Mexat® IV injection

Methotrexate USP Injection

DESCRIPTION

MEXAT® IV Injection is a preparation of Methotrexate. Methotrexate is a folate antagonist. Methotrexate inhibits dihydrofolate reductase (DHFR), the enzyme that reduces folic acid to tetrahydrofolic acid. Tetrahydrofolate must be regenerated via the DHFR-catalyzed reaction in order to maintain the intracellular pool of tetrahydrofolate one-carbon derivatives for both thymidylate and purine nucleotide biosynthesis. The inhibition of DHFR by folate antagonists (Methotrexate) results in a deficiency in the cellular pools of thymidylate and purines and thus in a decrease in nucleic acid synthesis. Therefore, Methotrexate interferes with DNA synthesis, repair, and cellular replication.

Methotrexate is most active against rapidly multiplying cells, because its cytotoxic effects occur primarily during the S phase of the cell cycle. Since cellular proliferation in malignant tissues is greater than in most normal tissues, Methotrexate may impair malignant growth without irreversible damage to normal tissues. As a result, actively proliferating tissues such as malignant cells, bone marrow, fetal cells, buccal and intestinal mucosa, and cells of the urinary bladder are in general more sensitive to DHFR inhibition effects of Methotrexate.

The cytotoxicity of Methotrexate results from three important actions: inhibition of DHFR, inhibition of thymidylate synthase, and alteration of the transport of reduced folates. The affinity of DHFR to Methotrexate is far greater than its affinity for folic acid or dihydrofolic acid, therefore, large doses of folic acid given simultaneously will not reverse the effects of Methotrexate. However, Leucovorin calcium, a derivative of tetrahydrofolic acid may block the effects of Methotrexate if given shortly after the antineoplastic agent.

Methotrexate has immunosuppressive activity. This may be a result of inhibition of lymphocyte multiplication. The mechanisms of action in the management of rheumatoid arthritis of the drug is not known, although suggested mechanisms have included immunosuppressive and/or anti-inflammatory effects.

INDICATIONS

Neoplastic Diseases:

- Choriocarcinoma: Methotrexate – as single chemotherapy or in combination with other drugs.
- Intermediate-, or high-grade Non-Hodgkin's Lymphoma as part of ProMACE-CytaBOM, ProMACE-MOPP, and Magrath protocols.
- Breast Cancer: as part of CMF (cyclophosphamide-methotrexate-fluorouracil) therapy.
- Acute Lymphoblastic Leukemia: as maintenance therapy.
- Head and Neck Cancer: in combination with other chemotherapies.
- Gastric Cancer: palliative combination chemotherapy.
- Metastasis of unknown primary: as palliative combination chemotherapy.
- Bladder Cancer (advanced): as part of the M-VAC Regimen.
- Burkitt's lymphoma.
- Advanced stages of childhood lymphoma (III and IV, St. Jude's Children's' Research Hospital Staging System).
- Advanced cases of mycosis fungoides (cutaneous T-cell lymphoma).

Disease Modifying Antirheumatic Drug (DMARD):

- Severe disabling psoriasis/psoriatic arthritis
- Severe disabling rheumatoid arthritis (RA)
- Severe disabling seronegative arthritis

DOSAGE AND ADMINISTRATION

Neoplastic Diseases-

Dosing Considerations:

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained.
- Methotrexate injection may be given by the intramuscular, intravenous (as a bolus) or intra-arterial routes. The preserved formulation contains benzyl alcohol and must not be used for intrathecal, interventricular, or high dose therapy.
- Methotrexate may only be administered by physicians experienced in the treatment of neoplasia. The oncologist should consult the current literature for the treatment regimen to be used. Typical dosages reported in the literature for the following malignancies are listed in the following section.

Recommended Dose and Dosage Adjustment:

Breast Cancer: The initial doses of CMF will be cyclophosphamide 100 mg/m² p.o. days 1 through 14, Methotrexate 40 mg/m² i.v. day 1, 8, and 5 - Fluorouracil 600 mg/m² i.v. day 1, 8. Cycle length will be 28 days ("2 weeks-on, 2 weeks-off"). In patients over 60 years of age, the dosage of Methotrexate will be 30 mg/m² i.v. day 1, 8. If total bilirubin exceeds 1.5 mg/dL, decrease the dose of Methotrexate only by 50%.

Bladder Cancer: Typical dosage regimens for bladder cancer are the CMV Regimen and the "M-VAC Regimen" which are represented in the following tables.

Table 1: CMV Regimen*

Drugs**		Days	
	1	2	8
Cisplatin‡		100	
Vinblastine	4		4
Methotrexate***	30		30

- All doses in mg/m² with cycles repeated on day 22.
- Patients> 70 years old receive 80% of all doses; if vomiting persists to day 8, no drug is given.
- For each cycle adjust cisplatin to 100% for Ccr>60 mL/min; 50% of dose for Ccr 50-60 mL/min; none for Ccr<50mL/min.
- No drug for a decrease on day 8 of>30mL/min compared to day 1 or Ccr<50mL/min or Cr> 1.8 mg/dL.
- Major dose modifications for both drugs depending on myelosuppression.
- All doses in mg/m² with cycles repeated every 28 - 32 days.
- Patients having prior pelvic irradiation equivalent to >2500 rad in 5 days, reduce the dose of doxorubicin 15mg/m².
- No doses given when the WBC <2500 cells/mm3, platelets>100,000 cells/mm³, or mucositis present.

Head and Neck Cancer: Methotrexate remains the standard of therapy for patients with recurrent or metastatic disease. It has been given in a wide variety of doses and schedules (a few of which are represented in the table below-

Table 3: Methotrexate Schedule

0.8 mg/kg every 4 days IV
25 - 50 mg every 4 to 7 days
60 mg/m² weekly IV or 40mg/m² biweekly IV
40 - 60 mg/m² weekly IV
80 mg/m² for 30 h every 2 wk with escalation to toxicity
40 mg/m² weekly IV
40-200 mg/m² IV on days 1, 4 weekly; Leucovorin on days 2,5
60 mg/m² IV weekly

Gastric Cancer: A regimen used in a clinical trial in Belgium in patients with resectable gastric cancer follows: Methotrexate (1.5 g/m² IV day 1, + 5-Fluorouracil (1.5 g/m² IV) + Leucovorin (15 mg/m² orally or IV every 6 hours for 72 hours) + Adriamycin (30 mg/m² IV, day 15). The schedule is repeated on day 29 for 6 cycles.

Choriocarcinoma and similar trophoblastic diseases: Methotrexate is administered orally or intramuscularly 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 periods 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 (beta-HCG), which should return to normal or less than 50 IU/24 hr usually after the third or fourth course and usually be followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of Methotrexate after normalization of beta-HCG is usually recommended. Before each course of the drug careful clinical assessment is essential. Cyclic combination therapy of Methotrexate with other antitumor drugs has been reported as being useful.

Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with Methotrexate has been recommended.

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

Table 2: M-VAC Regimen*

Drugs	Days			
	1	2	15	22***
Methotrexate	30		30	30
Vinblastine		3	33	3
Doxorubicin		30**		
Cisplatin		70		

Lymphomas: In Burkitt's tumor, Stages I-II, Methotrexate has produced prolonged remissions in some cases. Recommended dosage is 10 to 25 mg/day orally for 4 to 8 days. In Stage III, Methotrexate is commonly given concomitantly with other antitumor agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods. Lymph sarcomas in Stage III may respond to combined drug therapy with Methotrexate given in doses of 0.625 to 2.5 mg/kg daily.

The treatment of choice for localized histologically aggressive lymphoma is primary combination chemotherapy with or without involved-field radiation therapy. Frequently used regimens for intermediate, or high grade NHL that include Methotrexate include groups: the ProMACE/MOPP, ProMACE-CytaBOM, and Magrath Protocols. Represented in the table below for example, is the ProMACE CytaBOM Regimen.

Table 4: ProMACE CytaBOM Regimen

ProMACE CytaBOM	Day 1	Day 8	Day 14	Day 15-21
Cyclophosphamide 650 mg/m²I.V.	x	No therapy		
Doxorubicin 25 mg/m² I.V.	x			
Etoposide 120 mg/m² I.V.	x			
Cytarabine 300 mg/m² I.V.		x		
Bleomycin 5 mg/m² I.V.		x		
Vincristine 1.4 mg/m² I.V.		x		
Methrotrexate 120 mg/m² I.V.		x with Leucovorin rescue		
Prednisone 60 mg/m² PO	x----------x			
Co-trimoxazole 2 PO bid throughout 6 cycles of therapy				

In early stage childhood non-Hodgkin's lymphoma, Methotrexate is used effectively in combination chemotherapy regimens.

Mycosis Fungoides (cutaneous T-cell lymphoma): Therapy with Methotrexate appears to produce clinical responses in up to 50% of patients treated, but chemotherapy is not curative. Dosage is usually 2.5 to 10 mg daily by mouth for several weeks or months. Dose levels of drug and adjustment of dose regimen by reduction or cessation of drug are guided by patient response and haematologic monitoring. Methotrexate has also been given intramuscularly in doses of 50 mg once weekly or 25 mg 2 times weekly.

Leukemia: Acute lymphoblastic leukemia (ALL) 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.

Methotrexate alone or in combination with steroids was used initially for induction of remission in ALL. More recently corticosteroid therapy, in combination with other antileukemic drugs or in cyclic combinations with Methotrexate included, has appeared to produce rapid and effective remissions. When used for induction, Methotrexate in doses of 3.3 mg/m² in combination with 60 mg/m² of prednisone, given daily, produced remissions in 50% of patients treated, usually within a period of 4 to 6 weeks. Methotrexate in combination with other agents appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: Methotrexate is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m². It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, re-induction of remission can again usually be obtained by repeating the initial induction regimen.

A variety of combination chemotherapy regimens have been used for both induction and maintenance therapy in ALL. The physician should be familiar with recent advances in antileukemic therapy.

Psoriasis:

- Recommended Starting Dose Schedules: Weekly single oral, IM or IV dose schedule: 10 to 25 mg per week until adequate response is achieved.
- Divided oral dose schedule: 2.5 mg at 12 hour intervals for three doses.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded.

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

Rheumatoid Arthritis:

Recommended Starting Dosage Schedules

- Single oral doses of 7.5 mg once weekly.
- Divided oral dosages of 2.5 mg at 12 hour intervals for 3 doses given as a course once weekly.

Dosages in each schedule may be adjusted gradually to achieve an optimal response, but not ordinarily to exceed a total weekly dose of 20 mg.

Therapeutic response usually begins within 3 to 6 weeks and the patient may continue to improve for another 12 weeks or more.

Use in Patients with Renal Impairment:

Table 5: Dose Adjustments in Patients with Renal Insufficiency

Creatinine Clearance (mL/min)	% Standard Dose to Administer
>80	Full Dose
80	75
60	63
50	56
<50	Use alternative therapy

CONTRAINDICATIONS

• Hypersensitivity

SIDE EFFECTS

- Alimentary System: Gingivitis, stomatitis, enteritis, anorexia, nausea, vomiting, diarrhea, haematemesis, melena, gastrointestinal ulceration and bleeding, pancreatitis.
- Cardiovascular: Pericarditis and pericardial effusion (damage to heart, rarely), hypotension, and thromboembolic events.
- Central Nervous System: Paresthesia, Headaches, dizziness, drowsiness, speech impediment including dysarthria and aphasia; hemiparesis, paresis and convulsions.
- Haematopoietic: Anaemia, leukopenia, and/or thrombocytopenia.
- Hepatobiliary Disorders: Hepatotoxicity, acute hepatitis, chronic fibrosis and cirrhosis, decrease in serum albumin, liver enzyme elevations, hepatic failure.
- Skin: Erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis.

WARNING AND PRECAUTION

Methotrexate injection contains benzyl alcohol and must not be used for intrathecal, intraventricular, or high dose treatment. Methotrexate can cause serious toxic reactions which may result in death. Methotrexate can cause birth defect (deformed babies) or death of an unborn baby when used in pregnant women. Pregnant women with psoriasis or rheumatoid arthritis should not take Methotrexate.

USE IN PREGNANCY AND LACTATION

Methotrexate has been reported to cause fetal death and/or congenital anomalies. Pregnant patients with psoriasis or rheumatoid arthritis should not receive Methotrexate.

Because of the potential for serious adverse reactions from Methotrexate in breast fed infants, Methotrexate is contraindicated in nursing mothers.

PHARMACEUTICAL PRECAUTION

Storage Condition: Will be confirmed later

PACKAGING

MEXAT® IV Injection

SK+F ONCOLOGY

Manufactured by
ESKAYEF PHARMACEUTICALS LIMITED
RUPGANJ, NARAYANGANJ, BANGLADESH

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