Package leaflet: information for the user

Hydroxycarbamide 500 mg capsules, hard

Active substance: hydroxycarbamide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Hydroxycarbamide is and what it is used for

Hydroxycarbamide is used to prevent painful crises, sudden chest pain and severe anemia, caused by Sickle Cell disease, in patients with body weight of 33 kg and more.

Sickle Cell disease is an inherited blood disorder that affects the disc shaped red cells of the blood. Some cells become abnormal, rigid and take a crescent or sickle shape which leads to anemia.
The sickle cells also get stuck in blood vessels, blocking blood flow. This can cause acute pain crises and organ damage.
For severe painful crises, most patients require hospitalisation. Hydroxycarbamide will decrease the number of painful crises as well as the need for hospitalisation linked with the disease.

The active substance of Hydroxycarbamide, hydroxycarbamide, is a substance which inhibits growth and proliferation of some cells, such as blood cells. These effects lead to a reduction of circulating red, white and coagulation blood cells (myelosuppressive effect). In Sickle Cell disease, hydroxycarbamide helps also to prevent red blood cells from taking abnormal shape.

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. What you need to know before you take Hydroxycarbamide

Do not take Hydroxycarbamide
- if you are **allergic** to hydroxycarbamide or any of the other ingredients of this medicine (listed in section 6). 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 x 10^9 leukocytes/l)
  - deficiency of blood platelets (less than 100 x 10^9 thrombocytes/l)
  - severe anaemia.
- if you are pregnant or **breastfeeding**.

Warnings and precautions
Talk to your doctor or pharmacist before taking 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 B_{12} deficiency. However, this is not attributable to too little vitamin B_{12} 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 hydroxycarbamide 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 thrombocythaemia.
  Another white blood cell cancer can develop. The extent to which this relates to the underlying disease or treatment with hydroxycarbamide 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.

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. Hydroxycarbamide 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 Hydroxycarbamide 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 Hydroxycarbamide.

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

Men undergoing treatment with Hydroxycarbamide should not father a child during treatment and at least 6 months afterwards. Seek advice on sperm conservation before beginning therapy as hydroxycarbamide therapy can cause transient infertility. If pregnancy is desired, specialized counselling is recommended even after therapy.

Other medicines and Hydroxycarbamide
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

- Other **medicines against tumour diseases or radiotherapy**
  Side effects can be more intense and more common than after administration of Hydroxycarbamide 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 hydroxycarbamide 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.

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 this medicine exactly as your doctor has told you. 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.

- **Sickle Cell disease**
  The posology should be based on your 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 you respond 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 you still do 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

- **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.

Elderly people

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:

- soreness
- 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 medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine 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, may affect up to 1 in 10 people

- 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 B_{12} subside when therapy is discontinued.
- diarrhoea
- constipation

Uncommon, may affect up to 1 in 100 people

- 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, may affect up to 1 in 1,000 people
- allergic reactions
- hair loss
- rare disorders of nerve function including headache, dizziness, and convulsions
- 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)
- gangrene

Very rare, may affect up to 1 in 10,000 people
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

- disorientation, hallucinations

Side effects of frequency not known (frequency cannot be estimated from the available data):
- Skin tumor
- Weakness
- liver toxicity
- Reduced platelets (including CD4 lymphocytes)
- peripheral neuropathy
- inflammation of the pancreas.
- Mucosal inflammation
- digestion dysfunction

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 "Other medicines and Hydroxycarbamide").

High doses can cause moderate sleepiness.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Hydroxycarbamide

Keep this medicine out of the sight and reach of children.

Do not store above 25 °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.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Content of the pack and other 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-blister packs of 20, 25, 50, **100** and 120 capsules.

Not all pack sizes may be marketed.

Marketing Authorization Holder
Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
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Manufacturer
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