PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]METHOTREXATE INJECTION USP

Methotrexate Injection

Solution (Preservative-Free), 10 mg/mL and 25 mg/mL methotrexate (as methotrexate sodium), for intravenous, intramuscular, intra-arterial, intrathecal and intracerebroventricular use

Solution (with Preservative), 25 mg/mL methotrexate (as methotrexate sodium), for intravenous, intramuscular, intra-arterial use

USP

Antimetabolite and Antirheumatic

Pfizer Canada ULC
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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Neurologic	03/2024

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Methotrexate Injection USP is indicated for 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.
- Osteogenic sarcoma (adjuvant) - high dose methotrexate with leucovorin rescue (HDMTX-LV)
- Bladder Cancer (advanced) - as part of the M-VAC Regimen.
- Leptomeningeal spread of malignancies (carcinomatosis/leukemia/lymphoma) as a single chemotherapy or alternating with Ara-C
- Burkitt's lymphoma.
- Advanced stages of childhood lymphoma (III and IV, St. Jude's Childrens' Research Hospital Staging System).
- Advanced cases of mycosis fungoides (cutaneous T-cell lymphoma).

Methotrexate Injection USP is indicated as a Disease Modifying Antirheumatic Drug (DMARD) in the following diseases where standard therapeutic interventions fail:

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

In the treatment of psoriasis, Methotrexate Injection USP 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 after dermatologic consultation.

1.1 Pediatrics

Pediatrics (< 18 years of age): Safety and effectiveness in pediatric patients have not been established, other than in cancer chemotherapy. Therefore, Methotrexate Injection USP should not be used as a DMARD in pediatric patients.

1.2 Geriatrics

Experience suggests that use in the geriatric population is associated with differences in safety, see 4.2 Recommended Dose and Dose Adjustment and 7.1.4 Warnings and Precautions, Geriatrics.

2 CONTRAINDICATIONS

Methotrexate Injection USP is contraindicated:

- In patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**).
- In patients with severe renal impairment including end stage renal disease with and without dialysis (see **7 WARNINGS AND PRECAUTIONS: Renal**, **7.1 Special populations** and **4.2 Recommended dose and dosage adjustment: Special populations**).
- In pregnant patients with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus.
- In women of childbearing potential until pregnancy is excluded.
- In nursing mothers.
- In patients with psoriasis or rheumatoid arthritis with alcoholism, alcoholic liver disease or other chronic liver disease.
- In patients with psoriasis or rheumatoid arthritis who have overt or laboratory evidence of immunodeficiency syndromes.
- In patients with psoriasis or rheumatoid arthritis who have pre-existing blood dyscrasias, such as bone marrow hypoplasia, leucopenia, thrombocytopenia or significant anemia.
- With nitrous oxide anesthesia (see **7 WARNINGS AND PRECAUTIONS: Renal** and **9.4 Drug-Drug Interactions**).

Methotrexate Injection USP formulations containing benzyl alcohol are also contraindicated:

- To use for intrathecal, intracerebroventricular, or high-dose therapy.
- To use in neonates (children less than one month age).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Methotrexate Injection USP should be used only by physicians whose knowledge and experience includes the use of antimetabolite therapy because of the possibility of serious toxic reactions (see **7 WARNINGS AND PRECAUTIONS: General**).
- Methotrexate Injection USP formulations which contain benzyl alcohol are contraindicated in neonates and for intrathecal, intracerebroventricular, or high dose therapy (see **2 CONTRAINDICATIONS**).
- Methotrexate has been reported to cause fetal death and/or congenital anomalies (see **7.1.1 Pregnant Women**). Therefore, use is contraindicated for women of childbearing potential until

pregnancy is excluded and pregnant patients with psoriasis or rheumatoid arthritis (see **2 CONTRAINDICATIONS**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.
- Women of childbearing potential should not be started on Methotrexate Injection USP until pregnancy is excluded.

Neoplastic Diseases:

- Methotrexate Injection USP without preservative may be given by the intramuscular, intravenous (as a bolus), intra-arterial, intrathecal or intracerebroventricular (via Ommaya reservoir into the CNS) routes.
- Methotrexate Injection USP formulations which contain benzyl alcohol as preservative are contraindicated in neonates and for intrathecal, intracerebroventricular, or high-dose therapy (see **2 CONTRAINDICATIONS**).
- Methotrexate Injection USP may only be administered by physicians experienced in the treatment of neoplasia. Typical dosages reported in the literature for the following malignancies are listed in the following section.

Psoriasis and Rheumatoid Arthritis:

- The patient should be fully informed of the risks involved and should be under constant supervision of the physician (see **7 WARNINGS AND PRECAUTIONS**).
- All dosage schedules should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects (see **8 ADVERSE REACTIONS**). Maximal myelosuppression usually occurs in seven to ten days.
- Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken weekly in rheumatoid arthritis and psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity.

4.2 Recommended Dose and Dosage Adjustment

Breast Cancer: The initial doses of CMF will be cyclophosphamide 100 mg/m^2 p.o. days 1 through 14, methotrexate 40 mg/m^2 IV day 1, 8, and 5 - Fluorouracil 600 mg/m^2 IV 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/m^2 IV 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/m^2 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 <50 mL/min.
*** No drug for a decrease on day 8 of >30 mL/min compared to day 1 or Ccr <50 mL/min or Cr >1.8 mg/dL.
¶Major dose modifications for both drugs depending on myelosuppression.

Table 2: M-VAC Regimen*

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

* All doses in mg/m^2 with cycles repeated every 28 - 32 days.
** Patients having prior pelvic irradiation equivalent to >2500 rad in 5 days, reduce the dose of doxorubicin 15 mg/m^2.
*** No doses given when the WBC <2500 cells/mm^3, platelets >100,000 cells/mm^3, 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/m^2 weekly IV or 40 mg/m^2 biweekly IV
40 - 60 mg/m^2 weekly IV
80 mg/m^2 for 30 h every 2 wk with escalation to toxicity
40 mg/m^2 weekly IV
40 - 200 mg/m^2 IV on days 1, 4 weekly; leucovorin on days 2,5
60 mg/m^2 IV weekly

** excerpt from Devita, et al: CANCER *3rd Ed, p. 496*

For palliation of patients with advanced, incurable disease and acceptable renal function, it is appropriate to begin intravenous methotrexate with weekly doses of 40-50 mg/m^2 or biweekly doses of

15 to 20 mg/m^2 and escalate the dose in weekly increments until either mild toxicity or therapeutic response is achieved.

Gastric Cancer: A regimen used in a clinical trial in Belgium in patients with resectable gastric cancer follows: methotrexate (1.5 g/m^2 IV day 1) + 5-Fluorouracil (1.5 g/m^2 IV) + Leucovorin (15 mg/m^2 orally or IV every 6 hours for 72 hours) + Adriamycin (30 mg/m^2 IV, day 15). The schedule is repeated on day 29 for 6 cycles.

Choriocarcinoma and similar trophoblastic diseases: Methotrexate is administered 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 are usually recommended. Before each course of the drug, careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumour 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.

Lymphomas: In Burkitt's tumour, Stages I-II, methotrexate has produced prolonged remissions in some cases. In Stage III, 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.

Lymphosarcomas 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, 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**	**ıy 14**	**Days 15-21**
Cyclophosphamide 650 mg/m^2 I.V.	x			No therapy
Doxorubicin 25 mg/m^2 I.V.	x			
Etoposide 120 mg/m^2 I.V.	x			

Cytarabine 300 mg/m^2 I.V.	x
Bleomycin 5 mg/m^2 I.V.	x
Vincristine 1.4 mg/m^2 I.V.	x
Methotrexate 120 mg/m^2 I.V.	x with leucovorin rescue
Prednisone 60 mg/m^2 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. Dose levels of drug and adjustment of dose regimen by reduction or cessation of drug are guided by patient response and hematologic monitoring. Methotrexate has also been given intramuscularly in doses of 50 mg once weekly or 25 mg of methotrexate twice 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/m^2 in combination with 60 mg/m^2 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 twice weekly intramuscularly in total weekly doses of 30 mg/m^2. 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.

Meningeal Leukemia: In the treatment or prophylaxis of meningeal leukemia, methotrexate must be administered intrathecally.

For intrathecal administration, preservative free methotrexate is diluted to a concentration of 1 mg/mL in an appropriate sterile, preservative free medium such as 0.9% Sodium Chloride Injection, USP.

The cerebrospinal fluid volume is dependent on age and not on body surface area. The CSF is at 40% of the adult volume at birth and reaches the adult volume in several years.

Intrathecal methotrexate administration at a dose of 12 mg/m^2 (maximum 15 mg) has been reported to result in low CSF methotrexate concentrations and reduced efficacy in children and high concentrations and neurotoxicity in adults.

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

Table 5: Dosage regimen

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

In one study in patients under the age of 40, this dosage regimen appeared to result in more consistent CSF methotrexate concentrations and less neurotoxicity. Another study in children with acute lymphocytic leukemia compared this regimen to a dose of 12 mg/m^2 (maximum 15 mg), a significant reduction in the rate of CNS relapse was observed in the group whose dose was based on age.

Because the CSF volume and turnover may decrease with age, a dose reduction may be indicated in elderly patients.

For the treatment of meningeal leukemia, intrathecal methotrexate may be given at intervals of 2 to 5 days. However, administration at intervals of less than 1 week may result in increased subacute toxicity. Methotrexate is administered until the cell count of the cerebrospinal fluid returns to normal. At this point one additional dose is advisable. For prophylaxis against meningeal leukemia, the dosage 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.

Untoward side effects may occur with any given intrathecal injection and are commonly neurological in character. Large doses may cause convulsions. Methotrexate given by the intrathecal route appears significantly in the systemic circulation and may cause systemic methotrexate toxicity. Therefore, systemic antileukemic therapy with the drug should be appropriately adjusted, reduced, or discontinued. Focal leukemic involvement of the central nervous system may not respond to intrathecal chemotherapy and is best treated with radiotherapy.

Leptomeningeal Carcinomatosis: Intrathecal administration of methotrexate as a single-drug or in combination regimens, is the most common therapy for carcinomatous leptomeningitis.

Treatment is optimally administered through an Ommaya reservoir and is usually started with methotrexate (10 mg/m^2) given twice weekly until the cerebrospinal fluid cytology becomes negative. The treatment regimen is gradually decreased, first to a weekly course, and eventually to a single administration every two months.

Osteosarcoma: An effective adjuvant chemotherapy regimen requires the administration of several cytotoxic chemotherapeutic agents. In addition to high-dose methotrexate with leucovorin rescue, these agents may include doxorubicin, cisplatin, and the combination of bleomycin, cyclophosphamide and dactinomycin (BCD) in the doses and schedule shown in the table below. The starting dose for high-dose Methotrexate treatment is 12 grams/m^2. If this dose is not sufficient to produce a peak

serum methotrexate concentration of 1,000 micromolar (10^{-3} mol/L) at the end of the methotrexate infusion, the dose may be escalated to 15 grams/m^2 in subsequent treatments. If the patient is vomiting or is unable to tolerate oral medication, leucovorin is given IV or IM at the same dose and schedule.

Table 6: Doses and schedule

Drug*	**Dose***	**Treatment Week After Surgery**
Methotrexate Leucovorin	12 g/m^2 IV as 4 hour infusion (starting dose) 15 mg orally every six hours for 10 doses starting at 24 hours after start of methotrexate infusion.	4,5,6,7,11,12,15,16,29,30,44,45
Doxorubicin** as a single drug	30 mg/m^2/day IV x 3 days	8,17
Doxorubicin** Cisplatin**	50 mg/m^2 IV 100 mg/m^2 IV	20,23,33,36 20,23,33,36
Bleomycin** Cyclophosphamide** Dactinomycin**	15 units/m^2 IV x 2 days 600 mg/m^2 IV x 2 days 0.6 mg/m^2 IV x 2 days	2,13,26,39,42 2,13,26,39,42 2,13,26,39,42

* Link MP, Goorin AM, Miser AW, et al: The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. N *Engl J of Med* 1986; 314(No.25):1600-1606.

** See each respective package insert for full prescribing information. Dosage modifications may be necessary because of drug-induced toxicity.

When these higher doses of methotrexate are to be administered, the following safety guidelines should be closely observed.

GUIDELINES FOR METHOTREXATE THERAPY WITH LEUCOVORIN RESCUE

~~1.~~ Administration of Methotrexate Injection USP should be delayed until recovery if:

- The WBC count is less than 1500/microliter
- The neutrophil count is less than 200/microliter
- The platelet count is less than 75,000/microliter
- The serum bilirubin level is greater than 1.2 mg/dL
- The SGPT level is greater than 450 U
- Mucositis is present, until there is evidence of healing
- Persistent pleural effusion is present; this should be drained dry prior to infusion.

~~2.~~ Adequate renal function must be documented.

a) Serum creatinine must be normal, and creatinine clearance must be greater than 60 mL/min, before initiation of therapy.

b) Serum creatinine must be measured prior to each subsequent course of therapy. If serum creatinine has increased by 50% or more compared to a prior value, the creatinine clearance must be measured and documented to be greater than 60 mL/min (even if the serum creatinine is still within the normal range).

3. Patients must be well hydrated, and must be treated with sodium bicarbonate for urinary alkalinization.
    a) Administer 1,000 mL/m^2 of intravenous fluid over 6 hours prior to initiation of the Methotrexate Injection USP infusion. Continue hydration at 125 mL/m^2/hr (3 liters/m^2/day) during the Methotrexate Injection USP infusion, and for 2 days after the infusion has been completed.
    b) Alkalinize urine to maintain pH above 7.0 during Methotrexate Injection USP infusion and leucovorin calcium therapy. This can be accomplished by the administration of sodium bicarbonate orally or by incorporation into a separate intravenous solution.

4. Repeat serum creatinine and serum methotrexate 24 hours after starting Methotrexate Injection USP and at least once daily until the methotrexate level is below $5x10^{-8}$ mol/L (0.05 micromolar).

5. The table below provides guidelines for leucovorin calcium dosage based upon serum methotrexate levels (See table below).

    Patients who experience delayed early methotrexate elimination are likely to develop non-reversible oliguric renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved. If necessary, acute, intermittent hemodialysis with a high-flux dialyzer may also be beneficial in these patients.

6. Some patients will have abnormalities in methotrexate elimination, or abnormalities in renal function following methotrexate administration, which are significant but less severe than the abnormalities described in the table below. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, leucovorin rescue should be extended for an additional 24 hours (total 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with Methotrexate Injection USP (e.g., medications which may interfere with methotrexate binding to serum albumin, or elimination) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

Table 7: Leucovorin rescue schedules following treatment with higher doses of Methotrexate.

Clinical Situation	**Laboratory Findings**	**Leucovorin Dosage and Duration**
Normal Methotrexate Elimination	Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0.2 micromolar at 72 hours.	15 mg PO, IM or IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).
Delayed Late Methotrexate Elimination	Serum methotrexate level remaining above 0.2 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration.	Continue 15 mg PO, IM or IV q six hours, until Methotrexate level is less than 0.05 micromolar.

Clinical Situation	Laboratory Findings	Leucovorin Dosage and Duration
Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury	Serum methotrexate level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR; a 100% or greater increase in serum creatinine level at 24 hours after methotrexate administration (e.g., an increase from 0.5 mg/dL to a level of 1 mg/dL or more).	150 mg IV q three hours, until methotrexate level is less than 1 micromolar; than 15 mg IV q three hours, until methotrexate level is less than 0.05 micromolar.

Psoriasis:

Recommended starting dose schedule:

- Weekly single intramuscular or intravenous dose schedule: 10 to 25 mg per week until adequate response is achieved.

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 25 mg/week should not ordinarily be exceeded.

Once optimal clinical response has been achieved, the dosage schedule should be reduced to the lowest possible effective dose and to the longest possible rest period.

Rheumatoid Arthritis:

Recommended starting dosage schedule:

Dosages may be gradually adjusted to achieve optimal clinical 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. Upon achieving the therapeutically desired result, dosage should be reduced gradually to the lowest possible effective maintenance dose. The optimal duration of therapy is unknown; limited data from long-term studies indicate that the initial clinical improvement is maintained for at least 2 years with continued therapy.

Special Populations:

Hepatic impairment: Hepatic excretion of methotrexate is a minor route of elimination. However, the liver cells appear to retain certain amounts of the drug for prolonged periods even after a single therapeutic dose. Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function.

Renal Impairment: 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 inter subject pK variability. Methotrexate Injection USP is contraindicated in patients with severe renal impairment **(**see **2 CONTRAINDICATIONS**).

Table 8: 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

Pediatrics (< 18 years of age): Safety and effectiveness in pediatric patients have not been established, other than in cancer chemotherapy (see **7 WARNINGS AND PRECAUTIONS**: **Special Populations**, and **7.1.3 Pediatrics**).

Geriatrics (≥ 65 years of age): Due to diminished hepatic and renal function as well as decreased folate stores in elderly population, relatively low doses (especially in rheumatoid arthritis and psoriasis indications) should be considered and these patients should be closely monitored for early signs of toxicity. See **Table 1** for reduced doses in oncology patients with renal impairment.

4.3 Reconstitution

Parental products

Methotrexate Injection USP may be diluted with any of the solutions for IV infusion listed below in a concentration range of 0.4 mg/mL to 2 mg/mL.

Solutions:

0.9% Sodium Chloride Injection
5% Dextrose Injection
4% Dextrose and 0.18% Sodium Chloride Injection
Ringer's Injection

4.4 Administration

Dilution:

Methotrexate Injection USP may be diluted with any of the solutions for IV infusion listed below in a concentration range of 0.4 mg/mL to 2 mg/mL. Dilutions should be used within 24 hours if kept at room temperature. Unused solution should be discarded after this time in order to avoid risk of microbial contamination.

Solutions:

0.9% Sodium Chloride Injection
5% Dextrose Injection
4% Dextrose and 0.18% Sodium Chloride Injection
Ringer's Injection

Since methotrexate is poorly soluble in acid media, use of potassium chloride solution is not advisable.

If a preservative-free diluent is used, the solution should be used immediately because of the possibility of microbial growth. It is advisable to protect diluted solutions from light.

Due to the number of brands available, stability data of methotrexate in plastic syringes and bags are not available.
Unused preservative-free products should be discarded due to the possibility of microbial growth.

Dispensing of Pharmacy Bulk Vials:

Pharmacy Bulk Vials contain 25 mg/mL methotrexate (as methotrexate sodium) in 20 mL, 40 mL or 100 mL of sterile, **unpreserved**, isotonic solution (see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING: COMPOSITION**).

The availability of Pharmacy Bulk Vials is restricted to hospitals with a recognized intravenous admixture program. It is recommended that the vial remains in the carton until time of use. The Methotrexate Injection USP vial should be inspected for damage and visible signs of leaks. If there are signs of breakage or leakage from the vial, do not use. Incinerate the unopened package.

Pharmacy Bulk Vials are intended for multiple dispensing FOR INTRAVENOUS USE ONLY, employing a single puncture (see **12 SPECIAL HANDLING INSTRUCTIONS**).

The Pharmacy Bulk Vial content should be dispensed within eight hours. Any unused solution should be discarded. The diluted solutions prepared from the Pharmacy Bulk vial should be used within 24 hours from the time of the initial puncture of the Pharmacy Bulk Vial, when kept at room temperature.

Pharmacy Bulk Vials contain no preservatives. Care must be taken to minimize the potential for inadvertent introduction of micro-organisms during manipulation in the hospital environment.

Incompatibilities: Other drugs should not be mixed with methotrexate in the same infusion bottle. Methotrexate has been reported to be incompatible with cytarabine, fluorouracil, and prednisolone sodium phosphate; however, its incompatibility with fluorouracil has been questioned and subsequent studies documented in the literature indicate that methotrexate and cytarabine are physically and chemically stable in intravenous admixtures over a range of concentrations and in a variety of typical vehicles. A mixture of methotrexate with cytarabine and hydrocortisone sodium succinate in various infusion fluids has been reported to be visually compatible for at least 8 hours at 25°C, although precipitation did not occur on storage for several days. In general, compatibility of any medicinal product admixed with Methotrexate Injection USP must be assured prior to patient administration.

Contact with acidic solutions should be avoided since Methotrexate Injection USP is sparingly soluble in acid media and precipitation may occur (see **7 WARNINGS AND PRECAUTIONS** for clinical incompatibilities).

4.5 Missed Dose

If a scheduled dose is missed, contact your doctor for instructions.

5 OVERDOSAGE

Overdose with methotrexate has occurred with intrathecal administration, although intravenous and intramuscular overdose have also been reported.

Discontinue or reduce dosage at the first sign of ulceration or bleeding, diarrhea, or marked depression of the hematopoietic system. Leucovorin is indicated to diminish the toxicity and counteract the effect of overdosages of methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

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

There are published case reports of intravenous carboxypeptidase G2 treatment to hasten clearance of methotrexate in cases of overdoses.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 9: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-Medicinal Ingredients
Intramuscular, intravenous, intra-arterial, intrathecal, intracerebroventricular	Sterile solution (preservative-free) / 10 mg/mL (20 mg/2 mL) 25 mg/mL (50 mg/2 mL)	Sodium Chloride Sodium Hydroxide Hydrochloric Acid
Intravenous	Sterile solution (Pharmacy Bulk vial; preservative-free) / 25 mg/mL (500 mg/20 mL; 1 g/40 mL; 2.5 g/100 mL)	Sodium Chloride Sodium Hydroxide Hydrochloric Acid

Intramuscular, intravenous, intra-arterial	Sterile solution (with preservative) / 25 mg/mL (50 mg/2 mL; 500 mg/20 mL)	Benzyl alcohol as preservative Sodium Chloride Sodium Hydroxide Hydrochloric Acid

Methotrexate Injection USP is supplied in a carton containing 20 mg, 50 mg and 500 mg of methotrexate (as the sodium salt) as follows:

10 mg/mL methotrexate	20 mg/2 mL* (contains no preservative)
25 mg/mL methotrexate	50 mg/2 mL* (contains no preservative)
25 mg/mL methotrexate	50 mg/2 mL+ (contains preservative)
25 mg/mL methotrexate	500 mg/20 mL+ (contains preservative)

* Single-use vials
+ Multidose vials

Note: The 10 mg/mL presentation is available in packs of 5 vials. The 25 mg/mL presentations are available in packs of 5 vials (2 mL) or as single vials (2 mL and 20 mL).

~~(1)~~ Methotrexate Injection USP Pharmacy Bulk Vials which are packaged in a carton, are for intravenous use only and are supplied to hospitals with a recognized intravenous admixture program only, as follows:

Table 10: Methotrexate Injection USP Pharmacy Bulk Vials

25 mg/mL methotrexate	500 mg/20 mL	(contains no preservative)
25 mg/mL methotrexate	1 g/40 mL	(contains no preservative)
25 mg/mL methotrexate	2.5 g/100 mL	(contains no preservative)

Composition

Methotrexate Injection USP is a sterile, isotonic solution containing:

Methotrexate Sodium equivalent to 10 mg/mL Methotrexate with 7.0 mg/mL Sodium Chloride, (unpreserved), with Sodium Hydroxide and Hydrochloric Acid as pH adjusters.
Methotrexate Sodium equivalent to 25 mg/mL Methotrexate with 4.9 mg/mL Sodium Chloride, (unpreserved), with Sodium Hydroxide and Hydrochloric Acid as pH adjusters.
Methotrexate Sodium equivalent to 25 mg/mL Methotrexate with 2.6 mg/mL Sodium Chloride and 0.9% v/v Benzyl alcohol (preservative), with Sodium Hydroxide and Hydrochloric Acid as pH adjusters.

*Note: 50 mg/2 mL and 500 mg/20 mL Methotrexate Injection USP, with benzyl alcohol (as preservative) are supplied as multidose vials. Please see **11 STORAGE, STABILITY AND DISPOSAL** for special storage conditions once the vials are punctured.*

The vial stoppers are not made with natural rubber latex.

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

General

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 rheumatoid arthritis and psoriasis, and that daily use of the weekly recommended dose has led to fatal toxicity. Fatal toxicities related to intravenous dosing miscalculation have been reported. Special attention must be given to dose calculation.

Because of the possibility of serious toxic reactions (which can be fatal), Methotrexate Injection USP should be used only in neoplastic diseases (as indicated), or in patients with severe, recalcitrant, disabling psoriasis or rheumatoid arthritis that are 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.

The use of methotrexate high-dose regimens recommended for osteosarcoma requires meticulous care (see 4 **DOSAGE AND ADMINISTRATION**). High dosage regimens for other neoplastic diseases are investigational and a therapeutic advantage has not been established.

Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on Methotrexate Injection USP closely.

Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermittent hemodialysis with a high-flux dialyzer (see 5 **OVERDOSAGE**).

If Methotrexate Injection USP therapy is re-instituted, 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.

Methotrexate may induce "tumour lysis syndrome" in patients with rapidly growing tumours. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

Methotrexate exits slowly from third space compartments (e.g., pleural effusions or ascites). This results in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels.

Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) along with non-steroidal anti-inflammatory drugs (NSAIDs) (see 9 **DRUG INTERACTIONS**).

Bone marrow and mucosal toxicity depend on dose and duration of exposure of high levels (>$2x10^{-8}$ mol/L (0.02 micromolar)) of methotrexate. Since the critical time factor has been defined for these organs as being 42 hours in humans, this has the following implications:

- when high doses of methotrexate are employed (>1g/m^2), drug levels in serum should be monitored
- when drug levels exceeding 2 x 10^{-8} mol/L (0.02 micromolar) for >42 hours may forecast significant toxicity
- when toxicity can be minimized by appropriate administration of Leucovorin Calcium
- when high-dose methotrexate (HDMTX) is employed, it is imperative to alkalinise the urine in order to prevent crystallisation of methotrexate and its 7-hydroxy metabolite in the urine, which may lead to acute renal failure.

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

Methotrexate Injection USP should be used with extreme caution in the presence of debility.

The use of methotrexate high-dose regimens (≥500 mg/m^2) recommended for osteosarcoma requires meticulous care. High-dosing regimens for other neoplastic diseases are investigational and a therapeutic advantage has not been established.

Carcinogenesis and Mutagenesis

Malignant lymphomas may occur in patients receiving low-dose methotrexate. These lymphomas may regress following withdrawal of methotrexate without requiring treatment.

No controlled human data exist regarding the risk of neoplasia with methotrexate. 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. Assessment of the carcinogenic potential of methotrexate is complicated by conflicting evidence of an increased risk of certain tumours in rheumatoid arthritis. Benefit should be weighed against this potential risk before using Methotrexate Injection USP alone or in combination with other drugs, especially in children or young adults. (See 16 **NON-CLINICAL TOXICOLOGY**).

Driving and Operating Machinery

Some of the effects (e.g., dizziness and fatigue) may have an influence on the ability to drive or operate machinery.

Gastrointestinal

If vomiting, diarrhea, or stomatitis occurs, resulting in dehydration, Methotrexate Injection USP should be discontinued until recovery occurs. Diarrhea and ulcerative stomatitis require interruption of therapy; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur. Methotrexate Injection USP should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

Use caution when administering high-dose methotrexate to patients receiving proton pump inhibitor (PPI) therapy as concomitant use of some PPIs, such as omeprazole, esomeprazole, and pantoprazole, with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydromethotrexate, possibly leading to methotrexate toxicities (see **9.4 Drug-Drug Interactions**).

Hematologic

Methotrexate Injection USP should be used with caution in patients with impaired bone marrow function and previous or concomitant wide field radiotherapy. Methotrexate may produce marked bone marrow depression with resultant anemia, aplastic anemia, pancytopenia, leucopenia, neutropenia, and/or thrombocytopenia. In controlled clinical trials in rheumatoid arthritis (n=128), leucopenia (WBC <3000/mm^3) was seen in 2 patients, thrombocytopenia (platelets <100,000/mm^3) in 6 patients, and pancytopenia in 2 patients.

The nadir of circulating leukocytes, neutrophils and platelets usually occurs between 5 and 13 days after an IV bolus dose (with recovery between 14 to 28 days). Leukocytes and neutrophils may occasionally show two depressions, the first occurring in 4-7 days and a second nadir after 12-21 days, followed by recovery. Clinical sequel such as fever, infections and hemorrhage from various sites may be expected.

In psoriasis and rheumatoid arthritis, Methotrexate Injection USP should be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, Methotrexate Injection USP should be continued only if the potential benefit warrants the risk of severe myelosuppression. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotic therapy.

Hepatic/Biliary/Pancreatic

Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Acutely, liver enzyme elevations are frequently seen after methotrexate administration and are usually not a reason for modification of methotrexate therapy. Liver enzyme elevations are usually transient and asymptomatic, and also do not appear predictive of subsequent hepatic disease. Persistent liver abnormalities, and/or decrease of serum albumin may be indicators of serious liver toxicity. 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. 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. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population. 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. An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known. Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function.

Methotrexate has caused reactivation or worsening of hepatitis B and C infections, in some cases resulting in death. Some cases of hepatitis B reactivation have occurred after discontinuation of methotrexate. Prior to treatment with Methotrexate Injection USP, clinical and laboratory evaluation should be performed to evaluate preexisting hepatitis virus B and hepatitis virus C infection. Methotrexate Injection USP is not recommended for patients with active or chronic hepatitis B or C infection.

In psoriasis, liver damage and function tests, including serum albumin and prothrombin time, should be performed several times prior to dosing, but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy: 1) before the start of therapy or shortly after initiation of therapy (4-8 weeks); 2) after a total cumulative dose of 1.5 grams; and 3) after each additional 1.0 to 1.5 grams. Moderate fibrosis or any cirrhosis normally leads to discontinuation of 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 pre-therapy. Although these mild changes are usually not a reason to avoid or discontinue Methotrexate Injection USP therapy, the drug should be used with caution.

Clinical experience with liver disease in rheumatoid arthritis is limited, but the same risk factors would be anticipated. Liver function tests are also usually not reliable predictors of histological changes in this population.

In rheumatoid arthritis, advanced age at first use of methotrexate, and increasing duration of therapy have been reported as risk factors for hepatotoxicity. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid population. Liver function tests should be performed at baseline and at 4-8 week intervals in patients receiving Methotrexate Injection USP for rheumatoid arthritis. Pretreatment liver biopsy should be performed for patients with a history of excessive alcohol consumption, persistently abnormal baseline liver function test values, or chronic hepatitis B or C infection. During therapy, liver biopsy should be performed if there are persistent liver function test abnormalities, or there is a decrease in serum albumin below the normal range (in the setting of well controlled rheumatoid arthritis).

If the results of a liver biopsy show mild changes (Roenigk grades I, II, IIIa), Methotrexate Injection USP may be continued and the patient monitored according to the recommendations listed above. Methotrexate Injection USP 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).

There is a combined reported experience in 217 rheumatoid arthritis patients with liver biopsies both before and during treatment (after a cumulative dose of at least 1500 mg) and in 714 patients with a biopsy only during treatment. There are 64 (7%) cases of fibrosis and 1 (0.1%) case of cirrhosis. Of the 64 cases of fibrosis, 60 were deemed mild. The reticulin stain is more sensitive for early fibrosis and its use may increase these figures. It is unknown whether even longer use will increase these risks.

Immune

Methotrexate Injection USP should be used with extreme caution in the presence of active infection and is contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes (see 2 **CONTRAINDICATIONS**).

Immunization may be ineffective when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended. Hypogammaglobulinemia has been reported rarely.

Monitoring and Laboratory Tests

General: Patients undergoing Methotrexate Injection USP therapy should be informed of the early signs and symptoms of toxicity and closely monitored so that toxic effects are detected promptly. 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, and 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 leucovorin rescue is delayed for more than 42 to 48 hours.

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 leucovorin rescue).

Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests, and a chest X-ray. During initial or changing doses, or during periods of increased risk of elevated methotrexate blood levels (e.g., dehydration), more frequent monitoring may also be indicated.

During therapy of rheumatoid arthritis and psoriasis, monitor:

- **Hematologic:** Patients should have their blood tests checked at least monthly.
- **Hepatic:** Liver biopsies prior to Methotrexate Injection USP therapy are not indicated routinely. Liver function tests should be determined prior to the initiation of therapy with Methotrexate Injection USP and they should be monitored every 1 to 2 months. A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established. Transient liver function test abnormalities are observed frequently after methotrexate administration and are usually not cause for modification of Methotrexate Injection USP therapy. Persistent liver function test abnormalities just prior to dosing and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation.
- **Renal:** Renal function should be monitored every 1 to 2 months.
- **Respiratory:** Pulmonary function tests may be useful if methotrexate-induced lung disease (e.g. interstitial pneumonitis) is suspected, especially if baseline measurements are available.

During therapy of neoplastic disease:

More frequent monitoring is usually indicated during antineoplastic therapy for hematologic, hepatic, renal and respiratory.

Neurologic

There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had craniospinal irradiation. Serious neurotoxicity, frequently

manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intravenous methotrexate (1 g/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies.

Chronic leukoencephalopathy has also been reported in patients with osteosarcoma who received repeated doses of high-dose methotrexate with leucovorin rescue even without cranial irradiation. There are also reports of leukoencephalopathy in patients who received low oral doses (4-8 mg/week) of methotrexate therapy for rheumatoid arthritis or psoriatic arthritis.

Discontinuation of Methotrexate Injection USP does not always result in complete recovery.

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

After the intrathecal use of methotrexate, the central nervous system toxicity which may occur can be classified as follows: chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity, and fever; paresis, usually transient, manifested by paraplegia associated with involvement with one or more spinal nerve roots; leucoencephalopathy manifested by confusion, irritability, somnolence, ataxia, dementia, and occasionally major convulsions.

Intravenous administration of methotrexate may also result in acute encephalitis and acute encephalopathy with fatal outcome.

Cases of severe neurological adverse reactions that ranged from headache to paralysis, coma and stroke-like episodes have been reported mostly in juveniles and adolescents given methotrexate in combination with intravenous cytarabine.

Progressive multifocal leukoencephalopathy (PML): Cases of progressive PML, including fatal cases, have been reported with methotrexate use. PML is a rare and often fatal demyelinating disease attributed to the presence within the CNS of the John Cunningham virus (JCV) and its reactivation in people with suppressed immune function. Health professionals should consider PML in patients with new or worsening neurological, cognitive, or behavioural signs or symptoms and should take appropriate diagnostic measures. If PML is suspected, further methotrexate dosing must be suspended. If PML is confirmed, methotrexate should be permanently discontinued.

Renal

Methotrexate is contraindicated in patients with severe renal impairment including end stage renal disease with and without dialysis (see **2 CONTRAINDICATIONS** and **4.2 Recommended dose and dosage adjustment: Special populations**). Methotrexate therapy in patients with mild and moderate renal impairment should be undertaken with extreme caution, and at reduced dosages, because renal dysfunction will prolong methotrexate elimination. Methotrexate may cause renal damage that may lead to acute renal failure. High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function

including adequate hydration, urine alkalinization and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Nephritis has been reported on co-administration with nitrous oxide anesthesia in rheumatoid arthritis patients (see 2 **CONTRAINDICATIONS** and **9.4 Drug-Drug Interactions**).

Reproductive Health

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

Methotrexate cause embryotoxicity, abortion, and fetal defects in humans.

Pregnancy should be avoided if either partner is receiving Methotrexate Injections USP. The optimal time interval between cessation of methotrexate treatment of either partner and pregnancy has not been 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 Injection USP (see **2 CONTRAINDICATIONS**, **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**, **and 7.1.1 Pregnant Women**).

Respiratory

Methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, is a potentially dangerous lesion which may occur at any time during therapy and which has been reported at low doses. It is not always fully reversible and fatalities have been reported. Cases of pleural effusion with or without interstitial pneumonitis have also been reported at any time during therapy at low doses. Pulmonary symptoms (especially a dry nonproductive cough) or a nonspecific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate-induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest X-ray; infection (including pneumonia) needs to be excluded. This lesion can occur at all dosages.

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

Pulmonary alveolar haemorrhage has been reported with methotrexate. This event may also be associated with vasculitis and other comorbidities. Prompt investigations should be considered when pulmonary alveolar haemorrhage is suspected to confirm the diagnosis.

Skin

Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis (Lyell's Syndrome), Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular or intravenous methotrexate administration. Reactions were noted after single or multiple, low, intermediate or high

doses of methotrexate in patients with neoplastic diseases, rheumatoid arthritis or psoriasis. Recovery has been reported with discontinuation of therapy.

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

7.1 Special Populations

7.1.1 Pregnant Women

Methotrexate Injection USP is contraindicated in pregnant patients with psoriasis or rheumatoid arthritis (see 2 **CONTRAINDICATIONS and 3 SERIOUS WARNINGS AND PRECAUTIONS BOX**) and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus. 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. Methotrexate can cause fetal death, embryotoxicity, abortion, or teratogenic effects when administered to a pregnant woman.

Methotrexate Injection USP is contraindicated in women of childbearing potential until pregnancy is excluded and should be fully counselled on the serious risk to the fetus should they become pregnant while undergoing treatment (see 2 **CONTRAINDICATIONS**). Pregnancy should be avoided if either partner is receiving Methotrexate Injection USP. 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 Injection USP.

7.1.2 Breast-feeding

Methotrexate Injection USP is contraindicated in nursing mothers because of the potential for serious adverse reactions from methotrexate in breast-fed infants.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): Safety and effectiveness in pediatric patients have not been established, other than in cancer chemotherapy. Therefore, Methotrexate Injection USP should not be used as a DMARD in pediatric patients.

Overdose by intravenous miscalculation of dosage (particularly in juveniles) have occurred. Special attention must be given to dose calculation.

Methotrexate Injection USP formulations containing the preservative benzyl alcohol are contraindicated for use in neonates (children less than one month of age) (see 2 **CONTRAINDICATIONS**). The preservative benzyl alcohol has been associated with serious adverse events, including the “gasping syndrome”, and death in pediatric patients. Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity

administered and the hepatic capacity to detoxify the chemical. Premature and low-birth weight infants may be more likely to develop toxicity.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function, as well as decreased folate stores in this population, relatively low doses should be considered. Fatal toxicities related to inadvertent daily rather than weekly dosing have been reported, particularly in elderly patients. Elderly patients should be closely monitored for early signs of hepatic, bone marrow and renal toxicity.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In general, the incidence and severity of acute side effects are related to dose, frequency of administration, and the duration of the exposure to significant blood levels of methotrexate to the target organs. The most serious reactions are discussed under 7 **WARNINGS AND PRECAUTIONS** section. The most frequently reported adverse reactions include ulcerative stomatitis, leucopenia, 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.

Table 11: Adverse Drug Reactions by Organ System

Table 11 provides an overview of adverse reactions observed with methotrexate use

Blood and lymphatic system disorders	Leucopenia, anemia, aplastic anemia, thrombopenia, pancytopenia, agranulocytosis, lymphadenopathy and lymphoproliferative disorders (including reversible), neutropenia and eosinophilia have also been observed.
Cardiac disorders	Pericarditis and pericardial effusion (damage to heart, rarely).
Eye disorders	Conjunctivitis, blurred vision, serious visual changes of unknown etiology, and transient blindness/vision loss.
Gastrointestinal disorders	Gingivitis, stomatitis, enteritis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, pancreatitis, intestinal perforation, non-infectious peritonitis, glossitis.
General disorders and administration site conditions	Anaphylactoid reactions, vasculitis, fever, Injection site reaction, Injection site necrosis, conjunctivitis, infection, sepsis, nodulosis, hypogammaglobulinaemia, and sudden death.

Hepatobiliary disorders	Hepatotoxicity, acute hepatitis, chronic fibrosis and cirrhosis, decrease in serum albumin, liver enzyme elevations, hepatic failure.
Infection	Other reported infections included nocardiosis, histoplasmosis, cryptococcosis, and disseminated *H. simplex*, cytomegalovirus infection, including cytomegaloviral pneumonia.
Metabolism and nutrition disorders	Diabetes mellitus.
Musculoskeletal, connective tissue and bone disorders	Stress fractures, soft tissue necrosis, osteonecrosis, arthralgia, myalgia and osteoporosis.
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Tumour lysis syndrome. Malignant lymphomas.
Nervous system	Cerebrospinal fluid pressure increased, neurotoxicity, arachnoiditis, paresthesia, headache, dizziness, drowsiness, speech impediment including dysarthria and aphasia; hemiparesis, paresis and convulsions. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration, or unusual cranial sensations, leukoencephalopathy, or encephalopathy.
Renal and urinary disorders	Renal failure, severe nephropathy or renal failure, azotemia, dysuria, cystitis, hematuria, urogenital dysfunction. Proteinuria has also been observed.
Reproductive system and breast disorders	Defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge and gynecomastia; infertility, abortion, fetal defects, loss of libido/impotence.
Respiratory, thoracic and mediastinal disorders	Pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia, pulmonary fibrosis, *Pneumocystis carinii* pneumonia, pleural effusion. Dyspnea, chest pain, hypoxia, respiratory fibrosis, pharyngitis, and chronic interstitial obstructive pulmonary disease, alveolitis and pulmonary alveolar haemorrhage have occasionally occurred.
Skin disorders	Erythema, pruritus, photosensitisation, petechiae, loss of hair, skin necrosis, exfoliative dermatitis, painful erosion of psoriatic plaques, herpes zoster, vasculitis, urticaria, pigmentary changes, acne, ecchymosis, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), furunculosis and telangiectasia. Drug reaction with eosinophilia and systemic symptoms.
Vascular disorders	Hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein

	thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus), vasculitis.

Adverse Reactions Reported in Rheumatoid Arthritis:

- Alopecia (common)
- Diarrhea (common)
- Dizziness (common)
- Elevated liver enzymes (very common)
- Leucopenia (common)
- Nausea/vomiting (very common)
- Pancytopenia (common)
- Rash/pruritus/dermatitis (common)
- Stomatitis (common)
- Thrombocytopenia (common)

Adverse Reactions in Psoriasis:

The adverse reaction rates reported are very similar to those in the rheumatoid arthritis studies. Rarely, painful psoriatic plaque erosions may appear.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings

(See **7 WARNINGS AND PRECAUTIONS: Monitoring and Laboratory Tests**).

8.5 Post-Market Adverse Reactions

Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse events have also been reported during post-marketing experience with methotrexate:

Table 12: Post-Market Adverse Reactions

System Organ Class	Adverse Reaction
Blood and Lymphatic System Disorders	Agranulocytosis; Pancytopenia; Leukopenia; Neutropenia; Lymphadenopathy and lymphoproliferative disorders (including reversible); Eosinophilia; Anemia megaloblastic; Renal vein thrombosis; Lymphoma; Aplastic anemia; Hypogammaglobulinemia
Endocrine Disorders	Diabetes

General Disorders and Administration Site Conditions	Pyrexia; Chills; Malaise; Fatigue; Injection site reaction; Injection site necrosis; Anaphylactic reactions
Gastrointestinal Disorders	Intestinal perforation; Noninfectious peritonitis; Glossitis; Nausea; Pancreatitis
Hepatobiliary Disorders	Hepatic failure
Infections and Infestations	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
Musculoskeletal, Connective Tissue and Bone Disorders	Osteonecrosis
Nervous System Disorders	CSF pressure increased; Neurotoxicity; Arachnoiditis; Paraplegia; Stupor; Ataxia; Dementia; Dizziness; Paresthesia
Ophthalmologic Disorders	Transient blindness/vision loss
Pregnancy, Puerperium and Perinatal Conditions	Fetal death, Abortion
Renal and Urinary Disorders	Proteinuria
Reproductive System and Breast Disorders	Urogenital dysfunction
Respiratory, Thoracic and Mediastinal Disorders	Chronic interstitial pulmonary disease; Alveolitis; Dyspnea; Chest pain; Hypoxia; Cough; Plural effusion
Skin and Subcutaneous Tissue Disorders	Drug reaction with eosinophilia and systemic symptoms (DRESS); Dermatitis; Petechiae

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

The use of nitrous oxide anesthesia with methotrexate is contraindicated (see **2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS: Renal and 9.4 Drug-Drug Interactions**)

9.2 Drug Interactions Overview

Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that undergo tubular secretion, can markedly increase methotrexate serum levels. Laboratory studies demonstrate that methotrexate may be displaced from plasma

albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol and phenytoin.

9.3 Drug-Behaviour Interactions

Use of alcohol with Methotrexate Injection USP is contraindicated (see 2 **CONTRAINDICATIONS**). The effects of smoking on the pharmacokinetics of methotrexate have not been specifically studied.

9.4 Drug-Drug Interactions

Table 13 Established or Potential Drug-Drug Interactions

Proper/ Common name	Source of Evidence	Effect	Clinical comment
Amiodarone	C	Amiodarone administration to patients receiving methotrexate treatment for psoriasis has induced ulcerated skin lesions	Use with caution.
L-asparaginase	C	The administration of L-asparaginase has been reported to antagonize the effects of methotrexate.	Use with caution.
Ciprofloxacin	T	Renal tubular transport is diminished by ciprofloxacin.	Serum methotrexate levels and renal function should be carefully monitored when using this drug with Methotrexate Injection USP.
Cytarabine and other cytotoxic agents	C	Cases of severe neurological adverse reactions have been reported in patients given methotrexate in combination with intravenous cytarabine. See 7 WARNINGS AND PRECAUTIONS, Neurologic. Combined use of methotrexate with other cytotoxic agents has not been studied and may increases the incidence of adverse effects.	Caution should be used when cytotoxic agents are administered concomitantly with Methotrexate Injection USP
Disease Modifying Antirheumatic drugs (DMARDs)	T	Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, or sulfasalazine has not been studied and may increase the incidence of adverse effects.	Use with caution.
Diuretics	C	Bone marrow suppression and decreased folate levels have been described in the	Use with caution.

		concomitant administration of triamterene and methotrexate.	
Drugs Highly Bound to Plasma Proteins, such as sulfonylureas, aminobenzoic acid, salicylates, phenylbutazone, phenytoin, sulfonamides, some antibiotics such as penicillins, tetracycline, pristinamycin, probenecid, and chloramphenicol	T	Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by other highly bound drugs.	Use with caution.
Hepatotoxins such as leflunomide, azathioprine, sulfasalazine, retinoids	C	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.	Patients receiving concomitant therapy with Methotrexate Injection USP and other potential hepatotoxic agents should be closely monitored for possible increased risk of hepatotoxicity.
Leflunomide	T	Methotrexate in combination with leflunomide may increase the risk of pancytopenia.	Use with caution.
Mercaptopurine	T	Methotrexate increases the plasma levels of mercaptopurine.	Combination of Methotrexate Injection USP and mercaptopurine may require dose adjustment.
Nephrotoxic Drugs, such as cisplatin, aminoglycoside, Amphotericin B and Cyclosporin	T	Methotrexate clearance is decreased by cisplatinum. Although not documented, other nephrotoxic drugs could theoretically increase methotrexate toxicity by decreasing its elimination.	In the treatment of patients with osteosarcoma, use caution if high-dose Methotrexate Injection USP is administered in combination with a potentially nephrotoxic chemotherapy agent. Use with caution.
Nitrous oxide	C	The use of nitrous oxide anesthesia potentiates the effect of methotrexate on	In case of accidental co-administration, this effect

		folate metabolism, yielding increased toxicity such as severe, unpredictable myelosuppression, stomatitis, neurotoxicity (with intrathecal administration of methotrexate) and nephritis (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Renal).	can be reduced by the use of leucovorin rescue.
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)	C, CT	Concomitant administration of 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. These drugs have been reported to reduce the tubular secretion of methotrexate, in an animal model, and may enhance its toxicity by increasing methotrexate levels. The possibility of increased methotrexate toxicity with concomitant use of NSAIDs, including salicylates, in rheumatoid arthritis has not been fully explored. Despite the potential interactions, studies have usually included concurrent use of constant dosage regimens of NSAIDs without apparent problems. However, the doses used in rheumatoid arthritis (7.5 mg to 15 mg/week) are somewhat lower than those used in psoriasis. Larger doses could lead to toxicity.	NSAIDs should not be administered prior to or concomitantly with high doses of methotrexate. Caution should be used when NSAIDs, including salicylates, are administered concomitantly with lower doses of Methotrexate Injection USP.
Oral Antibiotics, such as such as tetracycline, chloramphenicol, and non-absorbable broad spectrum antibiotics	C, T	Oral antibiotics may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria. Neomycin, polymyxin B, nystatin and vancomycin decrease methotrexate absorption, whereas kanamycin increases methotrexate absorption. Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or an additive antifolate effect.	Use with caution.
Packed Red Blood Cells	C, CT	Patients receiving 24-hr methotrexate infusion and subsequent transfusions have	Care should be exercised whenever packed red

		showed enhanced toxicity probably resulting from prolonged high serum-methotrexate concentrations	blood cells and Methotrexate Injection USP are given concurrently.
Penicillins and Sulfonamides	C, CT, T	Penicillins and sulfonamides may reduce the renal clearance of methotrexate; hematologic and gastrointestinal toxicity have been observed in combination with methotrexate.	Use with caution.
Probenecid	T	Renal tubular transport is diminished by probenecid.	Serum methotrexate levels and renal function should be carefully monitored when using this drug with Methotrexate Injection USP.
Proton Pump Inhibitors (PPI) such as omeprazole, esomeprazole, and pantoprazole	C, CT	Case reports and published population pharmacokinetic studies suggest that concomitant use of some PPIs with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite 7-hydroxymethotrexate, possibly leading to methotrexate toxicities. In two of these cases, delayed methotrexate elimination was observed when high-dose methotrexate was co-administered with PPIs, but was not observed when methotrexate was co-administered with ranitidine. However, no formal drug interaction studies of methotrexate with ranitidine have been conducted.	Use caution when administering high- dose methotrexate to patients receiving PPI therapy. Concomitant use of PPIs and high-dose methotrexate should be avoided especially in patients with renal impairment.
Psoralen Plus Ultraviolet Light (PUVA) Therapy	C	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.	Use with caution.
Radiotherapy	C	Methotrexate given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.	Use with caution.
Theophylline	T	Methotrexate may decrease the clearance of theophylline.	Theophylline levels should be monitored when used concurrently with Methotrexate Injection USP

Vitamins, such as folic acid or folinic acid	T	Vitamin preparations containing folic acid or its derivatives may decrease responses to methotrexate. Preliminary animal and human studies have shown that small quantities of intravenously administered leucovorin enter the cerebrospinal fluid primarily as 5-methyl tetrahydrofolate and, in humans, remain 1 to 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high does of leucovorin may reduce the efficacy of intrathecally administered methotrexate. 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. Folate deficiency states may increase methotrexate toxicity.	Before taking a folate supplement, it is advisable to check B12 levels, particularly in adults over the age of 50, since folate administration can mask symptoms of B12 deficiency.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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 in high doses, followed by leucovorin rescue, is used as a part of the treatment of patients with non-metastatic osteosarcoma.

The original rationale for high-dose methotrexate therapy was based on the concept of selective rescue of normal tissues by leucovorin. More recent evidence suggests that high dose methotrexate may also overcome methotrexate resistance caused by impaired active transport, decreased affinity of dihydrofolic acid reductase for methotrexate, increased levels of dihydrofolic acid reductase resulting from gene amplification, or decreased polyglutamination of methotrexate. The actual mechanism of action is unknown.

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 are not known, although suggested mechanisms have included immunosuppressive and/or anti-inflammatory effects.

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.

10.2 Pharmacodynamics

Methotrexate has immunosuppressive and/or anti-inflammatory effects. The pharmacodynamics of methotrexate show large interpatient variability regardless of the route of administration or disease being treated.

10.3 Pharmacokinetics

Absorption

Methotrexate is generally completely absorbed following parenteral administration, and after intramuscular injection peak serum concentrations occur in 30 to 60 minutes.

Distribution

Methotrexate is widely distributed into body tissues with highest concentrations in the kidneys, gallbladder, spleen, liver and skin. Methotrexate in serum is approximately 50% protein-bound.

After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40% to 80% of body weight). 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% protein-bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given parenterally. High cerebrospinal fluid concentrations of the drug may be attained by intrathecal administration.

Metabolism

At low doses, methotrexate does not appear to undergo significant metabolism; following high-dose therapy after absorption, 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 syntheses. 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 tumours. 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.

Elimination

Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. Total clearance averages 12 L/h, but there is wide interindividual variation. Excretion of single daily doses occurs through the kidneys in amounts from 80% to 90% within 24 hours. Repeated daily doses result in more sustained serum levels and some retention of methotrexate over each 24-hour period, which may result in accumulation of the drug within the tissues. The liver cells appear to retain certain amounts of the drug for prolonged periods even after a single therapeutic dose. Methotrexate is retained in the presence of impaired renal function and may increase rapidly in the serum and in the tissue cells under such conditions. Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given parenterally. High concentrations of the drug, when needed, may be attained by direct intrathecal administration.

With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. 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. Methotrexate 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 leucovorin calcium during the final phase of methotrexate plasma elimination. Pharmacokinetic monitoring of methotrexate serum concentrations may help identify those patients at high risk for methotrexate toxicity and aid in proper adjustment of leucovorin dosing.

Half-Life

The terminal half-life reported for methotrexate is approximately 3 to 10 hours for patients receiving treatment for psoriasis, rheumatoid arthritis 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.

Special Populations and Conditions

- **Pediatrics:** 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.

- **Geriatrics:** The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses (especially in RA and psoriasis indications) should be considered and these patients should be closely monitored for early signs of toxicity.

- **Pregnancy and Breast-feeding:** Methotrexate has been detected in human breast milk and is contraindicated during breast-feeding. The highest breast milk to plasma concentration ratio reached was 0.08:1.

- **Hepatic Insufficiency:** Hepatic excretion of methotrexate is a minor route of elimination. However, the liver cells appear to retain certain amounts of the drug for prolonged periods even after a single therapeutic dose. Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function.

- **Renal Insufficiency** Since the renal excretion of methotrexate is the primary route of elimination with 80% to 90% of the single daily doses of methotrexate excreted through the kidneys within 24 hours, methotrexate is retained in the presence of impaired renal function and may increase rapidly in the serum and in the tissue cells under such conditions, thus in patients with renal impairment the health care provider may need to adjust the dose to prevent accumulation of drug.

11 STORAGE, STABILITY AND DISPOSAL

Keep in a safe place out of the reach of children.

Methotrexate Injection USP (preservative-free) and Methotrexate Injection USP (Pharmacy Bulk Vial, preservative-free): store single-use vials between 15°C and 25°C. Protect from light and freezing. Discard unused portion.

Methotrexate Injection USP (with benzyl alcohol as preservative): store multidose vials between 15°C and 25°C. After the vials are punctured, the vials should be stored between 2°C and 8°C for a maximum of four weeks (30 days). Protect from light and freezing. Aseptic techniques should be used when handling punctured vials to avoid contamination.

It is recommended that the vial remains in the carton until time of use. The Methotrexate Injection USP vial should be inspected for damage and visible signs of leaks. If there are signs of breakage or leakage from the vial, do not use. Incinerate the unopened package.

12 SPECIAL HANDLING INSTRUCTIONS

General: Individuals who have contact with anti-cancer drugs, or work in areas where these drugs are used, may be exposed to these agents in air or through direct contact with contaminated objects.

Safe Handling and Disposal: Good medical practice will minimize exposure of persons involved with frequent handling of this drug as outlined below:

Handling:

Methotrexate has no vesicant properties and does not show acute toxicity on topical contact with the skin or mucous membranes. However, persons involved with handling cytotoxic drugs should avoid contact with skin and inhalation of airborne particles.

Preparation of antineoplastic solutions should be done in a vertical laminar flow hood (Biological Safety Cabinet - Class II).

Personnel preparing methotrexate solutions should wear PVC gloves, safety glasses and protective clothing such as disposable gowns and masks.

Personnel regularly involved in the preparation and handling of antineoplastics should have bi-annual blood examinations.

Disposal:

Avoid contact with skin and inhalation of airborne particles by use of PVC gloves and disposable gowns and masks.

All needles, syringes, vials and other materials for disposal which have come in contact with Methotrexate Injection USP should be segregated in plastic bags, sealed and marked as hazardous waste. Incinerate at 1000°C or higher. Sealed containers may explode if a tight seal exists.

If incineration is not available, rinse all needles, syringes, tubing and other materials for disposal which have come in contact with methotrexate solutions with water and discard in the sewer system with running water.

Rinse vials with the appropriate quantity of water with the aid of a hypodermic syringe. Withdraw the solution and discard in the sewer system with running water. Dispose of rinsed equipment and vials in a safe manner.

Cleaning: Non-disposable equipment that has come in contact with Methotrexate Injection USP may be rinsed with water and washed thoroughly with soap and water.

Spillage/Contamination: Wear gloves, mask and protective clothing. Place spilled material in an appropriate container (i.e. cardboard for broken glass) and then in a polyethylene bag; absorb remains with gauze pads or towels; wash area with water and absorb with gauze or towels again and place in bag; seal, double bag and mark as a hazardous waste. Dispose of waste by incineration or by other methods approved for hazardous materials. Personnel involved in clean up should wash with soap and water.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

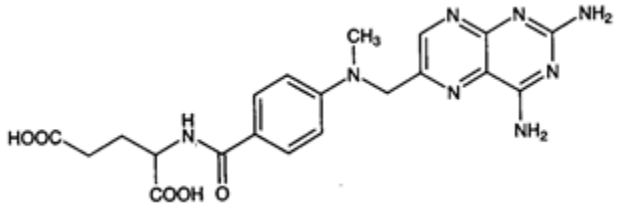
Drug Substance

Proper name: Methotrexate

Chemical name: N-[4-[[(2,4-diamino-6-pteridinyl)methylamino]benzoyl]-L-glutamic acid

Molecular formula and molecular mass: $C_{20}H_{22}N_8O_5$ (454.45 g/mol)

Structural formula:



Physicochemical properties:

Physical Form: A yellow to orange-brown crystalline powder. Contains not more than 12% water. Methotrexate is a mixture of 4-amino-10-methylfolic acid and closely related compounds and is equivalent to not less than 94.0% of $C_{20}H_{22}N_8O_5$ calculated on the anhydrous basis. The parenteral solution is prepared with the sodium salt, but potency is always expressed on the basis of the acid.

Solubility: Practically insoluble in water, chloroform, ether and alcohol, but freely soluble in dilute solutions of mineral acids, alkali hydroxides and carbonates.

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

The acute toxicity (LD_{50}) of methotrexate in mice ranges from 65 to 70 mg/kg intravenously. 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 acute oral toxicity (LD_{50}) in rats is 180 mg/kg; subcutaneously, it is 58 mg/kg. The tolerance to methotrexate in mice increased with age. 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.

Carcinogenicity:

In a 22-month carcinogenicity study in rats that received methotrexate at doses of 0.1, 0.2 and 0.4 mg/kg/day, 5 days/week every other week, little or no effect of the drug was observed. It has been concluded that methotrexate is apparently remarkably free from toxic effects when otherwise lethal doses are administered utilizing an intermittent dosage schedule providing for a recovery period of 9 days. For example, daily oral doses of 0.4 mg/kg are lethal doses both in dogs and rats when administered for up to two weeks; when 0.5 mg/kg and 0.4 mg/kg doses, respectively, were administered daily five times a week every other week for three months to dogs and ten months to rats, they were found to be essentially without toxicity.

Special Toxicology:

Methotrexate is often used clinically in doses that are nearly toxic and may cause severe depression of all blood cellular elements. Constant supervision is recommended and signs of gastrointestinal ulceration and bleeding, including bleeding from the mouth, bone marrow depression, primarily of the white cell series and alopecia are indications of toxicity. In general, toxicity is in direct proportion to dose and exposure time to methotrexate.

Toxicity of methotrexate to the bone marrow and gastrointestinal epithelium is not so much dependent on dosage as on the duration of exposure of these organs to the drug and its extracellular (plasma) concentration. For bone marrow and gastrointestinal tract, the critical time factor has been defined as about 42 hours and the critical plasma concentration as $2x10^{-8}M$. Both factors must be exceeded for toxicity to occur to these organs.

Doses of methotrexate resulting in plasma levels in excess of $2xl0^{-8}M$ circulating for greater than 42 hours will be toxic to both the bone marrow and gastrointestinal epithelium. This toxicity can be minimized by the appropriate administration of Leucovorin Calcium.

Methotrexate may be hepatotoxic, particularly at high dosage and with prolonged therapy. Liver atrophy, necrosis, cirrhosis, fatty changes and periportal fibrosis have been reported.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Methotrexate Injection USP
(meth-o-TREX-ate)

Read this carefully before you start taking **Methotrexate Injection USP** and each time you get an injection. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Methotrexate Injection USP.**

Serious Warnings and Precautions

- Methotrexate Injection USP should be prescribed by a healthcare professional who is experienced with the use of methotrexate.
- Methotrexate Injection USP dosage forms that contain benzyl alcohol as a preservative must not be used:
    - for intrathecal (into the spinal canal/fluid) or intracerebroventricular (into the cavities of the brain) infusions.
    - for high-dose treatment.
    - in newborn babies less than one month old.
- Methotrexate Injection USP can cause serious side effects that may result in death.
- **Pregnancy and breastfeeding - Female patients:**
    - Methotrexate Injection USP can harm your unborn baby, cause birth defects or cause you to lose the pregnancy.
    - Do not use Methotrexate Injection USP if you are pregnant, think you are pregnant or are planning to get pregnant during or after your treatment. If you want to get pregnant, talk to your healthcare professional.
    - If you are able to get pregnant, you:
        - will have a pregnancy test done before starting Methotrexate Injection USP. The result of this test must be negative. Pregnancy tests may be repeated during your treatment, especially if you miss using your birth control.
        - must use effective birth control during your treatment and for 6 months to 1 year after your last dose.
    - Avoid becoming pregnant while you are using Methotrexate Injection USP.
    - Tell your healthcare professional right away if you get pregnant or think you are pregnant during your treatment.
    - Methotrexate Injection USP passes into breastmilk. Do not breastfeed while you are using Methotrexate Injection USP. If you are currently breastfeeding, stop before you start Methotrexate Injection USP.
- **Pregnancy - Male patients:**
    - Do not father a child while you are using Methotrexate Injection USP.
    - Use effective birth control during your treatment and for at least 6 months to 1 year after your last dose. Female sexual partners should also use effective birth control.
    - If, during your treatment, your female sexual partner becomes pregnant or thinks she may be pregnant, tell your healthcare professional right away.
    - You should not donate sperm during treatment for at least 6 months to 1 year after your last dose.

What is Methotrexate Injection USP used for?

Methotrexate Injection USP is used in high doses to treat certain types of cancers, including breast cancer, Non-Hodgkin's lymphoma and leukemia.

Methotrexate Injection USP is used at lower doses to treat adults with the severe disabling conditions listed below when other treatments do not work. This means the conditions prevent the patient from carrying out their regular activities.

- Rheumatoid arthritis (joint inflammation caused by the immune system)
- Psoriasis (a chronic skin disease)
- Psoriatic arthritis (a kind of joint inflammation that affects people with psoriasis)
- Ankylosing spondylitis (inflammation in the joints and ligaments of the spine)
- Reactive arthritis (inflammation that can happen after another illness)
- Enteropathic arthritis (arthritis that happens in people who have inflammatory bowel disease, IBD)

How does Methotrexate Injection USP work?

Methotrexate Injection USP works by blocking an enzyme process in cancer cells so that they cannot grow. Methotrexate Injection USP also reduces the activity of the immune system (the body's own defence mechanism). It is used to modify and slow the worsening of psoriasis, rheumatoid arthritis and other disabling conditions. It will not cure them. Some normal cells in the body may be affected as well.

What are the ingredients in Methotrexate Injection USP?

Medicinal ingredients: methotrexate (as methotrexate sodium)
Non-medicinal ingredients: benzyl alcohol (as preservative), hydrochloric acid, sodium chloride, sodium hydroxide and water for injection

Methotrexate Injection USP comes in the following dosage forms:

Sterile solution:
<u>10 mg / mL</u>
20 mg / 2 mL (no preservative) as a single-use vial

<u>25 mg / mL</u>
50 mg / 2 mL (no preservative) as a single-use vial
50 mg / 2 mL (with preservative) as a multidose vial
500 mg / 20 mL (with preservative) as a multidose vial

Do not use Methotrexate Injection USP if:

- you are allergic to methotrexate, any of the non-medicinal ingredients, or any component of the container (see **What are the ingredients in Methotrexate for Injection, USP?**)
- you have severe kidney problems, kidney failure, or are on dialysis
- you are sexually-active, pregnant or planning to get pregnant. Both male and female patients must use effective birth control methods all the time while taking Methotrexate Injection USP and for a few months after the last dose.
- you are breastfeeding
- you have psoriasis or rheumatoid arthritis and the following:
    - suffer from alcoholism (drink excessive alcohol), or alcoholic liver disease or other severe liver disease
    - your immune system does not work as well as it should (immunodeficiency)

- blood or bone marrow problems:
    - low level of cells in the bone marrow (bone marrow hypoplasia)
    - low level of platelets (thrombocytopenia)
    - low red blood cells (anemia)
    - low white blood cells (neutropenia, leukopenia)
- you are going to receive a general anesthetic called nitrous oxide. It is also known as laughing gas.

Methotrexate Injection USP dosage forms that contain benzyl alcohol as a preservative must not be used:

- for intrathecal (into the spinal canal/fluid) or intracerebroventricular (into the cavities of the brain) infusions.
- for high-dose treatment.
- in newborn babies less than one month old.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Methotrexate Injection USP. **Talk about any health conditions or problems you may have, including if you:**

- have kidney problems. Your healthcare professional may want you to drink extra fluids so that you will have more urine to pass. This will help Methotrexate Injection USP to pass from your body.
- are dehydrated or experience a lot of vomiting, diarrhea, or sweating
- have or have had liver problems, including hepatitis B or hepatitis C infection
- have lung problems
- have problems with your immune system, or active infections
- have problems with your bone marrow
- have previously had radiation treatment to a large area of your body
- have gastrointestinal problems such as mouth sores or inflammation, peptic ulcer disease or ulcerative colitis (inflammatory bowel disease)
- have skin problems
- have a neurologic disorder
- drink alcohol
- have previously been treated with cisplatin
- have aciduria, a condition where uric acid builds up in the blood
- are experiencing weakness (debility)
- have fluid on your lungs (pleural effusion) or in your abdomen (ascites)
- are over 65 years of age. This is because side effects may be more likely.
- recently received or are going to receive a vaccine
- are obese
- have diabetes

Other warnings you should know about:

Sun and UV light exposure: Some patients who use Methotrexate Injection USP may become more sensitive to sunlight than they normally are. Avoid too much sun exposure and do not use a sunlamp until you see how you react to the sun, especially if you tend to burn easily. If you have been treated with radiation before, you may develop a reaction rash or sunburn to that area while using Methotrexate Injection USP. As well, your psoriasis sores can become worse if you are exposed to UV-rays during your treatment.

Serious blood and bone marrow problems: Methotrexate Injection USP can cause blood and bone marrow problems, which can increase your chance of getting infections and affect how your blood clots, which may lead to bleeding. To reduce the risk of infection or bleeding, you should:

- Avoid people with infections. Check with your healthcare professional right away if you think you are getting an infection or if you get a fever or chills, cough or hoarseness, lower back or side pain, or painful or difficult urination.
- Avoid anyone who has had the oral polio vaccine for at least 6 weeks. Do not get close to them or stay in the same room as them for very long. If this is not possible, wear a mask over your nose and mouth.
- Check with your healthcare professional right away if you notice any abnormal bleeding or bruising; black, tarry stools; blood in urine or stools; or red spots on your skin.
- Be careful when using a regular toothbrush, dental floss, or toothpick. Check with your healthcare professional before having any dental work done.
- Do not touch your eyes or the inside of your nose unless you have just washed your hands.
- Be careful not to cut yourself when you are using sharp objects such as scissors or a razor.
- Avoid contact sports or other situations where bruising or injury can happen.

Serious lung problems: Methotrexate Injection USP can cause sudden bleeding in the lungs. This is called **Pulmonary alveolar haemorrhage**. If you suddenly spit or cough up blood you must go to the hospital right away. You will need emergency care. This occurs in patients with some existing health problems. Some examples are rheumatic disorder (pain in your joints) or vasculitis (swelling in an artery or vein).

Progressive Multifocal Leukoencephalopathy (PML): Methotrexate Injection USP can cause a rare brain infection called PML.

Driving and operating machines: Methotrexate Injection USP can cause fatigue and dizziness. Before you drive or do tasks that require special attention, wait until you know how you respond to this medicine.

Fertility: Methotrexate Injection USP may affect your ability to have a child in the future (fertility).

- Females may have abnormal periods or have no period at all. Methotrexate Injection USP can affect egg production.
- Males may have a low sperm count. The sperm may also have changes in their DNA.
- These changes can happen during treatment and for a short period after your last dose.

Check-ups and testing: You will have regular visits with your healthcare professional before, during and at the end of your treatment. They will do blood and urine tests to check your liver and kidney health, do liver biopsies, lung tests and/or chest x-rays. Your healthcare professional will decide when to do these tests and will interpret the results.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions
Do not take Methotrexate Injection USP if you are going to receive a general anesthetic called nitrous oxide. It is also known as laughing gas.

The following may interact with Methotrexate Injection USP:

- medicines to reduce pain, fever or inflammation called Non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid (ASA), phenylbutazone and other pain killers
- certain Disease Modifying Antirheumatic drugs (DMARDs), such as gold taken by mouth or injection, penicillamine, hydroxychloroquine, sulfasalazine, leflunomide, azathioprine
- phenytoin, a medicine used to treat seizures
- probenecid, a medicine used to treat gout
- medicines used to treat bacterial and fungal infections including penicillins, tetracycline, vancomycin, nystatin, neomycin, trimethoprim/ sulfamethoxazole, ciprofloxacin, pristinamycin, chloramphenicol, amphotericin B, kanamycin, polymyxin B, sulfonamides
- theophylline, a medicine used to treat asthma
- the vitamin folic acid or vitamin preparations that contain folic acid
- medicines used to treat cancer including cytarabine, mercaptopurine, L-asparaginase, folinic acid and radiation therapy
- medicines used to treat acid related stomach problems called proton pump inhibitors (PPIs) including omeprazole, esomeprazole, and pantoprazole
- pyrimethamine, a medicine used to treat parasitic infections
- amiodarone, a medicine used to treat irregular heart beat
- medicines used to treat diabetes called sulfonylureas
- packed red blood cells, used for blood transfusions
- Psoralen Plus Ultraviolet Light (PUVA) therapy, a type of ultraviolet light treatment for severe skin conditions
- medicines called diuretics or “water pills” used to lower blood pressure and decrease swelling including triamterene
- some vaccines
- azathioprine, a medicine used to prevent transplant organ rejection
- aminobenzoic acid, a medicine used to treat Peyronie’s disease
- medicines used to treat acne called retinoids

Do not drink alcohol during your treatment with Methotrexate Injection USP. Alcohol can increase the chance of liver problems.

Tell any healthcare professional that is treating you that you are taking Methotrexate Injection USP.

How to take Methotrexate Injection USP:

Methotrexate Injection USP will be given to you by a healthcare professional in a healthcare setting.

- Do not take more or less of it, and do not take it more often than your healthcare professional has prescribed. The exact amount of medicine you need has been carefully worked out. Taking too much may increase the chance of side effects, while taking too little may not improve your condition.
- In most cases, Methotrexate Injection USP is taken once weekly on the same day of the week.
- In some cases, your healthcare professional may tell you to take Methotrexate Injection USP every 12 hours for 3 doses. You should only do this once a week. Do not take more than 3 doses each week.
- Methotrexate Injection USP should never be taken every day of the week when used to treat psoriasis, rheumatoid arthritis or in most cases of cancer.

- Taking Methotrexate Injection USP daily, or in a dose larger than prescribed can result in serious side effects, often requiring hospitalization, and sometimes resulting in death. Taking even small doses of Methotrexate Injection USP daily for less than a week can result in serious side effects, including death.
- Select a day of the week when you are most likely to remember to take Methotrexate Injection USP, and take it on that same day each week.
- Each time you refill your prescription, check to see whether the dose you need to take has changed.

Methotrexate Injection USP is often given together with certain other medicines. If you are using a combination of medicines, make sure that you take each one at the proper time and do not mix them. Ask your healthcare professional to help you plan a way to remember to take your medicines at the right times.

While you are using Methotrexate Injection USP, your healthcare professional may want you to drink extra fluids so that you will pass more urine. This will help the medicine to pass from your body, and will prevent kidney problems.

Usual dose:

The dose of Methotrexate Injection USP will be different for different patients. Your healthcare professional will tell you how much to take. Your dose will depend on:

- what the medicine is being used for
- your weight
- if you are taking other medicines

Your healthcare professional may start you on a lower dose, may change your dose, stop your treatment for a period of time or recommend that you stop treatment completely. This may happen if:

- you have kidney problems
- you are elderly
- you experience certain side effects
- your condition gets worse

Overdose:

If you take too much Methotrexate Injection USP you might get mouth ulcers, feel tired or weak, or experience bleeding, nausea, vomiting, diarrhea, skin rash or fever.

If you think you, or a person you are caring for, have taken too much Methotrexate Injection USP, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you missed a scheduled dose, contact your healthcare professional for instructions.

What are possible side effects from using Methotrexate Injection USP?

These are not all the possible side effects you may have when taking Methotrexate Injection USP. If you experience any side effects not listed here, tell your healthcare professional.

Methotrexate Injection USP might cause other unwanted effects that may not occur until months or years after the medicine is used. These delayed effects may include certain types of cancer, such as leukemia. Discuss these possible side effects with your healthcare professional.

Side effects may include:

- nausea, stomach pain
- loss of appetite
- weight loss
- hoarseness
- dizziness
- headaches
- hair loss
- mood changes
- confusion
- ringing in the ears
- sore eyes, blurred vision
- skin rashes, pin-point red spots on the skin, reddening or whitening of the skin, acne, boils
- fatigue, drowsiness, weakness
- chills and fever
- impotence, loss of interest in sex
- painful muscles and joints
- swelling in areas of the body that do not involve the injection sites, including vagina

Methotrexate Injection USP commonly causes nausea and vomiting. Even if you begin to feel ill, do not stop using this medicine without first checking with your healthcare professional. Talk to your healthcare professional for ways to manage these side effects.

Serious side effects, and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Gastrointestinal problems: diarrhea, vomiting, dehydration, abdominal pain, mouth ulcers			√
Infections: sore throat, fever, chills, swelling of lymph nodes/glands		√	
Lung problems including lung damage and Pneumonitis and Pneumonia (inflammation of the lungs): persistent dry, non-productive cough, shortness of breath, fever, chest pain, sweating, shaking chills		√	
LESS COMMON			

Serious side effects, and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Pericarditis, Pericardial effusion (inflammation of the lining of the heart or build up of fluid around the heart): chest pain or pressure, sharp, stabbing chest pain that gets worse when you cough, swallow, breathe deeply or lie flat, shortness of breath			√
Blood problems (low white or red blood cells or platelets): shortness of breath, weakness, frequent infections, cold sores, pale skin, rapid heart rate, fatigue, fever, heavy bleeding or bleeding for longer that usual if you hurt yourself, bruising easily			√
RARE			
Allergic reaction: skin rash, itching, chest tightness, wheezing, dizziness, hives, faintness, rapid heartbeat, shortness of breath, and/or a swollen face, lips or tongue			√
Gastrointestinal problems: blood in stool, bloody vomit, black tarry stools			√
Kidney problems: pain or difficulty urinating, lower back or side pain, blood in urine, changes in how often or how much you urinate, swelling of the hands, ankles or feet, nausea, vomiting		√	
Liver problems (including hepatitis): yellowing of your eyes or skin, itching, right upper stomach pain or swelling, nausea or vomiting, dark urine, pale stool			√
UNKNOWN			
Nervous system problems including Leukoencephalopathy /Encephalitis / Encephalopathy (brain disorders): abnormal			√

Serious side effects, and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
reflexes, paralysis, abnormal behaviours, loss of consciousness, headache, weakness or unable to move a muscle or group of muscles on one or both sides of the body, stroke-like episodes, difficulty speaking, coma, disorientation, changes or reduced senses of touch or temperature, numbness or feelings of prickling (pins and needles), short term blindness, seizures, vomiting, loss of speech and sight, changes in thinking, memory and orientation, personality changes			
Drug reaction with eosinophilia and systemic symptoms (DRESS) (serious skin reaction that may affect one or more organ): fever, severe rash, peeling skin, swollen lymph nodes/glands, flu-like feeling, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often less urine			√
Pulmonary alveolar hemorrhage (bleeding in the lungs): suddenly spit or cough up blood			√
Reactions at the injection site: blistering, itching, pain, redness, severe skin damage, tenderness, warmth in the area around the injection	√		
Sepsis and septic shock (blood infections): fever or dizziness, chills, high or very low body temperature, little or no urine, low blood pressure, rapid breathing and heart beat		√	
Convulsions: seizure, shaking or fits			√

Serious side effects, and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Diabetes (condition where the body does not produce enough insulin): excessive eating, thirst, and urination; unexplained weight loss, poor wound healing, infections		√	
Osteonecrosis of the jaw (tiny breaks in a bone leading to eventual collapse): broken bones, jaw pain		√	
Osteoporosis (thinning of the bones): broken bones, pain, back pain that gets worse when standing or walking		√	
Lymphoma (lymphatic system cancer): painless swelling of lymph nodes/glands, swollen tonsils, night sweats, itching, unexplained weight loss, persistent coughing/difficulty breathing or not being able to breathe		√	
Toxic Epidermal Necrolysis (TEN), Stevens Johnson syndrome (SJS), Erythema multiforme (severe skin reactions): redness, blistering and/or peeling of large areas of the skin, raised red or purple skin patches, possibly with blister or crust in the center; possibly swollen lips, mild itching or burning			√
Chemical arachnoiditis (rare pain disorder due to inflammation of a membrane surrounding the nerves of the spinal cord): headache, back pain, neck stiffness, fever		√	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue		√	
Lymphoproliferative disorders (excessive growth of white blood cells): enlarged lymph		√	

Serious side effects, and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
nodes/glands, abnormal bleeding, joint pain, bruising, diarrhea, nausea, vomiting, headache			
Reactivation of chronic infections like herpes zoster, tuberculosis, hepatitis B, hepatitis C (when a previous infection becomes active again): rash that is painful, itchy or tingling, cough, fever, weight loss, joint pain and inflammation, fatigue, loss of appetite, nausea, yellowing of the skin or whites of eyes, abdominal pain		√	
Thrombosis (blood clots): chest pain, shortness of breath, dizziness, face drooping, slurred speech, swelling, pain, arm or leg may be warm to the touch and appear red			√
Tumour lysis syndrome (the sudden, rapid death of cancer cells due to the treatment): nausea, shortness of breath, irregular heartbeat, heart rhythm disturbances, lack of urination, clouding of urine, muscle spasms or twitching, tiredness and/or joint pain, severe muscle weakness, and seizures. Metabolic disorders (kidney failure, abnormal heartbeat) and abnormal blood tests due to rapid breakdown of cancer cells			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store Methotrexate Injection USP without preservative between 15°C and 25°C and away from direct light. Avoid freezing. Discard any unused solution.

Store Methotrexate Injection USP with preservative (benzyl alcohol) between 15°C and 25°C. Once the vials have been punctured they can be stored between 2°C and 8°C for a maximum of four weeks (30 days). Protect from light and freezing. Aseptic techniques should be used when handling punctured vials to avoid contamination.

Keep vials of Methotrexate Injection USP in the carton until time of use. The Methotrexate Injection USP vial should be inspected for damage and visible signs of leaks. If there are signs of breakage or leakage from the vial, do not use.

Do not keep expired medicine or medicine that you no longer need. Be sure that any discarded medicine is out of the reach of children.

Keep out of reach and sight of children.

If you want more information about Methotrexate Injection USP

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website https://www.pfizer.ca, or by calling 1-800-463-6001

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