Public Assessment Report

Decentralised Procedure

Hydroxyurea 500 mg capsules, hard

Hydroxycarbamide 500 mg capsules, hard

PL 10880/0128-9

UK/H/1731/01/DC
UK/H/1732/01/DC

Hexal AG
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Hexal AG Marketing Authorisations (licences) for the medicinal products Hydroxyurea 500 mg capsules, hard and Hydroxycarbamide 500 mg capsules, hard (Product Licence numbers: PL 10880/0128-9). These medicines are available on prescription only.

Hydroxyurea 500 mg capsules, hard and Hydroxycarbamide 500 mg capsules, hard are used for the treatment of patients:

- With an aggressive white blood cell disease starting at the bone marrow (chronic myeloid leukemia) in a chronic or accelerated phase of the disease
- With a surplus of blood platelets (essential thrombocythaemia)
- With a surplus of certain blood cells (polycythaemia vera) associated with a high risk of vascular occlusion (thrombosis)

These medicines are also used to treat tumour diseases.

The data submitted in support of these applications for Hydroxyurea 500 mg capsules, hard and Hydroxycarbamide 500 mg capsules, hard raised no clinically significant safety concerns and it was therefore judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
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Module 1  

Information about decentralised procedure

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<th>Name of the product in the Reference Member State</th>
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| Type of application (Eudratrack details)       | Level 1 One complex, one abridged  
Level 2 Initial  
Level 3 10.3  
Level 4 Chemical substance  
Level 5 Prescription only |
| Name of the active substance (INN)             | Hydroxycarbamide |
| Pharmacotherapeutic classification (ATC code)  | Other antineoplastic agents (L01XX05) |
| Pharmaceutical form and strength              | Hard capsule, 500 mg |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1731/01/DC  
UK/H/1732/01/DC |
| Reference Member State                        | United Kingdom |
| Member States concerned                       | Germany |
| Date of start of the procedure                | 17 July 2008 |
| End date of decentralised procedure           | 6 August 2009 |
| Marketing Authorisation Number                | PL 10880/0128-9 |
| Name and address of the authorisation holder  | Hexal AG, Industriestrasse 25, 83607 Holzkirchen, Germany |
Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Hydroxyurea 500 mg capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One capsule contains 500 mg hydroxyurea.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsule, hard (capsule)

White capsule body with yellow cap

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Hydroxyurea is indicated for the treatment of patients with:
• chronic myeloid leukaemia (CML) in the chronic or accelerated phase of the disease.
• essential thrombocythaemia or polycythaemia vera with a high risk of thromboembolic complications.

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.

Chronic myeloid leukaemia
For chronic myeloid leukaemia (CML), hydroxyurea 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 × 10^9/l. The dose is then adjusted individually in order to maintain a white blood cell count of 5 - 10 × 10^9/l. The dose of hydroxyurea should be reduced if the white blood cell count drops below 5 × 10^9/l and increased if a white blood cell count of >10 × 10^9/l is observed.

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

An adequate trial period to determine the antineoplastic effect of hydroxyurea 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 10⁹/l, without lowering the white blood cell count below 4 x 10⁹/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 10⁹/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.

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

Dosages for elderly patients: Elderly patients can be more sensitive to the effects of hydroxycarbamide, and may require a lower dosage regimen.

Dosages in cases of 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 4.4).

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

4.3 Contraindications
Hydroxyurea is contraindicated in cases of severe bone marrow depression, leucocytopenia (< 2.5 x 10⁹ leucocytes/l), thrombocytopenia (< 100 x 10⁹ platelets/l) or severe anaemia.

Hydroxyurea is contraindicated for patients who are hypersensitive to hydroxycarbamide or any of the excipients. Treatment should be discontinued if hypersensitivity to hydroxyurea occurs.

Administration of hydroxyurea is contraindicated during lactation (see 4.6).

Concomitant use with yellow fever vaccine (see section 4.5).

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 10⁹/l, or the platelet count drops below 100 x 10⁹/l, treatment should be discontinued until the counts rise significantly towards normal (see 4.2).

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

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 B₁₂ or folic acid deficiency.

During treatment with hydroxyurea, 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.

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.

It is recommended that patients check for dermatological changes during treatment with hydroxycarbamide, as squamous cell carcinoma has been reported 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.

Cutaneous vasculitis 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. The digital distribution of these vasculitic ulcerations and progressive clinical behaviour of peripheral vasculitic insufficiency leading to digital infarct or gangrene were distinctly different than the typical skin ulcers generally described with hydroxycarbamide. 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 alternative cytoreductive agents should be initiated as indicated.

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.
If hydroxycarbamide is combined with nucleoside reverse transcriptase inhibitors (NRTI), the risk of adverse reactions due to NRTI can be increased (see also 4.5).

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 and maintain a high fluid intake.

Concomitant use with live attenuated vaccines (excepted yellow fever vaccines see Contraindications) (see section 4.5).

Contraceptive measures
Hydroxycarbamide may be genotoxic. Therefore, men under therapy are advised not to father a child and to use safe contraceptive measures during and for at least 1 year after therapy. They should be informed about the possibility of sperm conservation before the start of therapy.

Women of childbearing potential should use an effective contraceptive measure during treatment (See 4.6 Pregnancy and lactation) 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.

*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 hydroxyurea with nucleoside analogues is not recommended.

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 alternative cytoreductive agents should be initiated as indicated.

Concomitant use contraindicated (see section 4.3)
- Yellow fever vaccine: risk of generalised vaccinale disease mortal.
Concomitant use not recommended (see section 4.4)
- Live attenuated vaccines (except yellow fever): risk of systemic, possible fatal disease.
  This risk is increased in subjects who are already immunosuppressed by their underlying disease.
  Use an inactivated vaccine where this exists (poliomyelitis)

Concomitant use to take into consideration
Ciclosporine, Tacrolimus: Excessive immunosuppression with risk of lymphoproliferation.

4.6 Pregnancy and lactation

Fertility
Reversible azoospermia or oligospermia have been rarely observed in men. Male patients should be informed about the possibility of sperm conservation before the start of therapy.

Hydroxycarbamide may be genotoxic. Therefore, if a patient intends to become pregnant after a therapy with hydroxycarbamide a specialized consultation is recommended. Men under therapy are advised to use safe contraceptive measures during and at least 1 year after therapy.

Pregnancy
Animal experiments with hydroxycarbamide indicated teratogenic effects (see 5.3). In the human, according to a retrospective analysis of a cohort of 123 adult patients treated with hydroxycarbamide, twenty-three pregnancies have been reported from 15 women treated with hydroxycarbamide and partners of 3 men treated with hydroxycarbamide. Most (61%) had a normal outcome with regard to term and normal birth. In the other cases with known evolution, pregnancy had been interrupted either voluntarily or upon medical advice. Thus the data on a limited number of exposed pregnancies indicate no adverse effects on pregnancy or on the health of the foetus/newborn.

Nevertheless, based on the limited amount of information, hydroxycarbamide should not be used unless clearly necessary during pregnancy. The risk/benefit evaluation should be made on individual basis taking into account the other therapeutic options.

Women of child-bearing potential should take adequate birth-control measures during treatment with hydroxycarbamide.

If pregnancy still occurs during treatment, the possibility of specialized consultation should be used and a careful follow-up with adequate clinical and ultrasonographic examinations should be considered.

Lactation
As hydroxycarbamide is excreted into breast-milk, breast-feeding must be discontinued while taking the drug.

4.7 Effects on ability to drive and use machines
The patient’s ability to react may be impaired during treatment with hydroxyurea. 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 ($\geq 1/10$)
Common ($\geq 1/100$ to $<1/10$)
Uncommon ($\geq 1/1,000$ to $< 1/100$)
Rare ($\geq 1/10,000$ to $< 1/1,000$)
Very rare ($< 1/10,000$, not known, cannot be estimated from the available data)

**Blood and lymphatic system disorders**

Common: Bone marrow depression, leucopenia, megaloblastosis
Uncommon: Thrombocytopenia, anaemia

During treatment with hydroxycarbamide, megaloblastosis can occur that does not respond to treatment with folic acid or B12.

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

In patients 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 can reduce plasma clearance and utilisation of iron in red blood cells. However, it does not appear to alter the red blood cell survival time.

**Nervous system disorders**

Rare: Rare neurological disturbances including headache, dizziness, disorientation, hallucinations, convulsions

High doses may cause moderate drowsiness.

**Respiratory, thoracic and mediastinal disorders**

Rare: Acute pulmonary reactions consisting of diffuse pulmonary infiltrates, fever and dyspnoea, 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.
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, cutaneous ulcers (especially leg ulcers), pruritus, actinic keratosis, skin cancer (squamous cell cancer, basal cell carcinoma), violet papules, desquamation

Hydroxycarbamide may aggravate inflammation of the mucous membranes after exposure to radiation. 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 carcinoma, 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 treatment with hydroxycarbamide.

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.

Metabolism and nutrition disorders
Rare: Tumour lysis syndrome

General disorders
Uncommon: Drug fever, shivering, malaise
Rare: Hypersensitivity reactions

Hepatobiliary disorders
Uncommon: Increase in liver enzymes, bilirubin

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.

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  
3 years  

6.4 Special precautions for storage  
Do not store above 30 °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  
Hexal AG,  
Industriestrasse 25,  
83607 Holzkirchen,  
Germany.  

8 MARKETING AUTHORISATION NUMBER(S)  
PL 10880/0128  

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION  
02/09/2009  

10 DATE OF REVISION OF THE TEXT
1 NAME OF THE MEDICINAL PRODUCT
Hydroxycarbamide 500 mg capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One capsule contains 500 mg hydroxycarbamide.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsule, hard (capsule)
White capsule body with yellow cap

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Hydroxycarbamide is indicated for the treatment of patients with:
• chronic myeloid leukaemia (CML) in the chronic or accelerated phase of the disease.
• essential thrombocythaemia or polycythaemia vera with a high risk of thromboembolic complications.

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.

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.

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

Dosages for elderly patients: Elderly patients can be more sensitive to the effects of hydroxycarbamide, and may require a lower dosage regimen.

Dosages in cases of 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 4.4).

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. Treatment should be discontinued if hypersensitivity to hydroxycarbamide occurs.

Administration of hydroxycarbamide is contraindicated during lactation (see 4.6).

Concomitant use with yellow fever vaccine (see section 4.5).

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 4.2).

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

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 B₁₂ or folic acid deficiency.

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.

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.

It is recommended that patients check for dermatological changes during treatment with hydroxy carbamide, as squamous cell carcinoma has been reported 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.

Cutaneous vasculitis 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. The digital distribution of these vasculitic ulcerations and progressive clinical behaviour of peripheral vasculitic insufficiency leading to digital infarct or gangrene were distinctly different than the typical skin ulcers generally described with hydroxycarbamide. 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 alternative cytoreductive agents should be initiated as indicated.

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.
If hydroxycarbamide is combined with nucleoside reverse transcriptase inhibitors (NRTI), the risk of adverse reactions due to NRTI can be increased (see also 4.5).

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 and maintain a high fluid intake.

Concomitant use with live attenuated vaccines (excepted yellow fever vaccines see Contraindications) (see section 4.5).

Contraceptive measures

Hydroxycarbamide may be genotoxic. Therefore, men under therapy are advised not to father a child and to use safe contraceptive measures during and for at least 1 year after therapy. They should be informed about the possibility of sperm conservation before the start of therapy.

Women of childbearing potential should use an effective contraceptive measure during treatment (See 4.6 Pregnancy and lactation) 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.

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.

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 alternative cytoreductive agents should be initiated as indicated.

Concomitant use contraindicated (see section 4.3)
- Yellow fever vaccine: risk of generalised vaccinale disease mortal.
Concomitant use not recommended (see section 4.4)
- Live attenuated vaccines (except yellow fever): risk of systemic, possible fatal disease. This risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where this exists (poliomyelitis)

Concomitant use to take into consideration
Ciclosporine, Tacrolimus: Excessive immunosuppression with risk of lymphoproliferation.

4.6 Pregnancy and lactation

Fertility
Reversible azoo or oligospermia have been rarely observed in men. Male patients should be informed about the possibility of sperm conservation before the start of therapy.

Hydroxycarbamide may be genotoxic. Therefore, if a patient intends to become pregnant after a therapy with hydroxycarbamide a specialized consultation is recommended. Men under therapy are advised to use safe contraceptive measures during and at least 1 year after therapy.

Pregnancy
Animal experiments with hydroxycarbamide indicated teratogenic effects (see 5.3). In the human, according to a retrospective analysis of a cohort of 123 adult patients treated with hydroxycarbamide, twenty-three pregnancies have been reported from 15 women treated with hydroxycarbamide and partners of 3 men treated with hydroxycarbamide. Most (61%) had a normal outcome with regard to term and normal birth. In the other cases with known evolution, pregnancy had been interrupted either voluntarily or upon medical advice. Thus the data on a limited number of exposed pregnancies indicate no adverse effects on pregnancy or on the health of the foetus/newborn. Nevertheless, based on the limited amount of information, hydroxycarbamide should not be used unless clearly necessary during pregnancy. The risk/benefit evaluation should be made on individual basis taking into account the other therapeutic options.

Women of child-bearing potential should take adequate birth-control measures during treatment with hydroxycarbamide.

If pregnancy still occurs during treatment, the possibility of specialized consultation should be used and a careful follow-up with adequate clinical and ultrasonographic examinations should be considered.

Lactation
As hydroxycarbamide is excreted into breast-milk, breast-feeding must be discontinued while taking the drug.

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)

Blood and lymphatic system disorders

Common: Bone marrow depression, leucopenia, megaloblastosis
Uncommon: Thrombocytopenia, anaemia

During treatment with hydroxycarbamide, megaloblastosis can occur that does not respond to treatment with folic acid or B12.

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

In patients 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 can reduce plasma clearance and utilisation of iron in red blood cells. However, it does not appear to alter the red blood cell survival time.

Nervous system disorders

Rare: Rare neurological disturbances including headache, dizziness, disorientation, hallucinations, convulsions

High doses may cause moderate drowsiness.

Respiratory, thoracic and mediastinal disorders

Rare: Acute pulmonary reactions consisting of diffuse pulmonary infiltrates, fever and dyspnoea, 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.

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, cutaneous ulcers (especially leg ulcers), pruritus, actinic keratosis, skin cancer (squamous cell cancer, basal cell carcinoma), violet papules, desquamation

Hydroxycarbamide may aggravate inflammation of the mucous membranes after exposure to radiation. 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 carcinoma, 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 treatment with hydroxycarbamide.

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.

**Metabolism and nutrition disorders**
Rare: Tumour lysis syndrome

**General disorders**
Uncommon: Drug fever, shivering, malaise
Rare: Hypersensitivity reactions

**Hepatobiliary disorders**
Uncommon: Increase in liver enzymes, bilirubin

### 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
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.

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
3 years

6.4 Special precautions for storage
Do not store above 30 °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
Hexal AG,
Industriestrasse 25,
83607 Holzkirchen,
Germany.

8 MARKETING AUTHORISATION NUMBER(S)
PL 10880/0129

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/09/2009

10 DATE OF REVISION OF THE TEXT
02/09/2009
Module 3

Product Information Leaflet
PACKAGE LEAFLET: INFORMATION FOR THE USER

Hydroxyurea 500 mg capsules, hard
Hydroxycarbamide

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Hydroxyurea is and what it is used for
2. Before you take Hydroxyurea
3. How to take Hydroxyurea
4. Possible side effects
5. How to store Hydroxyurea
6. Further information

1. WHAT HYDROXYUREA IS AND WHAT IT IS USED FOR

Hydroxyurea is used for the treatment of patients:

- with an aggressive white blood cell disease starting at the bone marrow (chronic myeloid leukaemia) in a chronic or accelerated phase of the disease
- with a surplus of blood platelets (essential thrombocythaemia)
- with a surplus of certain blood cells (polycythaemia vera) associated with a high risk of vascular occlusion (thrombosis)

Hydroxyurea is a medicine to treat tumour diseases.

2. BEFORE YOU TAKE HYDROXYUREA

Do not take Hydroxyurea

- if you are hypersensitive (allergic) to hydroxycarbamide or any of the other ingredients of Hydroxyurea. Therapy should be discontinued if hypersensitivity to Hydroxyurea occurs.
- if the function of the bone marrow is considerably reduced, such as
  - reduced number of white blood cells (less than 2.5 x 10^9 leukocytes/l)
  - deficiency of blood platelets (less than 100 x 10^9 thrombocytes/l)
  - severe anaemia.
- if you are breastfeeding.
- if you are concomitantly treated with yellow fever vaccine.

Take special care with Hydroxyurea

- if you suffer from impaired liver and/or kidney function.
  Only little experience is available regarding this. Special caution is therefore required during treatment with Hydroxyurea, particularly at the beginning of therapy. The blood values as well as liver and kidney function are to be monitored by a doctor during treatment with Hydroxyurea.
• if you suffer from anaemia or if it occurs.
  Red blood cells can be replaced, if necessary. Their formation from abnormally large precursors is often
to be observed only when treatment is started and it resembles the anaemia due to vitamin B₁₂
deficiency. However, this is not attributable to too little vitamin B₁₂ or folic acid.
• if you notice skin changes.
  These require further observation, as certain types of skin cancer can occur in isolated cases.
• if you notice painful ulcers on the lower legs.
  These are usually difficult to treat and can require interruption of treatment. Discontinuation of
hydroxyurea usually enables the ulcers to slowly heal after some weeks.
• if you receive long-term treatment in cases of excessive formation of blood cells such as
  polycythaemia vera and thrombocytocaemia.
  Another white blood cell cancer can develop. The extent to which this relates to the underlying disease
or treatment with hydroxyurea is unknown to date.
• if you experience impaired blood formation in the bone marrow.
  A considerable reduction in white blood cells is the first and most common sign. A considerable
  reduction in blood platelets and anaemia occur less frequently and rarely without preceding leukopenia.
• if you are given other anticancer drugs or radiotherapy treatment.
• if you are concomitantly treated with live attenuated vaccines (expected yellow fever vaccines see “Do
  not take Hydroxyurea”).

The risk of an inflammation of the blood vessels of the skin, including blood vessel ulcerations and
deterioration, is increased. Severe skin blood vessel ulcers have been reported in patients with
myeloproliferative disease. Hydroxyurea should therefore be discontinued if such ulcerations develop.
In addition, alternative medicines should be used if necessary.

The following parameters should be observed in the blood count during treatment with Hydroxyurea, even
after the optimal dose has been established:
  - content of red blood pigment
  - differentiation of white blood cells
  - number of blood platelets
The control interval must be individualised, but is normally once a week.

It is important to monitor uric acid levels regularly. You should always drink sufficient liquid during
treatment with Hydroxyurea.

Appropriate contraceptive measures are to be taken if one partner is treated with Hydroxyurea.

Men undergoing treatment with Hydroxyurea should not father a child during treatment and up to 1 year
afterwards. Seek advice on sperm conservation before beginning therapy as hydroxyurea should therefore be discontinued if such ulcerations develop.
In addition, alternative medicines should be used if necessary.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including
medicines obtained without a prescription.

• Other medicines against tumour diseases or radiotherapy
  Side effects can be more intense and more common than after administration of Hydroxyurea alone.
  These side effects include the suppression of blood formation in the bone marrow, stomach and bowel
  complaints and inflammation in the mouth cavity. Enhancement of inflammatory reddening of the skin
caused by previous or concomitant radiotherapy is possible.

Laboratory tests have shown that hydroxyurea enhances the toxicity of certain medicines against
tumour diseases, e.g. of
- fluoropyrimidines (e.g. fluorouracil) and
cytarabine

It is not clear whether these interactions are additive in their toxicity during use in humans and whether the dose must be adjusted.

- **Medicines against viral diseases** (nucleoside analogues, medicines for the treatment of a HIV infection)
  Conditions such as, inflammation of the pancreas, liver damage, sometimes lethal, and severe peripheral nervous conditions have all been reported. Combination with medicines to treat viral diseases cannot be recommended.

- **Prior or concomitant interferon therapy**
The risk of an inflammation of the blood vessels of the skin, including blood vessel ulcerations and deterioration, is increased in patients who receive prior or concomitant interferon therapy.

- **Yellow fever vaccine**
  There is a risk of generalised vaccinale disease, which can be fatal, therefore concomitant use is contraindicated (see section “Do not take Hydroxyurea”).

- **Live attenuated vaccines (except yellow fever)**
  There is a risk of systemic, possible fatal disease. This risk is increased if you are already immunosuppressed by your underlying disease. An inactivated vaccine should be used where this exists (poliomyelitis).

- **Ciclosporine, Tacrolimus**
  Concomitant use is to be taken into consideration because of an excessive immunosuppression with risk of lymphoproliferation.

**Pregnancy and breast-feeding**
Hydroxyurea may impair the development of your unborn child. You must therefore **not use** Hydroxyurea during pregnancy. Women of childbearing potential should take contraceptive measures before starting and during treatment with Hydroxyurea. If a patient intends to become pregnant after a therapy with hydroxyurea a specialized consultation is recommended.

If a doctor deems the use absolutely necessary during pregnancy, he/she should inform you about the possible risk for your child. If you become pregnant during treatment with Hydroxyurea, inform your doctor without delay, and make use of the possibility of specialized counselling.

You must **not use** Hydroxyurea while **breast-feeding**. If treatment is recommended by a doctor, you must stop breast-feeding.

**Driving and using machines**
Reactivity can be impaired during treatment with Hydroxyurea. In this case, do not drive a car, and do not operate hazardous machines.

3. **HOW TO TAKE HYDROXYUREA**

Treatment should be conducted only by experienced specialists.

Always take Hydroxyurea exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
The capsules should be swallowed as a whole and must not disintegrate within the mouth.

The dosages stated in the following are based on the patient’s actual or ideal weight, whichever is the less. Your doctor determines the number of capsules and the duration of treatment.

- **Aggressive white blood cell disease**
  (chronic myeloid leukaemia)
  Depending on the number of white blood cells, the initial dose is usually 40 mg hydroxycarbamide per kg bodyweight daily.

  Your doctor will reduce the dose to 20 mg per kg daily if the number of white blood cells falls below 20 x 10⁹/l. The dose is then adjusted on an individual basis in order to keep the number of white blood cells at 5-10 x 10⁹/l.

  If the white blood cells are less than 5 x 10⁹ per litre, the dosage should be reduced, and it should be increased if they are above 10 x 10⁹/l.

  If the white blood cells fall below 2.5 x 10⁹/l or the blood platelets below 100 x 10⁹/l, your doctor should interrupt therapy until the values normalize.

  An appropriate test time to determine the efficacy of Hydroxyurea is 6 weeks. Your doctor will discontinue therapy if the disease is progressing. If there is a response, therapy can be continued indefinitely.

- **Surplus of blood platelets**
  (essential thrombocythaemia)
  For this disease, the initial dose is usually 15 mg hydroxycarbamide per kg bodyweight daily. This should keep the number of blood platelets below 600 x 10⁹/l without reducing the number of white blood cells below 4 x 10⁹/l.

- **Surplus of certain blood cells**
  (polycythaemia vera)
  In this case, treatment should be started with a dosage of 15-20 mg hydroxycarbamide per kg bodyweight daily. The dose is to be adjusted on an individual basis in order to keep the ratio between red blood cells and blood plasma below 45% and the number of blood platelets below 400 x 10⁹/l.

  This can be achieved in most patients with a continuous administered dose of 1 to 2 hard capsules daily on average. If the ratio of red blood cells to blood plasma and the number of blood platelets remain stable, treatment should be continued indefinitely.

**Children**
As these diseases only rarely occur in children, no dosage schemes can be established at present.

**Elderly patients**
Elderly patients can have a more pronounced reaction to the effect of hydroxycarbamide and possibly require a lower dosage.

**Patients with impaired liver or kidney function**
Recommendations cannot be given for these patients as no data exists to date.

**If you take more Hydroxyurea than you should**
If the dosage taken was several times more than the recommended dosage, the following acute skin and/or mucosal changes may be signs of an overdose:

- sorenness
- violet skin rash
- swellings on palms and soles, followed by scaling of hands and feet
- sore feet
- excessive generalised pigmentation
- severe acute inflammation of oral mucosa

Immediately inform a doctor if an overdose occurs. Immediate treatment consists of stomach irrigation, followed by supportive measures and monitoring of the blood formation.

**If you forget to take Hydroxyurea**

Do not take a double dose if you have forgotten the previous intake. Go back to your original directions for your next dose. If you are unsure contact your doctor.

**If you stop taking Hydroxyurea**

Your disease might worsen if therapy is discontinued. Therapy with hydroxycarbamide may be terminated or interrupted only on the orders of the attending doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, Hydroxyurea can cause side effects, although not everybody gets them.

The strength of suppressed blood formation of the bone marrow determines the dosage or whether therapy must be interrupted in rare cases.

Side effects affecting the stomach or the intestine only rarely require dose reduction or cessation of treatment.

Side effects can occur with the following frequencies:

**Common.** occurs in 1 to 10 per 100 users
- suppressed blood formation in the bone marrow
- reduced number of white blood cells (you are more prone to catch infections)
- changes in the red blood count (intraglobulistaosis)
  Possible changes in the red blood count which do not respond to treatment with folic acid or vitamin B12 subside when therapy is discontinued.
- diarrhoea
- constipation

**Uncommon.** occurs in 1 to 10 per 1,000 users
- reduced number of blood platelets (you are more prone to bruising, bleeding)
- anaemia (feeling tired)
- nausea, vomiting, loss of appetite
- inflammation of oral mucosa
- drug fever
- chills
- feeling unwell
- flaky, knotty inflamed skin, skin rash
- inflammatory reddening affecting face, arms and legs
- elevated liver enzymes
- elevated bilirubin
transient disorders of tubular kidney function with increase in uric acid, urea and creatinine in blood

Rare, occurs in 1 to 10 per 10,000 users
- allergic reactions
- hair loss
- rare disorders of nerve function including headache, dizziness, disorientation, hallucinations and fits
- development of an acute lung reaction with accumulation of liquid in the lung, fever, shortness of breath
- allergic reactions in the lungs
- difficult or painful urination (dysuria)
- Potentially life-threatening metabolic complications that can occur after treatment of cancer leading to increased uric acid level in the blood, which may result in gout or acute renal failure (tumour lysis syndrome)

Very rare, occurs in fewer than 1 per 10,000 users
In isolated cases after maintenance therapy for several years with daily intake of hydroxycarbamide:
- variable skin changes such as reddening and swelling
- excessive pigmentation on skin and nails
- thinning of skin and nails
- ulcers of the lower legs
- itching
- small, rough reddish patches on the skin, which may become skin cancer if not removed (actinic keratosis)
- skin cancer
- violet nodules
- skin scaling
- impaired kidney function
- cutaneous ulcers (especially ulcers of the lower legs)

Another white blood cell cancer can develop in patients with excessive formation of blood cells and continuously treated with hydroxycarbamide. It is not known whether this is attributable to the underlying disease or to the treatment with hydroxycarbamide.

Severe stomach complaints such as nausea, vomiting and loss of appetite, which can occur in combination with radiotherapy, can be controlled if administration of hydroxycarbamide is transiently stopped.

Hydroxycarbamide can enhance mucosal inflammations caused by radiation. Inflammatory reddening and excessive pigmentation can occur in pretreated tissue.

Inflammation of the blood vessels of the skin, including blood vessel ulcerations and deterioration, have occurred in patients with myeloproliferative disorders during therapy with hydroxycarbamide. This was reported most often in patients with a history of, or currently receiving, interferon therapy (see "Taking other medicines").

High doses can cause moderate sleepiness.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE HYDROXYUREA

Keep out of the reach and sight of children.

Do not store above 30 °C.
Do not use the medicine after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.

The medicine should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

**What Hydroxyurea contains**

- The *active substance* is **hydroxycarbamide**
  1 capsule, hard contains 500 mg hydroxycarbamide.

- The other ingredients are:
  **Capsule contents**
  Citric acid anhydrous, disodium hydrogen phosphate anhydrous, magnesium stearate

  **Capsule shell**
  Gelatin, ferric oxide, yellow, titanium dioxide

**What Hydroxyurea looks like and contents of the pack**

Capsule, hard with white lower part and yellow upper part

Hydroxyurea 500 mg capsules, hard are available in PVC/PVDC/aluminium-blister packs of 20, 25, 50, 100 and 120 capsules.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

**Marketing Authorisation**

Hexal AG,
Industriestrasse 25,
83607 Holzkirchen,
Germany.

**Manufacturer**

AMAREG GmbH,
Donaustraßer Str. 378,
93055 Regensburg,
Germany
or
Salutas Pharma GmbH,
Otto-von-Guericke-Allee 1,
39179 Barleben,
Germany
This leaflet was last approved in 08/2009 (to be amended after approval)
PACKAGE LEAFLET: INFORMATION FOR THE USER

Hydroxycarbamide 500 mg capsules, hard

Hydroxycarbamide

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if the symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Hydroxycarbamide is and what it is used for
2. Before you take Hydroxycarbamide
3. How to take Hydroxycarbamide
4. Possible side effects
5. How to store Hydroxycarbamide
6. Further information

1. WHAT HYDROXYCARBAMIDE IS AND WHAT IT IS USED FOR

Hydroxycarbamide is used for the treatment of patients:

- with an aggressive white blood cell disease starting at the bone marrow (chronic myeloid leukaemia) in a chronic or accelerated phase of the disease
- with a surplus of blood platelets (essential thrombocythaemia)
- with a surplus of certain blood cells (polycythaemia vera) associated with a high risk of vascular occlusion (thrombosis)

Hydroxycarbamide is a medicine to treat tumour diseases.

2. BEFORE YOU TAKE HYDROXYCARBAMIDE

Do not take Hydroxycarbamide

- if you are hypersensitive (allergy) to hydroxycarbamide or any of the other ingredients of Hydroxycarbamide. Therapy should be discontinued if hypersensitivity to Hydroxycarbamide occurs.
- if the function of the bone marrow is considerably reduced, such as
  - reduced number of white blood cells (less than $2.5 \times 10^9$ leukocytes/l)
  - deficiency of blood platelets (less than $100 \times 10^9$ thrombocytes/l)
  - severe anaemia.
- if you are breastfeeding.
- if you are concomitantly treated with yellow fever vaccine.

Take special care with Hydroxycarbamide

- if you suffer from impaired liver and/or kidney function.
  Only little experience is available regarding this. Special caution is therefore required during treatment with Hydroxycarbamide, particularly at the beginning of therapy. The blood values as well as liver and kidney function are to be monitored by a doctor during treatment with Hydroxycarbamide.
• if you suffer from anaemia or if it occurs. Red blood cells can be replaced, if necessary. Their formation from abnormally large precursors is often to be observed only when treatment is started and it resembles the anaemia due to vitamin B12 deficiency. However, this is not attributable to too little vitamin B12 or folic acid.
• if you notice skin changes. These require further observation, as certain types of skin cancer can occur in isolated cases.
• if you notice painful ulcers on the lower legs. These are usually difficult to treat and can require interruption of treatment. Discontinuation of hydroxyurea usually enables the ulcers to slowly heal after some weeks.
• if you receive long-term treatment in cases of excessive formation of blood cells such as polycythemia vera and thrombocytosis. Another white blood cell cancer can develop. The extent to which this relates to the underlying disease or treatment with hydroxyurea is unknown to date.
• if you experience impaired blood formation in the bone marrow. A considerable reduction in white blood cells is the first and most common sign. A considerable reduction in blood platelets and anaemia occur less frequently and rarely without preceding leukopenia.
• if you are given other anticancer drugs or radiotherapy treatment.
• if you are concomitantly treated with live attenuated vaccines (expected yellow fever vaccines see “Do not take Hydroxyurea”).

The risk of an inflammation of the blood vessels of the skin, including blood vessel ulcerations and deterioration, is increased. Severe skin blood vessel ulcers have been reported in patients with myeloproliferative disease. Hydroxyurea should therefore be discontinued if such ulcerations develop. In addition, alternative medicines should be used if necessary.

The following parameters should be observed in the blood count during treatment with Hydroxyurea, even after the optimal dose has been established:
  - content of red blood pigment
  - differentiation of white blood cells
  - number of blood platelets
The control interval must be individualised, but is normally once a week.

It is important to monitor uric acid levels regularly. You should always drink sufficient liquid during treatment with Hydroxyurea.

Appropriate contraceptive measures are to be taken if one partner is treated with Hydroxyurea.

Men undergoing treatment with Hydroxyurea should not father a child during treatment and up to 1 year afterwards. Seek advice on sperm conservation before beginning therapy as hydroxyurea therapy can cause transient infertility. If pregnancy is desired, specialized counselling is recommended even after therapy.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

• Other medicines against tumour diseases or radiotherapy
  Side effects can be more intense and more common than after administration of Hydroxyurea alone. These side effects include the suppression of blood formation in the bone marrow, stomach and bowel complaints and inflammation in the mouth cavity. Enhancement of inflammatory reddening of the skin caused by previous or concomitant radiotherapy is possible.

  Laboratory tests have shown that hydroxyurea enhances the toxicity of certain medicines against tumour diseases, e.g. of
- fluoropyrimidines (e.g. fluorouracil) and
cytarabine

It is not clear whether these interactions are additive in their toxicity during use in humans and whether the dose must be adjusted.

- **Medicines against viral diseases** (nucleoside analogues, medicines for the treatment of a HIV infection) Conditions such as, inflammation of the pancreas, liver damage, sometimes lethal, and severe peripheral nervous conditions have all been reported. Combination with medicines to treat viral diseases cannot be recommended.

- **Prior or concomitant interferon therapy**
The risk of an inflammation of the blood vessels of the skin, including blood vessel ulcerations and deterioration, is increased in patients who receive prior or concomitant interferon therapy.

- **Yellow fever vaccine**
There is a risk of generalised vaccinale disease, which can be fatal, therefore concomitant use is contraindicated (see section “Do not take Hydroxycarbamide”).

- **Live attenuated vaccines (except yellow fever)**
There is a risk of systemic, possible fatal disease. This risk is increased if you are already immunosuppressed by your underlying disease. An inactivated vaccine should be used where this exists (poliomyelitis).

- **Ciclosporine, Tacrolimus**
Concomitant use is to be taken into consideration because of an excessive immunosuppression with risk of lymphoproliferation.

**Pregnancy and breast-feeding**
Hydroxycarbamide may impair the development of your unborn child. You must therefore not use Hydroxycarbamide during pregnancy. Women of childbearing potential should take contraceptive measures before starting and during treatment with Hydroxycarbamide. If a patient intends to become pregnant after a therapy with hydroxycarbamide a specialized consultation is recommended.

If a doctor deems the use absolutely necessary during pregnancy, he/she should inform you about the possible risk for your child. If you become pregnant during treatment with Hydroxycarbamide, inform your doctor without delay, and make use of the possibility of specialized counselling.

You must not use Hydroxycarbamide while breast-feeding. If treatment is recommended by a doctor, you must stop breast-feeding.

**Driving and using machines**
Reactivity can be impaired during treatment with Hydroxycarbamide. In this case, do not drive a car, and do not operate hazardous machines.

**3. HOW TO TAKE HYDROXYCARBAMIDE**
Treatment should be conducted only by experienced specialists.

Always take Hydroxycarbamide exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
The capsules should be swallowed as a whole and must not disintegrate within the mouth.

The dosages stated in the following are based on the patient’s actual or ideal weight, whichever is the less. **Your doctor determines the number of capsules and the duration of treatment.**

- **Aggressive white blood cell disease**
  (chronic myeloid leukaemia)
  Depending on the number of white blood cells, the **initial dose is usually 40 mg hydroxycarbamide per kg bodyweight** daily.

  Your doctor will reduce the dose to 20 mg per kg daily if the number of white blood cells falls below 20 x 10^9/l. The dose is then adjusted on an individual basis in order to keep the number of white blood cells at 5-10 x 10^9/l.

  If the white blood cells are less than 5 x 10^9 per litre, the dosage should be reduced, and it should be increased if they are above 10 x 10^9/l.

  If the white blood cells fall below 2.5 x 10^9/l or the blood platelets below 100 x 10^9/l, your doctor should interrupt therapy until the values normalize.

  An appropriate test time to determine the efficacy of Hydroxycarbamide is 6 weeks. Your doctor will discontinue therapy if the disease is progressing. If there is a response, therapy can be continued indefinitely.

- **Surplus of blood platelets**
  (essential thrombocythaemia)
  For this disease, the **initial dose is usually 15 mg hydroxycarbamide per kg bodyweight** daily. This should keep the number of blood platelets below 600 x 10^9/l without reducing the number of white blood cells below 4 x 10^9/l.

- **Surplus of certain blood cells**
  (polycythaemia vera)
  In this case, treatment should be started with a dosage of **15-20 mg hydroxycarbamide per kg bodyweight** daily. The dose is to be adjusted on an individual basis in order to keep the ratio between red blood cells and blood plasma below 45% and the number of blood platelets below 400 x 10^9/l.

  This can be achieved in most patients with a **continuous administered dose of 1 to 2 hard capsules** daily on average. If the ratio of red blood cells to blood plasma and the number of blood platelets remain stable, treatment should be continued indefinitely.

**Children**
As these diseases only rarely occur in children, no dosage schemes can be established at present.

**Elderly patients**
Elderly patients can have a more pronounced reaction to the effect of hydroxycarbamide and possibly require a lower dosage.

**Patients with impaired liver or kidney function**
Recommendations cannot be given for these patients as no data exists to date.

**If you take more Hydroxycarbamide than you should**
If the dosage taken was several times more than the recommended dosage, the following acute skin and/or mucosal changes may be signs of an overdose:
  - soresness
• violet skin rash
• swellings on palms and soles, followed by scaling of hands and feet
• sore feet
• excessive generalised pigmentation
• severe acute inflammation of oral mucosa

Immediately inform a doctor if an overdose occurs. Immediate treatment consists of stomach irrigation, followed by supportive measures and monitoring of the blood formation.

If you forget to take Hydroxycarbamide
Do not take a double dose if you have forgotten the previous intake. Go back to your original directions for your next dose. If you are unsure contact your doctor.

If you stop taking Hydroxycarbamide
Your disease might worsen if therapy is discontinued.
Therapy with hydroxycarbamide may be terminated or interrupted only on the orders of the attending doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Hydroxycarbamide can cause side effects, although not everybody gets them.

The strength of suppressed blood formation of the bone marrow determines the dosage or whether therapy must be interrupted in rare cases.

Side effects affecting the stomach or the intestine only rarely require dose reduction or cessation of treatment.

Side effects can occur with the following frequencies:

Common, occurs in 1 to 10 per 100 users
• suppressed blood formation in the bone marrow
• reduced number of white blood cells (you are more prone to catch infections)
• changes in the red blood count (megaloblastosis)
  Possible changes in the red blood count which do not respond to treatment with folic acid or vitamin B12 subside when therapy is discontinued.
• diarrhoea
• constipation

Uncommon, occurs in 1 to 10 per 1,000 users
• reduced number of blood platelets (you are more prone to bruising, bleeding)
• anaemia (feeling tired)
• nausea, vomiting, loss of appetite
• inflammation of oral mucosa
• drug fever
• chills
• feeling unwell
• flaky, knotty inflamed skin, skin rash
• inflammatory reddening affecting face, arms and legs
• elevated liver enzymes
• elevated bilirubin
• transient disorders of tubular kidney function with increase in uric acid, urea and creatinine in blood

**Rare.** occurs in 1 to 10 per 10,000 users

• allergic reactions
• hair loss
• rare disorders of nerve function including headache, dizziness, disorientation, hallucinations and fits
• development of an acute lung reaction with accumulation of liquid in the lungs, fever, shortness of breath
• allergic reactions in the lungs
• difficult or painful urination (dysuria)
• Potentially life-threatening metabolic complications that can occur after treatment of cancer leading to increased uric acid level in the blood, which may result in gout or acute renal failure (tumour lysis syndrome)

**Very rare.** occurs in fewer than 1 per 10,000 users

In isolated cases after maintenance therapy for several years with daily intake of hydroxycarbamide:

• variable skin changes such as reddening and swelling
• excessive pigmentation on skin and nails
• thinning of skin and nails
• ulcers of the lower legs
• itching
• small, rough reddish patches on the skin, which may become skin cancer if not removed (actinic keratosis)
• skin cancer
• violet nodules
• skin scaling
• impaired kidney function
• cutaneous ulcers (especially ulcers of the lower legs)

Another white blood cell cancer can develop in patients with excessive formation of blood cells and continuously treated with hydroxycarbamide. It is not known whether this is attributable to the underlying disease or to the treatment with hydroxycarbamide.

Severe stomach complaints such as nausea, vomiting and loss of appetite, which can occur in combination with radiotherapy, can be controlled if administration of hydroxycarbamide is transiently stopped.

Hydroxycarbamide can enhance mucosal inflammations caused by radiation. Inflammatory reddening and excessive pigmentation can occur in pretreated tissue.

Inflammation of the blood vessels of the skin, including blood vessel ulcerations and deterioration, have occurred in patients with myeloproliferative disorders during therapy with hydroxycarbamide. This was reported most often in patients with a history of, or currently receiving, interferon therapy (see “Taking other medicines”).

High doses can cause moderate sleepiness.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. **HOW TO STORE HYDROXERCARBAMIDE**

Keep out of the reach and sight of children.

Do not store above 30 °C.
Do not use the medicine after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.

The medicine should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Hydroxycarbamide contains

- The active substance is hydroxycarbamide
  1 capsule, hard contains 500 mg hydroxycarbamide.

- The other ingredients are:
  Capsule contents
  Citric acid anhydrous, disodium hydrogen phosphate anhydrous, magnesium stearate

  Capsule shell
  Gelatin, ferric oxide, yellow, titanium dioxide

What Hydroxycarbamide looks like and contents of the pack

Capsule, hard with white lower part and yellow upper part

Hydroxycarbamide 500 mg capsules, hard are available in PVC/PVDC/aluminium-blisters packs of 20, 25, 50, 100 and 120 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation
Hexal AG,
Industriestrasse 25,
83607 Holzkirchen,
Germany.

Manufacturer
AMAREG GmbH,
Donaustaufer Str. 378,
93055 Regensburg,
Germany
or
Salutas Pharma GmbH,
Otto-von-Guericke-Allee 1,
39179 Barleben,
Germany
This leaflet was last approved in 08/2009 (to be amended after approval)
Module 4

Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING (carton)

1. NAME OF THE MEDICINAL PRODUCT

Hydroxyurea 500 mg capsules, hard

Hydroxycarbamide

2. STATEMENT OF ACTIVE SUBSTANCE

Each capsule, hard contains 500 mg of hydroxycarbamide.

3. LIST OF EXCIPIENTS

-

4. PHARMACEUTICAL FORM AND CONTENTS

20 capsules, hard
25 capsules, hard
50 capsules, hard
100 capsules, hard
120 capsules, hard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

-

8. EXPIRY DATE

EXP
9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG,
Industriestrasse 25,
83607 Holzkirchen,
Germany.

12. MARKETING AUTHORISATION NUMBER(S)

PL 10880/0128

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

-

16. INFORMATION IN BRAILLE

Hydroxyurea 500 mg
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(PVC/PVDC aluminium blisters)</td>
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</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<tbody>
<tr>
<td>Hydroxyurea 500 mg capsules, hard</td>
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</table>

<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
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<tbody>
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<td>Hexal AG</td>
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<table>
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<tr>
<th>3. EXPIRY DATE</th>
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<td>EXP</td>
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</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
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<tbody>
<tr>
<td>Batch</td>
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<table>
<thead>
<tr>
<th>5. OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL 10880/0128</td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

(carton)

1. NAME OF THE MEDICINAL PRODUCT

Hydroxycarbamide 500 mg capsules, hard

Hydroxycarbamide

2. STATEMENT OF ACTIVE SUBSTANCE

Each capsule, hard contains 500 mg of hydroxycarbamide.

3. LIST OF EXCIPIENTS

-

4. PHARMACEUTICAL FORM AND CONTENTS

20 capsules, hard
25 capsules, hard
50 capsules, hard
100 capsules, hard
120 capsules, hard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

-

8. EXPIRY DATE

EXP
9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

-

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Hexal AG,
Industriestrasse 25,
83607 Holzkirchen,
Germany.

12. MARKETING AUTHORISATION NUMBER(S)

PL 10880/0129

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

-

16. INFORMATION IN BRAILLE

Hydroxycarbamide 500 mg
MINIMUM PARTICULARS TO APPEAR ON BLISTERS

(PVC/PVDC aluminium blisters)

1. NAME OF THE MEDICINAL PRODUCT

Hydroxycarbamide 500 mg capsules, hard

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Hexal AG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PL 10880/0129
Module 5

Scientific discussion during initial procedure

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) considers that the applications for Hydroxyurea 500 mg capsules, hard and Hydroxycarbamide 500 mg capsules, hard in the treatment of chronic myeloid leukaemia, polycythaemia vera and essential thrombocythaemia are approvable.

EXECUTIVE SUMMARY

About the product
The active substance, hydroxycarbamide, is the hydroxyl derivative of urea and is also known as hydroxyurea. Hydroxycarbamide is an inhibitor of the enzyme ribonucleotide reductase, which is the enzyme which catalyses the conversion of ribonucleotide diphosphates into deoxyribonucleotide diphosphates. As this is one of the rate determining steps in the formation of DNA, hydroxycarbamide specifically inhibits both cell division and DNA repair and is particularly active against rapidly dividing cells, such as cancer cells.

General comments on the submitted dossier
This decentralized application concerns a generic version of Hydroxycarbamide 500 mg capsules.

The originator product is Hydrea™ capsules 500 mg by E.R. Squibb & Sons Ltd, UK, registered since 29 May 1986 (PL 0034/5044).

With UK as the Reference Member State in this Decentralized Procedure, HEXAL AG is applying for the Marketing Authorisations for Hydroxyurea 500 mg capsules, hard and Hydroxycarbamide 500 mg capsules, hard in Germany.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles.
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The applicant has submitted one bioequivalence study which, they state, was conducted under GCP guidelines.

SCIENTIFIC OVERVIEW AND DISCUSSION

QUALITY ASPECTS

Drug substance
The chemical-pharmaceutical documentation and Expert Report in relation to Hydroxyurea 500 mg capsules, hard and Hydroxycarbamide 500 mg capsules, hard are of sufficient quality in view of the present European regulatory requirements. The active substance, hydroxycarbamide, is the subject of a Ph Eur monograph and is controlled by a current certificate of suitability. The drug substance specification for drug substance is acceptable. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. An adequate re-test period has been defined based on conducted stability studies.

**Drug Product**

The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. The batch analysis results show that the finished products meet the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. The proposed shelf-life of 36 months is acceptable.

**NON CLINICAL ASPECTS**

The pharmacodynamic, pharmacokinetic and toxicological properties of hydroxycarbamide are well known. As hydroxycarbamide is a well known active substance, no further new non-clinical data are required and the applicant has provided none. An overview based on the literature is thus appropriate.

The non-clinical overview has been written by an expert who has a degree and doctorate in biochemistry. He has some experience in drug regulatory work. The overview, dated February 2008, refers to a total of 69 references from the published literature dated 1990 to 2007. The toxicological properties of hydroxycarbamide are well known. The nonclinical overview is acceptable.

**CLINICAL ASPECTS**

**Pharmacokinetics**

The applicant has submitted one bioequivalence study.

**Study design**

This was a single centre, single dose, open label, randomized, two way cross-over study, conducted under fasting conditions.

The study was conducted in line with GCP.

The design of the study is adequate. As the dosage is not given specifically with food conducting the study under fasting conditions is satisfactory.

**Test product:** Hydroxyurea 500 mg capsules, hard/Hydroxycarbamide 500 mg capsules, hard

**Reference product**

Hydrea™ 500 mg capsules
E.R. Squibb & Sons Ltd, UK
A single oral dose of hydroxycarbamide as 2 x 500 mg capsules was administered under fasting conditions in each study period. The washout period was at least three days.

The dose of 1 g was chosen for analytical reasons. As this dose is within the therapeutic dose range it is acceptable. As half life is 3-4 hours a washout of at least 3 days is also acceptable.

Population
Twenty-eight subjects (Caucasian, male and female and aged between 18-55 years) were enrolled and randomized. There were no withdrawals. One subject dropped out prior to period two due to personal reasons. PK analysis was done on data of 27 subjects and safety analysis on 28 subjects.

Analytical methods
Blood sampling points included: pre-dose and at 0.16, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 10, 12, 14, 16 and 18 hours post dose in each period.

Plasma concentrations of hydroxycarbamide were determined using a validated GCMS method. Considering Cmax is reached at approx. 0.5 to 2 hours and the half life is 3-4 hours the blood sampling schedule is appropriate.

Pharmacokinetic Variables & Statistical methods
- Primary parameters: AUC0-t and Cmax
- Secondary parameters: AUC0-∞, Tmax, Kel, T½ and residual area
Parametric ANOVA on ln-transformed AUC and Cmax; geometric CI for AUC and Cmax and non-parametric test for T½

Criteria for bioequivalence: 90% of geometric CI of the ratio test/reference of least square means from ANOVA on ln transformed AUC0-t and Cmax lie within 80-125%.

Results

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test (mean ± SD)</th>
<th>Reference (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-t (µg.h/ml)</td>
<td>84.57 ± 17.24</td>
<td>84.20 ± 15.52</td>
</tr>
<tr>
<td>AUC0-∞ (µg.h/ml)</td>
<td>87.39 ± 17.19</td>
<td>87.79 ± 15.55</td>
</tr>
<tr>
<td>Cmax (µg/ml)</td>
<td>24.72 ± 6.07</td>
<td>24.61 ± 7.44</td>
</tr>
<tr>
<td>Residual area (%)</td>
<td>3.35 ± 0.81</td>
<td>4.18 ± 2.21</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>0.62 ± 0.20</td>
<td>0.74 ± 0.39</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>3.31 ± 0.58</td>
<td>3.90 ± 1.83</td>
</tr>
</tbody>
</table>

Table 2. Test vs Reference
There were no clinically significant drug related adverse events or safety concerns during the study period.

There were no pre-dose concentrations of hydroxycarbamide detectable at any of the study periods confirming an adequate washout period.

Bioequivalence between the test and reference product has been shown and the CI lie within the acceptance range of 80-125% for both Cmax and AUC.

**Pharmacokinetic conclusion**

Based on the submitted bioequivalence study Hydroxyurea 500 mg capsules, hard/ Hydroxycarbamide 500 mg capsules, hard are considered bioequivalent with Hydrea 500 mg capsules.

**Pharmacodynamics**

No new data have been submitted and none are required for this application.

**Clinical efficacy**

No new data have been submitted for this generic application.

**Clinical safety**

No new data have been submitted for this generic application.

**Pharmacovigilance system**

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

**Risk Management Plan**

Hydroxycarbamide 500 mg capsules is a generic product. With the reference medicinal product no special important risks or potential risks have been identified which require additional risk minimization activities other than the global pharmacovigilance system.

**Periodic Safety Update Report (PSUR)**

The applicant has applied for a PSUR submission scheme of three years upon approval as hydroxycarbamide is a well known active substance which has been marketed for many years throughout the EU. The proposal is acceptable.
**Product literature**
All product literature (SPC, PIL and labelling) is satisfactory. The package leaflet was submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**BENEFIT RISK ASSESSMENT**
Bioequivalence has been shown between the test and the reference products. Approval is recommended.