METHOTREXATE TABLETS

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METHOTREXATE
TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Methotrexate 2.5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains methotrexate sodium equivalent to 2.5 mg methotrexate.

3. PHARMACEUTICAL FORM

Tablets for oral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Anti-neoplastic Chemotherapy

Methotrexate is indicated for the treatment of gestational choriocarcinoma, and in patients with chorioadenoma destruens and hydatidiform mole.

Methotrexate is indicated for the palliation of acute lymphocytic leukemia. It is also indicated in the treatment and prophylaxis of meningeal leukemia. Greatest effect has been observed in palliation of acute lymphoblastic (stem-cell) leukemias in children. In combination with other anticancer drugs or suitable agents methotrexate may be used for induction of remission, but it is most commonly used, as described in the literature, in the maintenance of induced remissions.

Methotrexate may be used alone or in combination with other anticancer agents in the management of breast cancer, epidermoid cancers of the head and neck, and lung cancer, particularly squamous cells and small cell types.

Methotrexate is also effective in the treatment of the advanced stages (III and IV, Peters Staging System) of lymphosarcoma, particularly in those cases in children; and in advanced cases of mycosis fungoides.

Psoriasis Chemotherapy (See section ***4.4 Special warnings and precautions for use***)

Because of high risk attending its use. Methotrexate 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 after dermatologic consultation.

4.2 Posology and method of administration

Oral dosage forms of methotrexate should not be split or crushed but should be taken whole.

Anti-neoplastic chemotherapy

Oral administration in tablet form is often preferred since absorption is rapid and effective serum levels are obtained.

Choriocarcinoma and similar trophoblastic diseases: Methotrexate 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 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 (CGH), which should return to normal or less than 50 IU/24 h, 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 after normalization of CGH 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 or be followed by 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.

Leukemia: Acute lymphatic (lymphoblastic) leukemia 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 leukemia, the prognosis for adequate response is less encouraging.

Methotrexate alone or in combination with steroids was used initially for induction of remission of lymphoblastic leukemias. More recently corticosteroid therapy in combination with other antileukemic drugs or in cyclic combinations with methotrexate included appear to produce rapid and effective remissions. When used for induction, methotrexate alone or 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. If and when relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen. Various experts have recently introduced a variety of dosing schedules for both induction and maintenance of remission with various combinations of alkylating and antifolic agents. Multiple drug therapy with several agents, including methotrexate given concomitantly is gaining increasing support in both the acute and chronic forms of leukemia. The physician should familiarize himself with the new advances in antileukemic therapy.

Acute granulocytic leukemia is rare in children but common in adults. This form of leukemia responds poorly to chemotherapy and remissions are short with relapses common, and resistance to therapy develops rapidly.

Meningeal leukemia: Patients with leukemia are subject to leukemic 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 (CSF) which contains leukemic cells in such cases. Therefore, the CSF should be examined in all leukemic patients.

For the treatment of meningeal leukemia, methotrexate is given at intervals of 2 to 5 days. Methotrexate is administered until the cell count of the CSF returns to normal. At this point one additional dose is advisable.

For prophylaxis against meningeal leukemia, the dosing is the same as for treatment except for the intervals of administration. On this subject, it is advisable for the physician to consult the medical literature.

Lymphomas: In Burkitt's Tumor, Stages I-II, methotrexate has produced prolonged remissions in some cases. Recommended dosing is 10 to 25 mg per 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 days rest periods. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrexate given in doses of 0.625 mg to 2.5 mg/kg daily. Hodgkin's Disease responds poorly to methotrexate and to most types of chemotherapy.

Mycosis fungoides: Therapy with methotrexate as a single agent appears to produce clinical remission in one half of the cases treated. Dosing is usually 2.5 to 10 mg daily by mouth for weeks or months. Dose levels of drug and adjustment of dose regimen by reduction or cessation of drug are guided by patient response and hematologic monitoring.

Psoriasis 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 complete blood count (CBC), urinalysis, serum creatinine, liver function studies, and liver biopsy if indicated) before beginning Methotrexate, periodically during methotrexate therapy, and before reinstituting methotrexate therapy after a rest period. Appropriate steps should be taken to avoid conception during and for at least eight weeks following methotrexate therapy.

There are two commonly used general types of dosing schedules:
1) Weekly oral intermittent large doses;
2) Divided dose intermittent oral schedule over a 36-hour period.

All schedules should be continually tailored to the individual patient. Dose schedules cited below pertain to an average 70 kg adult. An initial test dose one week prior to initiation of therapy is recommended to detect any idiosyncrasy.

Recommended starting dose schedules:

1. Weekly single oral: 10-25 mg per week until adequate response is achieved. With this dosage schedule, 25 mg per week should not ordinarily be exceeded.
2. Divided oral dose schedule: 2.5 mg every 12 hours for three 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, the dosing schedule should be reduced to the lowest possible amount of drug and to the longest possible dosing interval. The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

Use in elderly

Due to diminished hepatic and renal function as well as decreased folate stores in elderly patients, relatively low doses (especially in psoriasis indications) should be considered and these patients should be closely monitored for early signs of toxicity (See section ***4.4 Special warnings and precautions for use***). See Table 1 below for reduced doses in oncology patients.

Use in patients with renal impairment – dose adjustments

Methotrexate is excreted to a significant extent by the kidneys, thus in patients with renal impairment the health care provider may need to adjust the dose to prevent accumulation of drug. The table below provided recommended starting doses in renally impaired patients; dosing may need further adjustment due to wide intersubject pK variability.

Table 1. Dose Adjustments in Patients with Renal Impairment

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

Folate supplementation

In patients with rheumatoid arthritis, or psoriasis, folic acid or folinic acid may reduce methotrexate toxicities such as gastrointestinal symptoms, stomatitis, alopecia, and elevated liver enzymes.

Before taking a folate supplement, it is advisable to check B_{12} levels, particularly in adults over the age of 50, since folate administration can mask symptoms of B_{12} deficiency.

4.3 Contraindications

- Hypersensitivity to methotrexate or any excipients in the formulation.
- Breast feeding.

- Severe renal impairment.

Applies to patients with psoriasis only:

- Alcoholism, alcoholic liver disease, or other chronic liver disease.
- Overt or laboratory evidence of immunodeficiency syndromes.
- Preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia.
- Pregnancy.

4.4 Special warnings and precautions for use

General

Because of the possibility of serious toxic reactions (which can be fatal), methotrexate should be used only in neoplastic diseases (as indicated), or in patients with severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy. The patient should be informed by the physician of the risks involved and should be under a physician's constant supervision. Refer to Section 4.4, Special Populations, Geriatric Use and Pediatric Use for specific warnings.

It should be emphasized to the patient treated for psoriasis that the recommended dose must be taken weekly, and that mistaken daily use of the recommended dose has led to fatal toxicity (See sections ***4.2 Posology and method of administration*** and ***4.9 Overdose***).

Methotrexate has been reported to cause fetal death and/or congenital anomalies. It is not recommended for the treatment of neoplastic diseases in women of childbearing potential.

Like other cytotoxic drugs, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

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.

Methotrexate 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 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. Periodic liver biopsies are usually recommended for psoriatic patients who are under long-term treatment.

Methotrexate has caused reactivation of hepatitis B infection or worsening of hepatitis C infections, in some cases resulting in death. Some cases of hepatitis B reactivation have

occurred after discontinuation of methotrexate. Clinical and laboratory evaluation should be performed to evaluate preexisting liver disease in patients with prior hepatitis B or C infections. Based on these evaluations, treatment with methotrexate may not be appropriate for some patients.

Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis and pleural effusion, 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.

Diarrhea and ulcerative stomatitis require interruption of therapy, otherwise, hemorrhagic enteritis and death from intestinal perforation may occur. Methotrexate should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

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

Methotrexate exits slowly from third space compartments (e.g., pleural effusions, ascites). This results in a prolonged terminal 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 levels.

Methotrexate therapy in patients with impaired renal function should be undertaken with extreme caution, and at reduced doses, because impairment of renal function will decrease methotrexate elimination.

It is necessary to follow patients on methotrexate closely. Methotrexate has the potential for serious toxicity. Toxic effects may be related in frequency and severity to dose or frequency of administration, but has been seen at all doses and can occur at any time during therapy. Most adverse reactions are reversible if detected early. When such reactions do occur, the dosing should be reduced or discontinued and appropriate corrective measures should be taken. If methotrexate therapy is reinstituted, 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 (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 use of methotrexate high-dose regimens requires meticulous care. High dosing regimens for other neoplastic diseases are investigational and a therapeutic advantage has not been established.

Malignant lymphomas may occur in patients receiving low-dose methotrexate. These lymphomas may regress following withdrawal of methotrexate without requiring treatment. Discontinue methotrexate first and if the lymphoma does not regress, appropriate treatment should be instituted.

Folate deficiency states may increase methotrexate toxicity.

Organ System Toxicity

Gastrointestinal

If vomiting, diarrhea, or stomatitis occur, resulting in dehydration, supportive therapy should be instituted and methotrexate discontinuation, until recovery occurs, should be considered.

Hematologic

Methotrexate can suppress hematopoiesis and cause anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, and/or thrombocytopenia. Methotrexate should be used with caution, if at all, in patients with preexisting hematopoietic impairment (See section ***4.3 Contraindications***). In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit outweighs the risk of severe myelosuppression. In psoriasis, methotrexate should be stopped immediately if there is a significant drop in blood cell counts.

Hepatic

Methotrexate 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 administration and are usually not a reason for modification of methotrexate 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. It is recommended 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 therapy, the drug should be used with caution.

If the results of a liver biopsy show mild changes (Roenigk Grades I, II, IIIa), methotrexate may be continued and the patient monitored according to the recommendations listed above. Methotrexate 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 (Roenigk Grade IIIb or IV).

Infection or Immunologic States

Methotrexate 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.

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

Immunization

Vaccinations may be less immunogenic when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended.

Neurologic

Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.

Chronic leukoencephalopathy has also been reported in patients who received repeated doses of high-dose methotrexate with folinic acid rescue even without cranial irradiation. There are also reports of leukoencephalopathy in patients who received oral methotrexate.

Discontinuation of methotrexate does not always result in complete recovery.

A transient acute neurologic syndrome has been observed in patients treated with high dosing regimens. Manifestations of this neurologic syndrome may include behavioral abnormalities, focal sensorimotor signs, including transient blindness, and abnormal reflexes. The exact cause is unknown.

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 intrathecal methotrexate in combination with intravenous cytarabine, although adverse drug reaction (ADR) occurrence after oral administration of methotrexate, in combination with cytarabine, cannot be ruled out.

Pulmonary

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

Renal

Methotrexate 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 and renal function are recommended (See section ***4.2 Posology and method of administration***).

Concomitant use of proton pump inhibitors (PPIs) and high dose methotrexate should be avoided, especially in patients with renal impairment.

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 methotrexate 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.

Laboratory Monitoring

General

Patients undergoing methotrexate 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, hepatitis B or C infection testing, renal function tests; and a chest X-ray.

Psoriasis

During therapy of psoriasis, monitoring of the following parameters is recommended: hematology 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 blood levels (e.g., dehydration), more frequent monitoring may also be indicated.

Pulmonary Function Tests

Pulmonary function tests may be useful if lung disease (e.g., interstitial pneumonitis) is suspected, especially if baseline measurements are available.

Methotrexate Level

Serum methotrexate level monitoring can significantly reduce toxicity and mortality by allowing the adjustment of methotrexate dosing and the implementation of appropriate rescue measures.

Patients subject to the following conditions are predisposed to developing elevated or prolonged methotrexate 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 clearance in the absence of these features. It is important that patients be identified within 48 hours since methotrexate toxicity may not be reversible if adequate folinic acid rescue is delayed for more than 42 to 48 hours.

The method of monitoring methotrexate concentrations varies from institution to institution. Monitoring of methotrexate concentrations should include determination of a methotrexate level at 24, 48, or 72 hours, and assessment of the rate of decline in methotrexate concentrations (to determine how long to continue folinic acid rescue).

Special Populations

Pediatric Use

Safety and effectiveness in pediatric patients have been established only in cancer chemotherapy.

Geriatric Use

Fatal toxicities related to inadvertent daily rather than weekly dosing have been reported, particularly in elderly patients. It should be emphasized to the patient that the recommended dose is taken weekly for psoriasis (See section ***4.2 Posology and method of administration***).

4.5 Interactions with other medicinal products and other forms of interaction

Chemotherapeutic Agents

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

Cytarabine: Methotrexate given concomitantly with intravenous cytarabine may increase the risk of severe neurologic adverse events such as headache, paralysis, coma and stroke-like episodes. While these ADRs have most frequently been reported with intrathecal methotrexate, ADR occurrence with oral administration of methotrexate, in combination with cytarabine, cannot be ruled out.

L-asparaginase: The administration of L-asparaginase has been reported to antagonize the effect of MTX.

Mercaptopurine: Methotrexate increases the plasma levels of mercaptopurine. Combination of methotrexate and mercaptopurine may therefore require dose adjustment.

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs should not be administered prior to or concomitantly with the high doses of methotrexate. Concomitant administration of some NSAIDs with high-dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic (including bone marrow suppression and aplastic anemia) and gastrointestinal toxicity. NSAIDs and salicylates have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity by increasing methotrexate levels. Therefore, caution should be used when they are administered concomitantly with lower doses of methotrexate.

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. Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, has not been studied and may increase the incidence of adverse effects.

Proton Pump Inhibitors

Co-administration of proton pump inhibitors (PPIs) with methotrexate may decrease the clearance of methotrexate causing elevated methotrexate plasma levels with clinical signs and symptoms of methotrexate toxicity. Concomitant use of PPIs and high dose methotrexate should therefore be avoided, especially in patients with renal impairment.

Antibiotics

Ciprofloxacin: Renal tubular transport is diminished by ciprofloxacin; use of methotrexate with this drug should be carefully monitored.

Penicillins and sulfonamides: Penicillins and sulfonamides may reduce the renal clearance of methotrexate; hematologic and gastrointestinal toxicity has been observed in combination with high- and low-dose methotrexate.

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

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

Concurrent use of the anti-protozoal pyrimethamine may increase the toxic effects of methotrexate because of an additive antifolate effect.

Hepatotoxic Agents

The potential for increased hepatotoxicity when methotrexate 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 and other potential hepatotoxic (e.g., leflunomide, azathioprine, sulfasalazine, retinoids) should be closely monitored for possible increased risk of hepatotoxicity.

Nitrous Oxide Anesthesia

The use of nitrous oxide anesthesia potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe unpredictable myelosuppression, and stomatitis and neurotoxicity with intrathecal administration. This effect can be reduced by the use of folinic acid rescue (See section ***4.2 Posology and method of administration***).

Probenecid

Renal tubular transport is diminished by probenecid; use of methotrexate with this drug should be carefully monitored.

Vitamins

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate, however, folate deficiency states may increase methotrexate toxicity.

Amiodarone

Amiodarone administration to patients receiving methotrexate treatment for psoriasis has induced ulcerated skin lesions.

Drugs Highly Bound to Plasma Proteins

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by other highly bound drugs, such as sulfonylureas, aminobenzoic acid, salicylates, phenylbutazone, phenytoin, sulfonamides, some antibiotics such as penicillins, tetracycline, pristinamycin, probenecid, and chloramphenicol.

Leflunomide

Methotrexate in combination with leflunomide may increase the risk of pancytopenia.

Psoralen Plus Ultraviolet A Photochemotherapy (PUVA)

Skin cancer has been reported in few patients with psoriasis or mycosis fungoides (a cutaneous T-cell lymphoma) receiving a concomitant treatment with methotrexate plus PUVA therapy (methoxalen and ultraviolet light).

Theophylline

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

Diuretics

Bone marrow suppression and decreased folate levels have been described in the concomitant administration of triamterene and methotrexate.

4.6 Fertility, pregnancy and lactation

Fertility

Methotrexate has been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

Pregnancy

Methotrexate can cause fetal death, embryotoxicity, abortion, or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant patients with psoriasis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus (See section ***4.3 Contraindications***).

Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate.

The optimal time interval between the cessation of methotrexate treatment of either partner and pregnancy has not been clearly established. Published literature recommendations for time intervals vary from 3 months to one year.

The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.

Lactation

Methotrexate 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.

4.7 Effects on ability to drive and use machines

Some of the effects reported in Section 4.8, (e.g., dizziness, fatigue) may have an influence on the ability to drive or use machines.

4.8 Undesirable effects

In general, the incidence and severity of adverse drug reactions are related to dose and frequency of administration. Relevant sections should be consulted when looking for information about adverse reactions with methotrexate.

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness, and decreased resistance to infection. Ulcerations of the oral mucosa are usually the earliest signs of toxicity.

Other adverse reactions that have been reported with methotrexate are listed below by organ system and by frequency. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to methotrexate difficult. See section ***4.4 Special warnings and precautions for use*** for specific reference to medically important and long term events including those following long term treatment or high cumulative doses (e.g., hepatic toxicity).

Frequency categories are defined as: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data).

Table 2. Adverse Reactions Table

System Organ Class	Adverse Reaction
Infections and Infestations	
Rare	Sepsis
Not known	Infections (including fatal sepsis); Pneumonia; Pneumocystis carinii pneumonia; Nocardiosis; Histoplasmosis; Cryptococcosis; Herpes zoster; H. simplex hepatitis; Disseminated H. simplex; Cytomegalovirus infection (including cytomegaloviral pneumonia); Reactivation of hepatitis B infection; Worsening of hepatitis C infection
Neoplasms Benign, Malignant, and Unspecified (including cysts and polyps)	
Uncommon	Lymphoma (including reversible lymphoma)
Blood and Lymphatic System Disorders	
Uncommon	Bone marrow failure; Anemia; Thrombocytopenia
Very rare	Aplastic anemia
Not known	Agranulocytosis; Pancytopenia; Leukopenia; Neutropenia; Lymphadenopathy and lymphoproliferative disorders (including reversible); Eosinophilia; Anemia megaloblastic
Immune System Disorders	
Uncommon	Anaphylactoid reactions
Very rare	Hypogammaglobulinemia
Metabolism and Nutrition Disorders	
Rare	Diabetes
Psychiatric Disorders	
Rare	Mood alterated; Transient cognitive dysfunction
Nervous System Disorders	
Common	Paresthesia
Uncommon	Hemiparesis; Headaches
Rare	Paresis; Dysarthria; Aphasia; Drowsiness; Leukoencephalopathy (oral)
Very rare	Cranial nerve disorder
Not known	CSF pressure increased; Neurotoxicity; Arachnoiditis; Paraplegia; Stupor; Ataxia; Dementia; Dizziness
Eye Disorders	
Rare	Blurred vision; Serious visual changes
Very rare	Transient blindness/vision loss; Conjunctivitis
Cardiac Disorders	
Rare	Hypotension
Very rare	Pericardial effusion; Pericarditis
Vascular Disorders	
Rare	Thromboembolic events (including cerebral thrombosis, arterial thrombosis, pulmonary embolism, deep vein thrombosis, thrombophlebitis, retinal vein thrombosis)
Very rare	Vasculitis
Respiratory, Thoracic and Mediastinal disorders	
Uncommon	Interstitial pneumonitis (including fatalities); Pleural effusion
Rare	Respiratory fibrosis; Pharyngitis

Table 2. Adverse Reactions Table

System Organ Class	Adverse Reaction
Not known	Chronic interstitial pulmonary disease; Alveolitis; Dyspnea; Chest pain; Hypoxia; Cough
Gastrointestinal Disorders	
Uncommon	Pancreatitis; Decreased appetite; Vomiting; Diarrhea; Stomatitis
Rare	Gastrointestinal ulceration and bleeding; Melena; Enteritis; Gingivitis
Very rare	Hematemesis
Not known	Intestinal perforation; Non-infectious peritonitis; Glossitis; Nausea
Hepatobiliary Disorders	
Uncommon	Liver enzyme elevations
Rare	Chronic fibrosis and cirrhosis; Acute hepatitis; Hepatotoxicity
Very rare	Decrease in serum albumin
Not known	Hepatic failure
Skin and Subcutaneous Tissue Disorders	
Uncommon	Toxic epidermal necrolysis (Lyell's syndrome); Stevens-Johnson Syndrome; Alopecia
Rare	Erythema multiforme; Erythematous rashes; Painful erosion of psoriatic plaques; Photosensitivity; Skin ulceration; Urticaria; Acne; Ecchymosis; Pigmentation disorder; Pruritus
Very rare	Furunculosis; Telangiectasia
Not known	Drug reaction with eosinophilia and systemic symptoms; Dermatitis; Petechiae
Musculoskeletal, Connective tissue and Bone disorders	
Rare	Arthralgia/myalgia; Osteoporosis; Stress fractures
Not known	Osteonecrosis
Renal and Urinary Disorders	
Uncommon	Renal failure; Nephropathy
Rare	Dysuria
Very rare	Hematuria; Azotemia; Cystitis
Not known	Proteinuria
Pregnancy, Puerperium and Perinatal Conditions	
Uncommon	Fetal defects
Rare	Abortion
Not known	Fetal death
Reproductive System and Breast Disorders	
Rare	Menstrual dysfunction
Very rare	Defective oogenesis/spermatogenesis; Impotence; Infertility; Loss of libido; Transient oligospermia; Vaginal discharge
Not known	Urogenital dysfunction
General Disorders and Administration Site Conditions	
Rare	Nodule
Very rare	Sudden death
Not known	Pyrexia; Chills; Malaise; Fatigue

4.9 Overdose

In post-marketing experience, overdose with methotrexate has generally occurred with oral administration.

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 pharmacologic doses, particularly hematologic and gastrointestinal reactions. For example, leukopenia, thrombocytopenia, anemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In some cases, no symptoms were reported. There have been reports of death following chronic overdose in the self administered dosage for psoriasis (See sections ***4.2 Posology and method of administration*** and ***4.4 Special warnings and precautions for use***). In these cases, events such as sepsis or septic shock, renal failure, and aplastic anemia were also reported.

Recommended Treatment

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

In cases of massive overdose, hydration and urinary alkalization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Neither standard hemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. However, effective clearance of methotrexate has been reported with acute, intermittent hemodialysis using a high-flux dialyzer.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Methotrexate (4-amino-10 methyl folic acid) is an antimetabolite and an analogue of folic acid. The drug enters the cells via an active transport system for reduced folates and, due to a relatively irreversible binding, methotrexate inhibits dihydrofolic acid reductase. Dihydrofolates must be reduced to tetrahydrofolates by this enzyme before they can be utilized as carriers of one-carbon groups in the synthesis of purine nucleotides and thymidylate. Therefore, methotrexate interferes with DNA synthesis, repair, and cellular replication. The affinity of dihydrofolate reductase for methotrexate is far greater than its affinity for folic or dihydrofolic acid and, therefore, even very large amounts of folic acid given simultaneously will not reverse the effects of methotrexate. The drug seems also to cause an increase in intracellular deoxyadenosine triphosphate, which is thought to inhibit ribonucleotide reduction and polynucleotide ligase, an enzyme concerned in DNA synthesis and repair.

Actively proliferating tissues such as malignant cells, bone marrow, fetal cells, buccal and intestinal mucosa, spermatogonia, and cells of the urinary bladder are in general more sensitive to this effect of methotrexate. Due to increased cellular proliferation methotrexate may impair malignant growth without irreversible damage to normal tissues.

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

5.2 Pharmacokinetics properties

Absorption

Oral absorption appears to be dose-dependent. Peak serum levels are reached within one to five hours. The absorption of doses greater than 80 mg/m^2 is significantly less, possibly due to a saturation effect. Peak serum levels achievable following oral administration are slightly lower than those detected after intramuscular injection.

In leukemic pediatric patients, oral absorption of methotrexate also appears to be dose-dependent and has been reported to vary widely (23% to 95%). A twenty-fold difference between highest and lowest peak levels (C_{max}: 0.11 to 2.3 micromolar after a 20 mg/m^2 dose) has been reported. Significant interindividual variability has also been noted in time-to-peak concentration (T_{max} 0.67 to 4 hours after a 15 mg/m^2 dose) and fraction of dose absorbed. The absorption of doses greater than 40 mg/m^2 has been reported to be significantly less than that of lower doses. At doses of 30 mg/m^2 or less, methotrexate is generally well absorbed with a mean bioavailability of about 60%. In pediatric patients receiving methotrexate for acute lymphocytic leukemia (6.3 to 30 mg/m^2), the terminal half-life has been reported to range from 0.7 to 5.8 hours.

Distribution

Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% reversibly bound to protein.

Methotrexate is widely distributed into body tissues with highest concentrations in the kidneys, gallbladder, spleen, liver and skin. Methotrexate does not penetrate the blood-CSF barrier in therapeutic amounts when given orally.

Small amounts have been detected in saliva and breast milk. The drug crosses the placental barrier.

The drug enters slowly into third-space collections of fluid, such as pleural effusions, ascites and marked tissue edemas.

In dogs, synovial fluid concentrations after oral dosing were higher in inflamed than uninflamed joints. Although salicylates did not interfere with this penetration, prior prednisone treatment reduced penetration into inflamed joints to the level of normal joints.

Metabolism

At low doses, methotrexate does not appear to undergo significant metabolism; following high dose therapy methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms that can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues, and tumors. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. Accumulation of this metabolite may become significant at the high doses used in osteogenic sarcoma. The aqueous solubility of 7-hydroxymethotrexate is 3- to 5-fold lower than the parent compound. Methotrexate is partially metabolized by intestinal flora after oral administration.

Half-life – The terminal half-life reported for methotrexate is approximately three to ten hours for patients receiving treatment for psoriasis or low dose antineoplastic therapy (less than 30 mg/m^2). For patients receiving high doses of methotrexate, the terminal half-life is 8 to 15 hours.

Elimination

Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Non-linear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels. Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.

Total methotrexate clearance averages 12 L/h, but clearance rates vary widely and are generally decreased at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, a third space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

The potential for toxicity from high dose regimens or delayed excretion is reduced by the administration of folinic acid during the final phase of methotrexate plasma elimination.

Effects of Food

The bioavailability of orally administered methotrexate is not reduced by food and methotrexate may be administered without regard to meals.

5.3 Preclinical safety data

The intraperitoneal LD_{50} of methotrexate was 94 and 6 to 25 mg/kg for mice and rats, respectively. The oral LD_{50} of the compound in rats was 180 mg/kg. The tolerance to methotrexate in mice increased with age. In dogs, the intravenous dose of 50 mg/kg was lethal. The main targets after a single dose were the hemolymphopoietic system and gastrointestinal (GI) tract.

The toxic effects after repeated administration of methotrexate were investigated in mice and rats. The main targets of methotrexate in the above animal species were the hemolymphopoietic system, GI tract, lung, liver, kidney, testes, and skin. The tolerance of mice to chronic methotrexate doses increased with age.

Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf life

Refer to outer carton for expiration date.

6.2 Packages

2.5 mg Tablets – Blister of 28's and 30's.

Not all pack sizes may be marketed.

6.3 Special precautions for storage

Store below 30°C.

6.4 Special precautions for disposal and other handling

Procedures for proper handling and disposal of anticancer drugs should be considered.

7. PRODUCT OWNER

Pfizer Inc.
235 East 42nd Street
New York 10017
United States

MTX TAB-SIN-0322/0
Date of last revision: March 2022

Package leaflet: Information for the patient

Methotrexate 2.5 mg Tablets

Methotrexate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Methotrexate Tablets are and what they are used for

What Methotrexate Tablets are and how they work

Methotrexate Tablets contain the active ingredient methotrexate. Methotrexate is referred to as a cytotoxic medicine, most commonly used to kill cells in tumors.

What Methotrexate Tablets are used for

Methotrexate Tablets are used to treat severe, uncontrolled psoriasis. It is usually used for patients who have tried other treatments, but their condition has not improved.

Methotrexate Tablets help patients with psoriasis by killing the cells in the skin, which are growing too quickly. It is these fast growing cells, which cause the raised patches of skin in psoriasis.

Methotrexate Tablets can also be used to treat a wide range of tumors, in particular:

- gestational choriocarcinoma.
- chorioadenoma destruens and hydatidiform mole.
- acute lymphocytic leukemia.
- meningeal leukemia.
- breast cancer.
- head, neck and lung cancer.
- lymphosarcoma.
- mycosis fungoides.

Methotrexate Tablets can be given alone or in combination with other medicines.

You should consult your doctor if you are unsure why you have been given Methotrexate 2.5 mg Tablets.

You must talk to a doctor if you do not feel better or if you feel worse on treatment with this medicine.

2. What you need to know before you take Methotrexate Tablets

Your doctor may perform several tests such as blood tests, X-rays and physical examinations before treatment with Methotrexate Tablets is started, and at regular intervals during treatment.

Do not take Methotrexate Tablets if you:

- are allergic to methotrexate, or any of the other ingredients of this medicine (listed in section 6).
- are breast feeding.
- have severe kidney problems, including conditions requiring kidney dialysis.
- have an alcohol dependency, alcohol-related liver disease, or other chronic liver disease (only applicable for the treatment of psoriasis).
- have immunodeficiency disorder (only applicable for the treatment of psoriasis).
- have blood problems, including incomplete development of bone marrow, low levels of white blood cells, low levels of blood platelets (which can lead to bleeding and bruising), or severe low red blood cell counts (which can cause tiredness and pale skin) (only applicable for the treatment of psoriasis).
- are pregnant (see section on Pregnancy, breast feeding and fertility) (only applicable for the treatment of psoriasis).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Methotrexate Tablets and during your treatment if you experience signs or symptoms described in this section. This will help them decide if Methotrexate Tablets are suitable for you:

- have any mild or moderate kidney disease.
- have a stomach ulcer or ulcerative colitis (inflammation and ulceration of the gut).
- have any blood disorders including anemia.
- have diarrhea.
- have gastro-intestinal (digestive) problems.
- have severe mouth ulcers.
- have or have ever suffered from psychological symptoms such as behavioral abnormalities.
- are receiving radiotherapy (X-ray treatment) or UV radiation.
- have received any live virus vaccines recently or you are due to have any, as Methotrexate Tablets can reduce their effect.
- have any symptoms or signs of infection.

- have excess fluid, between the lungs and chest wall (pleural effusion) or abdominal swelling (ascites) causing breathlessness.
- develop a persistent or dry non-productive cough, or develop shortness of breath as it may be associated with serious lung disease.
- special care is also needed in children and the elderly.
- have or have ever had liver damage, dependence on alcohol or abnormal liver function tests.
- have diabetes.
- have an inactive chronic infection, such as hepatitis B or C.
- you or your partner are pregnant, suspect may be pregnant or planning to have a baby. See also section "Pregnancy, breast feeding and fertility".
- folate deficiency.
- severe skin problems.

If you experience symptoms of spitting or coughing up blood you should contact your doctor immediately.

If you, your partner or your care giver notice new onset or worsening of neurological symptoms including general muscle weakness, disturbance of vision, changes in thinking, memory and orientation leading to confusion and personality changes, contact your doctor immediately because these may be symptoms of a very rare, serious brain infection called leukoencephalopathy. Care giver should also contact your doctor immediately if you experience headache, paralysis, coma and stroke like episodes.

<u>Recommended follow-up examinations and precautions</u>

Even if Methotrexate Tablets is used in low doses, serious side effects can occur. In order to detect them in time, your doctor must perform monitoring examinations and laboratory tests.

Prior to the start of therapy

Before starting treatment, your blood will be screened for hepatitis. Furthermore, serum albumin, liver function and kidney function will be checked. The doctor may also decide to run other liver tests, some of these may be images of your liver and others may need a small sample of tissue taken from the liver in order to examine it more closely. Your doctor may also check to see if you have tuberculosis, and they may X-ray your chest or perform a lung function test.

During the treatment

Your doctor may perform the following examinations:

- examination of the oral cavity and the pharynx for changes in the mucous membrane such as inflammation or ulceration.
- blood tests/blood count with number of blood cells and measurement of serum methotrexate levels.
- blood test to monitor liver function.
- imaging tests to monitor liver condition.
- small sample of tissue taken from the liver in order to examine it more closely.

- blood test to monitor kidney function.
- respiratory tract monitoring and, if necessary, lung function test.

It is very important that you appear for these scheduled examinations.

If the results of any of these tests are conspicuous, your doctor will adjust your treatment accordingly.

Elderly patients

Elderly patients under treatment with Methotrexate Tablets should be monitored closely by a physician so that possible side effects can be detected as early as possible. Age-related impairment of liver and kidney function as well as low body reserves of the vitamin folic acid in old age require a relatively low dosage of methotrexate.

Pediatric use

Safety and effectiveness in pediatric patients have been established only in cancer chemotherapy.

Other medicines and Methotrexate Tablets

Some medicines may affect Methotrexate Tablets, or be affected by it. Please tell your doctor, pharmacist or nurse about all the medicines you have recently taken, are currently taking, or plan to take, including medicines obtained without a prescription, vitamins, and herbal medicines. This includes the following medicines, as the effect of Methotrexate Tablets may be altered when they are taken at the same time. The medicines listed in this leaflet may not be the only ones that could interact with Methotrexate Tablets.

- Vaccinations/live virus vaccines.
- Non-steroidal anti-inflammatory drugs (NSAIDs) (used for pain or inflammation) e.g., salicylates, phenylbutazone.
- Diuretics (water tablets) e.g., triamterene.
- Medicines used/taken for diabetes e.g., sulfonylureas.
- Antibiotics (used to treat bacterial infections) e.g., chloramphenicol, penicillin, sulfonamides, trimethoprim/sulfamethoxazole, ciprofloxacin, tetracyclines, anti-protozoal pyrimethamine and pristinamycin.
- Amiodarone (used to treat abnormal or irregular heartbeat).
- Retinoids, aminobenzoic acid (used to improve certain skin issues).
- Methoxalen and ultraviolet light (used to treat psoriasis, skin disorders or blood cancer).
- Phenytoin (used to treat epilepsy).
- Probenecid, sulfasalazine, leflunomide, azathioprine, gold (used to treat gout or arthritis).
- Radiotherapy.
- Vitamin preparations containing folic acid or similar products.
- Nitrous oxide (a gas used in general anesthesia).
- Cisplatin (used in chemotherapy).
- Cytarabine, L-asparaginase, mercaptopurine (used to treat cancer of the blood).

- Proton pump inhibitors (used to treat indigestion, stomach acid and ulcers).
- Theophylline (used to treat asthma, bronchitis, emphysema).
- Penicillamine (used to treat Wilson's disease).
- Hydroxychloroquine (used to treat malaria).

Methotrexate Tablets with food and drink

Alcohol should be avoided while receiving Methotrexate Tablets as it increases the risk of liver damage.

Pregnancy, breast feeding and fertility

If you are pregnant or breast feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

Do not use Methotrexate Tablets during pregnancy except if your doctor has prescribed it for cancer treatment. Methotrexate can cause birth defects, harm the unborn baby or cause miscarriage. It is therefore very important that Methotrexate Tablets is not given to pregnant women or to women who are planning to become pregnant unless used for cancer treatment when the potential benefit outweighs the risk to the fetus.

In women of child-bearing age, the possibility of a pregnancy must be ruled out, e.g., by pregnancy tests before treatment is started.

Do not use Methotrexate Tablets if you are trying to become pregnant. You must avoid becoming pregnant during treatment with Methotrexate Tablets and for at least 3 months after the end of treatment. Therefore, you must ensure that you are taking effective contraception for the whole of this period (see also section "Warnings and precautions").

If you become pregnant during treatment or suspect you might be pregnant, speak to your doctor as soon as possible. If you do become pregnant during treatment, you should be offered advice regarding the risk of harmful effects on the child through treatment.

If you want to become pregnant, you should speak with your doctor, who may refer you for specialist advice before the planned start of treatment.

Methotrexate Tablets may affect women's periods; they may become less frequent or stop completely. It can affect sperm and egg production with the potential to cause birth defects. You and your partner should avoid conception (becoming pregnant or fathering children) for at least 3months after your treatment with Methotrexate Tablets has stopped.

Male fertility

Methotrexate can affect the production of sperm, which is associated with the possibility of birth defects.

You should avoid fathering a child or to donate semen during treatment with Methotrexate Tablet and for at least 3 months after the end of treatment.

Breast feeding

Methotrexate passes into breast milk. You should not take Methotrexate Tablets if you are breast feeding.

Driving and using machines

Methotrexate Tablets may cause some side effects which could affect your ability to drive or use machinery for example drowsiness, tiredness, loss of coordination or blurred vision. If you experience these symptoms, do not drive or use any tools or machinery. The full list of side effects are listed in section 4.

Methotrexate Tablets contains lactose

Methotrexate Tablets contain lactose monohydrate (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Methotrexate Tablets

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Alcohol should be avoided while receiving methotrexate.

Do not crush or chew the tablets. Swallow the tablets whole with a full glass of water. The tablets may be taken with or without food.

The dose of Methotrexate Tablets will be different for different patients. The dose that is used may depend on a number of things, including what the medicine is being used for, the patient's size and whether or not other medicines are also being taken. The doctor may decrease your dose if you have problems with your kidneys. If you are taking or receiving Methotrexate Tablets at home, follow your doctor's orders or the directions on the label. If you have any questions about the proper dose of Methotrexate Tablets, ask your doctor or pharmacist.

Make sure that you understand how often your doctor wants you to take Methotrexate Tablets to treat your condition.

There are different doses for psoriasis and cancer. It is important not to take Methotrexate Tablets more often or in higher doses than your doctor has prescribed for your condition. Overdoses of methotrexate may cause serious illness or death.

Psoriasis

Methotrexate Tablet is taken once weekly; the prescribed dose is taken on a single day of the week. Select a day of the week when you are most likely to remember to take Methotrexate Tablets, and take it on that same day each week.

Alternatively, your doctor may also instruct you to take Methotrexate Tablets every 12 hours for 3 doses; you should only do this once a week and should not take more than 3 doses each week.

Take methotrexate only once a week, taking it more often may be fatal.

Cancer

For cancer, take the tablets at the same time of day and only on the days specified by your doctor.

Taking the tablets at the same time of the day will also help you to remember when to take the medicine.

The amount of methotrexate to be taken and how often it should be taken, will be calculated for you by your doctor based on your conditions and tolerance to the medicine. This dosage may be increased or reduced by your doctor as the treatment progresses depending on your response. It's important that you adhere strictly to your doctor's instructions.

If you take more Methotrexate Tablets than you should

If you accidentally take too many Methotrexate Tablets, contact your doctor at once or go to the nearest hospital emergency department, even if there are no symptoms. Always take the labeled medicine package with you, whether there are any Methotrexate Tablets left or not.

Overdose symptoms may include easy bruising or bleeding, unusual weakness, mouth sores, nausea, vomiting, black or bloody stools, coughing up blood or vomit that looks like coffee grounds, and decreased urinating. In some cases, no symptoms were reported.

Inappropriate intake resulting in overdose can sometimes lead to death.

The antidote in case of an overdose is folinic acid. In cases of massive overdose, hydration and urinary alkalization may be necessary.

If you forget to take Methotrexate Tablets

If you forget to take a dose, contact your doctor or pharmacist for advice.

Never take a double dose to make up for the dose you missed.

If you have any trouble remembering when to take your tablets, ask your doctor or pharmacist for help.

If you stop taking Methotrexate Tablets

Do not stop taking Methotrexate Tablets unless your doctor tells you to. Should you need to stop taking Methotrexate Tablets, your doctor will have decided which is the best method for you.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

If you vomit while taking Methotrexate Tablets

If you vomit shortly after taking a dose of Methotrexate Tablets, check with your doctor. You will be told whether to take the dose again or to wait until the next scheduled dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. However, Methotrexate Tablets is a very toxic medicine and some patients are unable to tolerate treatment.

Tell your doctor immediately if you experience any of the following symptoms after taking this medicine. Although they are very rare, these symptoms can be serious.

- **Severe skin rash that causes blistering**, (this can affect the mouth and tongue). These may be signs of a condition known as Stevens-Johnson Syndrome. Your doctor will stop your treatment in these cases.
- **Persistent cough, pain or difficulty breathing or become breathless**; Methotrexate Tablets can cause diseases of the lungs e.g., fluid in lungs.
- **Spitting or coughing blood**.
- **Skin rash and fever with swollen glands**, as these may be signs of a hypersensitivity reaction.
- **Sore throat, fever, chills or achiness**; Methotrexate Tablets can make you more likely to catch infections.
- **Severe allergic reaction (anaphylactic reaction)**; although very rare, you may experience a sudden itchy skin rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), wheeze, and you may feel you are going to faint. If this happens, you should seek medical attention immediately.

Other side effects that may occur are:

- Severe mouth ulcers and ulcers of the gut.
- Reduction in red blood cells which can make the skin pale and cause weakness or breathlessness.
- Reduction in blood platelets which increases risk of bleeding or bruising.
- Lung infection (pneumonia).
- Drowsiness.
- Severe skin reaction.
- Inflammation of vessels, often with skin rash.
- Tiny blood spots under the skin.
- Itchy skin.
- Shingles (herpes zoster).
- Abdominal pain.
- Convulsions.
- Loss of coordination.

- Difficulty in breathing or wheezing.
- Confusion.
- Liver damage (seen as yellowing of the skin and whites of the eye).
- Liver failure.
- Kidney damage.
- Low levels of white cell count (leukopenia).
- Low levels of neutrophils, a type of white blood cell that fights infection.
- Infection of the lungs, liver, brain, or entire body, reduced resistance to infection.
- Abnormal red blood cell function.
- Lung damage/scarred.
- Build-up of excess fluid in the lung.
- Build-up of fluid or excess fluid in the double layer around the heart.
- Abnormal low blood pressure.
- Inability to move.
- Inability to move in one half of the body.
- Dizziness.
- Headaches, blurred vision.
- Raised blood sugar levels (diabetes mellitus).
- Sensation of numbness or tingling, having less sensitivity to stimulation than normal.
- Loss of ability to speak or understand speech.
- Impaired vision.
- Short-term blindness.
- Brittle bones.
- Muscular pain.
- Slow thought process.
- Mood alteration.
- Black or tarry stools.
- Skin ulcers
- Erosions of inflamed areas, in psoriasis patients.
- Damaged skin becomes inflamed on re-exposure to radiation and sunlight.
- Reduced ability to become pregnant and reduced ability to father children.
- Menstrual disorders.
- Blood in the urine.
- Raised liver enzymes.
- Weakening or softening of bones.
- Loss of interest in, or inability to have sex.
- Soreness of the mouth, throat, lips and tongue.
- Inflamed blood vessels.
- Feeling sick, being sick and/or diarrhea.
- Pain or difficulty in passing urine.
- The need to pass urine more often than usual.
- Joint and muscle pain.
- Chills and fever.
- Changes in skin and nail coloration.
- Hair loss.
- Red spots on the skin, skin lesions, acne, boils.
- Redness and/or shedding of skin.

- Itchiness and rash.
- Sensitivity to light.
- Eye infection.
- Tiredness and lack of energy.
- Lymphoproliferative disorders (excessive growth of white blood cells).
- Bone damage.
- Reactivation of hepatitis B infection.
- Worsening of hepatitis C infection.
- Blood poisoning, which may be fatal.
- Bone marrow failure.
- Low levels of all types of blood cells.
- An excess of eosinophils, a type of white blood cell.
- Paralysis.
- Pain, tingling, numbness, weakness, or paralysis of the face including the eyes.
- Loss of intellectual function.
- Inflammation of the membrane around the heart.
- Problems due to the formation of blood clots in the blood vessels.
- Inflammation of the pancreas.
- Loss of appetite.
- Vomiting.
- Bloody vomit.
- Nausea.
- Inflammation of gums.
- Liver damage/scarred.
- Decreased in serum albumin (a protein that circulates in the blood).
- Abnormally high levels of nitrogen-containing compounds (such as urea, creatinine, various body waste compounds, and other nitrogen-rich compounds) in the blood.
- Excess protein in the urine.
- Harm to the unborn baby.
- Death of the unborn baby.
- Miscarriage.
- Urinary and genital tracts (reproductive organs) dysfunction.
- Unusual vaginal discharge.
- Sudden death.

Methotrexate Tablets may lead to problems with your blood, liver and kidneys. Your doctor will take blood samples to check for these problems and may ask to have a small sample of your liver taken for testing (liver biopsy).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Methotrexate Tablets

Keep this medicine out of the sight and reach of children. Accidental ingestion can be lethal for children.

Do not use this medicine after the expiry date which is stated on the carton and on the blister foil.

Store this medicine below 30°C.

Do not use any pack that is damaged or shows signs of tampering.

Anyone handling Methotrexate Tablets should wash their hands after administering a dose. To decrease the risk of exposure, parents and care givers should wear disposable gloves when handling Methotrexate Tablets.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Methotrexate Tablets contain

- The active substance is methotrexate. Each tablet contains 2.5 mg methotrexate.
- The other ingredients are lactose monohydrate, pregelatinised maize starch, magnesium stearate, sodium hydroxide and purified water.

What Methotrexate Tablets look like

Methotrexate 2.5 mg Tablets are round, convex, yellow, slightly mottled tablets, engraved with “2.5” on one side, scored in half on the other side and engraved with “M” above the score line and “1” below it.

MTX TAB-SIN-0322/PIL/1
Date of last revision: August 2022