SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

HYDMOXIA 500 mg hard capsules
Cytotoxic

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

Hard Capsules
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

Neoplastic Diseases:
HYDMOXIA is indicated for the treatment of melanoma and resistant chronic myelocytic leukemia. It is used for the treatment of cervical cancer and primary squamous cell cancers in the head and neck region (excluding the lips) in combination with radiotherapy.

Sickle Cell Anemia:
HYDMOXIA is indicated for the treatment of sickle cell anemia in adults. It reduces the number and severity of painful vaso-occlusive crises. It reduces the need for hospitalization, blood transfusion and the incidence of chest syndrome. It significantly prolongs the time between the first and second vaso-occlusive crisis.

4.2 Posology and method of administration

Posology/administration frequency and duration:
The treatment dose of HYDMOXIA is adjusted according to the ideal or actual body weight of the patient, whichever is the less.

Neoplastic Diseases

- Solid Tumors
Intermittent therapy
80 mg/kg is administered orally as a single dose every third day.
Continuous therapy
20-30 mg/kg is administered orally as a single daily dose.
The advantage of intermittent therapy is a reduction in drug toxicity (e.g. bone marrow depression).

Combined therapy with radiotherapy
(in head, neck and cervix cancers)
80 mg/kg is administered orally as a single dose every third day.
HYDMOXIA should be started to be administered at least 7 days before starting radiotherapy, it should be continued during and after radiotherapy, and it should be administered as long as the patient is kept under constant supervision, unless unexpected or severe side effects are observed.

- Resistant Chronic Myelocytic Leukemia
Continuous therapy
20 to 30 mg/kg orally administered as a single daily dose.
An adequate trial period for determining the antineoplastic effect of HYDMOXIA is six weeks. Treatment should be continued when a significant clinical response is obtained. If the leukocyte count falls below 2,500/mm^3 and the platelet count falls below 100,000/mm^3, the treatment should be interrupted. In these cases, the leukocyte and platelet count should be repeated after 3 days and treatment should be continued when the values increase to acceptable levels. Hematopoietic recovery is usually rapid. If hematopoietic recovery does not occur rapidly with combined HYDMOXIA and radiotherapy treatment, radiotherapy may also be discontinued. Anemia, even if severe, can be managed without interrupting HYDMOXIA therapy.

Dose adjustment:
HYDMOXIA should be administered with caution in patients who have recently received intensive radiotherapy or chemotherapy with other cytotoxic drugs.

Pain or discomfort from inflammation of the mucous membranes at the irradiated site 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.

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

Sickle Cell Anemia
The starting dose of HYDMOXIA is 15 mg/kg orally administered once a day. The patient's blood counts should be observed every 2 weeks (see section 4.4). If blood counts are within acceptable values*, the dose can be increased by 5 mg/kg/day every 12 weeks to reach the maximum tolerated dose (the highest dose without toxic blood counts** for 24 weeks) or the maximum dose of 35 mg/kg/day.

* acceptable values: neutrophils ≥ 2500 cells/mm3, platelets ≥ 95,000/mm^2, hemoglobin > 5.3 g/dL, or reticulocytes ≥ 95,000/mm^3 if hemoglobin concentration < 9g/dL

** toxic blood counts: neutrophils <2000 cells/mm^3, platelets <80,000/mm^2, hemoglobin <4.5 g/dL, or reticulocytes <80,000/mm^3 if hemoglobin concentration <9g/dL

If blood counts are between acceptable and toxic limits, do not increase the dose. If blood counts are considered toxic, interrupt HYDMOXIA treatment until they return to normal values. When the values return to normal, treatment can be resumed with a dose of 2.5 mg/kg/day lower than the dose at which toxicity is observed. The dose of HYDMOXIA may then be increased or decreased by 2.5 mg/kg/day every 12 weeks and titrated until a stable dose is achieved for 24 weeks without hematological toxicity. Any dose at which a patient develops hematological toxicity twice should not be attempted again. The dose should not exceed 35 mg/kg/day.

Dose adjustment:
Concomitant use of HYDMOXIA with other myelosuppressive drugs may require dose adjustment.

Method of administration:
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 (see Section 6.6). Some inert substances used as carriers in the capsule may not dissolve and remain on the water surface.

Additional information on special populations:
Renal impairment: Since renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of HYDMOXIA in this population.

Based on the results of a single-dose study of the effect on the pharmacokinetics of renal function in adult patients with sickle cell anemia, the starting dose of hydroxycarbamide should be reduced in patients with renal impairment.

Close monitoring of hematological parameters is also recommended.

Hepatic impairment: There are no data to form a specific guideline to support dose adjustment in patients with hepatic dysfunction. Close monitoring of hematological parameters is recommended.

Pediatric population: The safety and efficacy of hydroxycarbamide in children have not been established (see section 4.4).

Geriatric population: Elderly patients may require a lower dosage regimen (see section 4.4).

4.3 Contraindications

It is contraindicated in patients who are allergic to hydroxycarbamide or its other ingredients.

4.4 Special warning and precautions for use

In neoplastic diseases
HYDMOXIA treatment should not be initiated if bone marrow function is suppressed, i.e. there is leukopenia (<2500 /mm^3) or thrombocytopenia (<100.000/mm^3) or severe anemia. HYDMOXIA may produce bone marrow suppression; leukopenia is generally its first and most common manifestation. Thrombocytopenia and anemia 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 anemia must be corrected before initiating therapy with HYDMOXIA.
Patients who have received irradiation therapy in the past may have an exacerbation of post irradiation erythema when HYDMOXIA is given.

In sickle cell anemia patients
Hydroxycarbamide is a cytotoxic and myelosuppressive agent. If bone marrow function is markedly suppressed, i.e. neutrophils are <2000 cells/mm3, platelet counts <80,000/mm3, and hemoglobin levels <4.5 g/dL, or if reticulocytes are <80,000/mm3 when hemoglobin concentration is <9 g/dL, HYDMOXIA should not be given (see section 4.2). Neutropenia is usually the first and most common manifestation of hematological suppression. Thrombocytopenia and anemia are less common, and it is very rare to occur without leukopenia. Myelosuppression usually resolves quickly when HYDMOXIA treatment is discontinued.

Erythrocyte abnormalities: Megaloblastic erythropoiesis, which is self-limiting, is often seen early in the course of hydroxycarbamide therapy. The morphologic change resembles pernicious anemia, but is not related to vitamin B_{12} or folic acid deficiency. The macrocytosis may mask the incidental development of folic acid deficiency; therefore, prophylactic folic acid can be administered. 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.

Other
Fatal and nonfatal pancreatitis has been observed in HIV-infected patients during treatment with hydroxycarbamide and didanosine, with or without stavudine. Hepatotoxicity and fatal hepatic failure have been reported in post-marketing surveillance in HIV-infected patients treated with hydroxycarbamide and other antiretroviral agents. Fatal hepatic events were reported more frequently in patients treated with the combination of hydroxycarbamide, didanosine, and stavudine. Peripheral neuropathy, in some cases severe, has been reported in HIV-infected patients receiving hydroxycarbamide in combination with antiretroviral agents, including didanosine, with or without stavudine (see section 4.8).

Cutaneous vasculitic toxicities including vasculitic ulcerations and gangrene have occurred in patients with myeloproliferative disorders during therapy with hydroxycarbamide. These vasculitic toxicities have been reported more frequently in patients with a history of or on treatment with 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.

Renal impairment
HYDMOXIA should be used with caution in patients with renal dysfunction. Based on the results of a single-dose study of the pharmacokinetics of hydroxycarbamide in patients with sickle cell anemia, the starting dose of hydroxycarbamide should be reduced in patients with renal impairment (see section 4.2).

Patients should be warned about adequate fluid intake.

Pediatric use
Safety and effectiveness in children have not been established. There is evidence that pediatric patients with sickle cell anemia respond similarly to adults in terms of clinical and hematological effect.

Geriatric use
Elderly patients may be more sensitive to the effects of HYDMOXIA and a lower dosage regimen may be required.

Lactose
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.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of hydroxycarbamide with other myelosuppressive drugs or radiotherapy in patients with neoplastic disease may increase the likelihood of bone marrow suppression or other side effects (see sections 4.4 and 4.8).

Dose adjustment of uricosuric drugs may be necessary, as hydroxycarbamide may increase serum uric acid levels.

In vitro studies showed a significant increase in the cytotoxic effect of cytarabine in cells exposed to hydroxycarbamide. It has not been determined whether this interaction will cause synergistic toxicity in clinical practice or whether modification of cytarabine doses is required.

4.6 Fertility, pregnancy and lactation

General recommendation
Pregnancy Category: D

Women of childbearing potential/Contraception
It is known that hydroxycarbamide has a strong teratogenic effect in many animal species. Effects following prenatal ingestion of hydroxycarbamide include embryo-fetal death, multiple fetal malformations of the viscera and skeleton, growth retardation, and functional defects.

When HYDMOXIA is administered to a pregnant woman, it may harm the fetus. There are no adequate and well-controlled studies of the use of hydroxycarbamide in pregnant women. If HYDMOXIA has been used during pregnancy or if the patient becomes pregnant while being treated with HYDMOXIA, the patient should be informed of the potential harm to the fetus. Women of childbearing potential should be warned to avoid becoming pregnant while taking HYDMOXIA.

Pregnancy
HYDMOXIA should not be used during pregnancy unless necessary.

Lactation
Hydroxycarbamide passes into milk. The benefit of breastfeeding for the child and the benefit of HYDMOXIA treatment for the nursing mother should be taken into account when deciding whether to stop breastfeeding or stop HYDMOXIA treatment.

Reproductive ability/Fertility
In preclinical safety studies, hydroxycarbamide has been shown to reduce fertility in animals (see section 5.3). This possibility should be considered before giving medication to male or female patients who are considering having children.

4.7 Effects on ability to drive and use machines

The effect of hydroxycarbamide on the ability to drive and use machines has not been studied. Attention may be reduced as HYDMOXIA may cause sleep and other neurological effects (see section 4.8). Patients should be warned to be careful while driving and using machines.

4.8 Undesirable effects

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. In the ACTG 5025 study, 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).

Cutaneous vasculitic toxicities including vasculitic ulcerations and gangrene have occurred in patients with myeloproliferative disorders during therapy with hydroxycarbamide. These vasculitic toxicities have been reported more frequently in patients with a history of or undergoing treatment with interferon (see section 4.4).

Adverse effects in neoplastic diseases
Blood and lymphatic system disorders: Bone marrow suppression (leukopenia, anemia, thrombocytopenia) (see section 4.4)

Psychiatric disorders: Hallucination, disorientation

Nervous system disorders: Convulsions, dizziness, peripheral neuropathy, somnolence, rarely headache

Gastrointestinal disorders: Stomatitis, anorexia, nausea, vomiting, diarrhea and constipation

Skin and subcutaneous tissue disorders: Maculopapular rash, facial erythema, peripheral erythema, skin ulcers and dermatomyositis-like skin changes. After several years of long-term daily maintenance therapy with hydroxycarbamide, hyperpigmentation, erythema, atrophy of the skin and nails, scaling of the skin, purple papules and alopecia have been observed in some patients. Alopecia is rare. Rarely, skin cancer has also been reported.

Renal and urinary disorders: Increase in serum uric acid, BUN and creatinine levels; rarely dysuria.

General disorders and administration site conditions: Pyrexia, chills, malaise, asthenia, increase in liver enzymes; rarely acute pulmonary reactions (diffuse pulmonary infiltration/fibrosis and dyspnea)

Adverse reactions observed with combined hydroxycarbamide and irradiation therapy were similar to those reported with the use of hydroxycarbamide alone, primarily bone marrow depression (leukopenia and anemia) and gastric irritation. Nearly all patients receiving an adequate course of combined hydroxycarbamide 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.

Adverse effects in sickle cell anemia patients
In a multicenter hydroxycarbamide study in sickle cell anemia patients, the most common adverse events were hematological (see section 4.4), neutropenia and low reticulocyte and platelet levels necessitated temporary discontinuation of hydroxycarbamide therapy in almost all patients. Hematological improvement was usually within two weeks. Non-hematological events possibly associated with hydroxycarbamide were hair loss, skin rashes, fever, gastrointestinal discomfort, weight gain, bleeding, and paravirus B-19 infection. The frequency of these events was similar in patients treated with hydroxycarbamide and placebo. Melanonychia was also reported in patients receiving hydroxycarbamide for the treatment of sickle cell anemia.

Adverse Effects Reported in Clinical or Post-Marketing Experience
The following frequency groups were used:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data)

Infections and infestations
Not known: Gangrene, erythema infectiosum

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Not known: Skin cancer

Blood and lymphatic system disorders
Not known: Bone marrow failure, CD4 lymphocyte decreased, leukopenia, neutropenia, thrombocytopenia, platelet count decreased, anemia, reticulocyte count decreased

Metabolism and nutrition disorders
Not known: Anorexia

Psychiatric disorders
Not known: Hallucinations, disorientation

Nervous system disorders
Not known: Convulsions, dizziness, peripheral neuropathy, somnolence, headache

Vascular disorders
Not known: Bleeding

Respiratory, thoracic and mediastinal disorders
Not known: Pulmonary fibrosis, lung infiltration, dyspnea

Gastrointestinal disorders
Not known: Pancreatitis, nausea, vomiting, diarrhea, stomatitis, constipation, mucositis, stomach discomfort, dyspepsia, gastrointestinal disturbance

Hepatobiliary disorders
Not known: Hepatotoxicity, liver enzymes increased, bromosulphthalein test abnormal

Skin and subcutaneous tissue disorders
Not known: Cutaneous vasculitis, dermatomyositis, alopecia, maculopapular rash, papular rash, skin exfoliation, skin atrophy, rash, skin ulcer, erythema, skin hyperpigmentation, nail disorder, nail discoloration

Renal and urinary disorders
Not known: Dysuria, increased blood creatinine levels, increased blood urea levels, increased blood uric acid levels.

General disorders and administration site conditions
Not known: Pyrexia, asthenia, chills, malaise

Investigations
Not known: Weight gain

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 national reporting system.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents
ATC code: L01XX05

Mechanism of action
The antineoplastic mechanism of action of hydroxycarbamide is not fully known. Different studies in tissue culture, rats, and humans support that hydroxycarbamide acts as a ribonucleotide reductase inhibitor, inhibiting DNA synthesis without interfering with ribonucleic acid or protein synthesis.

The increase in effect due to the combined use of radiation and hydroxycarbamide in head and neck squamous cell (epidermoid) cancers is explained by three mechanisms: (1) Hydroxycarbamide is lethal to S-stage cells, which are normally radiation resistant, in Chinese hamster cells *in vitro*. (2) It keeps other cells in the cell cycle in the pre-G-1 or pre-DNA synthesis stage, where they are more sensitive to the effects of radiation. (3) By inhibiting DNA synthesis, it also shortens the lifespan of cells that are damaged by radiation but do not die, by preventing normal repair. RNA and protein synthesis remain unchanged.

The mechanism of action of hydroxycarbamide in sickle cell anemia is not fully known. An increase in hemoglobin F production may be associated with decreased neutrophil count, increased water content of erythrocytes, increased malformation of sickle-shaped cells, or altered adhesion of red blood cells to the endothelium. The exact mechanism of the cytotoxic and cytoreductive effects of hydroxycarbamide is not known.

Clinical efficacy and safety

Clinical studies

The efficacy of hydroxycarbamide has been evaluated in large clinical trials. The study was a randomized, double-blind, placebo-controlled study evaluating 299 adult patients (aged ≥ 18 years) with moderate to severe disease (≥ 3 painful crises per year). The study was based on the observation that fewer painful crises were observed in patients receiving hydroxycarbamide after the Data Safety Monitoring Committee had completed patient recruitment but before the planned 24-week follow-up was completed in all patients.

Compared with placebo treatment (N=147), hydroxycarbamide treatment (N=152) included the number of painful attacks in one year (mean 2.5 and 4.6 episodes, p=0.001), the number of painful attacks requiring hospitalization in one year (mean 1 and 2.5 hospitalizations; p=0.0027), incidence of chest syndrome (56 and 101 episodes, p=0.003), number of patients requiring transfusion (55 and 79 patients, p=0.002), and transfused blood units (423 and 670 units, p=0.003) significantly decreased. Painful crisis is defined as acute sickling pain lasting longer than 4 hours, requiring parenteral narcotic or NSAID, resulting in admission to a healthcare facility; chest syndrome, priapism, and hepatic sequestration are also included in this definition. Hydroxycarbamide significantly increased the mean time to the first (mean 2.76 and 1.35 months, p=0.014) and the second (mean 6.58 and 4.13 months, p=0.0024) painful crises.

There were no deaths due to hydroxycarbamide treatment and none of the patients developed neoplastic diseases during the study. Treatment was completely discontinued for medical reasons in 14 patients treated with hydroxycarbamide (myelotoxicity in 2 patients) and 6 patients treated with placebo (see section 4.8).

Fatal Hemoglobin: In patients with sickle cell anemia treated with hydroxycarbamide, fatal increases in hemoglobin (HbF) have been observed 4 to 12 weeks after treatment initiation. Generally, mean HbF levels are proportional to dose and plasma levels, possibly plateauing at higher doses. A definitive relationship between reduced seizure frequency and HbF or F-cell levels has not been proven. The dose-dependent cytoreductive effects of hydroxycarbamide, especially on neutrophils, were most strongly correlated with the decreasing frequency of crisis.

Animal Toxicity: In acute toxicology studies, the oral LD50 of hydroxycarbamide was 7330 mg/kg in mice and 5780 mg/kg in rats. The most consistent pathological findings in subacute and chronic toxicity studies in rats were mild to moderate bone marrow hypoplasia and pulmonary congestion with a significant dose-related staining of the lungs. At the highest dose levels (1260 mg/kg/day for

37 days, then 2520 mg/kg/day for 40 days), testicular atrophy with lack of spermatogenesis was seen (see section 4.4). In many animals, damage to hepatic cells by fat metamorphosis has been observed. Mild to significant bone marrow depression was a consistent finding in the dog, except at low dose levels.

Growth retardation, slight increase in blood glucose values, and hemosiderosis of the liver or spleen were found at higher dose levels (140-240 mg or 140-1260 mg/kg/week for 3 or 7 days every week for 12 weeks). Reversible spermatogenic arrest was also observed.

Bone marrow suppression, lymphoid atrophy of the spleen, and degenerative changes in the epithelium of the small and large intestine were found in monkeys. At higher, often lethal doses (400 to 800 mg/kg/day for 7 to 15 days), hemorrhage and congestion in the lungs, brain and urinary tract were observed. Pulse, blood pressure, orthostatic hypotension, electrocardiogram changes, and mild hemolysis and/or methemoglobinemia were observed in some laboratory animal species at doses higher than those used clinically.

5.2 Pharmacokinetic properties

General properties
Absorption:
Hydroxycarbamide is rapidly absorbed after oral administration. Peak plasma levels are reached in 1-4 hours after oral dosing. Disproportionately larger mean peak plasma concentrations and area under curve (AUC) were observed as doses increased. There are no data on the effect of meals on the absorption of hydroxycarbamide.

Distribution:
Hydroxycarbamide is rapidly and extensively distributed in the body and the estimated volume of distribution is close to total body water. Plasma-abdominal fluid ratios range from 2:1 to 7.5:1. Hydroxycarbamide collects in leukocytes and erythrocytes and crosses the blood-brain barrier.

Biotransformation:
50% of an oral dose is altered in unexplained metabolic pathways. One of the pathways is probably saturable hepatic metabolism. Another minor metabolic pathway is its degradation by urease in intestinal bacteria to acetohydroxamic acid.

Elimination:
The mean cumulative urinary recovery of hydroxycarbamide in patients with sickle cell anemia is approximately 40% of the administered dose.

Linearity/Nonlinearity:
In humans, hydroxycarbamide excretion is likely to be linearly via the kidney. In patients with malignancy, renal elimination is between 30-55% of the administered dose.

Characteristics in patients
There is no information on pharmacokinetic differences due to age, gender or race. No pharmacokinetic data are available in pediatric patients treated with hydroxycarbamide for sickle cell anemia.

Kidney impairment
Since renal excretion is a route of elimination, dose reduction should be considered in this population. The starting dose of hydroxyurea should be reduced in patients with renal impairment. The effect of renal impairment was evaluated in a single-dose, non-randomized, multicenter study on the pharmacokinetics of hydroxyurea in patients with sickle cell anemia. In studies in patients with normal (creatinine clearance >80 ml/min), mild (CrCl 50-80 ml/min) or severe (CrCl <30 ml/min) renal impairment, a single oral dose of 15 mg/kg with the combination of 200mg, 300mg and 400mg capsules of hydroxycarbamide was administered. Two doses of 15mg/kg were administered to patients with end-stage renal disease in 7 days. The first dose was given after 4 hours of hemodialysis, and the second dose was given before hemodialysis. In this study, drug exposure (AUC) in patients with creatinine clearance < 60 ml/min was 64% higher than in patients with normal creatinine clearance. These results support that the starting dose of hydroxycarbamide should be reduced in patients with renal impairment.

Hepatic impairment
There are no data to form specific guidelines to support dose adjustment in patients with impaired hepatic function.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis and Fertility Failure
Hydroxycarbamide is genotoxic and is predicted to be an interspecies carcinogen exposing humans to a carcinogenic risk. Secondary leukemia has been reported in patients receiving long-term hydroxycarbamide for myeloproliferative diseases such as polycythemia vera and thrombocythemia; It is unknown whether this secondary leukemogenic effect is due to hydroxycarbamide or to the patient's underlying disease. Skin cancer has also been reported in patients taking hydroxycarbamide for a long time.

It is mutagenic to bacteria, fungi, protozoa and mammalian cells *in vitro*. It is clastogenic *in vitro* (hamster, human lymphoblasts) and *in vivo* (rodents). Hydroxycarbamide causes the transformation of rodent embryo cells to a tumorigenic phenotype.

Long-term animal studies have not been conducted to evaluate its carcinogenic potential. High doses of aspermatogenesis were noted in rats and reversible spermatogenic arrest in dogs. Drugs that affect DNA synthesis, such as hydroxycarbamide, may be potential mutagens. This possibility should be considered before giving medication to male or female patients who are considering having children.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (from cow milk)
Citric acid
Disodium phosphate
Magnesium stearate

Hard gelatin capsule
Erythrosin - FD&C Red 3
Indigotine - FD&C Blue 2
Titanium dioxide
Quinoline yellow
Gelatin (bovine)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at room temperature below 30°C protected from moisture.

6.5 Nature and contents of container

HYDMOXIA 500 mg hard capsules are presented in blister packs of clear PVC/Aclar film, sealed with aluminum foil. in packages of 100 capsules (10 capsules in 1 blister, 10 blisters in a package) with a patient leaflet in a carton box.

6.6. Special precautions for disposal and other handling

Patients who take the capsule contents by emptying them into water (see section 4.2) should be warned that this is a potent drug that should be handled with care. Patients should be warned that when opening the capsule, the powder should not come into contact with the skin and mucous membranes and should not be inhaled. People who are not taking HYDMOXIA should not be exposed to it. Disposable gloves should be used when handling HYDMOXIA or blisters containing HYDMOXIA to decrease the risk of exposure. Anyone handling HYDMOXIA should wash their hands before and after contact with the capsules. If the powder is accidentally spilled, it should be wiped off immediately with a damp disposable cloth and discarded together with the empty capsules in a closed container such as a plastic bag. HYDMOXIA should be kept away from children and pets.

To minimize the risk of dermal exposure, always wear impermeable gloves when handling blisters containing capsules. In clinical settings, pharmacies, warehouses and home care settings; This includes all hand contact situations including unpacking, inspection, handling, dose preparation and administration.

The use and disposal procedure for anticancer drugs should be followed with caution. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

Saba İlaç San. ve Tic. A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No: 1
34303 Küçükçekmece - Istanbul/TURKEY

8. MARKETING AUTHORIZATION NUMBER

2019/200

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

Date of first authorization: 02.04.2019
Date of renewal :

10. DATE OF REVISION OF THE TEXT