mg/kg b.w./day.

As long as the patient responds to therapy either clinically or haematologically (e.g. increase of haemoglobin F (HbF), Mean Corpuscular Volume (MCV), neutrophil count) the dose of hydroxycarbamide should be maintained.

In case of non-response (re-occurrence of crises or no decrease in crisis rate) the daily dose may be increased by steps of 2.5 to 5 mg/kg b.w./day.

Under exceptional circumstances a maximum dose of 35 mg/kg b.w./day might be justified under close haematological monitoring.

In the event a patient does still not respond when treated with the maximum dose of hydroxycarbamide (35 mg/kg b.w./day) over three to six months, permanent discontinuation should be considered.

If blood counts are within the toxic range hydroxycarbamide should be temporarily discontinued until blood counts recover. Haematologic recovery usually occurs within two weeks. Treatment may then be reinstituted at a reduced dose. The dose of hydroxycarbamide may then be increased again under close haematological monitoring. A dose producing haematological toxicity should not be tried more than two times.

The toxic range may be characterised by the following results of blood tests:

Neutrophils	< 2,000/mm^3
Platelets	< 80,000/mm^3
Haemoglobin	< 4.5 g/dl
Reticulocytes	< 80,000/mm^3 if the haemoglobin concentration <9 g/dl

Long-term data on the continued use of hydroxycarbamide in patients with Sickle Cell Disease are available in children and adolescents, with a follow-up of 12 years in children and adolescents and over 13 years in adults. It is currently unknown how long patients should be treated with hydroxycarbamide. The duration of treatment is the responsibility of the treating physician and should be based on the clinical and haematological status of the individual patient.

Chronic myeloid leukaemia
For chronic myeloid leukaemia (CML), hydroxycarbamide is normally administered at an initial dose of 40 mg/kg daily, depending on the white blood cell count. The dose is reduced by 50 % (20 mg/kg daily) if the white blood cell count drops below 20 x 10^9/l. The dose is then adjusted individually in order to maintain a white blood cell count of 5 - 10 x 10^9/l. The dose of hydroxycarbamide should be reduced if the white blood cell count drops below 5 x 10^9/l and increased if a white blood cell count of >10 x 10^9/l is observed.

If the white blood cell count drops below 2.5 x 10^9/l, or the platelet count drops below 100 x 10^9/l, treatment should be discontinued until the counts significantly rise towards normal.

An adequate trial period to determine the antineoplastic effect of Hydroxycarbamide is six weeks. The treatment should be discontinued, if there is a significant progress of the disease. If there is a significant clinical response therapy may be continued indefinitely.

Essential Thrombocythaemia
In cases of essential thrombocythaemia, hydroxycarbamide is normally administered at an initial dose of 15 mg/kg/day and the dose is adjusted to maintain a platelet count of below 600 x 10^9/l, without lowering the white blood cell count below 4 x 10^9/l.

Polycythaemia vera
In cases of polycythaemia vera, hydroxycarbamide should be administered at an initial dose of 15-20 mg/kg/day. The hydroxycarbamide dose should be individually adjusted to keep the haematocrit value below 45% and the platelet count below 400 x 10^9 /l.

For most patients this can be achieved through continuous administration of hydroxycarbamide with an average daily dose of 500 to 1000 mg. If the haematocrit value and the platelet count can be sufficiently controlled, treatment should be continued indefinitely.

Paediatric population
Because of the rarity of these conditions in children, dose regimens have not been established.

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

Patients with impaired renal and/or hepatic function
There are no data available. Dose recommendations cannot be given for patients with impaired renal and/or hepatic function (see section 4.4).

Method of administration
The capsules must be swallowed whole and must not dissolve in the mouth.

4.3 Contraindications

Hydroxycarbamide is contraindicated in cases of severe bone marrow depression, leucocytopenia (< 2.5 x 10^9 leucocytes/l), thrombocytopenia (< 100 x 10^9 platelets/l) or severe anaemia.

Hydroxycarbamide is contraindicated for patients who are hypersensitive to hydroxycarbamide or any of the excipients listed in section 6.1. Treatment should be discontinued if hypersensitivity to Hydroxycarbamide occurs.

Administration of Hydroxycarbamide is contraindicated during pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Hydroxycarbamide can cause bone marrow depression with leucopenia as the first and most common symptom. Thrombocytopenia and anaemia are less common and rare without prior leucopenia.

A complete blood status test, including determination of the patient's haemoglobin count, total leucocyte (white blood cell) count and platelet count, should be performed regularly, even after the individual optimum dose has been established. The control interval should be individualised, but is normally once a week. If the white blood cell count drops below 2.5 x 10^9/l, or the platelet count drops below 100 x 10^9/l, treatment should be discontinued until the counts rise significantly towards normal (see section 4.2).

Severe anaemia must be corrected with whole blood replacement before initiating therapy with hydroxycarbamide.

In cases of anaemia before or during ongoing treatment, red blood cells can be transfused if necessary.

Also severe anaemia can usually be corrected without interrupting hydroxycarbamide therapy.

Self-limiting megaloblastic erythropoiesis is often observed early on in treatment with hydroxycarbamide. The morphological changes are similar to pernicious anaemia, but are not related to a vitamin B_{12} or folic acid deficiency.

The macrocytosis may mask the incidental development of folic acid deficiency; thus, prophylactic administration of folic acid may be warranted.

During treatment with Hydroxycarbamide, frequent monitoring of blood counts should be conducted as well as monitoring of hepatic and renal function.
There is limited experience of patients with impaired renal and/or hepatic function. 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.

During hydroxycarbamide therapy megaloblastosis may occur which does not respond to treatment with folic acid or vitamin B12. The bone marrow depression regresses after cessation of therapy.

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, lower leg ulcers, pruritus and hyperpigmentation of skin and nails have been observed in isolated cases after years of long-term daily maintenance therapy of hydroxycarbamide.

In patients who are receiving long-term treatment with hydroxycarbamide for myeloproliferative disorders, such as polycythaemia vera and thrombocythaemia, secondary leukaemia may develop. At present, the extent to which this is due to the underlying disorder or to treatment with hydroxycarbamide is not known.

Hydroxycarbamide may delay plasma iron clearance and reduce the rate of iron utilisation by erythrocytes but it does not appear to alter the red blood cell survival time.

Patients should be advised to protect skin from sun exposure, conduct self-inspection of the skin and be screened for secondary malignancies during routine follow-up visits as squamous cell carcinoma has been observed in isolated instances.

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

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 vasculitic ulcers reported in patients with myeloproliferative disease, hydroxycarbamide should be discontinued if these ulcerations develop and continued with an alternative medicinal agent.

Hydroxycarbamide should be administered with caution to patients who are being or have previously been treated with another antineoplastic drug or radiation therapy, as side effects can occur more frequently and are more serious than those reported for the use of hydroxycarbamide, other antineoplastic drugs or radiation therapy 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 elderly patients the dose may need to be adjusted due to a higher sensitivity to hydroxycarbamide (see section 4.2).

Fatal and non-fatal pancreatitis has occurred in HIV-infected patients during therapy with hydroxycarbamide and didanosine, with or without stavudine. Furthermore, cases of hepatotoxicity and hepatic failure resulting in death were reported in HIV-infected patients concurrently treated with hydroxycarbamide and other antiretroviral agents. Fatal hepatic events were reported most often in patients treated with the combination of hydroxycarbamide, didanosine and stavudine. This combination should be avoided.

Neuropathy, which was severe in some cases, has been reported in HIV-infected patients receiving hydroxycarbamide in combination with antiretroviral agents, including didanosine, with or without stavudine (see section 4.5).

Contraceptive measures
Suitable contraceptive measures are taken if a partner will be treated with hydroxycarbamide. Hydroxycarbamide may be genotoxic. Therefore, men under therapy are advised not to father a child and to use reliable contraceptive measures during and for at least 6 months after therapy. They should be informed about the possibility of sperm conservation before the start of therapy due to the potential for irreversible infertility. Women must not become pregnant during treatment.

Hydroxycarbamide must not be used in patients who are pregnant unless the benefits outweigh the potential risks (see section 4.6). The use of hydroxycarbamide is contraindicated within breast-feeding (see section 4.3).

Studies have shown that there is an analytical interference of hydroxycarbamide with the enzymes (urease, uricase, and lactic dehydrogenase), rendering falsely elevated results of these in patients treated with hydroxycarbamide.

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 treatment with other antineoplastic drugs or radiation therapy, as side effects can occur more often and be more serious than those reported for the use of hydroxycarbamide, other antineoplastic drugs or radiation therapy alone. These effects primarily include bone marrow depression, gastric irritation and mucositis.

An exacerbation of erythema caused by previous or concomitant radiation therapy may occur.

Almost all patients receiving an adequate course of combined hydroxycarbamide and irradiation therapy will demonstrate concurrent leukopenia. Platelet depression (< 100,000 cells/mm3) has occurred in the presence of marked leukopenia.

In vitro studies have demonstrated the ability of hydroxycarbamide to enhance the cytotoxicity in both cytarabine and fluoropyrimidines. It is unclear if this interaction clinically leads to cooperative toxicity or requires dose adjustment.

If hydroxycarbamide is combined with antiretroviral substances (nucleoside analogues) pancreatitis and liver damage, partly with lethal outcome, as well as peripheral neuropathy have been reported. A combination of Hydroxycarbamide with nucleoside analogues is not recommended.

4.6 Fertility, pregnancy and lactation
Hydroxycarbamide is genotoxic. Hydroxycarbamide has been demonstrated to be a potent teratogen in a wide variety of animal models. Embryo-foetal death, foetal malformation of the viscera and the skeleton, growth disorders and functional defects have been observed (see also section 5.3).

Pregnancy

Hydroxycarbamide must not be used during pregnancy. In case of a vital indication for the treatment of a pregnant patient specialised consultation should be offered due the potential harm to the foetus.

Women must not become pregnant during treatment. Adequate contraceptive measures are to be taken if a partner is treated with hydroxycarbamide (see section 4.4).

If pregnancy still occurs during treatment, the possibility of a genetic consultation should be offered due to the potential harm to the foetus.

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

Breastfeeding
As hydroxycarbamide is excreted into breast-milk, the use of hydroxycarbamide is contraindicated during breast-feeding due to the potential harm to the infant (see section 4.3). If treatment with hydroxycarbamide is necessary, breast-feeding must be discontinued.

4.7 Effects on ability to drive and use machines

The patient's ability to react may be impaired during treatment with Hydroxycarbamide. This should be considered when heightened attention is required, e.g. when driving and using machines.

4.8 Undesirable effects

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

The evaluation of undesirable effects is based on the following information on 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)
Not known* Reported post-marketing

Infections and infestations
Rare: Gangrene

Blood and lymphatic system disorders
Common: Bone marrow depression, leukopenia, megaloblastosis
Uncommon: Thrombocytopenia, anaemia
Not known: CD4 lymphocytes decreased, thrombocytes decreased

Psychiatric Disorders
Very rare*: Hallucination, disorientation

Nervous system disorders
Rare: neurological disturbances (e.g., headache, dizziness, convulsions)
Not known*: Peripheral neuropathy[1]

High doses may cause moderate drowsiness.

Respiratory, thoracic and mediastinal disorders
Rare: Acute pulmonary reactions consisting of diffuse pulmonary infiltrates and dyspnoea, fibrosis, allergic alveolitis

Gastrointestinal disorders
Common: Diarrhoea, constipation
Uncommon: Nausea, vomiting, anorexia, stomatitis
Severe gastric stress (nausea, vomiting, anorexia) caused by a combination of hydroxycarbamide and radiation therapy can usually be controlled by temporarily interrupting treatment with hydroxycarbamide.
Not known: Pancreatitis[1], mucositis, dyspepsia

Renal and urinary disorders
Uncommon: Transient impairment of renal tubular function accompanied by elevation in serum uric acid, urea and creatinine
Rare: Dysuria
Very rare: Renal impairment

Skin and subcutaneous tissue disorders
Uncommon: Maculopapular rash, facial erythema, acral erythema
Rare: Alopecia
Very rare: Dermatomyositis-like skin changes, hyperpigmentation or atrophy of skin and nails, leg ulcers, pruritus, actinic keratosis, skin cancer, violet papules, desquamation
Not known*: Skin exfoliation, skin tumour

Metabolism and nutrition disorders
Rare: Tumour lysis syndrome

General disorders and administration site conditions
Uncommon: Drug fever, shivering, malaise
Rare: Hypersensitivity reactions
Not known*: Asthenia

Hepatobiliary disorders
Uncommon: Increase in liver enzymes, bilirubin
Not known*: Hepatotoxicity[1]

[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. Patients treated with hydroxycarbamide in combination with didanosine, stavudine and indinavir showed a median decline in CD4 cells of approximately 100/mm^3 (see sections 4.4 and 4.5).

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 national reporting system listed in Appendix V.

4.9 Overdose

Acute mucocutaneous toxicity has been reported in patients receiving hydroxycarbamide at a dosage several times greater than that recommended. Soreness, violet erythema, oedema on palms and foot

soles followed by scaling of hands and feet, intense generalised hyperpigmentation of skin, and severe acute stomatitis were 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: L01X X05

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

In nearly all clinical studies conducted in Sickle Cell Disease, hydroxycarbamide reduced the frequency of vaso-occlusive episodes by 66% to 80%, in children and in adults. The same decrease was observed for the number of hospital admissions and the number of days of hospitalisation in the treated groups. The yearly frequency of acute chest syndrome was also reduced by 25 to 33% under hydroxycarbamide in several studies. Acute chest syndrome is a frequent life-threatening complication of Sickle Cell Disease and is characterised by chest pain or fever or dyspnoea with recent infiltrate on chest X-ray.
A sustained clinical benefit was demonstrated in patients remaining on hydroxycarbamide treatment for up to 8 years.
The specific mechanism of action of hydroxycarbamide is not fully understood. One of the mechanisms by which hydroxycarbamide acts is the elevation of foetal haemoglobin (HbF) concentrations in sickle cell patients. HbF interferes with the polymerisation of HbS and thus impedes the sickling of red blood cell. In all clinical studies, there was a significant increase in HbF from baseline after hydroxycarbamide use.
Recently, hydroxycarbamide has shown to be associated with the generation of nitric oxide suggesting that nitric oxide stimulates cyclic guanosine monophosphatase (cGMP) production, which then activates a protein kinase and increases the production of HbF. Other known pharmacological effects of hydroxycarbamide which may contribute to its beneficial effects in Sickle Cell Disease include decrease of neutrophils, increase of the water content of erythrocytes, increase of the deformability of sickled cells, and altered adhesion of red blood cells to the endothelium.
In addition hydroxycarbamide causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor, without interfering with the synthesis of ribonucleic acid or protein.
Beside the inconstant correlation between reduction of crisis rate and the increase in HbF, the cytoreductive effect of hydroxycarbamide, particularly the drop of neutrophils, was the factor with the strongest correlation to a reduced crisis rate.

5.2 Pharmacokinetic properties

The pharmacokinetic information is limited. Hydroxycarbamide is well absorbed and oral bioavailability is complete. Following oral administration, peak plasma concentrations are achieved within approx. 0.5 to 2 hours. Hydroxycarbamide is partially eliminated via the kidneys. 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

In preclinical toxicity studies the most common effects noted included bone marrow depression, lymphoid atrophy and degenerative changes in the epithelium of the small and large intestines. Cardiovascular effects and haematological changes were observed in some species. Also, in rats testicular atrophy with decreased spermatogenesis occurred, while in dogs reversible spermatogenic arrest was noted.

Hydroxycarbamide is unequivocally genotoxic in a wide range of test systems.
Conventional long-term studies to evaluate the carcinogenic potential of hydroxycarbamide have not been performed. However, hydroxycarbamide is presumed to be a transspecies carcinogen.

Hydroxycarbamide crosses the placenta barrier and has been demonstrated to be a potent teratogen and embryotoxic in a wide variety of animal models at or below the human therapeutic dose. Teratogenicity was characterised by partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, missing lumbar vertebrae. Embryotoxicity was characterized by decreased foetal viability, reduced live litter sizes, and developmental delays.

Hydroxycarbamide administered to male rats at 60 mg/kg b.w./day (about double the recommended usual maximum dose in humans) produced testicular atrophy, decreased spermatogenesis and significantly reduced their ability to impregnate females.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Citric acid anhydrous
Disodium hydrogen phosphate anhydrous
Magnesium stearate

Capsule shell:
Gelatine
Titanium dioxide (E171),
Ferric oxide, yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

PVC/PVDC/aluminium-blister

Packs containing 20, 25, 50, 100 and 120 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Name: Sandoz GmbH,Kundl
Address: Biochemiestrasse 106250.
Country: Austria.

8 MARKETING AUTHORISATION NUMBER(S)

To be confirmed

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be confirmed

10 DATE OF REVISION OF THE TEXT

To be confirmed