HIDROXIUREA KEMEX
HYDROXYUREA 500 mg
Hard Capsules

Made in Argentina Under prescription only

1. Name of the medicinal product
Hidroxiurea Kemex 500 mg Hard Capsules

2. Qualitative and quantitative composition
Each capsule contains:
Hydroxyurea 500 mg, Citric acid 5 mg, Disodium phosphate monobasic 20 mg, Magnesium stearate 8 mg, Lactose 272 mg.

3. Pharmaceutical form
Capsule, hard

4. Clinical particulars
4.1 Therapeutic indications
The treatment of chronic myeloid leukaemia.
The treatment of cancer of the cervix in conjunction with radiotherapy.

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.
Hydroxyurea should be started 7 days before concurrent irradiation therapy. If Hydroxyurea is used concomitantly with radiotherapy, adjustment of radiation dosage is not usually necessary.
An adequate trial period for determining the antineoplastic effect of Hydroxyurea is six weeks. Where there is a significant clinical response therapy may be continued indefinitely, provided that the patient is kept under adequate observation andshows no unusual or severe reactions. Therapy should be interrupted if the white cell count drops below $2.5x10^9$/L or the platelet count below $100x10^9$/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 Hydroxyurea and irradiation therapy, irradiation may also be interrupted. Anemia, even if severe, can be managed without interrupting Hydroxyurea therapy.
Severe gastric distress, such as nausea, vomiting, and anorexia, resulting from combined therapy may usually be controlled by interruption of Hydroxyurea 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, Hydroxyurea therapy may be temporarily interrupted; if it is extremely severe, irradiation dosage may, in addition, be temporarily postponed.

Continuous therapy
Hydroxyurea 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
Hydroxyurea 80 mg/kg in single doses should be given every third day. Using the intermittent regimes the likelihood of WBC depression is diminished, but if low counts are produced, 1 or more doses of Hydroxyurea should be omitted.
Concurrent use of Hydroxyurea 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 Hydroxyurea, 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 Hydroxyurea 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 (<$2.5wbcx10^9$/L), thrombocytopenia (<$100x10^9$/L), or severe anaemia.

4.4 Special warnings and precautions for use
Bone Marrow
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 Hydroxyurea 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 Hydroxyurea 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.
Hydroxyurea 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; Hydroxyurea should be used cautiously in such patients. The recovery from myelosuppression is rapid when Hydroxyurea therapy is interrupted.
Anaemia
Severe anaemia must be corrected with whole blood replacement before initiating therapy with Hydroxyurea. If, during treatment, anaemia occurs, correct without interrupting Hydroxyurea therapy. Erythrocytic abnormalities; megaloblastic erythropoeisis, which is self-limiting, is often seen early in the course of Hydroxyurea therapy. The morphologic change resembles pernicious anaemia, but is not related to vitamin B_{12} or folic acid deficiency. The macrocytosis may mask the incidental development of folic acid deficiency; regular determinations of serum folic acid are recommended. Hydroxyurea 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.
Irradiation
Patients who have received irradiation therapy in the past may have an exacerbation of post irradiation erythema when Hydroxyurea is given.
Renal
Hydroxyurea should be used with caution in patients with marked renal dysfunction.
HIV
Hydroxyurea 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).
Cancer
In patients receiving long-term therapy with Hydroxyurea for myeloproliferative disorders, such as polycythemia vera and thrombocythemia, secondary leukaemia has been reported. It is unknown whether this leukaemogenic effect is secondary to Hydroxyurea or associated with the patient's underlying disease. Skin cancer has also been reported in patients receiving long-term Hydroxyurea. Patients should be advised to protect skin from sun exposure, conduct self-inspection of the skin and be screened for secondary malignancies during routine follow-up visits.
Vasculitis toxicities
Cutaneous vasculitic toxicities including vasculitic ulcerations and gangrene have occurred in patients with myeloproliferative disorders during therapy with Hydroxyurea. 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 Hydroxyurea. Due to potentially severe clinical outcomes for the cutaneous vasculitic ulcers reported in patients with myeloproliferative disease, Hydroxyurea should be discontinued if cutaneous vasculitic ulcerations develop and alternative cytoreductive agents should be initiated as indicated.
Uric acid
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 Hydroxyurea, 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.
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.
Vaccinations
Concomitant use of Hydroxyurea 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 defence mechanisms may be suppressed by Hydroxyurea. Vaccination with a live vaccine in a patient taking Hydroxyurea 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 six months after treatment has finished and individual specialist advice sought (see section 4.5).

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 Hydroxyurea 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 Hydroxyurea and other antiretroviral agents. Fatal hepatic events were reported most often in patients treated with the combination of Hydroxyurea, didanosine and stavudine. This combination should be avoided. Peripheral neuropathy, which was severe in some cases, has been reported in HIV-infected patients receiving Hydroxyurea 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 Hydroxyurea 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 Hydroxyurea.
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 Hydroxyurea, 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 Hydroxyurea is a cytotoxic agent it has produced a teratogenic effect in some animal species.
In rats and dogs, high doses of Hydroxyurea reduced sperm production.
Hydroxyurea is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants from Hydroxyurea, a decision should be made whether to discontinue nursing or to discontinue Hydroxyurea, taking into account the importance of the drug to the mother.
Hydroxyurea can cause fetal harm when administered to a pregnant woman. Hydroxyurea 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.
Female patients of reproductive potential should be counselled to use effective contraception during therapy and for at least 6months after therapy.
Azoo- or oligospermia, sometimes reversible, have been observed in men. Male patient should be .informed about the possibility of sperm conservation before the start of therapy. Hydroxyurea may be genotoxic.
Men under therapy are advised to use effective contraceptive measures during and at least 1 year after therapy.

4.7 Effects on ability to drive and use machines
Hydroxyurea 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 Hydroxyurea.
Cutaneous vasculitic toxicities including vasculitic ulcerations and gangrene have occurred in patients with myeloproliferative disorders during therapy with Hydroxyurea. The risk of vasculitic toxicities is increased in patients who receive prior or concomitant interferon therapy.
In some patients, hyperpigmentation, nail pigmentation, atrophy of skin and nails, scaling, violet papules and alopecia have been observed following several years of long-term daily maintenance therapy with Hydroxyurea.
Cases of fatal and non-fatal pancreatitis and hepatotoxicity and severe peripheral neuropathy have been observed in HIV patients when Hydroxyurea was administered with antiretroviral agents, in particular didanosine plus stavudine. Patients treated with Hydroxyurea in combination with didanosine, stavudine and indinavir showed a median decline in CD4 cells of approximately $100/mm^3$ (see sections 4.4 and 4.5).
Adverse reactions observed with combined Hydroxyurea and irradiation therapy were similar to those reported with the use of Hydroxyurea alone, primarily bone marrow depression (leukopenia and anaemia) and gastric irritation. Nearly all patients receiving an adequate course of combined Hydroxyurea and irradiation therapy will develop leukopenia. Decreased platelet counts (<$100,000/mm^3$) have occurred rarely and usually in the presence of marked leukopenia.
Hydroxyurea may potentiate some adverse reactions usually seen with irradiation alone, such as

gastric distress and mucositis.

Hypersensitivity
Drug induced fever.
High fever (>39°C) requiring hospitalisation in some cases has been reported concurrently with gastrointestinal, pulmonary, muscloskeletal, hepatobiliary, dermatoloigical or cardiovascular manifestations. Onset typically occurred within 6 weeks of initiation and resolved promptly after discontinuation of Hydroxyurea. Upon readministration fever re-occurred within 24 hours.
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, anaemia
Metabolism and Nutrition Disorders	Very common	Anorexia
	Rare	Tumour lysis syndrome
Psychiatric Disorders	Common	Hallucination, disorientation
Nervous System Disorders	Common	Convulsion, dizziness, peripheral neuropathy[1], somnolence, headache
Respiratory, Thoracic, and Mediastinal Disorders	Common	Pulmonary fibrosis, pulmonary oedema, lung infiltration, dyspnoea
Gastrointestinal Disorders	Very common	Pancreatitis[1], nausea, vomiting, diarrhoea, stomatitis, constipation, mucositis, stomach discomfort, dyspepsia, abdominal pain, melaena
Hepatobiliary Disorders	Common	Hepatotoxicity[1], hepatic enzyme increased, cholestasis, hepatitis
Skin and Subcutaneous Tissue Disorders	Very common Not known	Cutaneous vasculitis, dermatomyositis, alopecia, rashmaculo-papular, rash papular, skin exfoliation, skinatrophy, skin ulcer, erythema, skin hyperpigmentation, nail disorder Nail pigmentation
Renal and Urinary Disorders	Very common	Dysuria, blood creatinine increased, blood ureaincreased, blood uric acid increased
General Disorders and Administration Site Conditions	Very common	Pyrexia, asthenia, chills, malaise
Reproductive system and breastdisorders	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 didanosineplus 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.

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

5.2 Pharmacokinetic properties
After oral administration Hydroxyurea 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. Hydroxyurea crosses the blood-brain barrier. Hydroxyurea is well distributed throughout the body.

5.3 Preclinical safety data
Hydroxyurea is unequivocally genotoxic and a presumed transpecies carcinogen which implies a carcinogenic risk to humans.

6. Pharmaceutical particulars
6.1 List of excipients
Citric acid
Disodium phosphate monobasic
Magnesium stearate
Lactose

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store at a temperature between 15°C and 30°C. Protect from moisture.

6.5 Nature and contents of container
Colorless transparent PVC blister and aluminum foil.
Carton containing 100 capsules.

6.6 Special precautions for disposal and other handling
People who are not taking Hydroxyurea should not be exposed to it. To decrease the risk of exposure, wear disposable gloves when handling Hydroxyurea. Anyone handling Hydroxyurea 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. Hydroxyurea should be kept away from children. Pregnant women should not handle Hydroxyurea.
To minimise the risk of dermal exposure, always wear impervious gloves when handling capsules containing Hydroxyurea. 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 authorisation holder
Laboratorio Kemex S.A.
Nazarre 3446 (C1417DXH)
Autonomous City of Buenos Aires, Argentina

8. Marketing authorisation number(s)
Certificate No. 49,378

9. Date of first authorisation/renewal of the authorisation
Date of first authorisation: 05 January 2001
Date of latest renewal: January 2006, January 2011, January 2016, January 2021, January 2026

10. Date of revision of the text
06/2022

"THIS MEDICATION MUST BE ADMINISTERED UNDER MEDICAL PRESCRIPTION AND CANNOT BE REPEATED WITHOUT A NEW PRESCRIPTION".
MEDICATION: KEEP AWAY FROM CHILDREN

05147.00

kemex laboratorio