Regulatory Affairs

HYDROXYUREA (hydroxycarbamide)

100 mg and 1,000 mg Film-coated tablets
500 mg Hard capsules

Summary of product characteristics (SmPC)

a) Table of contents

b) List of tables

2) Tradename

Hydroxyurea 100 mg film-coated tablets, 1,000 mg film-coated tablets and 500 mg hard capsules.

3) Description and composition

Pharmaceutical form(s)

100 mg film-coated tablets

White round film-coated tablet with one breaking notch on one side. On the same side debossment "|" on each half. Plain on the other side.

1,000 mg film-coated tablets

White oblong film-coated tablet with 3 breaking notches on both sides. On one side debossment "||" on each of the 4 parts, no debossment on the other side.

100 mg and 1,000 mg film-coated tablets are divisible (see section 4 Dosage regimen and administration - Method of administration).

500 mg hard capsules

Body-white opaque, Cap-yellow opaque.

Active substance

Film-coated tablets

100 mg film-coated tablets: Each film-coated tablet contains 100 mg hydroxycarbamide.

1,000 mg film-coated tablets: Each film-coated tablet contains 1,000 mg hydroxycarbamide.

Hard capsules

500 mg hard capsules: Each hard capsule contains 500 mg hydroxycarbamide.

Excipients

Film-coated tablets

100 mg and 1,000 film-coated tablets: Orange Flavour 769467, sodium stearyl fumarate, sucralose, opadry II 85F18422 and silicified microcrystalline cellulose.

Hard capsules

Capsules content:

Magnesium stearate, anhydrous citric acid and anhydrous disodium hydrogen phosphate.

Capsule shell:

Yellow ferric oxide (E172), titanium dioxide (E171), gelatin and water.

4) Indications

Hydroxycarbamide is indicated:

Sickle Cell Disease (SCD)

- For the prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in adults, adolescents, and children older than 2 years suffering from symptomatic sickle cell disease.

Chronic meyloid leukemia (CML), Essential thrombocythemia (ET) and Polycythemia (PV)

- For the treatment of patients with chronic myeloid leukemia in the chronic or accelerated phase of the disease.
- For the treatment of patients with essential thrombocythemia or polycythemia vera with a high risk of thromboembolic complications.

5) Dosage regimen and administration

Hydroxycarbamide is available in two dosage forms, film-coated tablets, and hard capsules.

Dosage regimen

Treatment with hydroxycarbamide should be initiated by a physician experienced in oncology or hematology.

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

General target population

Dosing recommendations in Sickle Cell Disease

In adults, adolescents, and children older than 2 years

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

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

In case of non-response (re-occurrence of crises or lack of reduction in crisis rate), the daily dose may be increased by steps of 2.5 to 5 mg/kg b.w./day using the most appropriate strength.

Under exceptional circumstances a maximum dose of 35 mg/kg b.w./day may be justified under close hematological monitoring (see section 6 Warnings and precautions).

If the patient does not respond to the maximum dose of hydroxycarbamide (35 mg/kg b.w./day) given over three to six months, permanent discontinuation of hydroxycarbamide should be considered.

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

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

- Neutrophils <1,500/mm^3
- Platelets <80,000/mm^3
- Hemoglobin <4.5 g/dL
- Reticulocytes <80,000/mm^3 if the hemoglobin concentration <9 g/dL

Long-term data on the continued use of hydroxycarbamide in patients with sickle cell disease are available in children and adolescents, with a follow-up of 12 years in children and adolescents and over 13 years in adults. It is currently unknown how long patients should be treated with hydroxycarbamide. The duration of treatment is the responsibility of the prescribing physician and should be based on the clinical and hematological status of each patient.

Special populations

Renal impairment

As renal excretion is a main pathway of elimination, a dose reduction of hydroxycarbamide should be considered in patients with renal impairment. In patients with creatinine clearance ≤ 60 mL/min, the initial hydroxycarbamide dose should be decreased by 50%. Close monitoring of blood parameters is advised in these patients. Hydroxycarbamide is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see sections 5 Contraindications, 6 Warnings and precautions and 11 Clinical pharmacology-pharmacokinetics).

Hepatic impairment

There are no data that support specific dose adjustments in patients with mild and moderate hepatic impairment. Close monitoring of blood parameters is advised in these patients. Due to safety considerations, hydroxycarbamide is contraindicated in patients with severe hepatic impairment (see sections 5 Contraindications and 6 Warnings and precautions).

Pediatric patients (less than 2 years of age)

The safety and efficacy of hydroxycarbamide in children with SCD, from birth up to 2 years have not yet been established. Limited data suggest that 20 mg/kg/day, reduced painful episodes and were safe in children less than 2 years of age but safety of long-term treatment remains to be established. Therefore, no recommendation on a posology can be made.

Geriatric patients (65 years of age or above)

No information is available regarding pharmacokinetic differences due to age (except pediatric patients.)

Dosing recommendations in patients with CML, ET and PV disease

Chronic myeloid leukemia

For chronic myeloid leukemia (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 to 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 counts 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. In these cases, the platelet count should be determined again after 3 days.

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 thrombocythemia

In cases of essential thrombocythemia (ET), hydroxycarbamide is normally administered at an initial dose of 15 mg/kg/daily 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.

If the platelet and/or white blood cell count can be adequately controlled and there is no evidence of resistance or intolerance, treatment with hydroxycarbamide should be continued indefinitely.

Polycythemia vera

In cases of polycythemia vera (PV), hydroxycarbamide should be administered at an initial dose of 15 to 20 mg/kg daily. The hydroxycarbamide dose should be individually adjusted to keep the hematocrit value below 45% and the platelet count below 400 x 10^9 /L.

In most patients this can be achieved through continuous administration of hydroxycarbamide with an average daily dose of 500 to 1,000 mg. If the hematocrit value and the platelet count can be sufficiently controlled and there is no evidence of resistance or intolerance, treatment should be continued indefinitely.

Concurrent treatment with hydroxycarbamide and myelosuppressive drugs may require adjustment of the dose of hydroxycarbamide.

Special populations

Pediatric population (below 18 years)

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

Geriatric patients (65 years of age or above)

Elderly patients may be more sensitive to the effects of hydroxycarbamide, and may require a lower dose regimen. Patients should be instructed to drink fluids abundantly.

Renal and Hepatic impairment

Hydroxycarbamide is largely excreted renally. This should be considered when dosing hydroxycarbamide in patients with renal impairment and the dose reduced as appropriate. There is little empirical data for patients with hepatic impairment. Therefore, no definitive dosage recommendation can be given (see section 6 Warnings and precautions). Close monitoring of blood parameters is recommended.

Method of administration

Film-coated Tablets

The 100 mg film coated tablet is divisible in two equal parts. The 1,000 mg film coated tablet is divisible in four equal parts.

Conforming to the individual prescribed dose, the tablet or the half or quarter of the tablet should be taken once daily, preferably in the morning before breakfast and, when necessary, with a glass of water or a very small amount of food.

For patients who are not able to swallow the tablets, these can be disintegrated immediately before use in a small quantity of water in a teaspoon. Adding a drop of syrup or mixing with food can mask a possible bitter taste.

Capsules

The capsules must be swallowed whole with plenty of liquid (e.g. a glass of water) and must not dissolve in the mouth.

6) Contraindications

Applicable for patients with Sickle cell disease

Hypersensitivity to hydroxycarbamide or to any of the excipients. Treatment should be discontinued if hypersensitivity to hydroxycarbamide occurs.

Severe hepatic impairment (Child-Pugh classification C).

Severe renal impairment (creatinine clearance <30 mL/min).

Breast-feeding (see section 9.2 Lactation).

Toxic ranges of myelosuppression (see sections 4 Dosage regimen and administration and 6 Warnings and precautions).

Applicable for patients with CML, ET and PV disease

Hypersensitivity to hydroxycarbamide or to any of the excipients. Treatment should be discontinued if hypersensitivity to hydroxycarbamide occurs.

Pregnancy and breast-feeding (see section 9 Pregnancy, lactation, females and males of reproductive potential).

Patients treated with hydroxycarbamide who are immunosuppressed, must not be immunized with live vaccines (see sections 6 Warnings and precautions and 8 Interactions).

Severe bone marrow depression, leukopenia (<2.5 x 10^9 leukocytes/L), thrombocytopenia (<100 x 10^9 platelets/L) or severe anemia (see sections 4 Dosage regimen and administration and 6 Warnings and precautions).

7) Warnings and precautions

Applicable for patients with CML, ET, PV and SCD diseases

Macrocytosis

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

Self-limiting megaloblastic erythropoiesis is often observed early in treatment with hydroxycarbamide. The morphological changes are similar to pernicious anemia but are not related to a vitamin B12 or folic acid deficiency.

Hydroxycarbamide causes macrocytosis, which may mask the incidental development of folic acid and vitamin B12 deficiency thus regular determinations of serum folic acid level are recommended. Prophylactic administration of folic acid is recommended.

Carcinogenicity

Hydroxycarbamide is unequivocally genotoxic in a wide range of test systems. Hydroxycarbamide is presumed to be a transspecies carcinogen. In patients who are receiving long-term treatment with hydroxycarbamide for myeloproliferative disorders, such as polycythemia vera and essential thrombocythemia, secondary leukemia may develop. At present, the extent to which this is due to the underlying disorder or to treatment with hydroxycarbamide is not known.

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

Leg ulcers and cutaneous vasculitis toxicities

In patients with leg ulcers, hydroxycarbamide should be used with caution. Leg ulcers are a common complication of sickle cell disease but have also been reported in patients treated 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. Due to potentially severe clinical outcomes for the cutaneous vasculitic ulcers reported in patients with myeloproliferative disease, hydroxycarbamide should be discontinued and/or its dose reduced if cutaneous vasculitic ulcerations develop. Rarely, ulcers are caused by leukocytoclastic vasculitis.

Patients with HIV

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

Neuropathy, which was severe in some cases, has been reported in HIV-infected patients receiving hydroxycarbamide in combination with antiretroviral agents, including didanosine, with or without stavudine (see section 8 Interactions). Patients treated with hydroxycarbamide in combination with didanosine, stavudine, and indinavir showed a median decline in CD4 cells of approximately 100/mm^3.

Test Interference

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

Interference with Continuous Glucose Monitoring Systems

Hydroxycarbamide may falsely elevate sensor glucose results from certain continuous glucose monitoring (CGM) systems which may lead to hypoglycemia if sensor glucose results are relied upon to dose insulin.

If CGM systems are to be used concurrently with hydroxycarbamide treatment, consult with the CGM prescriber about the need to consider alternative glucose monitoring methods [1].

Vaccinations

Concomitant use of hydroxycarbamide with a live virus vaccine may potentiate the replication of the vaccine virus and/or may increase some of the adverse reactions of the vaccine virus because normal defense mechanisms may be suppressed by hydroxycarbamide. Vaccination with a live vaccine in a patient taking hydroxycarbamide may result in severe infection. The patient's antibody response to vaccines may be decreased.

The use of live vaccines in patients with CML, PV and ET disease should be avoided during treatment and for at least six months after treatment has finished and individual specialist advice sought if necessary (see sections 4 Contraindications and 8 Interactions).

Treatment with hydroxycarbamide and concomitant immunization with live virus vaccines in patients with SCD, should only be performed if benefits clearly outweigh potential risks and individual specialist advice sought if necessary.

Radiation therapy and other anti-neoplastic agents

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

Hydroxycarbamide should be administered with caution to patients who are being or have previously been treated with another antineoplastic medicinal agent or radiation therapy, as undesirable effects can occur more frequently and are more serious than those reported for the use of hydroxycarbamide, other antineoplastic medicinal agents 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.

Embryo-Fetal Toxicity

Hydroxycarbamide is embryotoxic and teratogenic in rats and rabbits. Hydroxycarbamide is genotoxic. Pregnant women should be advised of the potential risk to a fetus (see section 5 contraindications). Female patients of childbearing potential should be advised to use an effective method of contraception during therapy and for at least 6 months after therapy [1].

Male patients should be advised to use an effective method of contraception during therapy and for at least 3 months after therapy [1]. Men treated with hydroxycarbamide are advised to seek counselling on sperm preservation before starting treatment due to the possibility of irreversible infertility.

Renal and hepatic impairment

Hydroxycarbamide should be used with caution in patients with mild to moderate, hepatic, and renal impairment (see section 4 Dosage regimen and administration). During treatment with hydroxycarbamide, frequent monitoring of blood counts should be conducted as well as monitoring of hepatic and renal function. Special care should be taken in the treatment of these patients, especially at the beginning of therapy.

Bone marrow depression and anemia

Hydroxycarbamide may cause bone marrow depression with leukopenia being the first and most common sign of bone marrow inhibition. Thrombocytopenia and anemia occur less frequently and rarely without preceding leukopenia. Neutropenia is the first and most common manifestation of hematological suppression. Treatment with hydroxycarbamide requires close clinical monitoring. The hematological status of the patient, as well as renal and hepatic functions should be determined prior to, and repeatedly during treatment.

In patients with sickle cell disease, who are on treatment with hydroxycarbamide, blood counts must be monitored once a month at treatment initiation (i.e., for the first two months) and if the daily dose of hydroxycarbamide is up to 35 mg/kg b.w. Patients who are stable on lower doses should be monitored every 2 months. Treatment with hydroxycarbamide should be discontinued if bone marrow function is markedly depressed. Recovery from myelosuppression is usually rapid when therapy is discontinued. Hydroxycarbamide therapy can then be re-initiated at a lower dose (see section 4 Dosage regimen and administration).

In patients with CML, PV and ET, a differential blood count, which determines hemoglobin content, leukocyte differentiation and platelet count, should be performed regularly, even after adjustment to the individually optimal dose. The control interval should be individually adjusted, but normally the control should be performed once a week. If the leukocyte count falls below 2.5 × 109/L or the platelet count falls below 100 × 109/L, therapy should be interrupted until the values have largely returned to normal (see section 4 Dosage regimen and administration). The bone marrow depression regresses when therapy is discontinued.

In patients with CML, PV, ET and SCD, severe anemia must be corrected with whole blood replacement before initiating therapy with hydroxycarbamide. In cases of severe anemia before or during ongoing treatment, red blood cells can be transfused if necessary. Also, severe anemia can usually be corrected without interrupting hydroxycarbamide therapy. Cases of hemolytic anemia in patients treated with hydroxycarbamide for myeloproliferative diseases have been reported. Patients who develop severe anemia should have laboratory tests evaluated for hemolysis. If diagnosis of hemolytic anemia is established, hydroxycarbamide should be discontinued. Hydroxycarbamide may delay plasma iron clearance and reduce the rate of iron utilization by erythrocytes, but it does not appear to alter the red blood cell survival time.

Safe administration and monitoring

Patients and/or parents or the legal responsible person must be able to follow directions regarding the administration of this medicinal product, their monitoring and care.

Driving and using machines

Hydroxycarbamide has minor influence on the ability to drive and use machines. Patients should be advised not to drive or operate machines if dizziness is experienced while taking hydroxycarbamide.

Applicable to patients with CML, PV and ET disease

Respiratory diseases

Interstitial lung disease including pulmonary fibrosis, lung infiltration, pneumonitis, and alveolitis/allergic alveolitis have been reported in patients treated for myeloproliferative neoplasm and may be associated with fatal outcome. Patient developing pyrexia, cough, dyspnea, or other respiratory symptoms should be closely monitored, investigated, and treated. Prompt discontinuation of hydroxycarbamide and treatment with corticosteroids appears to be associated with resolution of the pulmonary events (see section 7 Adverse drug reactions).

8) Adverse drug reactions

Patients with Sickle Cell Disease

Summary of safety profile

The safety profile of hydroxycarbamide in SCD was established from clinical trials and confirmed with long-term cohort studies including up to 1,903 adults and children of more than 2 years of age.

The most frequently reported adverse reaction is myelosuppression with neutropenia as the most common manifestation. Bone marrow depression is the dose-limiting toxic effect of hydroxycarbamide. When the maximum tolerated dose is not reached, transient myelotoxicity usually occurs in less than 10% of patients, while under the maximum tolerated dose more than 50% can experience reversible bone marrow suppression. These adverse reactions are expected based on the pharmacology of hydroxycarbamide. Gradual dose titration may help diminish these effects (see section 4 Dosage regimen and administration).

The clinical data reported in patients with sickle cell disease have not shown evidence of adverse reactions of hydroxycarbamide on hepatic and renal function.

Adverse drug reactions from clinical trials and post-marketing experience

Adverse drug reactions from clinical trials (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

This table also includes the adverse drug reactions derived from post-marketing experience with hydroxycarbamide via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

(i) Table 8)-1 Adverse drug reactions identified in Sickle Cell Disease

Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	
Not known:	Leukemia, skin cancers (in elderly patients)
Blood and lymphatic system disorders	
Very common:	Bone marrow depression[1] including neutropenia (<1.5 x 10^9/L), reticulocytopenia (<80 x 10^9/L), macrocytosis[2]
Common:	Thrombocytopenia (<80 x 10^9/L), anaemia (haemoglobin <4.5 g/dL)[3]
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness
Vascular disorders	
Not known:	Bleeding
Gastrointestinal disorders	
Uncommon:	Nausea
Not known:	Gastrointestinal disturbances, vomiting, gastrointestinal ulcer, severe hypomagnesemia
Hepatobiliary disorders	
Rare:	Elevated liver enzymes
Skin and subcutaneous tissue disorders	
Common:	Skin reactions (for example oral, ungual and cutaneous pigmentation) and oral mucositis
Uncommon:	Rash, melanonychia, alopecia
Rare:	Leg ulcers

Very Rare:	Systemic and cutaneous lupus erythematosus
Not known:	Cutaneous dryness
Reproductive system and breast disorders	
Very common:	Azoospermia[4], Oligospermia[4]
Not known:	Amenorrhoea
General disorders and administration site conditions	
Not known:	Fever
Investigations	
Not known:	Weight gain[5]

[1]Haematological recovery usually occurs within two weeks of withdrawal of hydroxycarbamide.

[2]The macrocytosis caused by hydroxycarbamide is not vitamin B12 or folic acid dependent.

[3]Mainly due to infection with Parvovirus, splenic or hepatic sequestration, renal impairment.

[4]Oligospermia and azoospermia are in general reversible but have to be taken into account when fatherhood is desired (see section 13 Non-clinical safety data). These disorders are also associated with the underlying disease.

[5]Weight gain may be an effect of improved general conditions.

Pediatric population (older than 2 years of age)

Frequency, type, and severity of adverse reactions in children is generally similar to adults.

Post marketing data from one observational study with hydroxycarbamide (Escort HU) on a large set of patients (n=1906) with SCD showed that patients aged 2 to 10 years were at higher risk for neutropenia and at lower risk for dry skin, alopecia, headache, and anemia. Patients aged 10 to 18 years were at lower risk for dry skin, skin ulcer, alopecia, weight increase and anemia compared to adults.

Patients with CML, ET and PV disease

Summary of safety profile

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

Adverse drug reactions from clinical trials and post-marketing experience

Adverse drug reactions from clinical trials (Table 7-2) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

This table also includes the adverse drug reactions derived from post-marketing experience with hydroxycarbamide via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

(ii) Table 8)-2 Adverse drug reactions identified in patients with CML, ET and PV disease

Infections and infestations	
Rare:	Gangrene
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	

Common:	Skin cancer
Blood and lymphatic system disorders	
Very common:	Bone marrow depression, leukopenia, thrombocytopenia, megaloblastosis, CD4 lymphocytes decreased, anaemia
Not known:	Haemolytic anaemia
Immune system disorders	
Very rare:	Systemic and cutaneous lupus erythematosus
Metabolism and nutrition disorders	
Rare:	Tumour lysis syndrome
Psychiatric disorders	
Common:	Hallucination, disorientation
Nervous system disorders	
Common:	Neurological disturbances (e.g., headache, dizziness, convulsions, and seizures), peripheral neuropathy[1]. High doses may cause moderate drowsiness
Respiratory, thoracic, and mediastinal disorders	
Common:	Acute pulmonary reactions consisting of diffuse pulmonary infiltrates and dyspnoea, fibrosis, allergic alveolitis
Not known:	Interstitial lung disease
Gastrointestinal disorders	
Very common:	Diarrhoea, constipation, pancreatitis[1], mucositis, stomatitis, dyspepsia, severe gastric stress (nausea, vomiting, anorexia)[2]
Hepatobiliary disorders	
Common:	Increase in liver enzymes and bilirubin, hepatotoxicity[1], cholestasis, hepatitis
Skin and subcutaneous tissue disorders	
Very common:	Maculopapular rash[3], facial erythema, acral erythema, alopecia, cutaneous vasculitis[4], dermatomyositis-like skin changes, hyperpigmentation or atrophy of skin and nails, lower leg ulcers, pruritus, actinic keratosis, violet papules, desquamation, skin exfoliation, skin tumour
Not known:	Nail pigmentation
Renal and urinary disorders	
Very common:	Dysuria, renal impairment, transient impairment of renal tubular function accompanied by elevation of serum uric acid, urea, and creatinine
Reproductive system and breast disorders	
Very common:	Azoospermia, oligospermia
General disorders and administration site conditions	
Very common:	Drug fever[5], shivering, malaise, hypersensitivity reactions, asthenia

[1]*Fatal and non-fatal pancreatitis and hepatotoxicity and severe peripheral neuropathy have been reported in HIV-infected patients who received hydroxycarbamide in combination with antiretroviral agents, in particular didanosine plus stavudine.*

[2]*These gastrointestinal side effects, which can be caused by a combined hydroxycarbamide and radiotherapy, are usually controllable by temporarily discontinuing hydroxycarbamide administration.*

[3]*Erythema, skin and nail atrophy, desquamation, violet papules, alopecia, dermatomyositis-like lesions, actinic keratosis, skin cancer, lower leg ulcers, pruritus and hyperpigmentation of the skin and nails have been observed after years of long-term daily maintenance therapy with hydroxycarbamide.*

[4]*In patients with myeloproliferative disorders, such as polycythemia vera and thrombocythemia, hydroxycarbamide caused vasculitic ulcerations and gangrene, especially in the case of previous or simultaneous interferon therapy (see section 6 Warnings and precautions).*

[5]*Some cases of high fever (>39°C) with simultaneous onset of gastrointestinal, pulmonary, musculoskeletal, hepatobiliary, dermatological, or cardiovascular manifestations requiring hospitalization have been reported. These symptoms typically occurred within 6 weeks of initiation of therapy and disappeared immediately after discontinuation of hydroxycarbamide therapy. After resuming therapy fever recurred within 24 hours.*

9) Interactions

Specific interaction studies have not been performed with hydroxycarbamide.

Anti-neoplastic drugs and radiation therapy:

Concurrent use of hydroxycarbamide and other myelosuppressive medicinal products or radiation therapy may increase bone marrow depression, gastro-intestinal disturbances or mucositis. An erythema caused by radiation therapy may be aggravated by hydroxycarbamide.

All patients receiving an adequate course of combined hydroxycarbamide, and radiation therapy will demonstrate concurrent leukopenia. Platelet depression (<100,000 cells/mm^3) has occurred in the presence of marked leukopenia.

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

HIV drugs:

Potentially fatal pancreatitis and hepatotoxicity, and severe peripheral neuropathy have been reported in HIV-infected patients who received hydroxycarbamide in combination with first generation antiretroviral medicinal products, particularly didanosine plus stavudine. Patients treated with hydroxycarbamide in combination with didanosine, stavudine, and indinavir showed a median decline in CD4 cells of approximately 100/mm^3. The combination of hydroxycarbamide with nucleoside analogues is not recommended (see section 6 Warnings and precautions).

Live vaccines:

During concomitant use of hydroxycarbamide with live vaccines, the risk of a fatal systemic vaccine reaction is increased because the normal immune defense mechanisms and the immune response with antibodies can be reduced or suppressed by hydroxycarbamide.

Concomitant use of hydroxycarbamide with live vaccines in immunosuppressed patients can lead to severe infections. The use of live vaccines should be avoided and, if necessary, advice should be obtained from a specialist (see sections 5 Contraindications and Warnings and precautions).

Interference with Continuous Glucose Monitoring Systems

Hydroxycarbamide may falsely elevate sensor glucose results from certain continuous glucose monitoring (CGM) systems which may lead to hypoglycemia if sensor glucose results are relied upon to dose insulin.

If CGM systems are to be used concurrently with hydroxycarbamide treatment, consult with the CGM prescriber about the need to consider alternative glucose monitoring methods [1].

10) Pregnancy, lactation, females and males of reproductive potential

a) Pregnancy

Risk SummaryStudies in animals have shown reproductive toxicity. 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. Patients on hydroxycarbamide should be made aware of the risks to the fetus.

Pregnancy recommendations for patients with SCD

There is limited amount of data from the use of hydroxycarbamide in pregnant women. Hydroxycarbamide is not recommended during pregnancy in patients with SCD. The patient should be instructed to immediately contact a doctor in case of suspected pregnancy.

The evaluation of the risk-benefit ratio should be made on an individual basis taking into consideration the respective risk of hydroxycarbamide therapy against the switch to a blood transfusion program.Pregnancy recommendations for patients with CML, PV and ET disease

Use of hydroxycarbamide is contraindicated in pregnant women (see section 5 Contraindications). If pregnancy still occurs during treatment, the possibility of a genetic consultation should be offered due to the potential harm to the fetus.

Animal data

Teratogenicity of hydroxycarbamide has been demonstrated in many animal species, including rat, mice, and rabbits. Teratogenicity was characterized by neural defects, partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, missing lumbar vertebrae and deformed extremities. Embryotoxicity was characterized by lower fetal viability/death of large number of embryos, smaller litter sizes, and delayed development.

b) Lactation

Risk summary

c) As hydroxycarbamide is transferred into breastmilk, the use of hydroxycarbamide is contraindicated during breast-feeding due to the potential harm to the infant (see section 5 Contraindications). If treatment with hydroxycarbamide is necessary, breast-feeding must be discontinued.Females and males of reproductive potential

Contraception

Hydroxycarbamide is genotoxic, which can have a hereditary genetic damaging effect, therefore, genetic counseling in advance is also recommended for those wishing to become pregnant after treatment with hydroxycarbamide.

Females of childbearing potential receiving hydroxycarbamide should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur. Female patients of childbearing potential should be advised to use an effective method of contraception during therapy and for at least 6 months after treatment (see section 6 Warnings and precautions) [1].

Male patients should be advised to use an effective method of contraception during therapy and for at least 3 months after treatment (see section 6 Warnings and precautions) [1].

Male and female patients on hydroxycarbamide wishing to conceive should stop treatment 3 or 6 months respectively, before pregnancy if possible.

Infertility

Fertility in males might be affected by treatment. The occurrence of azoospermia and oligospermia, which may sometimes be reversible, has been observed in males. Therefore, due to the risk of irreversible infertility, male patients should be informed of the possibility of semen preservation before starting treatment. Impaired fertility was observed in male rats (see section 13 Non-clinical safety data).

11) Overdosage

Acute mucocutaneous toxicity has been reported in patients receiving hydroxycarbamide at a dose several times greater than that recommended. Soreness, violet erythema, oedema on the palms and soles followed by scaling of the hands and feet, severe generalized hyperpigmentation of the skin, and severe acute stomatitis has been observed.

Immediate treatment consists of gastric lavage followed by symptomatic treatment and monitoring of the bone marrow function.

In patients with SCD, severe bone marrow depression was reported in isolated cases of hydroxycarbamide overdose between 2 and 10 times the prescribed dose (up to 8.57 times of the maximum recommended dose of 35 mg/kg b.w./day). It is recommended that blood counts are monitored for several weeks after overdose since recovery may be delayed.

12) Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XX05.

Mechanism of action (MOA)

All mechanisms of action of hydroxycarbamide are not fully understood.

One of the mechanisms is the increase in fetal hemoglobin (HbF) concentrations in patients with SCD. HbF interferes with the polymerization of sickle hemoglobin (HbS) and thus impedes the sickling of red blood cell and in turn decreases vasocclusion and hemolysis. In all clinical studies, there was a significant increase in HbF from baseline after hydroxycarbamide use. Increased HbF also increases red blood cell survival and total hemoglobin level and thus reduces anemia in these patients.

Hydroxycarbamide has shown to be associated with the generation of nitric oxide suggesting that nitric oxide stimulates cyclic guanosine monophosphatase (cGMP) production, which then activates a protein kinase and increases the production of HbF. Other known pharmacological effects of hydroxycarbamide which may contribute to its beneficial effects in SCD include decrease in neutrophils, increase in water content of red blood cells, increased deformability of sickled cells, and altered adhesion of red blood cells to the endothelium.

In addition, hydroxycarbamide causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor, without interfering with the synthesis of ribonucleic acid or protein.

Pharmacodynamics (PD)

Besides the inconstant correlation between reduction of crisis rate and the increase in HbF, the cytoreductive effect of hydroxycarbamide, particularly the decrease in neutrophils, was the factor with the strongest correlation with the reduction in crisis rate.

Sickle cell disease

In all clinical studies conducted in sickle cell disease, hydroxycarbamide reduced the frequency of vaso-occlusive episodes by 40% to 80%, in children and in adults. The same decrease was observed for the number of hospital admissions and the number of days of hospitalization in the treated groups. The yearly frequency of acute chest syndrome (ACS) was also reduced by 25 to 68% under hydroxycarbamide in several studies. Acute chest syndrome is a frequent life-threatening complication of sickle cell disease and is characterized by chest pain or fever or dyspnea with recent infiltrate on chest X-ray.

A sustained clinical benefit was demonstrated in patients remaining on hydroxycarbamide treatment for more than 8 years.

In 1906 patients included in the cohort study ESCORT HU, after twelve and twenty-four months of treatment with hydroxycarbamide and compared to the baseline, it was observed a significant increase of Hb level (+1.4 g/dL and 1.5 g/dL) and percentage of HbF (+14.65% and 15%). In parallel after one year of treatment there was a significant reduction of the number of painful crises lasting >48 h (-40% in children and -50% in adults), episodes of ACS (-68% in children and -57% in adults), and hospitalizations (-44% in children and -45% in adults) and the percentage of patients requiring blood transfusion decreased by 50%. The safety profile of hydroxycarbamide in adults and in children observed in ESCORT HU was consistent with previous published data with no new risk.

Pediatric population

In NOHARM trial children of mean age of 2.2 years old (from 1 to 3.99 years) were randomized to either hydroxycarbamide (n=104) or placebo (n=104). Treatment was administered once daily at 20 ± 2.5 mg/kg for 12 months. A composite SCD-related clinical outcome (vaso-occlusive painful crisis, dactylitis, acute chest syndrome, splenic sequestration, or blood transfusion) was less frequent with hydroxycarbamide (45%) than placebo (69%, p=0.001). Regarding the risk of increased infection in children with drug-induced neutropenia, it was rare in NOHARM and did not differ on hydroxycarbamide versus placebo treatment.

At the end of the NOHARM trial, children were enrolled in the NOHARM extension trial (John 2020), and randomly assigned in a 1:1 ratio either to receive hydroxycarbamide at a fixed standard dose (mean [±SD], 20±5 mg per kilogram per day) or to escalate hydroxycarbamide to the maximum tolerated dose. 187 children were randomized: 94 (age 4.6 ± 1.0) in the fixed dose group (19.2±1.8 mg /kg/d) and 93 (age 4.8 ± 0.9) in the dose escalation group (29.5±3.6 mg/kg/d). After 18 months, an increase in Hb level (+0.3 g/dL) and % HbF (+8%) was found in the escalation group. Clinical adverse events of any grade were more frequent in the fixed-dose group, including all sickle cell-related events (245 vs 105) and specific events: vaso-occlusive pain crisis (200 vs 86) and acute chest syndrome, or pneumonia (30 vs 8). The number of key medical interventions were also fewer in the dose-escalation group than in the fixed-dose group, both for transfusions (34 vs. 116) and hospitalizations (19 vs. 90).

In infants with SS/Sb0 aged 9 to 23 months, a decrease of episodes of pain (-52%, 177 events vs 375), dactylitis (- 80%, 24 vs 123), acute chest syndrome, (8 vs 27) and hospitalizations (- 28%, 232 vs 324) has been reported with hydroxycarbamide (n=96) compared to placebo (n=97) respectively in the randomized controlled trial Baby Hug. In 25 patients treated for 1 year in the uncontrolled ESCORT HU over 1 year, compared to 1 year prior to enrolment (n=25), reduction of vaso-occlusive crises: -42% and hospitalizations: -55%. The benefit risk ratio and long-term safety remain to be established in this population.

In the uncontrolled cohort ESCORT HU, a subset of 27 pediatric patients with severe chronic anemia, treated with hydroxycarbamide for 12 months, had hemoglobin levels less than 7 g/dL at baseline. Of these, only 6 (22%) patients had levels less than 7 g/dL at Month 12. While there have been a majority of patients (56%) who had a change from baseline equal to or exceeding 1 g/dL, due to the large proportion of missing data, potential for regression to the mean and that an effect of transfusions could not be excluded, no robust efficacy conclusions can be made from this uncontrolled study.

Pharmacokinetics (PK)

Patients with CML, ET or PV disease

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.

Patients with Sickle cell disease

Absorption

After oral administration of 20 mg/kg of hydroxycarbamide, a rapid absorption is observed with peak plasma levels of about 30 mg/L occurring after 0.75 and 1.2 h in children and adult patients with sickle cell disease, respectively. The total exposure up to 24 h post-dose is 124 mg. h/L in children and adolescents and 135 mg. h/L in adult patients. The oral bioavailability of hydroxycarbamide is almost complete as assessed in indications other than sickle cell disease.

Distribution

Hydroxycarbamide distributes rapidly throughout the human body, enters the cerebrospinal fluid, appears in peritoneal fluid and ascites, and concentrates in leukocytes and erythrocytes. The estimated volume of distribution of hydroxycarbamide approximates total body water. The volume of distribution at steady state adjusted for bioavailability is 0.57 L/kg in patients with sickle cell disease (amounting to approximately 72 and 90 L in children and adults, respectively). The extent of protein binding of hydroxycarbamide is unknown.

Biotransformation

The biotransformation pathways as well as the metabolites are not fully characterized. Urea is one metabolite of hydroxycarbamide.

Hydroxycarbamide at 30, 100 and 300 μM is not metabolized *in vitro* by cytochrome P450s of human liver microsomes. At concentrations ranging from 10 to 300 μM, hydroxycarbamide does not stimulate the *in vitro* ATPase activity of recombinant human P glycoprotein (PGP), indicating that hydroxycarbamide is not a PGP substrate. Hence, no interaction is to be expected in case of concomitant administration with substances being substrates of cytochromes P450 or P-glycoprotein.

Elimination

In a repeated dose study in adult patients with sickle cell disease approximately 60% of the hydroxycarbamide dose was detected in urine at steady state. In adults, the total clearance adjusted for bioavailability was 9.89 L/h (0.16 L/h/kg) thereof 5.64 and 4.25 L/h by renal and non-renal clearance, respectively. The respective value for total clearance in children was 7.25 L/h (0.20 L/h/kg) with 2.91 and 4.34 L/h by renal and non-renal pathways.

In adults with sickle cell disease, mean cumulative urinary hydroxycarbamide excretion was 62% of the administered dose at 8 hours, and thus higher than in cancer patients (35–40%). In patients with sickle cell disease, hydroxycarbamide was eliminated with a half-life of approximately six to seven hours, which is longer than reported in other indications.

Special populations

Geriatric patients (65 years of age or above), gender, race

No information is available regarding pharmacokinetic differences due to age (except pediatric patients), gender or race.

Pediatric patients (less than 2 years of age)

In pediatric and adult patients with SCD, the systemic exposure to hydroxycarbamide at steady state was similar by means of the area under the curve. The maximum plasma levels and the apparent volume of distribution related to body weight were well comparable between age groups. The time to reach maximum plasma concentration and the percentage of the dose excreted in urine were increased in children compared to adults. In pediatric patients, the half-life was slightly longer, and the total clearance related to body weight slightly higher than in adult patients (see section 4 Dosage regimen and administration).

Renal impairment

As renal excretion is a pathway of elimination, consideration should be given to decreasing the dose of hydroxycarbamide in patients with renal impairment. In an open single-dose study in adult patients with SCD, the influence of renal function on pharmacokinetics of hydroxycarbamide was assessed. Patients with normal (creatinine clearance CrCl >80 mL/min), mild (CrCl 60 to 80 mL/min), moderate (CrCl 30 to 60 mL/min), or severe (<30 mL/min) renal impairment received hydroxycarbamide as a single dose of 15 mg/kg b.w. by using 200 mg, 300 mg, or 400 mg capsules. In patients, whose CrCl was below 60 mL/min or patients with end-stage renal disease the mean exposure to hydroxycarbamide was approximately 64% higher than in patients with normal renal function. As evaluated in a further study, in patients with a CrCl <60 mL/min the area under the curve was approximately 51% higher than in patients with a CrCl ≥60 mL/min, which suggests that a dose reduction of hydroxycarbamide by 50% may be appropriate in patients with a CrCl <60 mL/min. Hemodialysis reduced the exposure to hydroxycarbamide by 33% (see sections 4 Dosage regimen and administration and 6 Warnings and precautions). Close monitoring of blood parameters is advised in these patients.

Hepatic impairment

There are no data that support specific guidance for dose adjustment in patients with hepatic impairment, but, due to safety considerations, hydroxycarbamide is contraindicated in patients with severe hepatic impairment (see section 5 Contraindications). Close monitoring of blood parameters is advised in patients with hepatic impairment.

13) Clinical studies

Hydroxycarbamide is an established product. No clinical trial is conducted by Novartis.

14) Non-clinical 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 intestine and colon.

Cardiovascular effects and hematological changes were observed in some species.

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.

Reproductive toxicity

See section 9 Pregnancy, lactation, females, and males of reproductive potential.

Administration of hydroxycarbamide to male rats at a dose of 60 mg/kg b.w./day (approximately twice the maximum recommended dose for humans) resulted in testicular atrophy, decreased spermatogenesis, and a significant decrease in their ability to fertilize females. In addition, hydroxycarbamide affected spermatogenesis and sperm motility in mice when administered repeatedly, while in dogs reversible spermatogenic arrest was noted.

15) Pharmaceutical information

Incompatibilities

Not applicable.Special precautions for storage

Film coated tablets: Do not store above 30°C

Hard capsules: Store below 30°C

Information might differ in some countries.

Shelf life

Film coated tablets: 3 Years

Hard capsules:

Instructions for use and handling

Keep medicinal products out of reach of children.

Hydroxycarbamide is a medicinal product that must be handled with care.

People who are not taking hydroxycarbamide and in particular pregnant women should avoid being in contact with hydroxycarbamide. Anyone handling hydroxycarbamide should wash their hands before and after contact with the product. To reduce the risk of exposure when taking/handling the product, disposable gloves should be worn.

For film-coated tablets in case the prescribed dose requires breaking the tablet in halves or quarters, this should be done out of the reach of food. Powder eventually spilled from the broken tablet should be wiped up with a damp disposable towel, which must be discarded. If the powder

inside the capsule leaks out, it should be wiped up immediately with the empty capsule shell using a damp disposable towel and disposed of in a plastic bag.

Special precautions for disposal

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

16) Marketing Authorization Holder

Novartis Nigeria Limited

53, Isaac John Street,

Ikeja GRA, Lagos.

NAFDAC Registration Number:

Hydroxyurea Film Coated Tablet 100 mg - A4-100407

Hydroxyurea Film Coated Tablet 1000 mg - A4-100408

Hydroxyurea Capsules – C4-1194