

SCHEDULING STATUS: S4

PROPRIETARY NAME (and dosage form):

METHOTREXATE® LEDERLE 2,5 Tablets

COMPOSITION:

METHOTREXATE LEDERLE Tablets contain 2,5 mg of methotrexate.

PHARMACOLOGICAL CLASSIFICATION:

Category A 26 - Cytostatic agents

PHARMACOLOGICAL ACTION:

Methotrexate has as its principle mechanism of action the competitive inhibition of the enzyme, dihydrofolic acid reductase. Dihydrofolates must be reduced to tetrahydrofolic acid by this enzyme in the process of DNA synthesis and cellular replication. Methotrexate inhibits the reduction of dihydrofolate and interferes with tissue-cell reproduction.

Actively proliferating tissues such as malignant cells, bone marrow, foetal cells, dermal epithelium, buccal and intestinal mucosa and cells of the urinary bladder are in general more sensitive to this effect of methotrexate.

Cellular proliferation in malignant tissue is greater than in most normal tissue and thus methotrexate may impair malignant growth without irreversible damage to normal tissues.

Orally administered methotrexate is absorbed rapidly in most, but not all patients, and reaches peak serum levels in 1-2 hours. After parenteral injection, peak serum levels are seen in about one-half of this period.

Approximately one-half of the absorbed methotrexate is reversibly bound to serum protein, but exchanges with body fluids easily and diffuses into the body tissue cells, but does not penetrate the blood - cerebrospinal fluid barrier.

Excretion of single daily doses occurs through the kidneys in amounts from 55% to 88% or higher within 24 hours. Repeated doses daily result in more sustained serum levels and some retention of methotrexate over each 24 hour period, which may result in accumulation of the medicine within the tissues. The liver cells appear to retain certain

amounts of the medicine for prolonged periods even after a single therapeutic dose. The elimination $t_{1/2}$ in rheumatoid arthritis is $\pm 3 - 10$ hours. At higher doses the $t_{1/2}$ is 8-15 hours.

Methotrexate is retained in the presence of impaired renal function and may increase rapidly in the serum and in the tissue cells under such conditions. Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally. High concentration of the medicine when needed may be attained by direct intrathecal administration.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This differential in reproduction rates is the basis for the use of methotrexate to control the psoriatic process.

The mechanism of action in rheumatoid arthritis is unknown, it may affect immune function.

INDICATIONS:

Anti-neoplastic chemotherapy: METHOTREXATE LEDERLE is indicated for the treatment of breast carcinoma, gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole. METHOTREXATE LEDERLE is also indicated for the palliation of acute and subacute lymphocytic and meningeal leukaemia. Efficiency has been observed in palliation of acute lymphoblastic (stem-cell) leukaemias.

In combination with corticosteroids METHOTREXATE LEDERLE may be used for induction of remission.

METHOTREXATE LEDERLE is also effective in the treatment of the advanced stages of lymphosarcoma, particularly in those cases in children, and in advanced cases of mycosis fungoides.

High Dosage Therapy (See "WARNINGS" below): Diseases treated with high doses, administered in the form of single-medicine or combination therapy, include osteogenic sarcoma, acute leukaemia, bronchogenic carcinoma and epidermoid carcinoma of the head and neck.

Psoriasis Chemotherapy (See "WARNINGS" below): Because of high risk attending its use, METHOTREXATE LEDERLE is only indicated in the symptomatic control of severe,

recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or dermatologic consultation.

Rheumatoid Arthritis: METHOTREXATE LEDERLE is indicated in the treatment of selected adult patients of severe, classical rheumatoid arthritis not adequately responsive to other forms of therapy, as confirmed by rheumatologic consultation. Aspirin, nonsteroidal anti-inflammatory agents, and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored. Steroids may be reduced gradually in patients who respond to METHOTREXATE LEDERLE. Combined use of METHOTREXATE LEDERLE with gold, penicillamine, hydroxychloroquine, sulphasalazine, or cytotoxic agents, has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

CONTRAINDICATIONS:

Pregnancy or women with childbearing potential (**see “Pregnancy and Lactation”**).

Because of the potential for serious adverse reactions from METHOTREXATE LEDERLE in breast-fed infants, it is contraindicated in nursing mothers (**see “Pregnancy and Lactation”**).

Patients with psoriasis or rheumatoid arthritis with alcoholism, alcoholic liver disease or other chronic liver disease should not receive METHOTREXATE LEDERLE.

Patients with psoriasis or rheumatoid arthritis who have overt or laboratory evidence of immunodeficiency syndromes should not receive METHOTREXATE LEDERLE.

Patients with psoriasis or rheumatoid arthritis who have pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anaemia, should not receive METHOTREXATE LEDERLE.

Patients with a known hypersensitivity to METHOTREXATE LEDERLE or any excipients in the formulation should not receive the drug.

INFORMATION FOR THE PATIENT:

The physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in rheumatoid arthritis and psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity. Prescriptions should not be filled on a when necessary basis.

Patients should be informed of the potential benefit and risk in the use of METHOTREXATE LEDERLE. The risk of effects on reproduction should be discussed with both male and female patients taking METHOTREXATE LEDERLE.

WARNINGS:

METHOTREXATE LEDERLE SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED IN ANTIMETABOLITE CHEMOTHERAPY.

1. Because of the possibility of serious toxic reactions (which can be fatal), METHOTREXATE LEDERLE should be used only in life-threatening neoplastic diseases, or in patients with psoriasis or rheumatoid arthritis with severe, recalcitrant, disabling disease that is not adequately responsive to other forms of therapy. Deaths have been reported with the use of METHOTREXATE LEDERLE in the treatment of malignancy, psoriasis, and rheumatoid arthritis. Because of the possibility of serious toxic reactions, the patient should be informed by the physician of the risks involved and should be under a physician's constant supervision.
2. METHOTREXATE LEDERLE given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.
3. Caution is recommended in the use of METHOTREXATE LEDERLE for non-neoplastic conditions because potential toxicity with long-term use of this agent.
4. Patients should be regularly monitored for bone marrow, liver, lung and kidney toxicities.
METHOTREXATE LEDERLE may produce marked depression of bone marrow, anaemia, leukopenia, thrombocytopenia and bleeding. Regular blood counts should be performed.
5. METHOTREXATE LEDERLE causes hepatotoxicity, liver fibrosis and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histologic changes, and fibrosis and cirrhosis have been reported; these latter lesions may not be preceded by symptoms or abnormal liver function tests in the

psoriasis population. For this reason, periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population (See “PRECAUTIONS, Organ System Toxicity, *Hepatic*”).

6. METHOTREXATE LEDERLE has caused foetal death and/or congenital anomalies, therefore, it is not recommended for the treatment of neoplastic diseases in women of childbearing potential, unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant psoriatic or rheumatoid arthritis patients should not receive METHOTREXATE LEDERLE. Adequate birth control should be practised in all childbearing women.
7. METHOTREXATE LEDERLE therapy in patients with impaired renal function should be undertaken with extreme caution, and at reduced dosages, because impairment of renal function will decrease METHOTREXATE LEDERLE elimination.
8. Diarrhoea and ulcerative stomatitis are frequent toxic effects and require interruption of therapy, otherwise haemorrhagic enteritis and death from intestinal perforation may occur. METHOTREXATE LEDERLE should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.
9. Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anaemia, and gastro-intestinal toxicity have been reported with concomitant administration of METHOTREXATE LEDERLE (usually in high dosage) along with nonsteroidal anti-inflammatory drugs (NSAIDs) (See “PRECAUTIONS, Drug Interactions”).
10. METHOTREXATE LEDERLE induced lung disease, including acute or chronic interstitial pneumonitis may occur at any time during therapy and has been reported at low doses. It is not always fully reversible and fatalities have been reported. Pulmonary symptoms (especially a dry, non-productive cough) may require interruption of treatment and careful investigation.
11. Malignant lymphomas, which may regress following withdrawal of METHOTREXATE LEDERLE, may occur in patients receiving low-dose METHOTREXATE LEDERLE and thus may not require cytotoxic treatment. Discontinue METHOTREXATE LEDERLE first and, if the lymphoma does not regress, appropriate treatment should be instituted.
12. METHOTREXATE LEDERLE may induce “tumour lysis syndrome” in patients with rapidly growing tumours. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.
13. Severe, occasionally fatal, skin reactions such as Stevens-Johnson Syndrome, toxic

epidermal necrolysis (Lyell's syndrome), have been reported following single or multiple doses of METHOTREXATE LEDERLE. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal METHOTREXATE LEDERLE administration. Recovery has been reported with discontinuation of therapy (See "PRECAUTIONS, Organ System Toxicity, Skin").

14. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with METHOTREXATE LEDERLE therapy.
15. METHOTREXATE LEDERLE exits slowly from third space compartments (e.g. pleural effusions or ascites). This results in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma METHOTREXATE LEDERLE levels.

METHOTREXATE LEDERLE HAS BEEN USED IN VERY HIGH DOSAGE FOLLOWED BY LEUCOVORIN (CITROVORUM FACTOR) RESCUE IN THE ADJUVANT TREATMENT OF CERTAIN NEOPLASTIC DISEASES. THIS PROCEDURE IS INVESTIGATIONAL AND HAZARDOUS.

IT SHOULD NOT BE ATTEMPTED OUTSIDE OF FACILITIES WHERE THE NECESSARY EXPERTISE AND RESOURCES HAVE BEEN ASSEMBLED. THE RECENT PUBLISHED LITERATURE SHOULD BE CONSULTED.

See also the section "SIDE EFFECTS AND SPECIAL PRECAUTIONS" and "Dosage and Directions for use- Leucovorin Rescue schedule following high-dose METHOTREXATE LEDERLE below.

CAUTION: Pharmacist. Because of its potential to cause severe toxicity, METHOTREXATE LEDERLE therapy requires close supervision of the patient by the physician. Pharmacists should dispense no more than a seven (7) day supply of the medicine at one time. Refill of such prescription should be by direct order of the physician only.

INTERACTIONS:

- **Nonsteroidal Anti-inflammatory Drugs (NSAIDs)**

Nonsteroidal anti-inflammatory drugs (NSAIDs) should not be administered prior to or concomitantly with the high doses of METHOTREXATE LEDERLE such as used in the treatment of osteosarcoma. Concomitant administration of NSAIDs with high-dose METHOTREXATE LEDERLE therapy has been reported to elevate and prolong serum

METHOTREXATE LEDERLE levels, resulting in deaths from severe haematologic and gastrointestinal toxicity. NSAIDs and salicylates have been reported to reduce the tubular secretion of METHOTREXATE LEDERLE in an animal model and may enhance its toxicity by increasing METHOTREXATE LEDERLE levels. Therefore, caution should be used when they are administered concomitantly with lower doses of METHOTREXATE LEDERLE.

In treating rheumatoid arthritis with METHOTREXATE LEDERLE; aspirin, NSAIDs, and/or low dose steroids may be continued.

The possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored. Steroids may be reduced gradually in patients who respond to METHOTREXATE LEDERLE. Combined use of METHOTREXATE LEDERLE with gold, penicillamine, hydroxychloroquine, sulfasalazine, or cytotoxic agents, has not been studied and may increase the incidence of adverse events. Despite the potential interactions, studies of METHOTREXATE LEDERLE in patients with rheumatoid arthritis have usually included concurrent use of constant dosage regimens of NSAIDs, without difficulty. It should be appreciated, however, that the METHOTREXATE LEDERLE doses used in rheumatoid arthritis (7,5 to 15 mg/week) are somewhat lower than those used in psoriasis and that larger doses could lead to unexpected toxicity.

- **Leflunomide**

METHOTREXATE LEDERLE in combination with leflunomide may increase the risk of pancytopenia.

- **Drugs Highly Bound to Plasma Proteins**

METHOTREXATE LEDERLE is partially bound to serum albumin, and toxicity may be increased because of displacement by other highly bound drugs, such as salicylates, phenylbutazone, phenytoin and sulphonamides.

- **Probenecid**

Renal tubular transport is also diminished by probenecid; use of METHOTREXATE LEDERLE with this agent should be carefully monitored.

- **Chemotherapeutic Agents**

Enhancement of nephrotoxicity may be seen when high-dose METHOTREXATE LEDERLE is administered in combination with a potentially nephrotoxic chemotherapeutic agent (e.g. cisplatin).

- **Oral Antibiotics**

Oral antibiotics such as tetracycline, chloramphenicol, and non-absorbable broad spectrum antibiotics, may decrease intestinal absorption of METHOTREXATE LEDERLE or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of METHOTREXATE LEDERLE by bacteria.

Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving METHOTREXATE LEDERLE, probably by decreased tubular secretion and/or additive antifolate effect.

- **Penicillins and Sulphonamides**

Penicillins and sulphonamides may reduce the renal clearance of METHOTREXATE LEDERLE; haematologic and gastrointestinal toxicity has been observed in combination with high- and low- dose METHOTREXATE LEDERLE. Use of METHOTREXATE LEDERLE with penicillin should be carefully monitored.

- **Hepatotoxins**

The potential for increased hepatotoxicity when METHOTREXATE LEDERLE is administered with other hepatotoxic agents has not been evaluated. However, hepatotoxicity has been reported in such cases. Therefore, patients receiving concomitant therapy with METHOTREXATE LEDERLE and other potential hepatotoxic agents (e.g. leflunomide, azathioprine, sulphasalazine, retinoids) should be closely monitored for possible increased risk of hepatotoxicity.

- **Theophylline**

METHOTREXATE LEDERLE may decrease the clearance of theophylline; theophylline levels should be monitored when used concurrently with METHOTREXATE LEDERLE.

- **Vitamins**

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered METHOTREXATE LEDERLE, however, folate deficiency

states may increase METHOTREXATE LEDERLE toxicity. High doses of leucovorin may reduce the efficacy of intrathecally administered METHOTREXATE LEDERLE.

- **Leucovorin**

Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1 - 3 orders of magnitude lower than the usual METHOTREXATE LEDERLE concentrations following intrathecal administration.

- **Mercaptopurine**

METHOTREXATE LEDERLE increases the plasma levels of mercaptopurine. Combination of METHOTREXATE LEDERLE and mercaptopurine may therefore require dose adjustment.

- **Radiotherapy**

METHOTREXATE LEDERLE given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

- **Cytarabine**

METHOTREXATE LEDERLE given concomitantly with cytarabine may increase the risk of severe neurologic adverse events such as headache, paralysis, coma and stroke-like episodes. (See "SIDE EFFECTS AND SPECIAL PRECAUTIONS")

PREGNANCY AND LACTATION:

See "CONTRAINDICATIONS".

METHOTREXATE LEDERLE can cause foetal death, embryotoxicity, abortion, or teratogenic effects when administered to a pregnant woman. METHOTREXATE LEDERLE is contraindicated in pregnant patients with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the foetus.

Women of childbearing potential should not be started on METHOTREXATE LEDERLE until pregnancy is excluded and should be fully counselled on the serious risk to the foetus (See "Precautions") should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving METHOTREXATE LEDERLE. The optimal time

interval between the cessation of METHOTREXATE LEDERLE treatment of either partner and pregnancy has not been clearly established. (See boxed "WARNINGS").

Published literature recommendations for time intervals vary from 3 months to one year.

METHOTREXATE LEDERLE has been detected in human breast milk and is contraindicated during breast-feeding. The highest breast milk-to-plasma concentration ratio measured was 0,08:1.

DOSAGE AND DIRECTIONS FOR USE:

Anti-neoplastic chemotherapy: Oral administration in tablet form is often preferred since absorption is rapid and effective serum levels are obtained.

For conversion of mg/kg body mass to mg/m² of body surface or the reverse a ratio of 1:30 is given as a guideline. The conversion factor varies between 1:20 and 1:40 depending on age and body build.

Choriocarcinoma and similar trophoblastic diseases: METHOTREXATE LEDERLE is administered orally in doses of 15 to 30 mg daily for a 5-day course. Such courses are usually repeated for 3 to 5 times as required, with rest period of one or more weeks interposed between courses, until any manifesting toxic symptoms subside. The effectiveness of therapy is ordinarily evaluated by 24 hour quantitative analysis of urinary chorionic gonadotropin hormone (CGH), which should return to normal or less than 50 IU/24 hr. usually after the 3rd or 4th course and usually be followed by a complete resolution of measurable lesions in 4 to 6 weeks.

One to two courses of METHOTREXATE LEDERLE after normalization of CGH is usually recommended. Before each course of the medicine careful clinical assessment is essential.

Cyclic combination therapy of METHOTREXATE LEDERLE with other antitumour medicines has been reported as being useful.

Since hydatidiform mole may precede or be followed by choriocarcinoma, prophylactic chemotherapy with METHOTREXATE LEDERLE has been recommended.

Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. METHOTREXATE LEDERLE is administered in these disease states in doses similar to those recommended for choriocarcinoma.

Breast carcinoma: Prolonged cyclic combination chemotherapy with cyclophosphamide, METHOTREXATE LEDERLE and fluorouracil has given good results when used as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary lymph nodes.

Leukaemia: Acute lymphatic (lymphoblastic) leukaemia in children and young adolescents is the most responsive to present-day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common. In chronic lymphatic leukaemia, the prognosis for adequate response is less encouraging.

METHOTREXATE LEDERLE alone or in combination with steroids was formerly used for induction of remission of lymphoblastic leukaemias. More recently corticosteroid therapy in combination with other antileukaemic medicines or in cyclic combination therapy including METHOTREXATE LEDERLE has produced rapid and effective remissions. When used for induction, METHOTREXATE LEDERLE in doses of $3,3 \text{ mg/m}^2$ in combination with prednisone 60 mg/m^2 given daily produced remission in 50 % of patients treated, usually within a period of 4 to 6 weeks. METHOTREXATE LEDERLE alone or in combination with other agents appears to be the medicine of choice for securing maintenance of medicine-induced remissions.

When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: METHOTREXATE LEDERLE is administered twice weekly by mouth in doses of 30 mg/m^2 .

If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regime. Various experts have recently introduced a variety of dosage schedules for both induction and maintenance of remission with various combinations of alkylating and antifolic agents. Multiple medicine therapy with several agents, including METHOTREXATE LEDERLE given concomitantly is gaining increasing support in both the acute and chronic forms of leukaemia. The physician should familiarise himself with the new advances in antileukaemic therapy.

Acute granulocytic leukaemia is rare in children but common in adults.

This form of leukaemia responds poorly to chemotherapy and remissions are short with relapses common, and resistance to therapy develops rapidly.

Meningeal leukaemia: Some patients with leukaemia are subject to leukaemic invasion of the central nervous system. This may manifest characteristic signs or symptoms or may remain silent and be diagnosed only by examination of the cerebrospinal fluid which contains leukaemic cells in such cases. Therefore, the CSF should be examined in all leukaemic patients.

The passage of METHOTREXATE LEDERLE from blood serum to the cerebrospinal fluid is minimal, for adequate therapy the medicine is administered intrathecally. Some clinicians have given such chemotherapy in a prophylactic regime but the value of this procedure has not been established.

A common approach is to treat such patients as may actually manifest leukaemic involvement by direct intrathecal instillation of METHOTREXATE LEDERLE.

The following dosage regimen is based on age instead of body surface area.

Age (years)	Dose (mg)
< 1	6
1	8
2	10
3 or older	12

Untoward side effects may occur with any given intrathecal injection and are commonly neurological in character.

METHOTREXATE LEDERLE given by intrathecal route appears significantly in the systemic circulation and may cause systemic METHOTREXATE LEDERLE toxicity. Therefore, systemic antileukaemic therapy with the medicine should be appropriately adjusted, reduced or discontinued. Focal leukaemic involvement of the central nervous system may not respond to intrathecal chemotherapy and is best treated with radiotherapy.

Lymphomas: In Burkitt's Tumour, Stages 1-11, METHOTREXATE LEDERLE has produced prolonged remissions in some cases. Recommended dosage is 10 to 25 mg per day orally for 4 to 8 days. In stage III, METHOTREXATE LEDERLE is commonly given concomitantly

with other antitumour agents. Treatment in all stages usually consists of several courses of the medicine interposed with 7 to 10 day rest periods. Lymphosarcomas in stage III may respond to combined medicine therapy with METHOTREXATE LEDERLE given in doses of 0,625 mg to 2,5 mg/ kg daily. Hodgkin's Disease responds poorly to METHOTREXATE LEDERLE and to most types of chemotherapy.

Mycosis fungoides: Therapy with METHOTREXATE LEDERLE appears to produce clinical remissions in one half of the cases treated. Dosage is usually 2,5 to 10 mg daily by mouth for weeks or months.

Dose levels of medicine and adjustment of dose regime by reduction or cessation of medicine are guided by patient response and haematologic monitoring. METHOTREXATE LEDERLE has also been given intramuscularly in doses of 50 mg once weekly or 25 mg twice weekly.

High-dosage therapy: As stated under "WARNINGS" above, the recent published literature should be consulted for details. Dosage regimens have varied considerably in different studies, the nature and severity of the disease and the previous experience of the investigator are some of the factors influencing the choice of dosage and the duration of therapy.

It must be emphasized that high dosages should be used only by qualified specialists and in hospitals where the necessary facilities are available.

LEUCOVORIN RESCUE SCHEDULES FOLLOWING TREATMENT WITH HIGHER DOSES OF METHOTREXATE LEDERLE

CLINICAL SITUATION	LABORATORY FINDINGS	LEUCOVORIN DOSAGE AND DURATION
Normal METHOTREXATE LEDERLE Elimination	Serum METHOTREXATE LEDERLE level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0,2 micromolar at 72 hours	15 mg PO. IM or IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of METHOTREXATE LEDERLE infusion).
Delayed Late METHOTREXATE	Serum METHOTREXATE LEDERLE level remaining	Continue 15 mg PO. IM or IV q six hours, until

CLINICAL SITUATION	LABORATORY FINDINGS	LEUCOVORIN DOSAGE AND DURATION
LEDERLE Elimination	above 0,2 micromolar at 72 hours, and more than 0,05 micromolar at 96 hours after administration.	METHOTREXATE LEDERLE level is less than 0,05 micromolar.
Delayed Early METHOTREXATE LEDERLE Elimination and/or Evidence of Acute Renal Injury	Serum METHOTREXATE LEDERLE level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR a 100 % or greater increase in serum creatinine level at 24 hours after METHOTREXATE LEDERLE administration (e.g., an increase from 0,5 mg/dl to a level of 1 mg/dl or more)	150 mg IV q three hours, until METHOTREXATE LEDERLE level is less than 1 micromolar; then 15 mg IV q three hours, until METHOTREXATE LEDERLE level is less than 0,05 micromolar

Alternatively, Isovorin® [Levofolinic acid, the pharmacologically active isomer of leucovorin (folinic acid)], can be used for METHOTREXATE LEDERLE rescue.

GUIDELINES FOR ISOVORIN® METHOTREXATE LEDERLE RESCUE DOSAGE AND ADMINISTRATION

Clinical Situation	Laboratory Findings	Levofolinic acid Dosage and duration
Normal METHOTREXATE LEDERLE Elimination	Serum METHOTREXATE LEDERLE level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0,2 micromolar at 72 hours.	7,5 mg PO, IM, or IV q 6 hours for 60 hours (10doses starting at 24 hours after start of METHOTREXATE LEDERLE infusion).

Clinical Situation	Laboratory Findings	Levofolinic acid Dosage and duration
Delayed Late METHOTREXATE LEDERLE Elimination	Serum METHOTREXATE LEDERLE level remaining above 0,2 micromolar at 72 hours, and more than 0,05 micromolar at 96 hours after administration.	Continue 7,5 mg PO, IM, or IV q 6 hours, until METHOTREXATE LEDERLE level is less than 0,05 micromolar.
Delayed Early METHOTREXATE LEDERLE Elimination and/or Evidence of Acute Renal Injury	Serum METHOTREXATE LEDERLE level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR a 100 % or greater increase in serum creatinine level at 24 hours after METHOTREXATE LEDERLE administration (e.g., an increase from 0,5 mg/dl to a level of 1 mg/dl or more).	75 mg IV q 3 hours, until METHOTREXATE LEDERLE level is less than 1 micromolar; Then 7,5 mg IV q 3 hours until METHOTREXATE LEDERLE level is less than 0,05 micromolar.

Psoriasis and Rheumatoid Arthritis Chemotherapy:

THE PATIENT SHOULD BE FULLY INFORMED OF THE RISKS INVOLVED AND SHOULD BE UNDER CONSTANT SUPERVISION OF THE PHYSICIAN.

Assessment of renal function, liver function, and blood elements should be made by history, physical examination, and laboratory tests (such as haemogram, urinalysis, serum creatinine, liver function studies and liver biopsy if indicated) before beginning METHOTREXATE LEDERLE and periodically during METHOTREXATE LEDERLE therapy, and before reinstating METHOTREXATE LEDERLE therapy after a rest period. Appropriate steps should be taken by male or female patients to avoid conception during and for at least eight weeks following METHOTREXATE LEDERLE therapy.

There are two commonly used general types of dosage schedules:

- 1) Weekly oral or parenteral intermittent large doses.
- 2) Divided dose intermittent oral schedule over a 36-hour period.

All schedules should be continually tailored to the individual patient. An initial test dose one week prior to initiation of therapy is recommended to detect any idiosyncrasy. A suggested dose range is 5-10 mg parenterally.

For the treatment of psoriasis the recommended starting dose schedules for a 70 kg Adult:

- 1) Weekly single oral dose schedule: 10-25 mg per week until adequate response is achieved. With this dosage schedule, 30 mg per week should ordinarily not be exceeded.
- 2) Divided oral dose schedule: 2,5 mg at 12-hour intervals for three doses or at 8-hour intervals for four doses each week. With this dosage schedule, 30 mg per week should not be exceeded.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response, but not to exceed the maximum stated for each schedule.

Once optimal clinical response has been achieved, each dosage schedule should be reduced to the lowest possible amount of medicine and to the longest possible rest period. The use of METHOTREXATE LEDERLE may permit the return to conventional topical therapy, which should be encouraged.

Rheumatoid Arthritis:

Oral, initially 2,5 to 5 mg every 12 hours for 3 doses once a week, the dosage being increased as necessary in increments of 2,5 mg per week up to a maximum of 20 mg per week.

OR

Oral, initially 10 mg once a week, the dosage being increased as necessary up to 20 mg per week.

Folate Supplementation:

In patients with rheumatoid arthritis, including polyarticular-course juvenile rheumatoid arthritis, or psoriasis, folic acid or folinic acid may reduce METHOTREXATE LEDERLE toxicities such as gastro-intestinal symptoms, stomatitis, alopecia, and elevated liver enzymes. See also "INTERACTIONS - Vitamins".

Before taking a folate supplement, it is advisable to check B₁₂ levels, particularly in adults over the age of 50, since folate administration can mask symptoms of B₁₂ deficiency.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

SIDE EFFECTS:

In general, the incidence and severity of acute side effects are related to dose and frequency of administration.

The most frequently reported side effects include ulcerative stomatitis, leukopaenia, nausea and abdominal distress. Other frequently reported side effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection.

Other adverse reactions that have been reported with METHOTREXATE LEDERLE are listed below by organ system.

Adverse reactions are listed in CIOMS frequency categories:

Very common:	≥ 10%
Common:	≥ 1% and < 10%
Uncommon:	≥ 0,1% and < 1%
Rare:	≥ 0,01% and < 0,1%
Very rare:	< 0,01%

System Organ Class	Side effect
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Infections and Infestations:

Uncommon:	Opportunistic infections, including fatal infections
Rare:	Sepsis
Frequency undetermined:	Infections, including pneumonia, <i>Pneumocystis carinii</i> pneumonia, Nocardiosis, Histoplasmosis, Cryptococcosis, <i>Herpes zoster</i> , <i>H. simplex</i> hepatitis, Disseminated <i>H. simplex</i> , Fatal sepsis, cytomegalovirus infection, including cytomegaloviral pneumonia.

Neoplasms benign and malignant (including cysts and polyps):

Uncommon:	Lymphoma, including reversible lymphoma
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Blood and lymphatic system disorders:

Uncommon:	Anaemia, Suppressed haematopoiesis, Thrombocytopaenia
Very rare:	Aplastic anaemia

Frequency undetermined: Lymphadenopathy and lymphoproliferative disorders
(including reversible), Pancytopenia, Neutropenia,
Agranulocytosis, Eosinophilia

Immune system disorders:

Uncommon: Anaphylactoid reactions

Very rare: Hypogammaglobulinaemia

Metabolism and nutritional disorders:

Rare: Diabetes

Psychiatric disorders:

Rare: Mood alterations, Transient cognitive dysfunction

Nervous system disorders:

Uncommon: Headaches, Hemiparesis

Rare: Drowsiness, Paresis, Speech impairment, including dysarthria
and aphasia

Very rare: Unusual cranial sensations

Eye disorders:

Rare: Blurred vision, Serious visual changes of unknown aetiology

Very rare: Conjunctivitis, Transient blindness/vision loss

Cardiac disorders:

Rare: Hypotension

Very rare: Pericardial effusion, Pericarditis

Vascular disorders:

Rare: Thromboembolic events (including thrombophlebitis, arterial
thrombosis, cerebral thrombosis, deep vein thrombosis,
pulmonary embolism, retinal vein thrombosis)

Very rare: Vasculitis

Respiratory, thoracic and mediastinal disorders:

Uncommon: Interstitial pneumonitis, including fatalities

Rare: Pharyngitis, Respiratory fibrosis
Very rare: Chronic obstructive pulmonary disease
Frequency undetermined: Alveolitis

Gastro-intestinal disorders:

Uncommon: Anorexia, Diarrhoea, Stomatitis, Vomiting, Pancreatitis
Rare: Enteritis, Gastro-intestinal ulceration and bleeding, Gingivitis,
Melaena
Very rare: Haematemesis

Hepato-biliary disorders:

Uncommon: Liver enzyme elevations
Rare: Acute hepatitis, Chronic fibrosis and cirrhosis, Hepatotoxicity
Very rare: Decrease in serum albumin
Frequency undetermined: Hepatic failure

Skin and subcutaneous tissue disorders:

Uncommon: Alopecia, Stevens-Johnson Syndrome, Toxic epidermal
necrolysis (Lyell's syndrome)
Rare: Acne, Ecchymosis, Erythema multiforme, Erythematous
rashes, Nodulosis, Painful erosion of psoriatic plaques,
Photosensitivity, Pigmentary changes, Pruritus, Skin
ulceration, Urticaria
Very rare: Furunculosis, Telangiectasia

Musculoskeletal, connective tissue and bone disorders:

Rare: Arthralgia/myalgia, Osteoporosis, Stress fractures

Renal and urinary disorders:

Uncommon: Severe nephropathy, Renal failure
Rare: Dysuria
Very rare: Azotaemia, Cystitis, Haematuria
Frequency undetermined: Proteinuria

Pregnancy, puerperium and perinatal conditions:

Uncommon: Foetal defects

Rare: Abortion
Frequency undetermined: Foetal death

Reproductive system and breast disorders:

Rare: Menstrual dysfunction
Very rare: Defective oogenesis/spermatogenesis, Impotence,
Infertility, Loss of libido, Transient oligospermia, Vaginal
discharge

General disorders and administration site conditions:

Very rare: Sudden death

• **Adverse Events in Juvenile Rheumatoid Arthritis (JRA) Studies**

The approximate incidences of adverse reactions reported in paediatric patients with JRA treated with oral, weekly doses of METHOTREXATE LEDERLE (5 to 20 mg/m²/wk or 0,1 to 1,1 mg/kg/wk), were as follows (virtually all patients were receiving concomitant nonsteroidal anti-inflammatory drugs, and some also were taking low doses of corticosteroids): elevated liver function tests, 14 %; gastro-intestinal reactions (e.g. nausea, vomiting, diarrhoea 11 %; stomatitis 2 %; leukopaenia 2 %; headache 1,2 %; alopecia 0,5 %; dizziness 0,2 %; and rash 0,2%. Although there is experience with dosing up to 30 mg/m²/wk in JRA, the published data for doses above 20 mg/m²/wk are too limited to provide reliable estimates of adverse reaction rates.

SPECIAL PRECAUTIONS:

NOTE: IT IS IMPORTANT THAT THE PHYSICIAN FAMILIARISES HIMSELF WITH THE WARNINGS LISTED UNDER THE HEADING "WARNINGS" ABOVE.

METHOTREXATE LEDERLE has a high potential toxicity, usually dose-related.

- METHOTREXATE LEDERLE has the potential for serious toxicity (See boxed "WARNINGS"). Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses and can occur at any time during therapy. It is therefore necessary to follow patients on METHOTREXATE LEDERLE closely. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium (See "OVERDOSAGE").

If METHOTREXATE LEDERLE therapy is reinstated, it should be carried out with caution, with adequate consideration of further need for the drug and with increased alertness as to possible recurrence of toxicity.

- Patients should be informed of the potential benefits and risks in the use of METHOTREXATE LEDERLE (including the early signs and symptoms of toxicity), the need to see their physician promptly if they occur, and of the need for close follow-up, including periodic laboratory tests, to monitor toxicity. The risk of effects on reproduction should be discussed with both male and female patients taking METHOTREXATE LEDERLE.
- It should be emphasized to the patient that the recommended dose is taken weekly in rheumatoid arthritis and psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity.
- The use of METHOTREXATE LEDERLE high-dose regimens recommended for osteosarcoma requires meticulous care. High dosage regimens for other neoplastic diseases are investigational and a therapeutic advantage has not been established.
- Malignant lymphomas, which may regress following withdrawal of METHOTREXATE LEDERLE, may occur in patients receiving low-dose METHOTREXATE LEDERLE and, thus, may not require cytotoxic treatment. Discontinue METHOTREXATE LEDERLE first and, if the lymphoma does not regress, appropriate treatment should be instituted.
- Folate deficiency states may increase METHOTREXATE LEDERLE toxicity.
- Pneumonitis, due to METHOTREXATE LEDERLE may occur in some patients. Acute depression of haematological function, and acute folinic acid deficiency may be produced with high doses.
- METHOTREXATE LEDERLE is excreted principally by the kidneys. Its use in the presence of impaired renal function may result in accumulation of toxic amounts or even additional renal damage.
The patient's renal status should be determined prior to and during METHOTREXATE LEDERLE therapy and proper caution exercised should

significant renal impairment be disclosed. Medicine dosage should be reduced or discontinued until renal function is improved or restored.

- METHOTREXATE LEDERLE should be used with extreme caution in the presence of infection, peptic ulcer, ulcerative colitis, debility, and in extreme youth and old age. If profound leukopaenia occurs during therapy, bacterial infection may occur or become a threat. Cessation of the medicine and appropriate antibiotic therapy is usually indicated. In severe bone marrow depression, blood or platelet transfusions may be necessary. Since it is reported that METHOTREXATE LEDERLE may have an immunosuppressive action, this factor must be taken into consideration in evaluating the use of the medicine where immune responses in a patient may be important or essential.
- Neurologic; Cases of severe neurological adverse reactions that ranged from headache to paralysis, coma and stroke-like episodes have been reported mostly in juveniles and adolescents given METHOTREXATE LEDERLE in combination with cytarabine.

In all instances where the use of METHOTREXATE LEDERLE is considered for chemotherapy, the physician must evaluate the need and usefulness of the medicine against the risks of toxic effects or adverse reaction. Most such adverse reactions are reversible if detected early. When such effects or reactions do occur, the medicine should be reduced in dosage or discontinued and appropriate corrective measures should be taken, according to the clinical judgement of the physician. Reinstitution of METHOTREXATE LEDERLE therapy should be carried out with caution, with adequate consideration of further need for the medicine and alertness as to possible recurrence of toxicity.

Laboratory Monitoring

- **General**

Patients undergoing METHOTREXATE LEDERLE therapy should be closely monitored so that toxic effects are detected promptly. Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests, and a chest X-ray.

- **Psoriasis, Rheumatoid Arthritis**

During therapy of rheumatoid arthritis and psoriasis, monitoring of the following parameters is recommended: haematology at least monthly, hepatic enzyme levels and renal function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. During initial or change in dosing, or during periods of increased risk of elevated METHOTREXATE LEDERLE blood levels (e.g. dehydration), more frequent monitoring may also be indicated.

- **Pulmonary Function Tests**

Pulmonary function tests may be useful if METHOTREXATE LEDERLE induced lung disease is suspected, especially if baseline measurements are available.

- **METHOTREXATE LEDERLE Level**

Serum METHOTREXATE LEDERLE level monitoring can significantly reduce METHOTREXATE LEDERLE toxicity and mortality.

Patients subject to the following conditions are predisposed to developing elevated or prolonged METHOTREXATE LEDERLE levels and benefit from routine monitoring of levels; e.g. pleural effusion, ascites, gastrointestinal tract obstruction, previous cisplatin therapy, dehydration, aciduria, impaired renal function.

Some patients may have delayed METHOTREXATE LEDERLE clearance in the absence of these features. It is important that patients be identified within 48 hours since METHOTREXATE LEDERLE toxicity may not be reversible if adequate leucovorin rescue is delayed for more than 42 to 48 hours.

Monitoring of METHOTREXATE LEDERLE concentrations should include determination of a METHOTREXATE LEDERLE level at 24, 48 or 72 hours, and assessment of the rate of decline in METHOTREXATE LEDERLE concentrations (to determine how long to continue leucovorin rescue).

Organ System Toxicity:

- **Gastro-intestinal**

If vomiting, diarrhoea, or stomatitis occur, which may result in dehydration, METHOTREXATE LEDERLE should be discontinued until recovery occurs.

- **Haematologic**

METHOTREXATE LEDERLE can suppress haematopoiesis and cause anaemia, aplastic anaemia, pancytopenia, leukopenia, neutropenia, and/or thrombocytopenia. In patients with malignancy and pre-existing haematopoietic impairment, the medicine should be used with caution, if at all. In psoriasis and rheumatoid arthritis, METHOTREXATE LEDERLE should be stopped immediately if there is a significant drop in blood cell counts. In the treatment of neoplastic diseases, METHOTREXATE LEDERLE should be continued only if the potential benefit warrants the risk of severe myelosuppression.

- **Hepatic**

METHOTREXATE LEDERLE has the potential for acute hepatitis and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally two years or more) and after a total cumulative dose of at least 1,5 grams. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes and advanced age.

Transient abnormalities of liver parameters are observed frequently after METHOTREXATE LEDERLE administration and are usually not a reason for modification of METHOTREXATE LEDERLE therapy. Persistent liver abnormalities, and/or decrease of serum albumin may be indicators of serious liver toxicity.

In psoriasis, liver damage and function tests, including serum albumin and prothrombin time, should be performed several times prior to dosing. Liver function tests are often normal in developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1) before start of therapy or shortly after initiation of therapy (2 - 4 months); 2) after a total cumulative dose of 1,5 grams and; 3) after each additional 1,0 to 1,5 grams. In case of moderate fibrosis or any cirrhosis, discontinue the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low grade portal inflammation are relatively common before the start of therapy. Although these mild changes are usually not a reason to avoid or discontinue METHOTREXATE LEDERLE therapy, the medicine should be used with caution.

In rheumatoid arthritis, age at first use of METHOTREXATE LEDERLE and duration of therapy have been reported as risk factors for hepatotoxicity. Persistent abnormalities in

liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid population.

Liver function tests should be performed at baseline and at 4 - 8 week intervals in patients receiving METHOTREXATE LEDERLE for rheumatoid arthritis. Pre-treatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

If the results of a liver biopsy show mild changes (Roanigk grades I, II, IIIa), METHOTREXATE LEDERLE may be continued and the patient monitored as per recommendations listed above. METHOTREXATE LEDERLE should be discontinued in any patient who displays persistently abnormal liver function tests and refuses liver biopsy or in any patient whose liver biopsy shows moderate to severe changes (Roanigk grade IIIb or IV).

- **Infection or Immunologic States**

METHOTREXATE LEDERLE should be used with extreme caution in the presence of active infection and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. Hypogammaglobulinaemia has been reported rarely.

- **Infection**

Pneumonia (in some cases leading to respiratory failure) may occur.

Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with METHOTREXATE LEDERLE therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered.

- **Immunization**

Immunization may be ineffective when given during METHOTREXATE LEDERLE therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunization in patients receiving METHOTREXATE LEDERLE therapy.

- **Pulmonary**

Pulmonary signs and symptoms, e.g. a dry non-productive cough, fever, cough, chest pain, dyspnoea, hypoxaemia, and an infiltrate on chest X-ray, or a non-specific pneumonitis occurring during METHOTREXATE LEDERLE therapy, may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Pulmonary lesions can occur at all dosages. Infection (including pneumonia) needs to be excluded.

- **Renal**

METHOTREXATE LEDERLE may cause renal damage that may lead to acute renal failure. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum METHOTREXATE LEDERLE and creatinine levels are essential for safe administration.

- **Skin**

Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome, and erythema multiforme, have been reported within days of oral, intramuscular, intravenous, or intrathecal METHOTREXATE LEDERLE administration.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation dermatitis and sunburn may be "recalled" by the use of METHOTREXATE LEDERLE.

Other Precautions: METHOTREXATE LEDERLE should be used with extreme caution in the presence of debility.

High-Dosage Therapy

The use of METHOTREXATE LEDERLE high-dose regimens recommended for osteosarcoma requires meticulous care. High dosage regimens for other neoplastic diseases are investigational and a therapeutic advantage has not been established. Large doses should not be used in patients with impaired renal function or a third-space reservoir, such as ascites or large pleural effusion, because rapid medicine excretion is important in limiting toxicity.

Careful monitoring of renal function and METHOTREXATE LEDERLE serum levels is required in order to reveal impending toxicity and the need for extended leucovorin calcium administration. Alkalinization of the urine and increased urine volume are recommended in order to prevent renal precipitation in acidic urine.

Paediatric Use:

Safety and effectiveness in paediatric patients have been established only in cancer chemotherapy and in polyarticular-course juvenile rheumatoid arthritis.

Published clinical studies evaluating the use of METHOTREXATE LEDERLE in children and adolescents (i.e., patients 2 to 16 years of age) with juvenile rheumatoid arthritis demonstrated safety comparable to that observed in adults with rheumatoid arthritis. See also "SIDE EFFECTS AND SPECIAL PRECAUTIONS".

Geriatric Use :

Due to diminished hepatic and renal function as well as decreased folate stores in elderly patients, relatively low doses should be considered, and these patients should be closely monitored for early signs of toxicity.

Carcinogenesis, Mutagenesis, And Impairment Of Fertility

No controlled human data exist regarding the risk of neoplasia with METHOTREXATE LEDERLE. METHOTREXATE LEDERLE has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that METHOTREXATE LEDERLE causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Non-Hodgkin's lymphoma and other tumours have been reported in patients receiving low-dose oral METHOTREXATE LEDERLE. However, there have been instances of malignant lymphoma arising during treatment with low-dose oral METHOTREXATE LEDERLE, which have regressed completely following withdrawal of METHOTREXATE LEDERLE, without requiring active anti-lymphoma treatment. Benefits should be weighed against the potential risks before using METHOTREXATE LEDERLE alone or in combination with other drugs, especially in children or young adults. METHOTREXATE LEDERLE causes embryotoxicity, abortion, and foetal defects in humans. It has also been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy

Effects On Activities Requiring Concentration And Performance:

Some of the effects mentioned under “SIDE EFFECTS AND SPECIAL PRECAUTIONS”, such as dizziness and fatigue, may affect the ability to drive or operate machinery.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms of overdose are listed under the headings "WARNINGS" and "SIDE EFFECTS AND SPECIAL PRECAUTIONS"

In post-marketing experience, overdose with METHOTREXATE LEDERLE has generally occurred with oral and intrathecal administration, although intravenous and intramuscular overdose has also been reported.

Reports of oral overdose indicate accidental daily administration instead of weekly (single or divided doses). Symptoms commonly reported following oral overdose include those symptoms and signs reported at pharmacological doses, particularly haematologic and gastro-intestinal reactions (e.g. leukopaenia, thrombocytopaenia, anaemia, pancytopaenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastro-intestinal ulceration, and gastro-intestinal bleeding). In some cases, no symptoms were reported. There have been reports of death following overdose. In these cases, events such as sepsis or septic shock, renal failure, and aplastic anaemia were also reported.

- ***Recommended Treatment***

Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdoses of METHOTREXATE LEDERLE. Leucovorin administration should begin as promptly as possible. As the time interval between METHOTREXATE LEDERLE administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum METHOTREXATE LEDERLE concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

In cases of massive overdose, hydration and urinary alkalinization may be necessary to prevent the precipitation of METHOTREXATE LEDERLE and/or its metabolites in the renal tubules.

Neither standard haemodialysis nor peritoneal dialysis has been shown to improve METHOTREXATE LEDERLE elimination. However, effective clearance of METHOTREXATE LEDERLE has been reported with acute, intermittent haemodialysis using a high-flux dialyser.

In general, where overdosage is suspected, the dose of leucovorin should be equal to or higher than the offending dose of METHOTREXATE LEDERLE and should best be administered within the first hour. Use of leucovorin calcium after an hour delay is much less effective.

IDENTIFICATION:

Round, convex, yellow, tablets which may be mottled, 6,4mm in diameter; engraved with script "2.5" on the one side, scored in half on the other side and engraved with a block letter "M" above the score and "1" below.

PRESENTATION:

Tablets packed in opaque, white PVC/Al blisters in a pack size of 100 tablets

STORAGE INSTRUCTIONS:

Store at or below 25°C. The tablets should be stored in the original packaging which prevents access of moisture and protected from light. Keep out of reach of children.

REGISTRATION NUMBER:

Ref. No. H2766 (Act 101/1965)

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd
85 Bute Lane
Sandton, 2196
South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

14 August 2009

BOTSWANA: S2 Reg No.: B9306105
NAMIBIA: S2 Reg No.: 14/26/0144
ZIMBABWE: PP Reg No.: 94/9.2.1/2829

