PRODUCT SUMMARY

1. TRADE NAME OF THE MEDICINAL PRODUCT

Methotrexate 100 mg/ml Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 100 mg methotrexate (sodium salt formed in situ).

Each vial of 10 ml of solution contains 1 g methotrexate (sodium salt formed in situ).
Each vial of 50 ml of solution contains 5 g methotrexate (sodium salt formed in situ).

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection.

Vials containing a clear yellow/orange solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Methotrexate is indicated in the treatment of neoplastic disease, such as trophoblastic neoplasms and leukaemia, and the symptomatic treatment of severe recalcitrant disabling psoriasis which is not adequately responsive to other forms of treatment.

Methotrexate Injection may be given by the intramuscular, intravenous, intra-arterial, intrathecal routes.

Note: Methotrexate Injection 1g/ 10ml and 5g/ 50ml are hypertonic and therefore are not suitable for intrathecal use. In addition the 500mg/ 20ml and 1 g/40 ml are not suitable for intrathecal use.

4.2. Posology and method of administration

Adults and Children

Antineoplastic Chemotherapy

Methotrexate is active orally and parenterally. Methotrexate Injection B.P. may be given by the intramuscular, intravenous, intra-arterial or intrathecal routes. Dosage is related to the patient's body weight or surface area. Methotrexate has been used with beneficial effect in a wide variety of neoplastic diseases, alone and in combination with other cytotoxic agents.

NOTE: Methotrexate Injection 1 g/ 10ml and 5g/ 50ml are hypertonic and thus it is not recommended for intrathecal use. In addition, the 500 mg/20 ml and 1 g/40 ml presentations are not suitable for intrathecal use.

Chorlocarcinoma and Similar Trophoblastic Diseases

Methotrexate is administered orally or intramuscularly in doses of 15-30mg daily for a 5 day course. Such courses may be repeated 3-5 times as required, with rest periods of one or more weeks interposed between courses until any manifesting toxic symptoms subside.

The effectiveness of therapy can be evaluated by 24 hours quantitative analysis of urinary chorionic gonadotrophin hormone (HCG). Combination therapy with other cytotoxic drugs, has also been reported as useful.

Hydatidiform mole may precede or be followed by choriocarcinoma, and Methotrexate has been used in similar doses for the treatment of hydatidiform mole and chorioadenoma destruens.

Breast Carcinoma

Prolonged cyclic combination with Cyclophosphamide, Methotrexate and Fluorouracil has given good results when used as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary lymph nodes. Methotrexate dosage was 40mg/m^2 intravenously on the first and eighth days.

Leukaemia

Acute granulocytic leukaemia is rare in children but common in adults and this form of leukaemia responds poorly to chemotherapy.

Methotrexate is not generally a drug of choice for induction of remission of lymphoblastic leukaemia. Oral Methotrexate 3.3mg/m^2 daily, and Prednisolone 40-60mg/m^2 daily for 4-6 weeks has been used. After a remission is attained, Methotrexate in a maintenance dosage of 20-30mg/m^2 orally or by I.M. injection has been administered twice weekly. Twice weekly doses appear to be more effective than daily drug administration. Alternatively, 2.5mg/kg has been administered I.V. every 14 days.

Meningeal Leukaemia

Some patients with leukaemia are subject to leukaemic invasions of the central nervous system and the CSF should be examined in all leukaemia patients.

Passage of Methotrexate from blood to the cerebrospinal fluid is minimal and for adequate therapy the drug should be administered intrathecally. Methotrexate may be given in a prophylactic regimen in all cases of lymphocytic leukaemia. The dose of intrathecal Methotrexate is constant regardless of age or body surface area in patients over the age of 3 years of age, the maximum intrathecal dose should be 12mg in such patients. Patients under the age of 3 years should be treated in accordance with combination chemotherapy protocols. The administration is at weekly intervals and is usually repeated until the cell count of cerebrospinal fluid returns to normal. At this point one additional dose is advised. Large doses may cause convulsions and untoward side effects may occur as with any intrathecal injection, and are commonly neurological in character.

NOTE: Methotrexate Injection 1g/ 10ml and 5g/ 50ml are not recommended for intrathecal use. In addition, the 500 mg/20 ml and 1 g/40 ml presentations are not suitable for intrathecal use.

Lymphomas

In Burkitt's Tumour, stages 1-2, Methotrexate has prolonged remissions in some cases. Recommended dosage is 10-25mg per day orally for 4 to 8 days. In stage 3, Methotrexate is commonly given concomitantly with other antitumour agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods, and in stage 3 they respond to combined drug therapy with Methotrexate given in doses of 0.625mg to 2.5mg/kg daily. Hodgkin's Disease responds poorly to Methotrexate and to most types of chemotherapy.

Mycosis Fungoides

Therapy with Methotrexate appears to produce clinical remissions in one half of the cases treated. Recommended dosage is usually 2.5 to 10mg daily by mouth for weeks or months and dosage should be adjusted according to the patient's response and haematological monitoring. Methotrexate has also been given intramuscularly in doses of 50mg once weekly or 25mg twice weekly.

Psoriasis Chemotherapy

Cases of severe uncontrolled psoriasis, unresponsive to conventional therapy, have responded to weekly single, oral, I.M. or I.V. doses of 10-25mg per week, adjusted according to the patient's response. An initial test dose one week prior to initiation of therapy is recommended to detect any idiosyncrasy. A suggested dose range is 5-10mg parenterally.

An alternative dosage schedule consists of 2.5 to 5mg of Methotrexate administered orally at 12 hour intervals for 3 doses each week or at 8-hour intervals for 4 doses each week; weekly dosages should not exceed 30mg.

A daily oral dosage schedule of 2 to 5mg administered orally for 5 days followed by
a rest period of at least 2 days may also be used. The daily dose should not exceed 6.25mg.

The patient should be fully informed of the risks involved and the clinician should pay particular attention to the appearance of liver toxicity by carrying out liver function tests before starting Methotrexate treatment, and repeating these at 2 to 4 month intervals during therapy. The aim of therapy should be to reduce the dose to the lowest possible level with the longest possible rest period. The use of Methotrexate may permit the return to conventional topical therapy which should be encouraged.

4.3. Contraindications

Significantly impaired renal function.

Significantly impaired hepatic function

Pre-existing blood dyscrasias, such as significant marrow hypoplasia, leukopenia, thrombocytopenia or anaemia.

Methotrexate is contraindicated in pregnancy.

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, breast feeding is contra-indicated in women taking methotrexate.

Patients with a known allergic hypersensitivity to methotrexate should not receive methotrexate.

4.4. Special warnings and precautions for use

Warnings

Methotrexate must be used only by physicians experienced in antimetabolite chemotherapy.

Because of the possibility of fatal or severe toxic reactions, the patient should be fully informed by the physician of the risks involved and be under his constant supervision.

Acute or chronic interstitial pnemonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Symptoms typically include dyspnoea, cough (especially a dry non-productive cough) and fever for which patients should be monitored at each follow-up visit. Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop persistent cough or dyspnoea.

Methotrexate should be withdrawn from patients with pulmonary symptoms and a thorough investigation should be made to exclude infection. If methotrexate induced lung disease is suspected treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted.

Deaths have been reported with the use of Methotrexate in the treatment of psoriasis.

In the treatment of psoriasis, Methotrexate should be restricted to severe recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established by biopsy and/or after dermatological consultation.

1. Full blood counts should be closely monitored before, during and after treatment. If a clinically significant drop in white-cell or platelet count develops, methotrexate should be withdrawn immediately. Patients should be advised to report all symptoms or signs suggestive of infection.

2. Methotrexate may be hepatotoxic, particularly at high dosage or with prolonged therapy. Liver atrophy, necrosis, cirrhosis, fatty changes, and periportal fibrosis have been reported. Since changes may occur without previous signs of gastrointestinal or haematological toxicity, it is imperative that hepatic function be determined prior to initiation of treatment and monitored regularly throughout therapy. If substantial hepatic function abnormalities develop, methotrexate dosing should be suspended for at least 2 weeks. Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function. Concomitant use of other drugs with hepatotoxic potential (including alcohol) should be avoided.

3. Methotrexate has been shown to be teratogenic; it has caused foetal death and/or congenital anomalies. Therefore it is not recommended in women of childbearing potential unless there is appropriate medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant psoriatic patients should not receive Methotrexate.

4. Renal function should be closely monitored before, during and after treatment. Caution should be exercised if significant renal impairment is disclosed. Reduce dose of methotrexate in patients with renal impairment. High doses may cause the precipitation of methotrexate or its metabolites in the renal tubules. A high fluid throughput and alkalinisation of the urine to pH 6.5 — 7.0, by oral or intravenous administration of sodium bicarbonate (5 x 625mg tablets every three hours) or acetazolamide (500mg orally four times a day) is recommended as a preventative measure . Methotrexate is excreted primarily by the kidneys. Its use in the presence of impaired renal function may result in accumulation of toxic amounts or even additional renal damage.

5. Diarrhoea and ulcerative stomatitis are frequent toxic effects and require interruption of therapy, otherwise haemorrhagic enteritis and death from intestinal perforation may occur.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.