EMERGENCY OVERVIEW
Methotrexate is (formely Amethopterin) is an antimetabolite used in treatment of certain neoplastic
diseases, severe psoriasis and adult rheumatoid arthritis.

Section 1. Identification

Identification of the product

Product Name: Methotrexate Tablet USP
Formula: \( \text{C}_{20}\text{H}_{20}\text{N}_{8}\text{O}_{5}\text{Na}_{2} \)
Molecular weight: 454.45
Chemical Name: \( N\{4\{2,4\text{diamino6pteridinyl}methyl\text{methylamino}\text{benzoyl}\}\text{Lglutamic acid} \)

Manufacturer / supplier identification

Company: Cadila Healthcare Ltd., Matoda, India
Address: Cadila Healthcare Limited, Plot No- 1A/1 & 2, Pharmez Special Economic Zone, Sarkhej- Bavla N.H. No. 8A, Near Village Matoda, Tal. Sanand, Dist. Ahmedabad-382 213, India
Contact for information: Tel: +91-79-26868100 Fax: +91-79-26868533
Emergency Telephone No. Tel: +91-79-26868101
Recommended use / Therapeutic Category

**Neoplastic Diseases**
Methotrexate tablets, USP are indicated in the treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole.
Methotrexate tablets, USP are used in maintenance therapy in combination with other chemotherapeutic agents. Methotrexate tablets, USP are used alone or in combination with other anticancer agents in the treatment of breast cancer, epidermoid cancers of the head and neck, advanced mycosis fungoides (cutaneous T cell lymphoma), and lung cancer, particularly squamous cell and small cell types. Methotrexate tablets, USP are also used in combination with other chemotherapeutic agents in the treatment of advanced stage non-Hodgkin’s lymphomas.

**Psoriasis**
Methotrexate is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation. It is important to ensure that a psoriasis “flare” is not due to an undiagnosed concomitant disease affecting immune responses.

**Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis**
Methotrexate is indicated in the management of selected adults with severe, active, rheumatoid arthritis (ACR criteria), or children with active polyarticular-course juvenile rheumatoid arthritis, who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose non-steroidal anti-inflammatory agents (NSAIDs).
Aspirin, NSAIDs, and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylates has not been fully explored. (Steroids may be reduced gradually in patients who respond to methotrexate. Combined use of methotrexate with gold, penicillamine, hydroxychloroquine, sulfasalazine, or cytotoxic agents, has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

Restriction on Use / Contraindications:
Methotrexate can cause fetal death or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant women 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. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients.
Section 2. Hazard(s) Identification

<table>
<thead>
<tr>
<th>Dose and Administration</th>
<th>Neoplastic Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral administration in tablet form is often preferred when low doses are being administered since absorption is rapid and effective serum levels are obtained.</td>
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</tbody>
</table>
| Choriocarcinoma and similar trophoblastic diseases: Methotrexate is administered orally or intramuscularly in doses of 15 to 30 mg daily for a five 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 (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 hCG is usually recommended. Before each course of the drug careful clinical assessment is essential. Cyclic combination therapy of methotrexate with other antitumor drugs has been reported as being useful. Since hydatidiform mole may precede choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended. Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate is administered in these disease states in doses similar to those recommended for choriocarcinoma. Leukemia: Acute lymphoblastic leukemia in pediatric patients 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 acute lymphoblastic leukemias. More recently corticosteroid therapy, in combination with other anti-leukemic drugs or in cyclic combinations with methotrexate included, has appeared to produce rapid and effective remissions. When used for induction, methotrexate in doses of 3.3 mg/m2 in combination with 60 mg/m2 of prednisone, given daily, produced remissions in 50% of patients treated, usually within a period of 4 to 6 weeks. Methotrexate in combination with other agents appears to be the drug of choice for securing maintenance of drug induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: Methotrexate is administered 2 times weekly either by mouth or intramuscularly in total weekly doses of 30 mg/m2. It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction 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 acute lymphoblastic leukemia. The physician should be familiar with the new advances in anti-leukemic therapy. Lymphomas: In Burkitt’s tumor, Stages I-II, methotrexate has produced prolonged remissions in some cases. Recommended dosage is 10 to 25 mg/day orally for 4 to 8 days. In Stage III, methotrexate is commonly given concomitantly with other antitumor agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods. Lymphosarcomas in Stage III may
respond to combined drug therapy with methotrexate given in doses of 0.625 to 2.5 mg/kg daily.

Mycosis Fungoides (cutaneous T cell lymphoma): Therapy with methotrexate as a single agent appears to produce clinical responses in up to 50% of patients treated. Dosage in early stages is usually 5 to 50 mg once weekly. Dose reduction or cessation is guided by patient response and hematologic monitoring. Methotrexate has also been administered twice weekly in doses ranging from 15 to 37.5 mg in patients who have responded poorly to weekly therapy.

**Psoriasis, Rheumatoid Arthritis, and Juvenile Rheumatoid Arthritis**

Adult Rheumatoid Arthritis: Recommended Starting Dosage Schedules
1. Single oral doses of 7.5 mg once weekly.
2. Divided oral dosages of 2.5 mg at 12 hour intervals for 3 doses given as a course once weekly Polyarticular-Course Juvenile Rheumatoid Arthritis: The recommended starting dose is 10 mg/m2 given once weekly.

For either adult RA or polyarticular-course JRA dosages may be adjusted gradually to achieve an optimal response. Limited experience shows a significant increase in the incidence and severity of serious toxic reactions, especially bone marrow suppression, at doses greater than 20 mg/wk in adults. Although there is experience with doses up to 30 mg/m2/wk in children, there are too few published data to assess how doses over 20 mg/m2/wk might affect the risk of serious toxicity in children. Experience does suggest, however, that children receiving 20 to 30 mg/m2/wk (0.65 to 1 mg/kg/wk) may have better absorption and fewer gastrointestinal side effects if methotrexate is administered either intramuscularly or subcutaneously.

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

The optimal duration of therapy is unknown. Limited data available from long-term studies in adults indicate that the initial clinical improvement is maintained for at least two years with continued therapy. When methotrexate is discontinued, the arthritis usually worsens within 3 to 6 weeks.

The patient should be fully informed of the risks involved and should be under constant supervision of the physician. Assessment of hematologic, hepatic, renal, and pulmonary function should be made by history, physical examination, and laboratory tests before beginning, periodically during, and before reinstituting methotrexate therapy. Appropriate steps should be taken to avoid conception during methotrexate therapy. All 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. Maximal myelosuppression usually occurs in seven to ten days.

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

Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 30 mg/week should not ordinarily be exceeded. Once optimal clinical response has been achieved, each dosage schedule should be reduced to the lowest possible amount of drug and to the longest possible rest period.
The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

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

Published clinical studies evaluating the use of methotrexate in children and adolescents (i.e. patients 2 to 16 years of age) with JRA demonstrated safety comparable to that observed in adults with rheumatoid arthritis.

**Adverse Effects**

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

Other adverse reactions that have been reported with methotrexate are listed below by organ system. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to methotrexate difficult.

Alimentary System: gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.

Blood and Lymphatic System Disorders: suppressed hematopoiesis causing anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia and/or thrombocytopenia, lymphadenopathy and lymphoproliferative disorders (including reversible). Hypogammaglobulinemia has been reported rarely.

Cardiovascular: pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

Central Nervous System: headaches, drowsiness, blurred vision, transient blindness, speech impairment including dysarthria and aphasia, hemiparesis, paresis and convulsions have also occurred following administration of methotrexate. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration, unusual cranial sensations, leukoencephalopathy, or encephalopathy.

Hepatobiliary: disorders, hepatotoxicity, acute hepatitis, chronic fibrosis and cirrhosis, decrease in serum albumin, liver enzyme elevations.

Infection: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. Pneumocystis carinii pneumonia was the most common opportunistic infection. There have also been reports of infections, pneumonia, sepsis, nocardiosis, histoplasmosis, cryptococcosis, herpes zoster, H. simplex hepatitis, and disseminated H. simplex.

Musculoskeletal System: stress fracture.

Ophthalmic: conjunctivitis, serious visual changes of unknown etiology.

Pulmonary System: respiratory fibrosis, respiratory failure, interstitial pneumonitis; deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred.

Skin: erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson Syndrome, skin necrosis, skin ulceration, and
exfoliative dermatitis.
Urogenital System: severe nephropathy or renal failure, azotemia, cystitis, hematuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal defects. Other rarer reactions related to or attributed to the use of methotrexate such as nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death, reversible lymphomas, tumor lysis syndrome, soft tissue necrosis and osteonecrosis. Anaphylactoid reactions have been reported.

**Adverse Reactions in Double-Blind Rheumatoid Arthritis Studies**
The approximate incidences of methotrexate attributed (i.e. placebo rate subtracted) adverse reactions in 12 to 18 week double-blind studies of patients (n=128) with rheumatoid arthritis treated with low-dose oral (7.5 to 15 mg/week) pulse methotrexate, are listed below. Virtually all of these patients were on concomitant non-steroidal anti-inflammatory drugs and some were also taking low dosages of corticosteroids. Hepatic histology was not examined in these short-term studies.

- Incidence greater than 10%: Elevated liver function tests 15%, nausea/vomiting 10%.
- Incidence 3% to 10%: Stomatitis, thrombocytopenia, (platelet count less than 100,000/mm³).
- Incidence 1% to 3%: Rash/pruritus/dermatitis, diarrhea, alopecia, leukopenia (WBC less than 3000/mm³), pancytopenia, dizziness.

Two other controlled trials of patients (n=680) with Rheumatoid Arthritis on 7.5 mg – 15 mg/wk oral doses showed an incidence of interstitial pneumonitis of 1%. Other less common reactions included decreased hematocrit, headache, upper respiratory infection, anorexia, arthralgias, chest pain, coughing, dysuria, eye discomfort, epistaxis, fever, infection, sweating, tinnitus, and vaginal discharge.

**Adverse Reactions in Psoriasis**
There are no recent placebo-controlled trials in patients with psoriasis. There are two literature reports (Roeningk, 1969 and Nyfors, 1978) describing large series (n=204, 248) of psoriasis patients treated with methotrexate. Dosages ranged up to 25 mg per week and treatment was administered for up to four years. With the exception of alopecia, photosensitivity, and “burning of skin lesions” (each 3% to 10%), the adverse reaction rates in these reports were very similar to those in the rheumatoid arthritis studies. Rarely, painful plaque erosions may appear.

**Adverse Reactions in JRA Studies**
The approximate incidences of adverse reactions reported in pediatric patients with JRA treated with oral, weekly doses of methotrexate (5 to 20 mg/m²/wk or 0.1 to 0.65 mg/kg/wk) were as follows (virtually all patients were receiving concomitant non-steroidal anti-inflammatory drugs, and some also were taking low doses of corticosteroids): elevated liver function tests, 14%; gastrointestinal reactions (e.g. nausea, vomiting, diarrhea), 11%; stomatitis, 2%; leukopenia, 2%; headache, 1.2%; alopecia, 0.5%; dizziness, 0.2%; and rash, 0.2%. Although there is experience with dosing up to 30 mg/m²/wk in JRA, the published data for doses above 20 mg/m²/wk are too limited to provide reliable estimates of adverse reaction rates.
Over Dose Effect

Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered 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 alkalization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Generally speaking, neither hemodialysis nor peritoneal dialysis have been shown to improve methotrexate elimination. However, effective clearance of methotrexate has been reported with acute, intermittent hemodialysis using a high flux dialyzer (Wall, SM et al: Am J Kidney Dis 28(6): 846-854, 1996).

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

Reports of oral overdose often indicate accidental daily administration instead of weekly (single or divided doses). Symptoms commonly reported following oral overdose include those symptoms and signs reported at pharmacologic doses, particularly hematologic and gastrointestinal reaction. For example, leukopenia, thrombocytopenia, anemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In some cases, no symptoms were reported. There have been reports of death following overdose. In these cases, events such as sepsis or septic shock, renal failure, and aplastic anemia were also reported.

Contraindications

Methotrexate can cause fetal death or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant women 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. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients. Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers.

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

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

Patients with psoriasis or rheumatoid arthritis who have preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anemia, should not receive methotrexate.

Patients with a known hypersensitivity to methotrexate should not receive the drug.
Drug Interactions

Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity.

Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity.

Despite the potential interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of constant dosage regimens of NSAIDs, without apparent problems. It should be appreciated, however, that the doses used in rheumatoid arthritis (7.5 to 20 mg/week) are somewhat lower than those used in psoriasis and that larger doses could lead to unexpected toxicity.

Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain drugs, such as salicylates, phenyl butazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid; use of methotrexate with this drug should be carefully monitored.

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

Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with methotrexate. Use of methotrexate with penicillins should be carefully monitored.

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

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

Certain side effects such as mouth sores may be reduced by folate supplementation with methotrexate.

Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by an additive antifolate effect.
Pregnancy Comments
Methotrexate can cause fetal death or teratogenic effects when administered to a pregnant woman. Methotrexate is contraindicated in pregnant women 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. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients.

Pregnancy Category
Pregnancy Category X.

Section 3. Composition / information on ingredients

<table>
<thead>
<tr>
<th>Component</th>
<th>Exposure Limit</th>
<th>CAS No.</th>
</tr>
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<tbody>
<tr>
<td>Principle Component:</td>
<td></td>
<td></td>
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<tr>
<td>Methotrexate Disodium (USDMR FERTMON)</td>
<td>2 µg/m³</td>
<td>59 – 05 – 2</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Inactive Ingredients:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcrystalline cellulose 102 (COMPRECEL M102D+) (MTNGTAT )</td>
</tr>
<tr>
<td>Lactose Monohydrate (PHARMATOSE 200 M, DMV)</td>
</tr>
<tr>
<td>Anhydrous Lactose (SUPERTAB 21AN)</td>
</tr>
<tr>
<td>Pregelatinized Starch 1500LM(COLORC ON)</td>
</tr>
<tr>
<td>Anhydrous Lactose (SUPER</td>
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</tbody>
</table>
Section 4. First-aid measures

General
- **After inhalation:** Supply fresh air; consult doctor in case of complaints.
- **After skin contact:** Immediately wash with water and soap and rinse thoroughly.
- **After eye contact:** Rinse opened eye for several minutes under running water.
- **After swallowing:** Rinse mouth. Do not induce vomiting.
- **Information for doctor:**
  - **Most important symptoms and effects, both acute and delayed**: No further relevant information available.
  - **Indication of any immediate medical attention and special treatment needed**: No further relevant information available.

Overdose Treatment
If take too much methotrexate call doctor or go to nearest emergency room. To take a medicine called an antidote as soon as possible.

Section 5. Fire-fighting measures

**Extinguishing media**
- **Suitable extinguishing agents:**
  - CO₂, powder or water spray. Fight larger fires with water spray or alcohol resistant foam.
- **Special hazards arising from the substance or mixture**
  - Formation of toxic gases is possible during heating or in case of fire.
- **Advice for firefighters**
  - **Protective equipment:** Wear self-contained respiratory protective device.

**Specific hazards arising from the chemical**
- CO₂, Powder or water spray.
- Fight larger fires water spray or alcohol resistant foam.
- Formation of toxic gases is possible during heating or in case of fire.

**Special protective equipment and precautions for firefighters**
- Wear self-contained respiratory protective device.
Specific methods
Use standard firefighting procedures and consider the hazards of other involved materials.

General fire hazards
No unusual fire or explosion hazards noted

Section 6. Accidental Release Measures

Personal precautions, protective equipment and emergency procedures
Avoid formation of dust.

Environmental
Do not allow to enter sewers/surface or ground water.

Methods and material for containment and cleaning up:

Waste treatment methods
· Recommendation
Must not be disposed of together with household garbage. Do not allow product to reach sewage system.

· European waste catalogue
Waste disposal key numbers from EWC have to be assigned depending on origin and processing.

· Uncleaned packaging:
· Recommendation: Dispose of in accordance with national regulations.

Section 7. Handling and Storage

Storage:
Store methotrexate at room temperature between 68’to 77’ F (20’to 25’ C).
Keep methotrexate away from light.
Keep methotrexate and all medicines out of the reach of children.

Section 8. Exposure controls / personal protection

Respiratory Protection
Use a NIOSH/MSHA approved respirator if there is a risk of exposure to dust/fume at levels exceeding the exposure limits. No personal respiratory protective equipment normally required.

Skin protection
For prolonged or repeated skin contact use suitable protective gloves.

Eye/face protection
If contact is likely, safety glasses with side shields are recommended.

Protective Clothing
Protective clothing is not normally necessary, however it is good practice to use apron.
Biological limit values
No biological exposure limits noted for the ingredient(s).

Exposure guidelines
General ventilation normally adequate.

Thermal hazards
Wear appropriate thermal protective clothing, when necessary.

General hygiene considerations
Keep away from foodstuffs, beverages and feed. Wash hands before breaks and at the end of work. Routinely wash work clothing and protective equipment to remove contaminants. For advice on suitable monitoring methods, seek guidance from a qualified environment, health and safety professional.

Engineering controls
Engineering controls should be used as the primary means to control exposures. General room ventilation is adequate unless the process generates dust, mist or fumes. Keep airborne contamination levels below the exposure limits listed above in this section.

Section 9. Physical and chemical properties

Appearance
Yellow, round, uncoated tablets, with debossing “L2” on one side and scoring on other side.

Solubility
Freely soluble in water

Section 10. Stability and Reactivity

Conditions to avoid Stable
Contact with incompatible materials.

Reactivity
The product is stable and non-reactive under normal conditions of use, storage and transport.

Chemical stability
Material is stable under normal conditions.

Hazardous reactions
No dangerous reaction known under conditions of normal use.

Decomposition products
None known. Formation of toxic gases is possible during Heating or in case of fire.

Incompatible materials
Strong Oxidizing agent
Section 11. Toxicological information

General
Handling of formulated product is not expected to cause any toxicological affects. The data pertains to the ingredient in formulations, rather than this specie formulation.

Ingestion
Health injuries are not known or expected under normal use. Expected to be a low ingestion hazard. However, ingestion is not likely to be a primary route of occupational exposure.

Other

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Related to the physical, chemical and Toxicological characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspiration Hazard</td>
<td>None anticipated from normal handling of this product.</td>
</tr>
<tr>
<td>Dermal Irritation/ Corrosion</td>
<td>None anticipated from normal handling of this product. Based on clinical use, inadvertent contact of this product with skin may produce mild irritation and redness. Ocular Irritation/ Corrosion</td>
</tr>
</tbody>
</table>
| Sensitization | None anticipated from normal handling of this product. In clinical use, hypersensitivity reactions to methotrexate are reported to be rare. Reproductive Effects Folic acid antagonists such as methotrexate interfere with embryogenesis and are recognized teratogens. Embryonic mesenchymal tissue is sensitive to these compounds. In animals, methotrexate produced embryotoxic and teratogenic effects at relatively low dosages, typically in the low mg/kg/day range. The lowest LOAEL for teratogenicity was 0.1 mg/kg/day in rats, the most sensitive species. Impotence has been reported in three men with rheumatoid arthritis who were treated with weekly doses of 12.5 mg methotrexate. The sexual dysfunction was reversible when the drug was discontinued. Toxic effects of methotrexate on gonadal function are inferred from studies in which this agent, along with other agents used for cancer therapy, have been associated with oligospermaia in men and amenorrea in women. At least 19 children or fetuses with a very uncommon and characteristic pattern of congenital anomalies have been born to women treated with methotrexate during the first trimester of pregnancy The most characteristic malformation induced by methotrexate is a "clover-leaf" skull with a large head, swept-back hair, low-set ears, prominent eyes, and wide nasal bridge. Limb defects and absent ossification centers have also been reported, as well as CNS abnormalities including anencephaly, hydrocephaly, and meningomyelocele. Mutagenicity Methotrexate was negative for mutagenicity in several bacterial assays (Ames test, E. coli), but was clastogenic in a mouse lymphoma cell assay and an SCE assay in human lymphocytes. Carcinogenicity Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Non-Hodgkin's lymphoma and other tumors have been reported in patients receiving low-dose oral methotrexate. However, there have been instances of malignant lymphoma arising during treatment with low-dose oral methotrexate, which have regressed completely following withdrawal of methotrexate, without requiring active anti-lymphoma treatment. Target Organ Effects This material should be
considered irritating to the skin, eyes and respiratory tract. Based on clinical use, possible target organs may include the bone marrow, gastrointestinal system, central nervous system, cardiovascular system, lungs, liver, kidney, skin, gonads, and the foetus.

**Information on toxicological effects**

**Acute toxicity**  
Active Ingredient: LD50 Oral (rat): 135 mg/kg LD50 Oral (mouse): 146 mg/kg

**Section 12. Ecological information**  
Not determined for the product.

**Section 13. Disposal Consideration**  
Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

**Section 14. Transport Information**  
The product is not hazardous when shipping via air (IATA), ground (DOT), or sea (IMDG).

**Section 15. Regulatory Information**  
Generic Medicine. Approved by USFDA & the ANDA Number is 207812

**Section 16. Other information**  
None

**Date of issue: 30/01/17**  
**Supersedes edition: New Edition**

The information contained herein is based on the state of our knowledge. It characterizes the product with regard to the appropriate safety precautions. It does not represent a guarantee of the properties of the product.