

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

HYDROXYCARBAMIDE 500 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Hydroxycarbamide 500 mg

Excipient with known effect:

Lactose 42.2 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules.

Size 0 hard gelatin capsule with an opaque pink body and an opaque light green cap, containing a white to off-white homogeneous powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Significant tumor response to hydroxycarbamide has been demonstrated in melanoma, resistant chronic myelocytic leukemia, and recurrent metastatic or inoperable carcinoma of the ovary. Hydroxycarbamide used concomitantly with irradiation therapy is intended for use in the local control of primary squamous cell (epidermoid) carcinomas of the head and neck, excluding the lip, and carcinoma of the cervix.

4.2 Dose and Method of Administration

Posology/duration and frequency of administration

Because of the rarity of melanoma, resistant chronic myelocytic leukemia, carcinoma of the ovary, and carcinomas of the head and neck in children, dosage regimens have not been established. All dosage should be based on the patient's actual or ideal weight, whichever is less.

Elderly patients may require a lower dose regimen.

Concurrent use of hydroxycarbamide with other myelosuppressive agents may require adjustments of dosages.

Solid Tumors:

Intermittent therapy:

80 mg/kg administered orally as a *single* dose every *third* day.

Continuous therapy:

20 to 30 mg/kg administered orally as a *single* dose *daily*.

The intermittent dosage schedule offers the advantage of reduced toxicity since patients on this dosage regimen have rarely required complete discontinuance of therapy because of toxicity.

Concomitant therapy with irradiation: (Carcinoma of the head and neck)

80 mg/kg administered orally as a *single* dose every *third* day.

Administration of hydroxycarbamide should be begun at least seven days before initiation of irradiation and

continued during radiotherapy as well as indefinitely afterwards provided that the patient may be kept under adequate observation and evidences no unusual or severe reactions.

Irradiation should be given at the maximum dose considered appropriate for the particular therapeutic situation; adjustment of irradiation dosage is not usually necessary when hydroxycarbamide is used concomitantly.

Resistant Chronic Myelocytic Leukemia: Continuous therapy:

20 to 30 mg/kg administered orally as a *single* dose *daily* is recommended.

An adequate trial period for determining the antineoplastic effectiveness of hydroxycarbamide is 6 weeks of therapy. When there is regression in tumor size or arrest in tumor growth, therapy should be continued indefinitely. Therapy should be interrupted if the white blood cell count drops below 2500/mm³, or the platelet count drops below 100,000/mm³. In these cases, the counts should be rechecked after three days, and therapy resumed when the counts rise significantly toward normal values. Since the hematopoietic rebound is prompt, it is usually necessary to omit only a few doses. If prompt rebound has not occurred during combined hydroxycarbamide and irradiation therapy, irradiation may also be interrupted. However, the need for postponement of irradiation has been rare; radiotherapy has usually been continued using the recommended dosage and technique. Anemia, if it occurs, should be corrected with whole blood replacement, without interrupting hydroxycarbamide therapy. Because hematopoiesis may be compromised by extensive irradiation or by other antineoplastic agents, it is recommended that hydroxycarbamide be administered cautiously to patients who have recently received extensive radiation therapy or chemotherapy with other cytotoxic medicines.

Pain or discomfort from inflammation of the mucous membranes at the irradiated site (mucositis) is usually controlled by measures such as topical anesthetics and orally administered analgesics. If the reaction is severe, hydroxycarbamide therapy may be temporarily interrupted; if it is extremely severe, irradiation dosage may, in addition, be temporarily postponed. However, it has rarely been necessary to terminate these therapies.

Severe gastric distress, such as nausea, vomiting and anorexia resulting from combined therapy may usually be controlled by temporary interruption of hydroxycarbamide administration; rarely has the additional interruption of irradiation been necessary.

Method of administration

The capsule should be swallowed whole with sufficient liquid.

Note: If the patient prefers, or is unable to swallow capsules, the contents of the capsules may be emptied into a glass of water and taken immediately. Some inert material used as a vehicle in the capsule may not dissolve, and may float on the surface.

Patients who take the medicine by emptying the contents of the capsule into water should be reminded that this is a potent medication that must be handled with care. Patients must be cautioned not to allow the powder to come in contact with the skin and mucous membranes, including avoidance of inhaling the powder when opening the capsules. People who are not taking hydroxycarbamide should not be exposed to it. To decrease the risk of exposure, wear disposable gloves when handling hydroxycarbamide, or bottles containing hydroxycarbamide. Anyone handling hydroxycarbamide should wash their hands before and after contact with the bottle or capsules. If the powder is spilled, it should be immediately wiped up with a damp disposable towel and discarded in a closed container, such as a plastic bag, as should the empty capsules. Hydroxycarbamide should be kept away from children and pets.

Additional information on special populations

Renal Insufficiency

There are no data that support specific guidance for dosage adjustment in patients with impaired renal function. Since renal excretion is a pathway of elimination, consideration should be given to decreasing the

dosage in this population. Close monitoring of hematologic parameters is advised.

Hepatic Insufficiency

There are no data that support specific guidance for dosage adjustment in patients with impaired hepatic function. Close monitoring of hematologic parameters is advised.

Pediatric Use

Safety and effectiveness in children have not been established.

Use in the Elderly

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

4.3 Contraindications

Hydroxycarbamide is contraindicated in patients who have demonstrated a previous hypersensitivity to hydroxycarbamide or any other component of its formulation.

Hydroxycarbamide is contraindicated in patients with marked bone marrow depression, i.e. leucopenia (<2500 WBC/mm³) or thrombocytopenia (<100,000/mm³), or severe anemia.

4.4 Special warning and precautions for use

Warnings

Treatment with hydroxycarbamide should not be initiated if bone marrow function is markedly depressed (see section 4.3). Bone marrow suppression may occur, and leucopenia is generally its first and most common manifestation. Thrombocytopenia and anemia occur less often, and are seldom seen without a preceding leucopenia. However, the recovery from the myelosuppression is rapid when therapy is interrupted. It should be borne in mind that bone marrow depression is more likely in patients who have previously received radiotherapy or cytotoxic cancer chemotherapeutic agents; hydroxycarbamide should be used cautiously in such patients.

Patients who have received irradiation therapy in the past may have an exacerbation of post- irradiation erythema.

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

Since hydroxycarbamide may cause drowsiness and other neurologic effects, alertness may be impaired in driving and operating machinery (see section 4.7).

Patients should be advised to maintain adequate fluid intake. Patients should consult with their physician regarding missed doses.

Fatal and nonfatal pancreatitis have occurred in HIV-infected patients during therapy with hydroxycarbamide and didanosine, with or without stavudine. Hepatotoxicity and hepatic failure resulting in death have been reported during post-marketing surveillance in HIV-infected patients 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. Peripheral 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.

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. Patients developing pyrexia, cough, dyspnea, or other respiratory symptoms should be closely

monitored, investigated and treated. Promptly discontinue hydroxycarbamide and treat with corticosteroids to resolve the pulmonary events (see section 4.8).

Erythrocytic Abnormalities

Megaloblastic erythropoiesis, which is self-limiting is often seen early in the course of hydroxycarbamide therapy. The morphological change resembles pernicious anemia, but is not related to Vitamin B12 or folic acid deficiency. The macrocytosis may mask the incidental development of folic acid deficiency; thus, prophylactic administration of folic acid may be warranted. Hydroxycarbamide may also 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.

Hydroxycarbamide should be used with caution in patients with marked renal dysfunction.

In patients receiving long-term therapy with hydroxycarbamide for myeloproliferative disorders, such as polycythemia vera and thrombocythemia, secondary leukemia has been reported. It is unknown whether this leukemogenic effect is secondary to hydroxycarbamide or associated with the patients' underlying disease.

Cutaneous vasculitic toxicities including vasculitic ulcerations and gangrene have occurred in patients with myeloproliferative disorders during therapy with hydroxycarbamide. These vasculitic toxicities were reported most often in patients with a history of or currently receiving 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.

Paediatric Use

Safety and effectiveness in children have not been established.

Use in the Elderly

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

Precautions

When appropriate, patients should be counseled concerning the use of contraceptive measures during therapy.

Concurrent use of hydroxycarbamide and other myelosuppressive agents or radiation therapy may increase the level of bone marrow depression or other adverse reactions (see sections 4.4 and 4.8).

Patients should be informed to maintain adequate fluid intake and to consult the physician regarding missed doses.

Therapy with hydroxycarbamide requires close supervision. The complete status of the blood, including bone marrow examination, if indicated, as well as kidney function and liver function should be determined prior to, and repeatedly during treatment. The determination of the hemoglobin level, total leukocyte counts, and platelet counts should be performed at least once a week throughout the course of hydroxycarbamide therapy. If the white blood cell count decreases to less than 2500/mm³, or the platelet count to less than 100 000/mm³, therapy should be interrupted until the values rise significantly toward normal levels. Anemia, if it occurs, should be managed with whole blood replacement, without interrupting hydroxycarbamide therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent use of hydroxycarbamide and other myelosuppressive agents or radiation therapy may increase the likelihood of bone marrow depression or other adverse events (see section 4.4 and 4.8).

In vitro studies have shown a significant increase in cytarabine activity in hydroxycarbamide- treated cells.

Whether this interaction will lead to synergistic toxicity in the clinical setting or the need to modify cytarabine doses has not been established.

Studies have shown that there is an analytical interference of hydroxycarbamide with the enzymes (urease, uricase, and lactic dehydrogenase) used in the determination of urea, uric acid and lactic acid, rendering falsely elevated results of these in patients treated with hydroxycarbamide. Since hydroxycarbamide may raise the serum uric acid level, dosage adjustment of uricosuric medication may be necessary.

There is an increased risk of fatal systemic vaccine disease with the concomitant use of live vaccines. Live vaccines are not recommended in immunosuppressed patients.

Vaccinations

Concomitant use of hydroxycarbamide with a live virus vaccine may potentiate the replication of the vaccine virus and/or may increase the adverse reaction 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. Patient's antibody response to vaccines may be decreased. The use of live vaccines should be avoided and individual specialist advice sought.

4.6 Fertility, pregnancy and lactation

General principles

Pregnancy category is D.

Pregnancy

Hydroxycarbamide can cause fetal harm when administered to a pregnant woman and has been demonstrated to be a potent teratogenic agent in animals. Malformations have been observed in the offspring of rabbits and rats given doses equivalent to one-third to twice the maximum human dose, respectively. There are no adequate and well-controlled studies in pregnant women. If this medicine is used during pregnancy or if the patient becomes pregnant while on hydroxycarbamide therapy, the patient should be apprised of the potential hazard of the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while taking hydroxycarbamide.

Breast-feeding

Hydroxycarbamide is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from hydroxycarbamide, breast feeding is not recommended during hydroxycarbamide therapy.

4.7 Effects on ability to drive and use machines

Since hydroxycarbamide may cause drowsiness and other neurologic effects, alertness may be impaired. Patients are advised not to drive or operate machinery if these symptoms occur or until their individual susceptibility is known.

4.8 Undesirable effects

Hematological

Adverse reactions have been primarily bone marrow depression (leucopenia, anemia, and occasionally thrombocytopenia (see section 4.4))

Gastrointestinal

Adverse gastrointestinal symptoms include stomatitis, anorexia, nausea, vomiting, diarrhea, and constipation.

Dermatological

Dermatologic reactions include maculopapular rash, facial erythema, and peripheral erythema, skin ulceration, dermatomyositis-like skin rashes, cutaneous lupus erythematosus. Alopecia occurs rarely.

Hyperpigmentation, erythema, atrophy of skin and nails, scaling, violet papules, and alopecia have been observed in some patients after several years of long-term daily maintenance therapy with hydroxycarbamide. Skin cancer has also been reported rarely.

Neurological

Large doses may produce moderate drowsiness. Neurological disturbances have occurred rarely and were limited to headache, dizziness, disorientation, hallucinations, and convulsions.

Renal

Hydroxycarbamide occasionally may cause temporary impairment of renal tubular function accompanied by elevations in serum uric acid, BUN, and creatinine levels. Dysuria occurs rarely.

Musculoskeletal and connective tissue disorders

Systemic lupus erythematosus.

Respiratory

Interstitial lung disease, pneumonitis, alveolitis, allergic alveolitis, cough.

Hypersensitivity

Drug-induced Fever

High fever ($>39^{\circ}\text{C}$) requiring hospitalization in some cases has been reported concurrently with gastrointestinal, pulmonary, musculoskeletal, hepatobiliary, dermatological or cardiovascular manifestations. Onset typically occurred within 6 weeks of initiation and resolved promptly after discontinuation of hydroxycarbamide. Upon re-administration fever re-occurred within 24 hours.

Other

Fever, chills, malaise, asthenia, azoospermia, oligospermia, cholestasis, hepatitis, tumor lysis syndrome, and elevation of hepatic enzymes have also been reported.

The association of hydroxycarbamide with the development of acute pulmonary reactions consisting of diffuse pulmonary infiltrates, fibrosis, pulmonary edema, fever, and dyspnea has been rarely reported.

Cutaneous vasculitic toxicities including vasculitic ulcerations and gangrene have occurred in patients with myeloproliferative disorders during therapy with hydroxycarbamide. These vasculitic toxicities were reported most often in patients with a history of or currently receiving interferon therapy (see section 4.4)

Fatal and nonfatal pancreatitis and hepatotoxicity, and severe peripheral neuropathy have been reported in HIV-infected patients who received hydroxycarbamide in combination with antiretroviral agents, in particular didanosine plus stavudine. Patients treated with hydroxycarbamide in combination with didanosine, stavudine, and indinavir showed a median decline in CD4 cells of approximately $100/\text{mm}^3$ (see section 4.4).

Combined Hydroxycarbamide and Irradiation Therapy

Adverse reactions observed with combined hydroxycarbamide and irradiation therapy are similar to those reported with the use of hydroxycarbamide alone. These effects primarily include bone marrow depression (anemia and leucopenia), and gastric irritation. Almost all patients receiving an adequate course of combined hydroxycarbamide and irradiation therapy will demonstrate concurrent leucopenia. Decreased platelet counts ($<100,000/\text{mm}^3$) have occurred rarely and only in the presence of marked leucopenia. Gastric distress has also been reported with irradiation alone and in combination with hydroxycarbamide therapy.

It should be borne in mind that therapeutic doses of irradiation alone produce the same adverse reactions as hydroxycarbamide; combined therapy may cause an increase in the incidence and severity of these side effects.

Although inflammation of the mucous membranes at the irradiated site (mucositis) is attributed to irradiation alone, some investigators believe that the more severe cases are due to combination therapy.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Acute mucocutaneous toxicity has been reported in patients receiving hydroxycarbamide at a dosage several fold in excess of the usual recommended dosage. Soreness, violet erythema, edema on palms and foot soles followed by scaling of hands and feet, intense generalized hyperpigmentation of skin, and severe acute stomatitis were observed.

In the case of overdosage implement immediate gastric lavage, followed by supportive cardiorespiratory therapy. Long term monitoring of the hemopoietic system is necessary.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents

ATC code: L01XX05

Mechanism of Action

The precise mechanism by which hydroxycarbamide produces its cytotoxic effects cannot, at present, be described. However, the reports of various studies in tissue culture, rats and man lend support to the hypothesis that hydroxycarbamide causes an immediate inhibition of DNA synthesis without interfering with the synthesis of ribonucleic acid or of protein. This hypothesis explains why, under certain conditions, hydroxycarbamide may induce teratogenic effects.

Three mechanisms of action have been postulated for the increased effectiveness of concomitant use of hydroxycarbamide therapy with irradiation on squamous cell (epidermoid) carcinomas of the head and neck. *In vitro* studies utilizing Chinese hamster cells suggest that hydroxycarbamide (1) is lethal to normally radio-resistant S-stage cells and (2) holds other cells of the cell cycle in the G1 or pre-DNA synthesis stage where they are most susceptible to the effects of irradiation. The third mechanism of action has been theorized on the basis of *in vitro* studies of HeLa cells; it appears that hydroxycarbamide by inhibition of DNA synthesis, hinders the normal repair process of cells damaged but not killed by irradiation, thereby decreasing their survival rate; RNA and protein synthesis have shown no alteration.

5.2 Pharmacokinetic properties

After oral administration in man, hydroxycarbamide is readily absorbed from the gastrointestinal tract. The medicine reaches peak serum concentrations within 2 hours. Approximately 80% of an oral or intravenous dose of 7 to 30 mg/kg may be recovered in the urine within 12 hours.

Hydroxycarbamide crosses the blood-brain barrier.

5.3 Preclinical safety data

Animal Pharmacology and Toxicology

The oral LD₅₀ of hydroxycarbamide is 7330 mg/kg in mice and 5780 mg/kg in rats, given as a single doses. In subacute and chronic toxicity studies in the rat, the most consistent pathological findings were an apparent dose-related mild to moderate bone marrow hypoplasia as well as pulmonary congestion and mottling of the lungs. At the highest dosage levels (1260 mg/kg/day for 37 days then 2520 mg/kg/day for 40 days), testicular atrophy with absence of spermatogenesis occurred. In several animals hepatic cell damage with fatty metamorphosis was noted. In the dog, mild to marked bone marrow depression was a consistent finding

except at the lower dosage levels. Additionally, at the higher dose levels (140 to 420 mg or 140 to 1260 mg/kg/week given 3 or 7 days weekly for 12 weeks), growth retardation, slightly increased blood glucose values, and hemosiderosis of the liver or spleen were found, reversible spermatogenic arrest was noted. In the higher, often lethal, doses (400 to 800 mg/kg/day for 7 to 15 days), hemorrhage and congestion were found in the lungs, brain, and urinary tract. Cardiovascular effects (change in heart rate, blood pressure, orthostatic hypotension, EKG changes) and hematological changes (slight hemolysis, slight methemoglobinemia) were observed in some species of laboratory animals at doses exceeding clinical levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Hydroxycarbamide is unequivocally genotoxic and a presumed transpecies carcinogen which implies a carcinogenic risk to humans. In patients receiving long-term hydroxycarbamide for myeloproliferative disorders, such as polycythemia vera and thrombocythemia, secondary leukemia has been reported; it is unknown whether this leukemogenic effect is secondary to hydroxycarbamide or the patients' underlying disease. Skin cancer has also been reported in patients receiving long-term hydroxycarbamide.

Azoospermia or oligospermia, sometimes reversible, have been observed in men. Male patients should be informed about the possibility of sperm conservation before the start of therapy.

Hydroxycarbamide may be genotoxic. Men under therapy are advised to use safe contraceptive measures during and at least 1 year after therapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients

Lactose Monohydrate

Citric Acid

Disodium Phosphate

Magnesium Stearate

Size 0 Pink Op/Light Green OpC248 Capsule

Capsule Composition

Gelatin

Titanium dioxide

Erythrosin - FD&C Red 3

Indigotine - FD&C Blue 2

Quinoline yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C.

Keep out of the reach and sight of children.

6.5 Nature and contents of container

PVC/Aclar film sealed with Aluminum Foil (PVC/PCTFE/Alu & Alu/Alu Blister)

In packages of 100 capsules with its package leaflet in a carton box.

6.6. Special precautions for disposal and other handling

To minimize the risk of dermal exposure, always wear impervious gloves when handling bottles containing

hydroxycarbamide capsules. This includes all handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility and dose preparation and administration.

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

Date of first authorization: 04 April 2019

Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

10.06.2019