child during and for six months after treatment. Methotrexate is reported to be genotoxic and has caused increased number of abnormal and immobile spermatozoa.
Since treatment with methotrexate can lead to severe and possibly irreversible disorders in spermatogenesis, men should seek advice about the possibility of sperm preservation before starting the therapy. The possible risks of effects on reproduction should be discussed with patients of childbearing potential.
Use in pregnancy - Category D
Use of methotrexate is contraindicated throughout pregnancy. Methotrexate has been shown to be teratogenic. Methotrexate has caused embryo toxicity, abortion, foetal death and/or congenital abnormalities when administered to pregnant women.
Methotrexate is not recommended in women of childbearing potential unless there is appropriate medical evidence that the benefits are expected to outweigh the considered risks.
Women of childbearing potential should not be started on methotrexate until existing pregnancy is excluded with certainty, e.g. by pregnancy test prior to initiating therapy. Both male and female patients should be fully counselled on the serious risk to the foetus if pregnancy occurs whilst undergoing treatment.
Pregnancy should be avoided and reliable effective contraception used if either partner is receiving methotrexate, during and for a minimum of six months after therapy has ceased, although the optimal time interval between the cessation of methotrexate treatment of either partner, and pregnancy, has not been clearly established.
Teratogenicity: There is evidence of a teratogenic risk in humans (craniofacial, cardiovascular and extremital malformations) and in several animal species.
Use in lactation: Methotrexate passes into breast milk and is contraindicated during breastfeeding. Because of the potential for serious adverse reactions from methotrexate in breast fed infants, it is contraindicated in nursing mothers.

A14. SIDE EFFECTS
The most common adverse reactions include ulcerative stomatitis, leukopenia, nausea and abdominal distress. Although very rare, anaphylactic reactions to methotrexate have occurred. Others reported are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection. In general, the incidence and severity of side effects are considered to be dose-related. Adverse reactions as reported for the various systems are as follows:
Skin: Severe, occasionally fatal, dermatologic reactions including erythema multiforme, Stevens-Johnson syndrome, skin necrosis, exfoliative dermatitis, epidermal necrolysis. Erythematous rashes, pruritus, urticaria, dermatitis, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis. Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Skin ulceration in psoriatic patients and rarely painful erosion of psoriatic plaques have been reported. The recall phenomenon has been reported in both radiation and solar damaged skin.
Blood: Bone marrow depression, leukopenia, thrombocytopenia, anaemia hypogammaglobulinaemia, haemorrhage from various sites, septicaemia, lymphoproliferative disorders (frequency very rare).
Alimentary System: Gingivitis, pharyngitis, stomatitis, mucostitis, anorexia, vomiting, diarrhoea, haematemesis, melaena, gastrointestinal ulceration and bleeding, pancreatitis, enteritis, hepatic toxicity resulting in active liver atrophy, necrosis, fatty metamorphosis, periportal fibrosis, or hepatic cirrhosis. In rare cases the effect of methotrexate on the intestinal mucosa has led to malabsorption or toxic megacolon.
Hepatic: Hepatic toxicity resulting in significant elevations of liver enzymes, acute liver atrophy, necrosis, fatty metamorphosis, hepatitis, periportal fibrosis, or cirrhosis or death may occur, usually following chronic administration.
Urogenital System: Renal failure, azotaemia, cystitis, haematuria, defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, infertility, abortion, foetal defects, severe nephropathy. Vaginitis, vaginal ulcers, cystitis, haematuria and nephropathy have also been reported.
Pulmonary System: Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported (Special warnings and special precautions for use). Acute pulmonary oedema has also been reported after oral and intrathecal use. Pulmonary fibrosis is rare. A syndrome consisting of pleuritic pain and pleural thickening has been reported following high doses. Frequency Not Known: Pulmonary alveolar haemorrhage*
*(has been reported for methotrexate used in rheumatologic and related indications).
Central Nervous System: Headaches, drowsiness, blurred vision, aphasia, cognitive disorder, hemiparesis and convulsions have occurred possibly related to haemorrhage or to complications from intraarterial catheterization. Convulsion, paresis, Guillain-Barre syndrome and increased cerebrospinal fluid pressure have followed intrathecal administration.
Other reactions related to, or attributed to the use of methotrexate such as pneumonitis, metabolic changes, precipitation of diabetes, osteoporotic effects, abnormal changes in tissue cells and even sudden death have been

reported.
There have been reports of leukoencephalopathy following intravenous methotrexate in high doses, or low doses following cranial-spinal radiation.
Cardiac disorders: Pericarditis, pericardial effusion
Ear disorders: Tinnitus
Eye disorders: Conjunctivitis
Infections and infestations: Opportunistic infections (sometimes fatal e.g. fatal sepsis) have also been reported in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases,
Pneumocystis carinii pneumonia being the most common. Other reported infections include, pneumonia, nocardiosis, histoplasmosis, cryptococcosis, Herpes Zoster, Herpes Simplex, hepatitis and cytomegalovirus infection, including cytomegaloviral pneumonia.
Musculoskeletal and connective tissue disorders: Arthralgia/myalgia, Osteonecrosis of jaw (secondary to lymphoproliferative disorders) – frequency unknown.
Psychiatric disorders: Mood altered
Vascular disorder: Vasculitis, hypotension, thromboembolic events (e.g. thrombophlebitis, pulmonary embolism, arterial, cerebral, deep vein or retinal vein thrombosis).
Adverse reactions following intrathecal methotrexate are generally classified into three groups, acute, subacute, and chronic. The acute form is a chemical arachnoiditis manifested by headache, back or shoulder pain, nuchal rigidity, and fever. The subacute form may include paresis, usually transient, paraplegia, nerve palsies, and cerebellar dysfunction. The chronic form is a leukoencephalopathy manifested by irritability, confusion, ataxia, spasticity, occasionally convulsions, dementia, somnolence, coma, and rarely, death. There is evidence that the combined use of cranial radiation and intrathecal methotrexate increases the incidence of leukoencephalopathy.
Additional reactions related to or attributed to the use of methotrexate such as osteoporosis, abnormal (usually 'megaloblastic') red cell morphology, precipitation of diabetes, other metabolic changes, and sudden death have been reported.

A15. SYMPTOMS AND TREATMENT OF OVERDOSE
Cases of overdose have been reported, sometimes fatal, due to erroneous daily intake instead of weekly intake of oral methotrexate In these cases, symptoms that have been commonly reported are hematological and gastrointestinal reactions.
Calcium folinate (calcium leucovorin) is a potent agent for neutralizing the immediate toxic effects of methotrexate on the haematopoietic system. Where large doses or overdoses are given, calcium folinate may be administered by intravenous infusion in doses up to 75 mg within 12 hours, followed by 12 mg intramuscularly every 6 hours for 4 doses. Where average doses of methotrexate appear to have an adverse effect 6-12 mg of calcium folinate may be given intramuscularly every 6 hours for 4 doses. In general, where overdosage is suspected, the dose of calcium folinate should be equal to or higher than, the offending dose of methotrexate and should be administered as soon as possible; preferably within the first hour and certainly within 4 hours after which it may not be effective.
Other supporting therapy such as blood transfusion and renal dialysis may be required. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high flux dialyser.

A16. EFFECTS ON ABILITY TO DRIVE AND USE MACHINE
Central nervous system symptoms, such as fatigue and dizziness can occur during treatment with methotrexate which may have minor or moderate influence on the ability to drive and use machines.

A17. PRECLINICAL SAFETY DATA
Not applicable

A18. INSTRUCTION FOR USE
Methotrexate may be administered by intramuscular, intravenous or intrathecal routes.
"For Intravenous injection, Methotrexate Injection should be diluted in dextrose 5% solution or sodium chloride 0.9% solution"
METHOTREXATE INJECTION 100 MG/ML SHOULD BE USED INTRAVENOUS INFUSION ONLY. IT SHOULD NOT BE USED INTRATHECALLY AS THE SOLUTION IS HYPERTONIC.
Methotrexate 100 mg/ml solution for injection is a hypertonic presentation and therefore not suitable for intrathecal use, non-isotonic solutions of methotrexate injection should not be administered intrathecally
For intrathecal injection, Methotrexate Injection should be diluted to a strength of 1 mg/mL with an appropriate preservative-free medium such as 0.9% Sodium Chloride Injection.
For conversion of mg/kg bodyweight to mg/m^2 of body surface area or the reverse, a ratio of 1:30 is given as a guideline. The conversion factor varies between 1:20 and 1:40 depending on age and body build.
As with all antineoplastic agents, trained personnel should prepare Methotrexate Injection. This should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). Protective gown, mask, gloves and appropriate eye protection should be worn when handling methotrexate. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed thoroughly with soap and water. It is

recommended that pregnant personnel not handle cytotoxic agents such as methotrexate. Luer-Lock fitting syringes are recommended. Large bore needles are recommended to minimise pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation.
Items used to prepare Methotrexate Injection, or articles associated with body waste, should be disposed of by placing in a double sealed polythene bag and incinerating at 1100°C.
Incompatibilities: Methotrexate has been reported to be incompatible with cytarabine, fluorouracil and prednisolone.
Spills and disposal: If spills occur, restrict access to the affected area. Wear two pairs of gloves (latex rubber), a respirator mask, a protective gown and safety glasses. Limit the spread of the spill by covering with absorbent material such as absorbent towel or adsorbent granules. Collect up the towel of absorbent/adsorbent material and other debris from spill and place in a leak proof plastic container and label accordingly. Cytotoxic waste should be regarded as hazardous or toxic and clearly labelled 'CYTOTOXIC WASTE FOR INCINERATION AT 1100°C'. Waste material should be incinerated at 1100°C for at least 1 second. Cleanse the remaining spill area with copious amounts of water.

A19. STORAGE CONDITION
Store below 30°C. Protect from light.
Chemical and physical in-use stability has been demonstrated in dextrose 5% and sodium chloride 0.9% infusion solutions for 24 hours at room temperature (20-25) when protected from light. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. For single use only. Discard unused portion

A20. Shelf Life
Unopened vial
24 months
Methotrexate Solution for Injection have been assigned 24 months' shelf life when stored below 30°C in the original package in order to protect from light.

Reconstituted solution:
After dilution: Chemical and physical in-use stability has been demonstrated in dextrose 5% and sodium chloride 0.9% infusion solutions for 24 hours at room temperature (20-25) when protected from light.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

A21. Therapeutic Code
ATC code: L01BA01

Nature and contents of container:
(TREXOL - Methotrexate Solution for Injection 25 mg/ml)
Methotrexate Solution for Injection 25 mg/ml is filled in 2 ml amber tubular glass vial Type-I with reinforced Non-PVC Base which are stoppered with 13 mm Grey butyl rubber stopper and tampered with 13 mm flip off seal. Each vial is packed into secondary carton along with a package insert.
(TREXOL - Methotrexate Solution for Injection 100 mg/ml)
Methotrexate Solution for Injection 100 mg/ml is filled in 5 ml amber tubular glass vial Type-I with reinforced Non-PVC Base which are stoppered with 20 mm Bromo butyl rubber stopper and tampered with 20 mm flip off seal. Each vial is packed into secondary carton along with a package insert.
Methotrexate Solution for Injection 100 mg/ml is filled in 10 ml amber moulded glass vial Type I with reinforced Non-PVC Base which are stoppered with 20 mm Grey westarrubber stopper and tampered with 20 mm flip off seal. Each vial is packed into secondary carton along with a package insert.

Date of revision : 16-03-2022

MAL Number:
Trexol 50 mg - MAL22046018AZ
Trexol 500 mg/1000 mg - MAL22046019AZ

Product Registration Holder: **Unimed Sdn Bhd**
53, Jalan Tembaga SD 5/2B, Bandar Sri Damansara,
52200, Kuala Lumpur, Malaysia

Manufactured by: **VENUS REMEDIES LIMITED**
Hill Top Industrial Estate, Jharmajri, EPIP
Phase-I (Extn.), Bhatoli Kalan, Baddi, Distt. Solan,
Himachal Pradesh, 173205, India
www.venusremedies.com

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B81/MT1000/4778

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TREXOL

Methotrexate Solution For Injection

(Controlled Medicine / Ubat Terkawal)

A4. Product Description
TREXOL - Methotrexate Solution for Injection 25 mg/ml & 100 mg/ml is a yellowish solution, free from visible extraneous particulate matter.

After dilution: Yellowish solution

Each ml contains Methotrexate USP 25 mg.
Each ml contains Methotrexate USP 100 mg.
Excipients: Sodium Chloride USP 4.5 mg, Water for Injection USP q.s. (Sodium Hydroxide USP is used for pH adjustment)

A5. PHARMACODYNAMICS
Methotrexate is an antimetabolite which acts principally by competitively inhibiting the enzyme, dihydrofolate reductase. In the process of DNA synthesis and cellular replication, folic acid must be reduced to tetrahydrofolic acid by this enzyme, and inhibition by methotrexate interferes with tissue cell reproduction. Actively proliferating tissues such as malignant cells are generally more sensitive to this effect of methotrexate. It also inhibits antibody synthesis.
Methotrexate also has immunosuppressive activity, in part possibly as a result of inhibition of lymphocyte multiplication. The mechanism(s) of action in the management of rheumatoid arthritis of the drug is not known, although suggested mechanisms have included immunosuppressive and/or anti-inflammatory effect.

A6. PHARMACOKINETICS
In doses of 0.1 mg (of methotrexate) per kg, methotrexate is completely absorbed from the gastrointestinal tract; larger oral doses may be incompletely absorbed. Peak serum concentrations are achieved within 0.5 - 2 hours following intravenous, intramuscular or intraarterial administration. Serum concentrations following oral administration of methotrexate may be slightly lower than those following intravenous injection.
Methotrexate is actively transported across cell membranes. The drug is widely distributed into body tissues with highest concentrations in the kidneys, gall bladder, spleen, liver and skin. Methotrexate is retained for several weeks in the kidneys and for months in the liver. Sustained serum concentrations and tissue accumulation may result from repeated daily doses. Methotrexate crosses the placental barrier and is distributed into breast milk. Approximately 50% of the drug in the blood is bound to serum proteins.
Methotrexate does not appear to be appreciably metabolised. The drug is excreted primarily by the kidneys via glomerular filtration and active transport. Small amounts are excreted in the faeces, probably via the bile.
Methotrexate has a biphasic excretion pattern. If methotrexate excretion is impaired accumulation will occur more rapidly in patients with impaired renal function. In addition, simultaneous administration of other weak organic acids such as salicylates may suppress methotrexate clearance.

A7. INDICATION
-Antineoplastic chemotherapy: Treatment of breast cancer, gestational choriocarcinoma and in patients with chorioadenoma destruens and hydatidiform mole. Palliation of acute and subacute lymphocytic and meningeal leukaemia. Greatest effect has been observed in palliation of acute lymphoblastic (stem cell) leukaemias. In combination with corticosteroids, methotrexate may be used for induction of remission. The drug is now most commonly used for the maintenance of induced remissions. Methotrexate is also effective in the treatment of the advanced stages (III and IV, Peters Staging System) of lymphosarcoma, particularly in children and in advanced cases of mycosis fungoides.
-High dose therapy: The use of very high doses is made possible by vials for injection containing 1000 mg. Diseases treated with these doses administered in the form of single-drug or combination therapy, include osteogenic sarcoma, acute leukaemia, bronchogenic carcinoma and epidermoid carcinoma of the head and neck.
-Psoriasis chemotherapy: Because of the high risk attending to its use, Methotrexate Injection is only indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultations.

A8. RECOMMENDED DOSE
Dose and Method of Administration:

Font used and size :

Times new roman with font size 5

Dosage: Because of its potential to cause severe toxicity, methotrexate therapy requires close supervision with particular caution to distinguish between daily and weekly dosage regimens. Weekly dosage prescriptions should specify a particular day of the week.

Antineoplastic Chemotherapy
Breast carcinoma: Prolonged cyclic combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil has given good results when used as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary lymph nodes. Methotrexate dosage was 40 mg/m2 intravenously on only the first and eighth days.
Choriocarcinoma and similar trophoblastic diseases.
Methotrexate is administered intramuscularly in doses of 15 mg to 30 mg daily for a five day course. Such courses are usually repeated three to five times as required with a rest period 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 (-hCG), which should return to normal or less than 50 units/24 hour usually after the 3rd or 4th course and usually followed by a complete resolution of measurable lesions in 4 to 6 weeks. One to two courses of methotrexate after normalisation of β-hCG is 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 or be followed by choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended. Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate is administered in these disease states in doses similar to those recommended for choriocarcinoma.
Leukaemia: Acute lymphatic (lymphoblastic) leukaemia in children and young adolescents is the most responsive to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common. In chronic lymphatic leukaemia, the prognosis for adequate response is less encouraging. Methotrexate alone or in combination with steroids was used initially for induction of remission of lymphoblastic leukaemias. More recently, corticosteroid therapy in combination with other antileukaemic drugs or in cyclic combination therapy including methotrexate, has produced rapid and effective remissions. When used for induction, in doses of 3.3 mg/m^2 in combination with prednisolone 60 mg/m^2 given daily, remission occurred in 50% of patients treated, usually within a period of 4 to 6 weeks.
Methotrexate alone, or in combination with other agents, appears to be the drug of choice for securing maintenance of drug induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, by administering methotrexate 2 times weekly intramuscularly in 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, reinduction of remission can again usually be obtained by repeating the initial induction regimen.
Meningeal leukaemia: Patients with leukaemia are subject to leukaemic invasion of the central nervous system. This may manifest characteristic signs or symptoms or may remain silent and be diagnosed only by examination of the cerebrospinal fluid, which contains leukaemic cells in such cases. Therefore, the CSF should be examined in all leukaemic patients. Since passage of methotrexate from blood serum to the cerebrospinal fluid is minimal, for adequate therapy the drug is administered intrathecally.
It is now common practice to administer methotrexate intrathecally as prophylaxis in all cases of lymphocytic leukaemia.
By intrathecal injection the distribution of methotrexate is in the CSF, the volume of which is dependent on age and not body surface area. The CSF is at 40% of adult volume at birth and reaches adult volume in several years. The recommended dose by age is:

Age (Yrs)	<1	1	2	3 + Older
Dose (mg)	6 mg	8 mg	10 mg	12 mg

There is some indication that infants less than 4 months and adults 70 years may have increased acute toxicity with doses recommended and dose reduction may be indicated. The solution is made in a strength of 1 mg/mL with an appropriate, sterile, preservative-free medium such as 0.9% Sodium Chloride Injection BP. Remove a volume of cerebrospinal fluid equivalent to the volume of methotrexate being administered.
For the treatment of meningeal leukaemia, intrathecal methotrexate may be given at intervals of 2 to 5 days however, there is some indication that doses given at intervals of less than one week may result in increased toxicity. Do not exceed the maximum recommended single dose of 15 mg.
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 leukaemia, 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.
Large doses may cause convulsions. Untoward side effects may occur with any given intrathecal injection and are commonly neurological in character. Methotrexate given by intrathecal route appears significantly in the systemic circulation and may cause systemic methotrexate toxicity. Therefore, systemic antileukaemic therapy with drug should be appropriately adjusted,

reduced or discontinued. Focal leukaemic involvement of the CNS may not respond to intrathecal chemotherapy and is best treated with radiotherapy.
Lymphomas: In Burkitt's tumour, stages I-II, methotrexate has produced prolonged remission in some cases. Recommended dosage is 10 to 25 mg per day orally for 4 to 8 days. 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 mg to 2.5 mg/kg daily. Hodgkin's Disease responds poorly to methotrexate and to most types of chemotherapy.
Mycosis fungoides: As an alternative to oral therapy, methotrexate 50 mg intramuscularly weekly or 25 mg intramuscularly twice weekly may be given.
High-dose therapy: Dosage regimens have varied considerably in different studies, the nature and severity of the disease and the previous experience of the investigator are some of the factors influencing the choice of dosage and the duration of therapy. It must be emphasised that high dosages should be used only by qualified specialists and in hospitals where the necessary facilities are available.
Psoriasis chemotherapy: The patient should be fully informed of the risks involved and should be under constant supervision of the physician.
Assessment of renal function, liver function and blood elements should be made by history, physical examination and laboratory tests (such as full blood count, urinalysis, serum creatinine, liver function studies and liver biopsy if indicated) before beginning methotrexate, periodically during methotrexate therapy and before reinstituting methotrexate therapy after a rest period. Appropriate steps should be taken to avoid conception during and for at least 6 months following methotrexate therapy.
The commonly used injectable dosage schedule is by weekly parenteral intermittent large doses.
All schedules should be continually tailored to the individual patient. Dose schedules cited below pertain to an average 70 kg adult. An initial test dose one week prior to initiation of therapy is recommended to detect any idiosyncrasy. A suggested dose range is 5 mg to 10 mg parenterally.
Recommended starting dose schedules:
Weekly single IM or IV dose schedule: 10 mg to 25 mg per week until adequate response is achieved. With this dosage schedule, 50 mg per week should ordinarily not be exceeded.
Dosage may be gradually adjusted to achieve optimal clinical response, but not to exceed the maximum stated for each schedule. Once optimal clinical response has been achieved the 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.

DOSAGE ADJUSTMENT
Renal Impairment: Methotrexate is excreted primarily by the kidneys. In patients with renal impairment the dose may need to be adjusted to prevent accumulation of drug.

Method of Administration:
Intramuscular, intravenous or intrathecal routes
For Intravenous injection, Methotrexate Injection should be diluted in dextrose 5% solution or sodium chloride 0.9% solution.
METHOTREXATE INJECTION 100 MG/ML SHOULD BE USED INTRAVENOUS INFUSION ONLY. IT SHOULD NOT BE USED INTRATHECALLY AS THE SOLUTION IS HYPERTONIC.
Methotrexate 100 mg/ml solution for injection is a hypertonic presentation and therefore not suitable for intrathecal use, non-isotonic solutions of methotrexate injection should not be administered intrathecally
For intrathecal injection, Methotrexate Injection should be diluted to a strength of 1 mg/mL with an appropriate preservative-free medium such as 0.9% Sodium Chloride Injection.
For conversion of mg/kg bodyweight to mg/m^2 of body surface area or the reverse, a ratio of 1:30 is given as a guideline. The conversion factor varies between 1:20 and 1:40 depending on age and body build.
Instructions for handling: As with all antineoplastic agents, trained personnel should prepare Methotrexate Solution For Injection. This should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). Protective gown, mask, gloves and appropriate eye protection should be worn when handling methotrexate. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed thoroughly with soap and water. It is recommended that pregnant personnel not handle cytotoxic agents such as methotrexate.
Luer-Lock fitting syringes are recommended. Large bore needles are recommended to minimise pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation.
Items used to prepare Methotrexate Solution For Injection, or articles associated with body waste, should be disposed of by placing in a double sealed polythene bag and incinerating at 1100°C.
Spills and disposal: If spills occur, restrict access to the affected area. Wear two pairs of gloves (latex rubber), a respirator mask, a protective gown and safety glasses. Limit the spread of the spill by covering with absorbent material such as absorbent towel or adsorbent granules. Collect up the towel

of absorbent/adsorbent material and other debris from spill and place in a leak proof plastic container and label accordingly. Cytotoxic waste should be regarded as hazardous or toxic and clearly labelled 'CYTOTOXIC WASTE FOR INCINERATION AT 1100°C'. Waste material should be incinerated at 1100°C for at least 1 second. Cleanse the remaining spill area with copious amounts of water.

A9.Route of Administration: Parenteral

A10. CONTRAINDICATION
Methotrexate is contraindicated in: Patients with significantly impaired renal function (creatinine clearance less than 30 ml/min) for methotrexate doses <100 mg/m^2, and moderate renal impairment (creatinine clearance less than 60 ml/min) for methotrexate doses >100 mg/m^2 (see section posology and method of administration).
Patients with significantly impaired hepatic function: Patients with pre-existing blood dyscrasias, such as significant marrow hypoplasia, leukopenia, thrombocytopenia or anaemia.
Patients with active infections: Patients with overt or laboratory evidence of immunodeficiency syndrome(s).
Methotrexate is contraindicated in pregnancy (see section Fertility, pregnancy and breast-feeding).
Because of the potential for serious adverse reactions from methotrexate in breast fed infants, breast feeding is contraindicated in women taking methotrexate (see section Fertility, pregnancy and breast-feeding).
Patients with a known allergic hypersensitivity to methotrexate or any of the other ingredients should not receive methotrexate.

A11. WARNING AND PRECAUTIONS
Warnings: Methotrexate must be used only by physicians experienced in antimetabolite chemotherapy.
Because of the possibility of fatal or severe toxic reactions, the patient should be fully informed by the physician of the risks involved and be under his constant supervision.
The prescriber should specify the day of intake on the prescription. The prescriber should make sure patients understand that methotrexate should only be taken once a week. Patients should be instructed on the importance of adhering to the once-weekly intakes.
Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Symptoms typically include dyspnoea, cough (especially a dry non-productive cough), thoracic pain, and fever for which patients should be monitored at each follow-up visit. Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop persistent cough or dyspnoea.
In addition, pulmonary alveolar haemorrhage has been reported with methotrexate used in rheumatologic and related indications. 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.
Methotrexate should be withdrawn from patients with pulmonary symptoms and a thorough investigation should be made to exclude infection. If methotrexate induced lung disease is suspected treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted.
When a patient presents with pulmonary symptoms, the possibility of Pneumocystis carinii pneumonia should be considered.
Methotrexate has the potential for serious, sometimes fatal toxicity. The toxic effects may be related in frequency and severity to the dose or frequency of administration but have been seen at all doses. Because the toxic reactions can occur at any time during therapy, the patients have to be observed closely and must be informed of early signs and symptoms of toxicity.
Use caution when administering high-dose methotrexate to patients receiving proton pump inhibitor (PPI) therapy. Case reports and published population pharmacokinetic studies suggest that 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 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.

PRECAUTIONS
Methotrexate has a high potential toxicity, usually dose related, and should be used only by physicians experienced in antimetabolite chemotherapy, in patients under their constant supervision. The physician should be familiar with the various characteristics of the drug and its established clinical usage.
Before beginning methotrexate therapy or reinstituting methotrexate after a rest period, assessment of renal function, liver function and blood elements should be made by history, physical examination and laboratory tests.
It should be noted that intrathecal doses are transported into the cardiovascular system and may give rise to systemic toxicity. Systemic toxicity of methotrexate may also be enhanced in patients with renal dysfunction, ascites, or other effusions due to prolongation of serum half-

life. In rare cases, following intrathecal administration, a tumour lysis syndrome has been observed.
Fertility and reproduction
Fertility: Methotrexate has been reported to cause impairment of fertility, oligospermia, menstrual dysfunction and amenorrhoea in humans, during and for a short period after cessation of therapy, affecting spermatogenesis and oogenesis during the period of its administration - effects that appear to be reversible on discontinuing therapy. In addition, methotrexate causes embryotoxicity, abortion and foetal defects in humans.
For contraception advice for men see section Fertility, pregnancy and breast-feeding: Patients undergoing therapy should be subject to appropriate supervision so that signs or symptoms of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay. This may occur abruptly and on apparent safe dosage, and any profound drop in blood cell count indicates immediate stopping of the drug and appropriate therapy. In patients with malignant disease who have pre-existing bone marrow aplasia, leukopenia, thrombocytopenia or anaemia, methotrexate should be used with caution, if at all.
In general, the following laboratory tests are recommended as part of essential clinical evaluation and appropriate monitoring of patients chosen for or receiving methotrexate therapy: complete haemogram; haematocrit; urinalysis; renal function tests; liver function tests and chest X-ray.
Methotrexate is bound in part to serum albumin after absorption, and toxicity may be increased because of displacement by certain drugs such as salicylates, sulphonamides, phenytoin, and some antibacterials such as tetracycline, chloramphenicol and para-aminobenzoic acid. These drugs, especially salicylates and sulphonamides, whether antibacterial, hypoglycaemic or diuretic, should not be given concurrently until the significance of these findings is established.
Vitamin preparations containing folic acid or its derivatives may alter response to methotrexate.
Since it is reported that methotrexate may have an immunosuppressive action, this factor must be taken into consideration in evaluating the use of the drug where immune responses in a patient may be important or essential.

A12. INTERACTIONS WITH OTHER MEDICAMENTS
Methotrexate is extensively protein bound and may be displaced by certain drugs such as salicylates, hypoglycaemics, diuretics, sulphonamides, diphenylhydantoins, tetracyclines, chloramphenicol and p-aminobenzoic acid, and the acidic anti-inflammatory agents, so causing a potential for increased toxicity when used concurrently.
Concomitant use of other drugs with nephrotoxic or hepatotoxic potential (including alcohol) should be avoided.
Vitamin preparations containing folic acid or its derivatives may decrease the effectiveness of methotrexate.
Caution should be used when NSAIDs and salicylates are administered concomitantly with methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate and thereby may enhance its toxicity. Concomitant use of NSAIDs and salicylates has been associated with fatal methotrexate toxicity.
However, patients using constant dosage regimens of NSAIDs have received concurrent doses of methotrexate without problems observed.
Treatment with more than one DMARD in various regimens is being tried but there is little evidence available to assess benefit. A meta-analysis of 5 different combinations of DMARDs demonstrated that although efficacy might be greater than single DMARDs, toxicity was also increased.
Renal tubular transport is also diminished by probenecid and penicillins; use of these with methotrexate should be carefully monitored.
A potential interaction may exist between methotrexate and proton-pump inhibitors (e.g. omeprazole, pantoprazole). Omeprazole may inhibit methotrexate clearance resulting in potentially toxic methotrexate levels.
Severe bone marrow depression has been reported following the concurrent use of methotrexate and co-trimoxazole or trimethoprim. Concurrent use should probably be avoided.
The use of nitrous oxide potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe, unpredictable myelosuppression and stomatitis and in cases of intrathecal administration increased severe, unpredictable neurotoxicity. Whilst this effect can be reduced by administering calcium folinate, the concomitant use of nitrous oxide and methotrexate should be avoided (see section posology and method of administration).
An increased risk of hepatitis has been reported following the use of methotrexate and the acitretin metabolite, etretinate. Consequently, the concomitant use of methotrexate and acitretin should be avoided.
Methotrexate may increase the bioavailability of mercaptopurine by interference with first-pass metabolism.
Concomitant application of methotrexate and theophylline can reduce theophylline clearance.

A13 PREGNANCY AND LACTATION
Effects on fertility: Methotrexate has been reported to cause impairment of fertility, defective oogenesis or spermatogenesis, oligospermia, menstrual dysfunction and amenorrheain humans, during and for a short period after cessation of therapy.
Men treated with methotrexate should use contraception and not father a