creatinine levels. Abnormal BSP retention has been reported. Fever, chills, malaise and elevation of hepatic enzymes have also been reported.

Adverse reactions observed with combined ***Cytodrox*** and irradiation therapy are similar to those reported with the use of ***Cytodrox*** alone. These effects primarily include bone marrow depression (anemia and leukopenia) and gastric irritation. Almost all patients receiving an adequate course of combined ***Cytodrox*** and irradiation therapy will demonstrate concurrent leukopenia. Platelet depression (less than 100,000 cells/mm^3) has occurred rarely and only in the presence of marked leukopenia. Gastric distress has also been reported with irradiation alone and in combination with ***Cytodrox*** therapy.

It should be borne in mind that therapeutic doses of irradiation alone produce the same adverse reactions as ***Cytodrox***; 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.

STORAGE

Store below 30°C.
Protect from moisture.

PRESENTATION

Cytodrox Strip of 10 capsules

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Hydroxyurea Capsules USP 500 mg

Cytodrox

COMPOSITION

Each capsule contains
Hydroxyurea USP ..... 500 mg

DESCRIPTION

Cytodrox is an antineoplastic agent, available for oral use as capsules providing 500 mg Hydroxyurea. The precise mechanism by which hydroxyurea produces its cytotoxic effects cannot at present, be described. However, the reports of various studies in tissue culture in rat and man lend to support the hypothesis that ***Cytodrox*** causes an immediate inhibition of DNA synthesis without interfering with the synthesis of ribonucleic acid or of protein.

INDICATIONS AND USAGE

Significant tumor response to ***Cytodrox*** has been demonstrated in melanoma, resistant chronic myelocytic leukamia, and recurrent, metastatic, or inoperable carcinoma of the ovary.

Cytodrox used concomittently with irradiation therapy is intented for use in the local control of primary squamous cell (epidermoid) carcinomas of the head and neck, excluding the lip.

DOSAGE AND ADMINISTRATION

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

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 vehicle in the capsule may not dissolve, and float on the surface.

SOLID TUMORS

Intermittent Therapy – 80 mg/kg administered orally as *single* dose every *third* day.

Continuous Therapy – 20-30 mg/kg administered as a *single* dose *daily*. The intermittent dosage schedule offers the advantage of reduced toxicity since patient on this dosage regimen have rarely required complete discontinuation of therapy because of toxicity.

Concomittent Therapy with Irradiation

Carcinoma of the head and neck –80 mg/kg administered orally as a single dose every third day.

Administration of ***Cytodrox*** should be begun at least seven days before initiation of irradiation and continued

Cipla

125 NI

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 ***Cytodrox*** is used concomitantly.

RESISTANT CHRONIC MYELOCYTIC LEUKAMIA

Until the intermittent therapy regimen has been evaluated, *continuous* therapy (20-30 mg/kg administered orally as a single dose daily) is recommended.

An adequate trial period for determining the antineoplastic effectiveness of ***Cytodrox*** is six weeks of therapy. When there is regression in the tumor size or arrest in the tumor growth, therapy should be continued indefinitely. Therapy should be interrupted if the white cell count drops below 2500/mm^3 or the platelet count below 100,000/mm^3. In these cases, the counts should be rechecked after three days, and therapy resumed when count rise significantly towards 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 ***Cytodrox*** and irradiation therapy, irradiation may also be interrupted. Anaemia, if it occurs, should be corrected with whole blood replacement, without interrupting ***Cytodrox*** therapy. Because hematopoiesis may be compromised by extensive irradiation or by other antineoplastic agents, it is recommended that ***Cytodrox*** be administered cautiously to patients who have recently received extensive radiation therapy or chemotherapy with other cytotoxic drugs.

Pain or discomfort from inflammation of the mucous membranes at the irradiated site (mucositis) is usually controlled by measures such as topical anaesthetics and orally administerd analgesics. If the reaction is severe, ***Cytodrox*** 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 temporary interruption of ***Cytodrox*** administeration; rarely has the additional interruption of irradiation been necessary.

CONTRAINDICATIONS

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

WARNINGS

Treatment with ***Cytodrox*** should not be initiated if bone marrow function is markedly depressed. Bone marrow suppression may occur, and leukopenia is generally its first and most common manifestation. Thrombocytopenia and anaemia occur less often, and are shown seldom seen without a preceeding leukopenia. However, the recovery from 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 of cytotoxic cancer chemotherapeutic agents; ***Cytodrox*** should be used cautiously in such patients.

Patients who have received irradiation therapy in the past may have an exacerbation of postirradiation erythema. Severe anaemia must be corrected with whole blood replacement before initiating therapy with ***Cytodrox***.

Erythrocytic abnormalities: Megaloblastic erythropoiesis, which is self limiting, is often seen early in the course of ***Cytodrox*** therapy. The morphological change resembles pernicious anemia, but is not related to vitamin B12 or folic acid deficiency. ***Cytodrox*** 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.

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

Elderly patients may be more sensitive to the effects of ***Cytodrox***, and may require a low dose regimen.

Usage in Pregnancy

Hydroxyurea affects the DNA synthesis hence, may be a potential mutagenic agent.The physician should consider this possibility before administering this drug to male or female patients who may contemplate conception Hydroxyurea is a known teratogenic agent in animals. Therefore, ***Cytodrox*** should not be used in women who are or may become pregnant unless in the judgement of the physician the potential benefits may outweigh the possible hazards.

PRECAUTIONS

Therapy with ***Cytodrox*** 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 hemoglobin level, total leukocyte counts, and platelet counts should be performed at least once a week throughout the course of ***Cytodrox*** therapy. If the white blood cell count decreases to less than 2500/mm^3, or the platelet count to less than 100,000/mm^3, therapy should be interrupted until the values rise significantly towards normal levels. Anemia, if it occurs, should be managed with blood replacement, without interrupting ***Cytodrox*** therapy.

ADVERSE REACTIONS

Adverse reactions have been primarily *bone marrow depression* (leukopenia, anemia, and occasionally thrombocytopenia), and less frequently *gastrointestinal symptoms* (stomatitis, anorexia, nausea, vomiting, diarrhea, and constipation), and *dermatological reactions* such as maculopapular rash and facial erythema. Dysuria and alopecia occcur very rarely. Large doses may produce moderate drowsiness. *Neurological disturbances* have occurred extremely rarely and were limited to headache, dizziness, disorientation, hallucinations, and convulsions. ***Cytodrox*** occasionally may cause *temporary impairment of renal tubular function* accompanied by elevations in serum uric acid, BUN, and