PRODUCT INFORMATION

TREXJECT IN, methotrexate (as sodium)
Solution for subcutaneous or intramuscular injection, pre-filled syringe

7.5 mg/0.15 mL, 10 mg/0.2 mL, 12.5 mg/0.25 mL, 15 mg/0.3 mL, 17.5 mg/0.35 mL, 20 mg/0.4 mL, 22.5 mg/0.45 mL and 25 mg/0.5 mL

WARNING

Methotrexate must only be prescribed by physicians experienced in anti-metabolic therapy and the treatment of severe rheumatoid arthritis or psoriasis.

Patients should be fully informed of the risk of fatal or severe toxic reactions involved with the administration of methotrexate and should be under constant supervision of the physician.

Deaths have been reported with the use of methotrexate. In the treatment of psoriasis and rheumatoid arthritis, methotrexate should be restricted to severe, recalcitrant, disabling disease which is not adequately responsive to other forms of therapy and only when the diagnosis has been established.

Methotrexate may produce depression of the bone marrow, anaemia, aplastic anaemia, leukopenia, neutropenia, thrombocytopenia and bleeding.

At high or prolonged doses, methotrexate may be hepatotoxic. Liver atrophy, necrosis, cirrhosis, fatty changes and periportal fibrosis have been reported. Since changes may occur without previous signs of gastro-intestinal or haematological toxicity, it is imperative that hepatic function be determined prior to initiation of treatment and monitored regularly throughout therapy. Special caution is indicated in the presence of liver damage or impaired hepatic function. Concomitant use of other drugs with hepatotoxic potential and alcohol should be avoided.

Potentially fatal opportunistic infections, especially Pneumocystis jirovecii pneumonia, may occur with methotrexate therapy.

Use in pregnancy
Category D. This category specifies drugs, which have caused an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Methotrexate has caused foetal death and/or congenital anomalies. It should not be used in pregnant women or in those who might become pregnant. Methotrexate is contraindicated in the treatment of psoriasis and rheumatoid arthritis in pregnant women. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counselled on the serious risk to the foetus should they become pregnant while undergoing treatment.

Pregnancy should be avoided if either partner is receiving methotrexate, during and for a minimum of 3 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.

Methotrexate is usually contraindicated in patients with impaired renal function.

Serious adverse reactions including bone marrow suppression, aplastic anaemia, gastrointestinal toxicity and death have been reported with concomitant administration of methotrexate (usually in high doses) with some nonsteroidal anti-inflammatory drugs (NSAIDs).

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

Pulmonary toxicity including acute or chronic interstitial pneumonitis and pulmonary fibrosis, which can progress rapidly and is potentially fatal, has been associated with methotrexate therapy. It may occur acutely at any time during therapy and has been reported at low doses. Methotrexate should be discontinued and careful clinical evaluation be performed in patients developing symptoms of pulmonary toxicity (eg. Dry, non-productive cough, dyspnoea). Management of methotrexate-induced pulmonary toxicity is mainly supportive. Methotrexate-induced pulmonary toxicity may not be fully reversible. Pulmonary lesions can occur at all dosages. Infection (including pneumonia) needs to be excluded. Patients should be closely monitored for pulmonary symptoms.

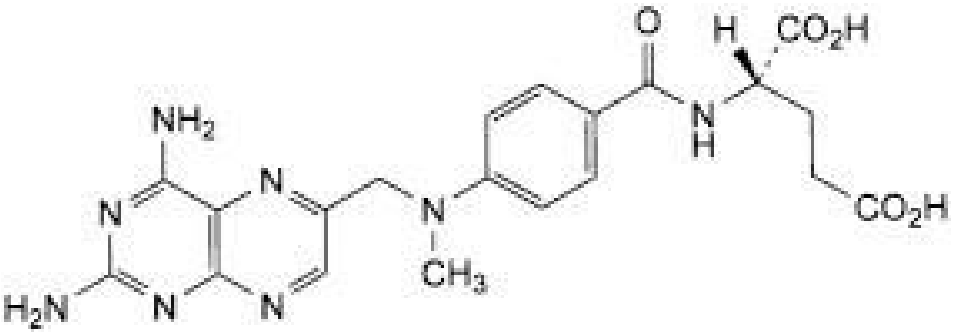
Use in children: Aside from its established use in cancer chemotherapy the safety and efficacy of using methotrexate to treat severe rheumatoid arthritis and psoriasis in children has not been fully elucidated.

Both the physician and the pharmacist should emphasise to the patient the importance of the weekly dosing regimen: mistaken daily use may cause serious and sometimes life- threatening or fatal toxicity. For the same reason great care should be taken with dispensing to ensure the correct dose of methotrexate is given to the patient.

NAME OF THE MEDICINE

TREXJECT IN, Methotrexate (as sodium)

The structural formula is represented below.



Molecular Formula: $C_{20}H_{22}N_8O_5$

Molecular Weight: 454.4

CAS Number: 59-05-2

DESCRIPTION

Methotrexate is (2*S*)-2-[(4-{[(2,4-diaminopteridin-6-yl)methyl]methylamino}benzoyl)amino] pentanedioic acid. It is a yellow to orange, crystalline powder, practically insoluble in water, alcohol, ether and ethylene chloride. It dissolves in dilute solutions of mineral acids and in dilute solutions of alkali hydroxides and carbonates.

TREXJECT IN is a sterile, clear, yellow-brown solution of Methotrexate sodium in Water for Injections, practically free from visible particles. Sodium Chloride is included for isotonicity. Sodium Hydroxide is included for pH adjustment. TREXJECT IN Injection contains no anti- microbial preservative.

One mL of solution contains 50 mg of methotrexate as methotrexate sodium, 4 mg of sodium chloride, approximately 10 mg of sodium hydroxide and water for injections to a total volume of 1 mL. The volume of injection is sufficient to permit administration of the nominal volume declared on the label.

TREXJECT IN Injection has a pH of 7.5 to 9.0.

PHARMACOLOGY

Methotrexate is an antimetabolite antineoplastic agent, which exerts its cytotoxic effect through competitive inhibition of dihydrofolate reductase, the enzyme that reduces folic acid to tetrahydrofolic acid. Inhibition of tetrahydrofolic acid results in interference with DNA synthesis and cellular reproduction.

Tissues with high rates of cellular proliferation, eg. bone marrow, foetal cells, dermal epithelium, buccal and intestinal mucosa and cells of the urinary bladder are generally more sensitive to this effect of methotrexate.

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

In patients with rheumatoid arthritis, effects of methotrexate on articular swelling and tenderness can be seen as early as three to six weeks. Although methotrexate clearly ameliorates symptoms of inflammation (pain, swelling, stiffness) there is no evidence that it reduces remission of rheumatoid arthritis nor has a beneficial effect been demonstrated on bone erosion and other radiological changes which result in impaired joint use, functional disability and deformity. Most studies of methotrexate in patients with rheumatoid arthritis are relatively short term (three to six months). Data from long-term studies indicate that an initial clinical improvement is maintained for at least two years with continued therapy.

Pharmacokinetics

Absorption

Methotrexate is incompletely absorbed after oral administration. Absorption is significantly higher after intramuscular and subcutaneous administration with no differences between both routes. Peak serum levels may be achieved within 0.25 and 1 hour following intramuscular (IM) administration and 0.25 to 1.5 hours following subcutaneous (SC) administration.

Distribution

Approximately 50% of the absorbed methotrexate is reversibly bound to serum proteins. Methotrexate is widely distributed into body tissues and concentrates in the kidneys, liver and gastrointestinal tract. It also distributes into third-space accumulation of fluid, e.g. ascites or pleural effusions. Methotrexate does not reach therapeutic concentrations in the cerebrospinal fluid (CSF) when given orally or parenterally.

Metabolism

Approx. 10 % of the administered methotrexate dose is metabolised intrahepatically. The principle metabolite is 7-hydroxymethotrexate.

Elimination

Methotrexate is predominantly excreted by the kidneys and small amounts appear in the faeces. Excretion of methotrexate is reduced in the presence of impaired renal function.

MC-MTX.7/PH

Study MC-MTX.7/PH was an open-label, single dose, 2-period crossover Phase 1 study comparing IM and SC doses of MTX 15 mg (using the 10 mg/mL injection solution). The primary objective of the study was to evaluate the PK characteristics, and the rate and extent of absorption of MTX 15 mg given by IM versus SC administration.

The primary PK results of Study MC-MTX.7/PH showed that the SC and IM routes of administration for MTX were bioequivalent in terms of the extent of drug exposure (based on AUC) but with higher peak plasma levels achieved from the IM injection (0.5 versus 1 hour). In addition, the mean Cmax for SC administration is approximately 60% of that seen following IM injection of MTX.

Primary Pharmacokinetic Parameter Results for Study MC-MTX.7/PH

Parameter	MTX s.c. (test)	MTX i.m. (reference)	Geometric mean ratio s.c./i.m. (%)	90% CI (%)
Tmax h	1 (1.7)	0.5 (1.7)		
AUC_{0-t} (µg*h/L)	1020.79 (1.23)	1043.33 (1.18)	97.84	91.07 – 105.11
$AUC_{0-\infty}$ (µg*h/L)	1058.89 (1.22)	1088.86 (1.18)	97.25	91.00 – 103.92
Cmax (µg/L)	221.76 (1.39)	381.28 (1.37)	58.16	47.61 - 71.06
AUC = area under the plasma concentration time curve; Cmax = maximum plasma concentration				

The secondary PK results for 7-OH MTX showed a similar pattern to the primary PK observations. The mean AUC for 7-OH MTX achieved following SC and IM administration were similar, and the geometric mean Cmax was also similar (44.84 µg/L for SC and 52.85 µg/L for IM administration).

MC-MTX.9/PH

Trial MC-MTX.9/PH compared the pharmacokinetics of two different MTX concentrations (10 mg/mL versus 50 mg/mL) in 24 healthy volunteers where one treatment arm was given via the SC route and the other given via the IM route. Each treatment arm consisted of a unique set of patients with no cross-over. The results show an equal extent of absorption of MTX with both concentrations after both routes of administration. The rate of absorption expressed by Cmax was different with about 15-20% higher maximum MTX concentrations achieved after administration of the higher concentrated solution. No clinical consequences are anticipated as the total exposure to MTX was equivalent. Both formulations were equally well tolerated.

Model-independent pharmacokinetic characteristics of methotrexate (geometric mean [SD])

Treatment	**50 mg/mL (test)**	**10 mg/mL (reference)**	**50 mg/mL (test)**	**10 mg/mL (reference)**
Route of administration	SC	SC	IM	IM
Number of subjects	12	12	12	12
AUC [µg*h/L]	1451.713 (1.13)	1488.010 (1.11)	1169.934 (1.17)	1273.756 (1.22)
Point estimate test/reference (90% CI)	97.56 (89.90 - 105.88)		91.85 (84.63 - 99.68)	
C_{max} [µg/L]	298.529 (1.39)	259.737 (1.28)	431.359 (1.51)	357.456 (1.44)

Point estimate test/reference (90% CI)	114.93 (90.96 - 145.22)	120.67 (95.51 - 152.48)

AUC = area under the plasma concentration time curve; C_{max} = maximum plasma concentration

Using a cross group comparison, which does not permit extraction of variability due to subject differences or period effects, it appears the 50 mg/mL product has a higher C_{max} and slightly lower AUC when given by i.m. injection compared to s.c. injection. This difference in the AUC after IM administration of the 10 mg/mL and 50 mg/mL is not expected to have any clinical consequence. The differences between the i.m. and s.c. routes for the two injection concentrations in the cross study-arm comparisons are similar, suggesting there are population differences contributing to this finding.

Studies comparing Oral with Parenteral Administration

Four published studies in adult patients with RA have compared oral MTX 7.5-30 mg/week with equivalent doses administered by either IM or SC injection. The mean bioavailability in 15 adult patients with RA after oral MTX 30 mg/week, as demonstrated by Hoekstra *et al* (2004), was 0.64 (range 0.21-0.96) which was statistically significantly different to the SC administration of the same dose. Seideman *et al* (1993) reported the AUC in nine patients where IM and oral doses met bioequivalence criteria (90% CI 92-121% for the AUC ratio). In the study of 21 RA patients conducted by Hamilton *et al* (1997) the 24-hour AUC was significantly lower with oral versus IM therapy at a mean MTX dose of 17 mg/week (p=0.027), but this was not seen at the lower 7.5 mg weekly dose of MTX. Auvinet *et al* (1992) observed a 10 mg/week oral dose that was 60% bioavailable relative to the same SC dose involving 8 adult patients with RA, which is consistent with the results reported by Hamilton and Hoekstra. Another study by Herman *et al* (1989) reported oral bioavailability of a 10 mg dose as 70% compared with the same dose given by IM injection in a study involving 41 RA patients. Overall, the published data indicates that a lower AUC is seen with oral therapy versus parenteral administration for doses of MTX as low as 10 mg, consistently when the dose is >15 mg. (See also **DOSAGE AND ADMINSTRATION**.)

CLINICAL TRIALS

Rheumatoid Arthritis

Subcutaneous Use

MC-MTX.6/RH

A double-blind, multicentric, randomised clinical trial (Study no. MC-MTX.6/RH) was conducted to evaluate the efficacy of subcutaneously administered MTX in comparison with oral treatment in patients with active rheumatoid arthritis (RA). A total of 384 patients aged 18 to 75 years with active RA defined by a disease activity score (DAS) 28 $\geq$ 4, who have never been treated with MTX before and who were familiar with subcutaneous self- administration through confirmed practice phase were included into this trial.

Patients were randomised into an oral arm (A; n = 190) or a subcutaneous arm (B; n = 194). Patients within arm A received 2 tablets of MTX 7.5 mg and one dummy pre-filled syringe per week. Patients within arm B received one pre-filled syringe containing 15 mg MTX and two dummy tablets per week. The patients were treated for 24 weeks with a constant dose of 15 mg MTX, except for patients who had not achieved a 20% improvement according to American College of Rheumatology criteria (ACR20) at week 16. In this case the study medication of the patients was changed from 15 mg oral to 15 mg SC (Arm A) or from 15 mg SC to 20 mg SC (Arm B), respectively.

The primary endpoint for this trial was the demonstration of superiority of MTX after SC administration vs oral administration after 24 weeks based on the ACR20 response. Sample size was determined by assuming a 15% point increase in ACR20 response rate after 24 weeks (55% in the MTX oral arm vs 70% in the SC group) within the Full-Analysis-Set. The two-tailed significance level was 5%. The power of the statistical test was fixed at 80%.

Of all patients, 78.2% in the SC group and 70.1% in the oral group were ACR20 responders at week 24. This difference was statistically significant (Cochran-Mantel-Haenszel test; P = 0.0412). The estimate of common relative risk was 1.12 (95% CI: 1.01-1.24). Furthermore, significantly more patients in the SC group were ACR70 responders compared to the oral group at week 24 (41 vs 33.2%; P = 0.03).

Time to initial ACR20 response was evaluated using Kaplan-Meier methods. No difference was seen between the two treatment groups. In both arms the median number of weeks to reach an ACR20 response for the first time was 6 weeks.

A low rate of withdrawal was observed in both groups with approximately 10% of the patients. Less patients discontinued study for insufficient clinical response in the SC group than in the oral group (1.1% vs 2.1%) but more patients withdrew from the study due to adverse events in the SC group (9.6% vs 5.3%).

TREXJECT IN given subcutaneously was thus shown to be well tolerated and statistically more efficacious than when given orally in terms of percentage of patients with ACR20.

Intramuscular use

The efficacy and safety of intramuscular administration of MTX has been proven in a number of published randomised clinical trials. The same dose regimens as for subcutaneous administration have been used.

Psoriasis

A favourable efficacy and safety profile has been established for MTX in a number of clinical trials, as well as in common practice. For the treatment of psoriasis, MTX is usually given once weekly either orally, intramuscularly or subcutaneously. The methotrexate start-dose in randomized controlled trials varied from 5 to 25 mg/week, most commonly being either 7.5 mg or 15 mg. Guidelines vary from 5 to 15 mg/week. The majority of studies have demonstrated a remission or an improvement in skin condition within 16 - 24 weeks after introducing methotrexate treatment. A higher starting dose (15 mg/week) in two studies has contributed to an achievement of maximum response after 8 - 12 weeks of treatment.

INDICATIONS

Psoriasis therapy (see WARNING box)

TREXJECT IN may be of value in the symptomatic control of severe, recalcitrant, disabling psoriasis in adults which is not adequately responsive to other forms of treatment. However, due to the high risk associated with its use, methotrexate should be used after the diagnosis has been definitely established, as by biopsy and/or after dermatologic consultation.

Rheumatoid arthritis therapy (see WARNING box)

Management of severe, recalcitrant, active rheumatoid arthritis in adults not responding to, or intolerant of, an adequate trial of NSAIDs and one or more disease modifying drugs.

Aspirin, NSAIDs and/or low dose steroids may be continued, although the possibility of increased toxicity with concomitant use of NSAIDs including salicylate has not been fully explored.

Steroids may be reduced gradually in patients who respond to methotrexate.

Combined use of methotrexate with gold or penicillamine, has not been studied and may increase the incidence of adverse effects. Rest and physiotherapy as indicated should be continued.

CONTRAINDICATIONS (see WARNING box)

Methotrexate is contraindicated in patients with:

- hypersensitivity to methotrexate or to any of the excipients (see **DESCRIPTION**),
- alcoholism or hepatic disorders, including alcoholic liver disease or other chronic liver disease,
- severe renal impairment (creatinine clearance less than 20 ml/min),
- pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia,
- serious, acute or chronic infections such as tuberculosis, HIV or with overt or laboratory evidence of other immunodeficiency syndromes,
- patients with peptic ulcer disease or ulcerative colitis and ulcers of the oral cavity,
- poor nutritional status
- concurrent vaccination with live vaccines.

Methotrexate is contraindicated in pregnancy and breast-feeding.

TREXJECT IN should not be used on the day of a surgery with anaesthesia.

An increased risk of hepatitis has been reported to result from combined use of methotrexate and retinoids like acitretin. Therefore, the combination of methotrexate and such medicinal products is also contraindicated.

PRECAUTIONS (see WARNING box)

Methotrexate must only be prescribed by physicians experienced in anti-metabolic therapy and the treatment of severe rheumatoid arthritis or psoriasis.

Methotrexate has a high potential for toxicity, which is usually dose-related. The physician should be familiar with the various characteristics of the drug and its established clinical usage. Because the toxic effects can occur at any time during methotrexate therapy, patients must be kept under appropriate supervision so that signs or symptoms of possible toxicity or adverse reactions may be detected as early as possible. This is especially important in patients where drug elimination could be impaired (renal impairment, pleural effusion, ascites). When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken. If methotrexate therapy is reinstituted, it should be carried out with utmost caution, with adequate consideration of further need for the drug, and with increased alertness as to possible recurrence of toxicity.

Pre-treatment and periodic haematologic evaluations are essential to the use of methotrexate in the treatment of severe rheumatoid arthritis and psoriasis because of its haematopoietic suppressive effects, manifesting as anaemia, aplastic anaemia, pancytopenia, leukopenia, neutropenia and/or thrombocytopenia. This may occur abruptly and on apparent safe dosage, and any profound drop in blood-cell count indicates immediate cessation of the drug and appropriate therapy.

Recommended examinations and safety measures before and during use

Before commencing or reinstituting methotrexate therapy after a rest period

Complete blood count with differential blood count and platelets, liver enzymes, bilirubin, serum albumin, chest x-ray and renal function tests. If clinically indicated, exclude tuberculosis and hepatitis.

During therapy (every 1 to 2 months)

An increased monitoring frequency should be considered also when the dose is increased.

1. Examination of the mouth and throat for mucosal changes.

2. Complete blood count with differential blood count and platelets: Haemopoietic suppression caused by methotrexate may occur abruptly and with apparently safe dosages. Any profound drop in white-cell or platelet counts indicates immediate withdrawal of the medicinal product and appropriate supportive therapy. Patients should be advised to report all signs and symptoms suggestive of infection. Patients taking simultaneous administration of haematotoxic medicinal products (e.g. leflunomide) should be monitored closely with blood count and platelets.

3. Liver function tests: Particular attention should be given to the appearance of liver toxicity. Treatment should not be instituted or should be discontinued if any abnormality of liver function tests, or liver biopsy, is present or develops during therapy. Such abnormalities should return to normal within two weeks after which treatment may be recommenced at the discretion of the physician. There is no evidence to support use of a liver biopsy to monitor hepatic toxicity in rheumatological indications.

For psoriasis patients the need of a liver biopsy prior to and during therapy is controversial. Further research is needed to establish whether serial liver chemistry tests or propeptide of type III collagen can detect hepatotoxicity sufficiently. The evaluation should be performed case by case and differentiate between patients with no risk factors and patients with risk factors such as excessive prior alcohol consumption, persistent elevation of liver enzymes, history of liver disease, family history of inheritable liver disease, diabetes mellitus, obesity, and history of significant exposure to hepatotoxic drugs or chemicals and prolonged methotrexate treatment or cumulative doses of 1.5 g or more. If the results of a liver biopsy show mild changes (Roenigk grades I, II, IIIa), methotrexate may be continued and the patient monitored according to the recommendations listed above. Methotrexate should be discontinued in any patient who displays persistently abnormal liver function tests and refuses liver biopsy, or in any patient whose liver biopsy shows moderate to severe changes (Roenigk grade IIIb or IV).

Check of liver-related enzymes in serum: Temporary increases in transaminases to twice or three times of the upper limit of normal have been reported by patients at a frequency of 13 – 20 %. In the case of a constant increase in liver-related enzymes, a reduction of the dose or discontinuation of therapy should be taken into consideration.

Due to its potentially toxic effect on the liver, additional hepatotoxic medicinal products should not be taken during treatment with methotrexate unless clearly necessary and the consumption of alcohol should be avoided or greatly reduced (see **INTERACTIONS WITH OTHER MEDICINES**). Closer monitoring of liver enzymes should be exercised in patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide). The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide).

4. Methotrexate may cause renal damage that may lead to acute renal failure. Close attention to renal function is recommended.

   As methotrexate is eliminated mainly by renal route, increased serum concentrations are to be expected in the case of renal insufficiency, which may result in severe undesirable effects. The renal status of the patient should be determined prior to and periodically during methotrexate therapy. Caution should be exercised if significant renal impairment is present. Drug dosage should be reduced or discontinued until renal function is improved or restored.

   Where renal function may be compromised (e.g. in the elderly), monitoring should take place more frequently. This applies in particular, when medicinal products are administered concomitantly, which affect the elimination of methotrexate, cause kidney damage (e.g. non-steroidal anti-inflammatory medicinal products) or which can potentially lead to impairment of blood formation. Dehydration may also intensify the toxicity of methotrexate.

5. Assessment of respiratory system: Methotrexate has been associated with pulmonary toxicity, which is potentially fatal. Patients should be closely monitored for pulmonary symptoms and, if necessary lung function test should be performed. Pulmonary affection requires a quick diagnosis and discontinuation of methotrexate. Pulmonary symptoms (especially a dry, non-productive cough) or a non-specific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Although clinically variable, the typical patient with methotrexate-induced lung disease presents with fever, cough, chest pain, dyspnoea, hypoxaemia and an infiltrate on X-ray; infection needs to be excluded. This lesion can occur at all dosages (see WARNING box). Infection (including pneumonia) needs to be

excluded.

6. Methotrexate may, due to its effect on the immune system, impair the response to vaccination and affect the result of immunological tests. Particular caution is also needed in the presence of inactive, chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) for reasons of eventual activation. Vaccination using live vaccines must not be carried out under methotrexate therapy.

If vomiting, diarrhoea or stomatitis occur, resulting in dehydration, methotrexate should be discontinued until recovery occurs.

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

Methotrexate causes hepatotoxicity, liver fibrosis and cirrhosis, but generally only after prolonged use. Liver enzyme elevations are frequently seen. These are usually transient and asymptomatic and do not appear predictive of subsequent hepatic disease. Liver biopsy after sustained use often shows histological 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.

The risk of developing acute hepatitis and chronic hepatotoxicity in psoriatic patients seems to be correlated not only to the cumulative dose of methotrexate but also to the presence of concurrent conditions such as alcoholism, obesity, diabetes, and advanced age. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally 2 years or more) and after a total cumulative dose of at least 1.5 grams.

Methotrexate therapy has immunosuppressive activity, which can potentially lead to serious or even fatal infections. Bacterial infection may occur or be a threat if profound leukopenia occurs during therapy. In this instance, the drug should be discontinued and appropriate antibiotic therapy instituted. If severe bone marrow depression occurs, blood or platelet transfusions may be required.

Pneumonia (in some cases leading to respiratory failure) may occur. Potentially fatal opportunistic infections, especially Pneumocystis jirovecii pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of Pnemocystis jirovecii pneumonia should be considered.

Immunisation may be ineffective when given during methotrexate therapy. Immunisation with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunisation in patients receiving methotrexate therapy (see **INTERACTIONS WITH OTHER MEDICINES**).

Severe, occasionally fatal, skin reactions have been reported following single or multiple doses of methotrexate. Reactions have occurred within days of oral, intramuscular, intravenous, or intrathecal administration. Recovery has been reported with discontinuation of therapy.

Even following low dose there have been occasional reports of significant CNS toxicity. Patients should be closely monitored for neurologic symptoms and if these occur treatment should be

discontinued and appropriate therapy instituted.

Encephalopathy/leukoencephalopathy have been reported in oncologic patients receiving methotrexate therapy and cannot be excluded for methotrexate therapy in non-oncologic indications.

Effects on fertility

Animal studies show that methotrexate impairs fertility (see **Genotoxicity**).

Use in pregnancy (Category D)

Methotrexate has caused foetal death and/or congenital abnormalities. Pregnant psoriatic or rheumatoid arthritis patients should not receive methotrexate. Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counselled on the serious risk to the foetus should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate, during and for at least 12 weeks after cessation of therapy.

Use in lactation

Methotrexate has been detected in human breast milk and is contraindicated during breastfeeding. Women should be advised not to breast feed while being treated with methotrexate.

Paediatric Use

TREXJECT IN is not recommended for use in paediatric patients.

Use in the Elderly

Due to diminished hepatic and renal functions as well as decreased folate states in elderly patients, relatively low doses should be considered and these patients should be closely monitored.

Genotoxicity

Methotrexate has been reported to cause chromosome damage. Methotrexate may cause defective oogenesis and spermatogenesis. Therefore, in men and women of fertile age, steps should be taken to avoid conception during methotrexate therapy. The risk of genetic abnormalities may persist after discontinuing methotrexate therapy. Thus, it is advised that both men and women avoid intercourse leading to conception for an indefinite period (at least 12 weeks) after discontinuing methotrexate to ensure the re-establishment of normal germinal cells.

Carcinogenicity

As conventional carcinogenicity studies have not been performed and data from chronic toxicity studies in rodents are inconsistent, methotrexate is considered not classifiable as to its carcinogenicity to humans

Effects on ability to drive and use machines

Central nervous symptoms such as tiredness and dizziness can occur during treatment, TREXJECT IN has minor or moderate influence on the ability to drive and use machines.

INTERACTIONS WITH OTHER MEDICINES

Alcohol, hepatotoxic medicinal products, haematotoxic medicinal products

The probability of methotrexate exhibiting a hepatotoxic effect is increased by regular alcohol consumption and when other hepatotoxic medicinal products are taken at the same time. Patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide) should be monitored with special care. The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide, azathioprine, retinoids, sulfasalazine).

Combined treatment with methotrexate and retinoids like acitretin increases the risk of hepatotoxicity (see CONTRAINDICATIONS).

Leflunomide

The incidence of pancytopenia and hepatotoxicity can be increased when leflunomide is combined with methotrexate.

Medicinal products with high plasma protein binding

As methotrexate is partly bound to serum proteins, its toxicity may be increased as a result of displacement by certain drugs such as salicylates, phenylbutazone, sulphonamides, sulphonylureas, phenytoin, tetracyclines, chloramphenicol and para-aminobenzoic acid. These drugs, particularly salicylates and sulphonamides, should not be given concurrently until the significance of these findings is established.

Antibiotics

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

The excretion of methotrexate from the body can be markedly reduced by the concurrent use of penicillins, glycopeptides, ciprofloxacin, cefalotin and sulfonamides. There is a considerable risk of methotrexate toxicity. Use of methotrexate with penicillins and these antibiotics should be carefully monitored.

Hypolipidaemic compounds such as cholestyramine provided preferential binding sites compared to serum proteins when given in combination with methotrexate. This may lead to decreased methotrexate serum levels.

Products containing folic acid or folinic acid

Concomitant treatment with folinic acid or folic acid may decrease the incidence or severity of adverse effects from methotrexate therapy but also the efficacy of methotrexate. Medicinal products containing folic acid or folinic acid (including certain vitamin preparations) should not be given to patients on the same day as methotrexate treatment.

Probenecid, weak organic acids, pyrazoles and non-steroidal anti-inflammatory agents

Caution should be used when NSAIDs or 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 for interactions, studies of methotrexate in patients with rheumatoid arthritis have usually included concurrent use of dosage regimens of NSAIDs, without apparent problems. It should be appreciated, however, that the doses used in these studies and in the treatment of rheumatoid arthritis (generally 7.5 to 15 mg/week) are somewhat lower than those used in psoriasis and that larger doses could lead to unexpected toxicity. Therefore, until more is known about the NSAID/methotrexate interaction, it is recommended that methotrexate dosage be carefully controlled during treatment with NSAIDs.

Probenecid and pyrazoles (phenylbutazone) may increase the methotrexate plasma half-life and thereby increase blood levels.

Proton-pump inhibitors

A potential interaction may exist between methotrexate and proton pump inhibitors (eg omeprazole, pantoprazole). Concomitant administration of methotrexate and omeprazole has led to delayed renal elimination of methotrexate. In combination with pantoprazole inhibited renal elimination of the metabolite 7-hydroxymethotrexate with myalgia and shivering was reported in one case.

Allopurinol

Concomitant use of allopurinol with methotrexate may result in an increased incidence of bone marrow depression.

Medicinal products which cause folate deficiency

Folate deficiency states may increase methotrexate toxicity. Trimethoprim alone and sulfamethoxazole/trimethoprim have been reported rarely to increase the toxic effects (e.g. bone marrow suppression) of methotrexate, probably by decreased tubular secretion and/or an additive antifolate effect. Increased toxic effects (e.g. bone marrow suppression) have also been reported in patients receiving methotrexate and pyrimethamine.

Assay for folate: Methotrexate may inhibit the organism used in the assay and interfere with detection of folic acid deficiency.

Medicinal products with adverse reactions on the bone marrow

In the case of medication with medicinal products, which may have adverse reactions on the bone marrow (e.g. sulphonamides, trimethoprim-sulphamethoxazole, chloramphenicol, pyrimethamine); attention should be paid to the possibility of pronounced impairment of blood formation.

Other antirheumatic medicinal products

An increase in the toxic effects of methotrexate is, in general, not to be expected when TREXJECT

IN is administered simultaneously with other antirheumatic medicinal products (e.g. gold compounds, penicillamine, hydroxychloroquine, sulphasalazine, azathioprin, cyclosporin).

Sulfasalazine

Although the combination of methotrexate and sulphasalazine can cause an increase in efficacy of methotrexate and as a result more undesirable effects due to the inhibition of folic acid synthesis through sulphasalazine, such undesirable effects have only been observed in rare individual cases in the course of several studies.

Amiodarone

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

Theophylline

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

Mercaptopurine

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

PUVA Therapy

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

Vaccines

Methotrexate is an immunosuppressant and may reduce immunological response to concurrent vaccination. Severe antigenic reactions may occur if a live vaccine is given concurrently.

Caffeine- or theophylline-containing beverages

An excessive consumption of caffeine- or theophylline-containing beverages (coffee, caffeine-containing soft drinks, black tea) should be avoided during methotrexate therapy.

INSTRUCTIONS TO PATIENTS

1. Patients should be informed of the potential benefit and risk in the use of methotrexate. The risk of effects on reproduction should be discussed with both male and female patients taking methotrexate.

2. Patients should be informed of the early signs and symptoms of toxicity, of the need to see their doctor promptly if they occur, and the need for close follow-up, including periodic laboratory tests to monitor toxicity.

3. If the clinical situation permits, the treating physician can delegate the subcutaneous administration to the patient or caregiver. In this case, appropriate instruction for self-injection or injection by a caregiver should be provided to the patient. See separate Product information for TREXJECT (with embedded sc needle).

4. Patients receiving methotrexate should avoid excessive unprotected exposure to sun or sunlamps because of possible photosensitivity reactions.

5. Adverse reactions to methotrexate, such as dizziness and fatigue may affect the ability to drive or operate machinery.

ADVERSE EFFECTS

The major toxic effects of methotrexate occur on normal, rapidly proliferating tissues, particularly the bone marrow and gastrointestinal tract. Ulcerations of the oral mucosa are usually the earliest signs of toxicity.

In clinical study MC-MTX.6/RH the overall incidence of adverse events (AEs) over the total period of study within the Safety-Analysis-Set was similar for both treatment groups, with AEs reported in 66.3% of patients in the SC group and 61.7% in the oral group.

As expected, the most commonly reported AEs in both treatment groups belonged to the category gastrointestinal disorders with a total of 42% of study patients. No statistically significant differences were observed between rates of gastrointestinal AEs in both treatment groups (SC group 45.6% vs oral group: 38.3%). The overall incidence of serious adverse events was also similar for both treatment groups (5.7% vs 4.3%).

More patients reported nausea and anorexia in the SC group but stomatitis occurred more often in the oral group. Comparing the frequency distribution of at least moderate adverse events, no significant differences were found regarding nausea, stomatitis and anorexia.

The incidence of diarrhoea was significantly increased in the oral group. All other adverse events were not significantly increased in one or another treatment group.

Other sources report ulcerative stomatitis, leukopenia, nausea and abdominal distress as the most common adverse reactions. Others reported include malaise, undue fatigue, chills and fever, dizziness, drowsiness, tinnitus, and decreased resistance to infection. The incidence and severity of side effects generally appear to be dose- and frequency-related. Adverse reactions have been reported for the various systems:

Skin: dermatitis, erythematous rashes, pruritus, urticaria, photosensitivity, depigmentation/ hyperpigmentation, alopecia, vasculitis, petechiae, ecchymosis, telangiectasia, acne, folliculitis, furunculosis, nail changes. Burning and erythema may appear in psoriatic areas for 1 to 2 days following each dose. Rarely, painful plaque erosions may appear. Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Skin ulceration has been reported in psoriatic patients. Anaphylactic reactions and skin ulceration/necrosis consistent with toxic epidermal necrolysis, soft tissue necrosis and osteonecrosis have also been reported. Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens- Johnson syndrome, exfoliative

dermatitis, skin necrosis, and erythema multiforme have been reported in children and adults within days of oral, intramuscular, intravenous or intrathecal methotrexate administration. Reactions were

noted after single or multiple low, intermediate or high doses of methotrexate.

Blood and lymphatic system: bone marrow depression, leukopenia, neutropenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenia, anaemia (including aplastic anaemia), hypogammaglobulinaemia, decrease in serum albumin. Clinical sequelae such as fever, infections, haemorrhage from various sites, septicaemia, lymphadenopathy and lymphoproliferative disorders may be expected. Megaloblastic anaemia has also been reported, mainly in elderly patients receiving long-term methotrexate therapy. Folate supplementation may permit continuation of methotrexate therapy with resolution of anaemia.

Cardiovascular system: Pericarditis, vasculitis, pericardial effusion, hypotension and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis and pulmonary embolus) have been reported with methotrexate therapy.

Alimentary system: mucositis (gingivitis, pharyngitis, stomatitis, glossitis), anorexia, nausea, vomiting, diarrhoea, abdominal distress, haematemesis, melena, gastrointestinal ulceration and bleeding, intestinal perforation, pancreatitis, enteritis, acute and chronic hepatic toxicity resulting in acute liver atrophy, necrosis, fatty metamorphosis, acute hepatitis, periportal fibrosis, or hepatic cirrhosis', elevated liver enzymes, decreased serum albumin and hepatic failure. In rare cases, the effect of methotrexate on the intestinal mucosa has led to malabsorption or toxic megacolon. Alteration of liver function tests (increases in transaminases and LDH levels) is commonly reported but usually resolves within one month of cessation of therapy.

Urogenital system: renal failure, dysuria, azotaemia, cystitis, haematuria, defective oogenesis or spermatogenesis, transient oligospermia, urogenital or menstrual dysfunction, infertility, abortion, foetal defects, foetal death, severe nephropathy, vaginitis, vaginal discharge.

Pulmonary system: interstitial pneumonitis, interstitial fibrosis, reversible eosinophilic pulmonary infiltrates, respiratory fibrosis, respiratory failure, chronic interstitial obstructive pulmonary disease, alveolitis, death. Manifestations of methotrexate-induced pulmonary toxicity commonly include fever, cough (especially dry and non-productive), dyspnoea, chest pain, hypoxaemia and/or radiological evidence of pulmonary infiltrates (usually diffuse and/or alveolar).

Central nervous system: headaches, drowsiness, blurred vision, speech impairment including dysarthria and aphasia, and coma. Aphasia, hemiparesis and convulsions have occurred possibly related to haemorrhage or to complications from intra-arterial catheterization. Following low doses, occasional patients have reported transient subtle cognitive dysfunction, mood alteration or unusual cranial sensations.

Ophthalmic: conjunctivitis, eye discomfort, blurred vision and serious visual changes of unknown aetiology including transient blindness have been reported in patients receiving methotrexate.

Infections: There have been case reports of sometimes fatal opportunistic infections in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases. Pneumocystis jirovecii pneumonia was the most common infection. Other reported infections include pneumonia, sepsis, nocardiosis, histoplasmosis, cryptococcosis, *Herpes Zoster*, *H.simplex* hepatitis, disseminated *H.simplex*, fatal sepsis and cytomegalovirus, including cytomegaloviral pneumonia.

Carcinogenicity: Cytotoxic drugs have been reported to be associated with an increased risk of development of secondary tumours in humans. Evidence of chromosomal damage to animal somatic cells and human bone marrow cells has been reported with methotrexate. Reports of lymphoma, including reversible lymphomas have been documented in patients treated with methotrexate.

Other reactions related to or attributed to the use of methotrexate, such as metabolic changes, precipitation of diabetes, osteoporotic effects (including aseptic necrosis of the femoral head), abnormal changes in tissue cells, arthralgia/myalgia, proteinuria, nodulosis, stress fractures, loss of libido, impotence, encephalopathy/leukoencephalopathy and even sudden death, have been reported.

Radiation dermatitis and sunburn may be "recalled". A few cases of anaphylactoid reactions have been reported.

DOSAGE AND ADMINISTRATION

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.

TREXJECT IN should only be prescribed by physicians who are familiar with the various characteristics of the medicinal product and its mode of action. TREXJECT IN is injected once weekly by a healthcare professional. If the clinical situation permits, the treating physician can delegate subcutaneous administration to the patient or caregiver. See separate Product information for TREXJECT (with embedded sc needle).

The patient is to be explicitly informed about the fact of administration once weekly. It is advisable to determine a fixed, appropriate weekday as the day of injection.

Methotrexate elimination is reduced in patients with a third distribution space (ascites, pleural effusions). Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration (see **Pharmacokinetics** and **PRECAUTIONS**).

Assessment of renal function, liver function and blood elements should be made by history, physical examination and laboratory tests (such as haemogram, 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. Additional monitoring may also be required when changing from oral to parenteral routes of administration. Appropriate steps should be taken to avoid conception for at least 12 weeks following methotrexate therapy.

If changing the oral application to parenteral administration a reduction of the dose may be required due to the variable bioavailability of methotrexate after oral administration. (See also **PHARMACOLOGY**, Studies comparing Oral with Parenteral Administration.) Folic acid supplementation may be considered according to current treatment guidelines.

No dose adjustment is necessary when switching from the intramuscular to the subcutaneous route or vice versa.

Dosage of TREXJECT IN for adult patients with rheumatoid arthritis:

A weekly dose of 7.5 to 25 mg is recommended, depending on response and tolerability. The recommended initial dose is 7.5 mg of methotrexate once weekly, administered subcutaneously or intramuscularly. Depending on the individual activity of the disease and tolerability by the patient, the initial dose may be increased gradually by 2.5 mg per week. A weekly dose of 25 mg should not be exceeded. Dosage should not ordinarily exceed 20 mg/week due to significant increase in toxicity, especially bone marrow suppression.

Response to treatment can be expected after approximately 4 – 8 weeks.

Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Dosage of TREXJECT IN for patients with psoriasis vulgaris:

A weekly dose of 7.5 to 25 mg is recommended, depending on response and tolerability. The recommended initial dose is 7.5 mg of methotrexate once weekly, administered subcutaneously or intramuscularly. The dose is to be increased gradually but should not exceed a weekly dose of 25 mg of methotrexate. Dosage should not ordinarily exceed 20 mg/week due to significant increase in toxicity, especially bone marrow suppression.

Response to treatment can generally be expected after approximately 2-6 weeks.

Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Patients with renal impairment:
TREXJECT IN should be used with caution in patients with impaired renal function. The dose should be adjusted as follows:

Chronic kidney disease stage	**Estimated glomerular filtration rate***	**Creatinine clearance (mL/min)**	**Dose**
I, II	≥ 60	≥ 60	100%
III	30 - 60	30 - 60	50%
IV, V	< 30	< 30	TREXJECT IN® must not be used
** Normalized to an average body surface area of 1.73m²*			

Patients with hepatic impairment:
Methotrexate should be administered with great caution, if at all, to patients with significant current or previous liver disease, especially if due to alcohol. If bilirubin is > 5 mg/dl µmol/l), methotrexate is contraindicated.

Use in elderly patients:
Dose reduction should be considered in elderly patients due to reduced liver and kidney function as well as lower folate reserves which occur with increased age.

Use in patient with a third distribution space (pleural effusions, ascitis):

As the half-life of Methotrexate can be prolonged to 4 times the normal length in patients who possess a third distribution space dose reduction or, in some cases, discontinuation of methotrexate administration may be required.

Duration and method of administration:
The medicine is for single use only.

TREXJECT IN solution for injection is administered by the intramuscular or subcutaneous route by a healthcare professional. TREXJECT IN is not approved for intravenous use.

The overall duration of the treatment is decided by the physician.

Instructions for handling:

The following protective recommendations are given due to the toxic nature of this substance:

- personnel should be trained in good handling technique
- pregnant staff should be excluded from working with this drug
- personnel handling methotrexate injection should wear disposable gloves
- all items used for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for disposal in a cytotoxic waste bin
- accidental contact with the skin or eyes should be treated immediately by copious lavage with water or sodium bicarbonate solution; medical attention should be sought.

OVERDOSAGE

Discontinue methotrexate at the first sign of ulceration or bleeding, diarrhoea or marked depression of the haematopoietic system.

Symptoms following overdosage would be expected to produce effects, which are an extension of the pharmacological effects. The toxic reactions expected would include those listed under **ADVERSE EFFECTS.**

Calcium folinate (leucovorin calcium) is a potent agent for neutralising the immediate toxic effects of methotrexate on the haematopoietic system. In general, when overdosage is suspected, the dose of calcium folinate should be equal to or higher than the offending dose of methotrexate, and should be given as soon as possible, preferably within the first hour after which it is much less effective. Calcium folinate may be administered by IV infusion in doses of up to 75 mg within 12 hours, followed by 12 mg IM every 6 hours for 4 doses. When average doses of methotrexate appear to have an adverse effect, 6 to 12 mg of calcium folinate may be given IM every 6 hours for 4 doses.

Concomitant hydration and alkalinisation of the urine with sodium bicarbonate is recommended to prevent precipitation of methotrexate or its metabolite in the renal tubules. Patients undergoing methotrexate therapy should be advised to increase fluid intake. Neither standard haemodialysis nor peritoneal dialysis have been shown to significantly improve methotrexate elimination. Some clearance of methotrexate may be obtained by haemodialysis if the patient is totally anuric and no

other therapeutic options are available. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high-flux dialyzer.

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 alkalinisation, 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 haemodialysis with a high-flux dialyzer may also be beneficial in these patients.

For advice on the management of overdose please contact the Poisons Information Centre anywhere in Australia on 13 11 26.

PRESENTATION AND STORAGE CONDITIONS

TREXJECT IN is supplied in a pre- -filled syringe of colourless glass (type I) of 1 mL capacity for subcutaneous or intramuscular administration by a healthcare professional.

Plunger stoppers of chlorobutyl rubber (type I) and HDPE polystyrene or polypropylene rods form the syringe plunger. Each syringe is marked with graduation marks, the name and strength of the medicine, and the expiry date and batch number. The syringe barrel includes a colour coded plastic back stop for each strength as described below:-

Pack sizes:

1. Syringe with 0.15 mL solution for injection, equivalent to 7.5 mg methotrexate.
   The syringe barrel is made of glass and has a **red** colour coded plastic backstop.

2. Syringe with 0.20 mL solution for injection, equivalent to 10 mg methotrexate.
   The syringe barrel is made of glass and has a **green** colour coded plastic backstop.

3. Syringe with 0.25 mL solution for injection, equivalent to 12.5 mg methotrexate.
   The syringe barrel is made of glass and has a **light blue** colour coded plastic backstop.

4. Syringe with 0.30 mL solution for injection, equivalent to 15 mg methotrexate.
   The syringe barrel is made of glass and has a **purple** colour coded plastic backstop.

5. Syringe with 0.35 mL solution for injection, equivalent to 17.5 mg methotrexate.
   The syringe barrel is made of glass and has a **pink** colour coded plastic backstop.

6. Syringe with 0.40 mL solution for injection, equivalent to 20 mg methotrexate.
   The syringe barrel is made of glass and has a **dark red** colour coded plastic backstop.

7. Syringe with 0.45 mL solution for injection, equivalent to 22.5 mg methotrexate.
   The syringe barrel is made of glass and has a **dark green** colour coded plastic backstop.

8. Syringe with 0.50 mL solution for injection, equivalent to 25 mg methotrexate.
   The syringe barrel is made of glass and has a **blue** colour coded plastic backstop.

TREXJECT IN is available in packs of 1, 4, 6, 12 and 24 syringes.

Not all presentations and pack sizes may be marketed.

Store below 25°C. Keep the pre-filled syringes in the outer carton in order to protect from light.

TREXJECT IN is intended for single use in one patient on one occasion only. Discard any residue in accordance with **Instructions for handling**, above.

NAME AND ADDRESS OF THE SPONSOR

Link Medical Products Pty Ltd
5 Apollo Street
Warriewood NSW 2102 Australia

Tel: (61) 2 9997 7176

Website: http://www.linkhealthcare.com.au

POISON SCHEDULE OF THE MEDICINE:

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

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