HYDMOXIA 500 mg Hard Capsules

1. NAME OF THE MEDICINAL PRODUCT

HYDMOXIA 500 mg Hard Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains

Active substance: Hydroxycarbamide 500 mg

Excipients with known effect:

Lactose monohydrate (from cow milk) 42.2 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, Hard

Capsule content: white to off-white homogeneous powder

Capsule: Size 0 hard gelatin capsule with an opaque pink body and an opaque light green cap

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Significant tumor response to HYDMOXIA (hydroxyurea capsules, USP) has been demonstrated in melanoma, resistant chronic myelocytic leukemia, and recurrent metastatic or inoperable carcinoma of the ovary. HYDMOXIA 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 Posology and method of administration

Posology

Adults

Treatment regimens can be continuous or intermittent. The continuous regimen is particularly suitable for chronic myeloid leukaemia, while the intermittent regimen, with its diminished effect on the bone marrow, is more satisfactory for the management of cancer of the cervix.

HYDMOXIA should be started 7 days before concurrent irradiation therapy. If HYDMOXIA is used concomitantly with radiotherapy, adjustment of radiation dosage is not usually necessary.

An adequate trial period for determining the antineoplastic effect of HYDMOXIA is six weeks. Where there is a significant clinical response therapy may be continued indefinitely, provided that the patient is kept under adequate observation and shows no unusual or severe reactions. Therapy should be interrupted if the white cell count drops below 2.5×10^9/L or the platelet count below 100×10^9/L (see section 4.4).

In these cases, the counts should be reevaluated after three days and therapy resumed when the counts return to acceptable levels. Hematopoietic rebound is usually rapid. If rapid rebound has not occurred during combined HYDMOXIA and irradiation therapy, irradiation may also be interrupted. Anemia, even if severe, can be managed without interrupting HYDMOXIA therapy.

Severe gastric distress, such as nausea, vomiting, and anorexia, resulting from combined therapy may usually be controlled by interruption of HYDMOXIA administration.

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, HYDMOXIA therapy may be temporarily interrupted; if it is extremely severe, irradiation dosage may, in addition, be temporarily postponed.

Continuous therapy

HYDMOXIA 20-30 mg/kg should be given daily in single doses. Dosage should be based on the patient's actual or ideal weight, whichever is the less. Therapy should be monitored by repeat blood counts.

Intermittent therapy

HYDMOXIA 80 mg/kg in single doses should be given every third day. Using the intermittent regimens, the likelihood of WBC depression is diminished, but if low counts are produced, 1 or more doses of HYDMOXIA should be omitted.

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

Special Populations

Children

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

Elderly

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

Renal Impairment

Since renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of HYDMOXIA in this population.

Method of administration

For oral use.

NB: 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. The contents of capsules should not be inhaled or allowed to come into contact with the skin or mucous membranes. Spillages must be wiped immediately.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Marked leucopenia (<2.5 wbc×10^9/L), thrombocytopenia (<100×10^9/L), or severe anemia.

4.4 Special warning and precautions for use

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. If bone marrow function is depressed, treatment with HYDMOXIA should not be initiated. The determination of haemoglobin level, total leukocyte counts, and platelet counts should be performed at least once a week throughout the course of hydroxycarbamide therapy. If WBC falls below 2.5x10^9/L or platelet count to <100x10^9/L, therapy should be interrupted. Counts should be rechecked after 3 days and treatment resumed when they rise significantly towards normal.

HYDMOXIA may produce bone marrow suppression; leukopenia is generally its first and most common manifestation. Thrombocytopenia and anaemia occur less often and are seldom seen without a preceding leukopenia. Bone marrow depression is more likely in patients who have previously received radiotherapy or cytotoxic cancer chemotherapeutic agents; HYDMOXIA should be used cautiously in such patients. The recovery from myelosuppression is rapid when HYDMOXIA therapy is interrupted.

Severe anaemia must be corrected with whole blood replacement before initiating therapy with hydroxycarbamide. If, during treatment, anaemia occurs, correct without interrupting HYDMOXIA therapy. Erythrocytic abnormalities; megaloblastic erythropoeisis, which is self-limiting, is often seen early in the course of hydroxycarbamide therapy. The morphologic change resembles pernicious anaemia, but is not related to vitamin B12 or folic acid deficiency. The macrocytosis may mask the incidental development of folic acid deficiency; regular determinations of serum folic acid are recommended. Hydroxycarbamide may also delay plasma iron clearance and reduce the rate of iron utilisation by erythrocytes but it does not appear to alter the red blood cell survival time.

Patients who have received irradiation therapy in the past may have an exacerbation of postirradiation erythema when HYDMOXIA is given.

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

Hydroxycarbamide is not licensed for use in combination with antiretroviral agents for HIV disease and it may cause treatment failure and toxicities (in some cases fatal) in HIV patients (see section 4.5).

In patients receiving long-term therapy with hydroxycarbamide for myeloproliferative disorders, such as polycythemia, secondary leukaemia has been reported. It is unknown whether this leukaemogenic effect is secondary to hydroxycarbamide or associated with the patient's underlying disease. 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.

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. The digital distribution of these vasculitic ulcerations and progressive clinical behaviour of peripheral vasculitic insufficiency leading to digital infarct or gangrene were distinctly different than the typical skin ulcers generally described with Hydroxycarbamide. Due to potentially severe clinical outcomes for the cutaneous vasculitic ulcers reported in patients with myeloproliferative disease, hydroxycarbamide should be discontinued if cutaneous vasculitic ulcerations develop and alternative cytoreductive agents should be initiated as indicated.

The possibility of an increase in serum uric acid, resulting in the development of gout or, at worst, uric acid nephropathy, should be borne in mind in patients treated with hydroxycarbamide, especially when used with other cytotoxic agents. It is therefore important to monitor uric acid levels regularly and maintain a high fluid intake during treatment.

This product contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Vaccinations

Concomitant use of HYDMOXIA 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 HYDMOXIA may result in severe infection. The patient's antibody response to vaccines may be decreased. The use of live vaccines should be avoided during treatment and for at least 6 months after treatment has finished and individual specialist advice sought (see section 4.5).

Respiratory disorders

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, dyspnoea or other respiratory symptoms should be closely monitored, investigated and treated. Promptly discontinue of hydroxyurea and treatment with corticosteroids appears to be associated with resolution of the pulmonary events (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

The myelosuppressive activity may be potentiated by previous or concomitant radiotherapy or cytotoxic therapy. Fatal and non-fatal pancreatitis has occurred in HIV-infected patients during therapy with hydroxycarbamide and didanosine, with or without stavudine. Hepatotoxicity and hepatic failure resulting in death were 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. (see section 4.4).

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.

Vaccinations

There is an increased risk of severe or fatal infections with the concomitant use of live vaccines. Live vaccines are not recommended in immunosuppressed patients (see section 4.4).

4.6 Fertility, pregnancy and lactation

Drugs which affect DNA synthesis, such as hydroxycarbamide, may be potent mutagenic agents. The physician should carefully consider this possibility before administering this drug to male or female patients who may contemplate conception. Since HYDMOXIA is a cytotoxic agent it has produced a teratogenic effect in some animal species.

In rats and dogs, high doses of hydroxycarbamide reduced sperm production.

Hydroxycarbamide is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants from hydroxycarbamide, a decision should be made whether to discontinue nursing or to discontinue HYDMOXIA, taking into account the importance of the drug to the mother.

HYDMOXIA can cause fetal harm when administered to a pregnant woman. HYDMOXIA should not normally be administered to patients who are pregnant, or to mothers who are breast feeding, unless the potential benefits outweigh the possible hazards.

When appropriate both male and female patients should be counseled concerning the use of contraceptive measures before and during treatment with HYDMOXIA.

4.7 Effects on ability to drive and use machines

Hydroxycarbamide may cause drowsiness. Patients receiving it should not drive or operate machinery unless it has been shown not to affect physical or mental ability.

4.8 Undesirable effects

Bone-marrow suppression is the major toxic effect of 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.

In some patients, hyperpigmentation, atrophy of skin and nails, scaling, violet papules and alopecia have been observed following several years of long-term daily maintenance therapy with hydroxycarbamide.

Cases of fatal and non-fatal pancreatitis and hepatotoxicity and severe peripheral neuropathy have been observed in HIV patients when hydroxycarbamide was administered 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/mm³ (see sections 4.4 and 4.5).

Adverse reactions observed with combined HYDMOXIA and irradiation therapy were similar to those reported with the use of HYDMOXIA alone, primarily bone marrow depression (leukopenia and anaemia) and gastric irritation. Nearly all patients receiving an adequate course of combined HYDMOXIA and irradiation therapy will develop leukopenia. Decreased platelet counts (<100,000/mm³) have occurred rarely and usually in the presence of marked leukopenia. HYDMOXIA may potentiate some adverse reactions usually seen with irradiation alone, such as gastric distress and mucositis.

The list is presented by system organ class, MedDRA preferred term, and frequency using the following frequency categories: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (<1/10000), and not known (cannot be estimated from the available data).

System Organ Class	Frequency	MedDRA Term
Infections and Infestations	Rare	Gangrene
Neoplasms Benign and Malignant (including cysts and polyps)	Common	Skin cancer
Blood and Lymphatic System Disorders	Very common	Bone marrow failure, CD4 lymphocytes decreased, leukopenia, thrombocytopenia, platelet count decreased, anemia
Metabolism and Nutrition Disorders	Very common	Anorexia
Psychiatric Disorders	Common	Hallucination, disorientation
Nervous System Disorders	Common	Convulsion, dizziness, peripheral neuropathy1, somnolence, headache
Respiratory, Thoracic, and Mediastinal Disorders	Common	Pulmonary fibrosis, pulmonary edema, lung infiltration, dyspnea
	Unknown	Interstitial lung disease, pneumonitis, alveolitis, allergic alveolitis, cough
Gastrointestinal Disorders	Very common	Pancreatitis1, nausea, vomiting, diarrhoea, stomatitis, constipation, mucositis, stomach discomfort, dyspepsia, abdominal pain, melaena
Hepatobiliary Disorders	Common	Hepatotoxicity1, hepatic enzyme increased, cholestasis, hepatitis

Skin and Subcutaneous Tissue Disorders	Very common	Cutaneous vasculitis, dermatomyositis, alopecia, rash maculo-papular, rash papular, skin exfoliation, skin atrophy, skin ulcer, erythema, skin hyperpigmentation, nail disorder
	Very rare	Systemic and cutaneous lupus erythematosus
Renal and Urinary Disorders	Very common	Dysuria, blood creatinine increased, blood urea increased, blood uric acid increased
General Disorders and Administration Site Conditions	Very common	Pyrexia, asthenia, chills, malaise
Reproductive system and breast disorders	Very common	azoospermia, oligospermia
1 Fatal and non-fatal pancreatitis and hepatotoxicity and severe peripheral neuropathy have been reported in HIV-infected patients who received hydroxyurea in combination with antiretroviral agents, in particular didanosine plus stavudine.		

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Health Product Pharmacovigilance Center at: http://thaihpvc.fda.moph.go.th

4.9 Overdose

Immediate treatment consists of gastric lavage, followed by supportive therapy for the cardiorespiratory systems if required. In the long term, careful monitoring of the haemopoietic system is essential and, if necessary, blood should be transfused.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents

ATC code: L01XX05

Hydroxycarbamide is an orally active antineoplastic agent. Although the mechanism of action has not yet been clearly defined, hydroxycarbamide appears to act by interfering with synthesis of DNA.

5.2 Pharmacokinetic properties

After oral administration hydroxycarbamide is readily absorbed from the gastrointestinal tract. Peak plasma concentrations are reached in 2 hours; by 24 hours the serum concentrations are virtually zero. Approximately 80% of an oral or intravenous dose of 7 to 30 mg/kg may be recovered from the urine within 12 hours. Hydroxycarbamide crosses the blood-brain barrier. Hydroxycarbamide is well distributed throughout the body.

5.3 Preclinical safety data

Hydroxycarbamide is unequivocally genotoxic and a presumed trans-species carcinogen which implies a carcinogenic risk to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate (from cow milk)

Anhydrous citric acid

Disodium hydrogen phosphate anhydrous

Magnesium Stearate

Hard gelatin capsule

Erythrosin - FD&C Red 3

Indigotine - FD&C Blue 2

Titanium dioxide

Gelatin (bovine)

Quinoline yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C. Protect from moisture.

6.5 Nature and contents of container

HYDMOXIA 500 mg Hard Capsules are presented in blisters of PVC/Aclar sealed with Aluminum Foil; in packages of 100 capsules (10 capsules in 1 blister, 10 blisters in a package) with its patient leaflet in a carton box.

6.6. Special precautions for disposal and other handling

People who are not taking HYDMOXIA should not be exposed to it. To decrease the risk of exposure, wear disposable gloves when handling HYDMOXIA. Anyone handling HYDMOXIA should wash their hands before and after contact with the capsules. If the powder is spilled, it should be immediately wiped with a damp disposable towel and discarded in a closed container, such as a plastic bag, as should the empty capsules. HYDMOXIA should be kept away from children. Pregnant women should not handle HYDMOXIA.

To minimize the risk of dermal exposure, always wear impervious gloves when handling capsules containing HYDMOXIA. 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

American Taiwan Biopharm Co., Ltd.

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Chomphon, Chatuchak, Bangkok, Thailand. 10900

8. MARKETING AUTHORIZATION NUMBER

1C 15097/63 (NG)

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

01.10.2020

10. DATE OF REVISION OF THE TEXT

08.10.2021