NEW ZEALAND DATA SHEET
METHOTREXATE SANDOZ (METHOTREXATE)

WARNING

Methotrexate must only be used by physicians experienced in anti-metabolite chemotherapy, or in the case of non-oncological conditions, by a specialist physician.

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, by biopsy and/or after consultation.

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

2. 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.

3. Malignant lymphomas, which may regress following withdrawal of methotrexate, may occur in patients receiving low-dose methotrexate and, thus, may not require cytotoxic treatment. Discontinue methotrexate first and, if the lymphoma does not regress, appropriate treatment should be instituted.

4. Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy.

5. **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 unless the potential benefits can be expected to outweigh the considered risks. 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.

6. Methotrexate is usually contraindicated in patients with impaired renal function.

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

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

9. 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 (e.g. 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.

10. **Use in children**

    Aside from its established use in cancer chemotherapy; the safety and efficacy of using methotrexate in children has not been fully elucidated.

11. 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 strength of methotrexate is given to the patient.

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

13. **Use in lacatation**

    Women should be advised not to breastfeed while being treated with methotrexate.

1. PRODUCT NAME

Methotrexate Sandoz 20 mg/mL solution for injection, pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL of solution for injection contains 20 mg methotrexate (as 21.94 mg methotrexate disodium).

1 pre-filled syringe of 0.375 mL solution for injection contains 7.5 mg methotrexate.

1 pre-filled syringe of 0.5 mL solution for injection contains 10 mg methotrexate.

1 pre-filled syringe of 0.625 mL solution for injection contains 12.5 mg methotrexate.

1 pre-filled syringe of 0.75 mL solution for injection contains 15 mg methotrexate.

1 pre-filled syringe of 0.875 mL solution for injection contains 17.5 mg methotrexate.

1 pre-filled syringe of 1 mL solution for injection contains 20 mg methotrexate.

1 pre-filled syringe of 1.125 mL solution for injection contains 22.5 mg methotrexate.

1 pre-filled syringe of 1.25 mL solution for injection contains 25 mg methotrexate.

1 pre-filled syringe of 1.375 mL solution for injection contains 27.5 mg methotrexate.

1 pre-filled syringe of 1.5 mL solution for injection contains 30 mg methotrexate.

1 pre-filled syringe of 2.0 mL solution for injection contains 40 mg methotrexate.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Clear, yellowish solution for injection.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

- Active rheumatoid arthritis in adult patients where treatment with disease modifying antirheumatic drugs (DMARDs) is indicated.
- Polyarthritic forms of severe, active juvenile idiopathic arthritis (JIA) when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate
- Severe forms of psoriasis vulgaris, particularly of the plaque type, which cannot be sufficiently treated with conventional therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis.

4.2. DOSE AND METHOD OF ADMINISTRATION

Methotrexate should only be prescribed by physicians who are familiar with the various characteristics of the medicinal product and its mode of action. The administration should routinely be done by health professionals. If the clinical situation permits the treating physician can, in selected cases, delegate the administration to the patient her/himself. In these cases, detailed administration instructions from the physician are obligate.

Methotrexate is only administered once weekly.

Methotrexate Sandoz® is injected once weekly! Patients have to be clearly informed that Methotrexate Sandoz® must be administered once weekly! It is recommended to specify a certain day of the week as “day for injection”.

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

Dosage in patients with rheumatoid arthritis

The recommended initial dose is 7.5 mg of methotrexate once weekly, administered either subcutaneously, intramuscularly or intravenously. Depending on the individual activity of the disease and tolerability by the patient, the dose may be increased gradually by 2.5 mg per week. A weekly dose of 25 mg should not be exceeded.

However, doses exceeding 20 mg/week can be associated with 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 in children and adolescents with polyarthritic forms of juvenile idiopathic arthritis

The recommended dose is 10-15 mg/m² body surface area (BSA)/week. In therapy-refractory cases the weekly dosage may be increased up to 20mg/m^2 body surface area/week. However, an increased monitoring frequency is indicated if the dose is increased.

Due to limited data availability about intravenous use in children and adolescents, parenteral administration is limited to subcutaneous and intramuscular injection.

Patients with JIA should always be referred to a rheumatology unit specializing in the treatment of children/adolescents.

Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety are available for this population.

Dosage in patients with severe forms of psoriasis and psoriatic arthritis

It is recommended that a test dose of 5 - 10 mg should be administered parenterally, one week prior to therapy to detect idiosyncratic adverse reactions.

The recommended initial dose is 7.5 mg of methotrexate once weekly, administered either subcutaneously, intramuscularly or intravenously.

The dose should be increased as necessary but should not exceed a maximum weekly dose of 30 mg of methotrexate.

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.

Dosage in patients with renal impairment

Methotrexate should be used with caution in patients with impaired renal function. The dose should be adjusted as follows:

Creatinine clearance (mL/min)

> 50 100% of dose

20-50 50% of dose

< 20 Methotrexate must not be used

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 (85.5 µmol/l), methotrexate is contraindicated.

Method and duration of administration

The medicinal product is for single use only.

Methotrexate Sandoz® can be given by subcutaneous, intramuscular or, intravenous route. In adults, intravenous administration should be given as a bolus injection. The overall duration of the treatment is decided by the physician.

Methotrexate Sandoz® treatment of rheumatoid arthritis, juvenile idiopathic arthritis, severe psoriasis vulgaris and psoriatic arthritis represents long-term treatment.

Rheumatoid arthritis

Treatment response in patients with rheumatoid arthritis can be expected after 4-8 weeks. Symptoms may return after treatment discontinuation.

Severe forms of psoriasis vulgaris and psoriatic arthritis

Response to treatment can generally be expected after 2-6 weeks. Depending on the clinical picture and the changes of laboratory parameters, the therapy is then continued or discontinued.

Special note

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.

Folic acid or folinic acid supplementation may be considered according to current treatment guidelines.

Any contact of methotrexate with skin and mucosa is to be avoided. In case of contamination, the affected parts are to be rinsed immediately with plenty of water.

The solution is to be visually inspected prior to use. Only clear solutions practically free from particles should be used.

4.3. CONTRAINDICATIONS

Methotrexate Sandoz® is contraindicated in:

- hypersensitivity to methotrexate or to any of the excipients
- alcohol abuse
- severe renal impairment.
- In the treatment of psoriasis and rheumatoid arthritis, methotrexate is contraindicated in pregnant women and in patients with poor nutritional status, bone marrow depression, hepatic disorders or those with pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia
- serious, acute or chronic infections such as tuberculosis and HIV, ulcers of the oral cavity and known active gastrointestinal ulcer disease
- in patients with overt or laboratory evidence of immunodeficiency syndrome(s)
- breast-feeding
- in rheumatoid arthritis patients with active, infectious disease or psoriasis patients with serious infections, and in psoriasis and rheumatoid arthritis patients with peptic ulcer disease or ulcerative colitis. Methotrexate is contraindicated in psoriatic and rheumatoid arthritis patients suffering severe renal disorders, alcoholism or hepatic disorders including alcoholic liver disease or other chronic liver disease.
- concurrent vaccination with live vaccines
- an increased risk of hepatitis has been reported to result from combined use of methotrexate and etretinate. Therefore, the combination of methotrexate and acitretin is also contraindicated.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients must be clearly informed, that Methotrexate Sandoz® must be administered once a week, not every day.

Methotrexate must only be used by physicians experienced in antimetabolite chemotherapy or, in the case of non-oncological conditions, by a specialist physician.

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 effects may be detected as early as possible. This is especially important in patients undergoing high dose therapy or in those 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 chemotherapy because of its haematopoietic suppressive effects, manifesting as anaemia, aplastic anaemia, pancytopenia, leucopenia, 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. Methotrexate should be used with caution, if at all, in patients with malignant disease who have pre-existing bone marrow aplasia, leucopenia, thrombocytopenia, or anaemia.

Check the following before and during use

As methotrexate is excreted primarily by the kidney, its use in the presence of impaired renal function may lead to drug accumulation with resultant toxicity or even additional renal damage. 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. The urine should be kept alkaline throughout therapy with methotrexate (methotrexate is a weak acid and tends to precipitate at urine pH below 6.0)

Methotrexate may cause renal damage that may lead to acute renal failure. Close attention to renal function including adequate hydration, urine alkalinisation, and measurement of serum methotrexate and renal function are recommended.

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

Methotrexate has been associated with pulmonary toxicity, which is potentially fatal. Patients should be closely monitored for pulmonary symptoms. Methotrexate should be discontinued and careful clinical evaluation should be performed in patients developing pulmonary manifestations (especially a dry, non-productive cough). 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 boxed Warning**)**. Infection (including pneumonia) needs to be excluded.

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.

The following laboratory tests should be carried out as part of the essential clinical evaluation and appropriate monitoring of patients on methotrexate therapy; complete haemogram; haematocrit; urinalysis; renal and liver function tests. A chest x-ray is recommended. The tests should be performed prior to, during and after therapy. During therapy for psoriasis, monitoring of the following parameters is recommended: haematology at least monthly, liver and renal function every one to three months. More frequent monitoring is usually indicated during antineoplastic therapy. It is important to perform liver biopsy or bone marrow aspiration studies where high dose or long term therapy is being followed. Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.

During therapy of rheumatoid arthritis and psoriasis, monitoring of the following parameters is recommended: haematology at least monthly, hepatic enzyme levels and renal function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. During initial or change in dosing, or during periods of increased risk of elevated methotrexate blood levels (e.g. dehydration), more frequent monitoring may also be indicated.

Methotrexate should be used with extreme caution in the presence of infection, peptic ulcer, ulcerative colitis, debility, and in extreme youth and old age.

Methotrexate should be used with extreme caution in the presence of active infection, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes.

Like other cytotoxic drugs, methotrexate may induce “tumour lysis syndrome” in pateints with rapidly growing tumours. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication.

Methotrexate exits slowly from the third-space compartments (e.g. 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 and to monitor plasma methotrexate levels.

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, advanced age and arsenical compounds. 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.

In psoriasis, liver damage and function tests, including serum albumin and prothrombin time, should be performed several times prior to dosing. Liver function tests are often normal in developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. It is recommended to obtain a liver biopsy at: 1) before start of therapy or shortly after initiation of

therapy (2 – 4 months); 2) after a total cumulative dose of 1.5 grams; and 3) after each additional 1.0 to 1.5 grams. In case of moderate fibrosis or any cirrhosis, discontinue the drug; mild fibrosis normally suggests a repeat biopsy in 6 months. Milder histologic findings such as fatty change and low grade portal inflammation are relatively common before the start of therapy. Although these mild changes are usually not a reason to avoid or discontinue methotrexate therapy, methotrexate should be used with caution.

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

If the results of a liver biopsy show mild changes (Roenigk grades I, II, IIIa), methotrexate 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).

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 leucopenia 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 carinii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pnemocystis carinii* 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 Section 4.5 Interactions with other medicines and other forms of interactions).

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.

When considering the use of methotrexate for chemotherapy, clinicians must evaluate the need and potential value of the drug against the risks, adverse effects or toxic effects. Most adverse effects are reversible if detected early. When such reactions do occur, the dosage should be reduced or drug discontinued and appropriate corrective measures taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermittent haemodialysis with a high-flux dialyser. Caution should be exercised when reinstituting methotrexate therapy and adequate consideration given to the need for further drug administration and alertness to the possible recurrence of toxicity.

Transient abnormalities of liver function tests (elevated transaminases) are observed frequently but persistent abnormalities and/or significant decreases in serum albumin may indicate serious

liver toxicity and require evaluation. Liver biopsy is currently believed to be the only reliable measure of methotrexate-induced hepatotoxicity.

When to perform a liver biopsy in rheumatoid arthritis patients has not been established, either in terms of cumulative methotrexate dose or duration of therapy. There is a combined reported experience in 217 patients with rheumatoid arthritis with liver biopsy both before and during treatment (after a cumulative dose of at least 1500 mg) and in 714 patients with a biopsy only during treatment. There were 64 (7%) cases of fibrosis and only one (0.1%) case of cirrhosis. Of the 64 cases of fibrosis, 60 were deemed mild. The reticulin stain is more sensitive for early fibrosis and its use may increase these figures. It is unknown whether even longer use will increase these risks. When methotrexate is discontinued, a "flare" of arthritis usually occurs within three to six weeks.

Both the physician and the pharmacist should emphasise to the patient the importance of the weekly dosage regimens; mistaken daily use may cause serious and sometimes life-threatening or fatal toxicity (see boxed Warning and Section 4.4 Special warnings and precautions for use).This medicinal product contains less than 1 mmol sodium (23 mg) per dose and is i.e. essentially "sodium-free".

Paediatric use

Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety are available for this population.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

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 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 and sulfonamides. There is a considerable risk of methotrexate toxicity. Use of methotrexate with penicillins and sulfonamides 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.

In inflammatory arthritis, such as rheumatoid arthritis, concomitant treatment with folinic acid or folic acid may decrease the incidence or severity of adverse effects from methotrexate

therapy. It is not known whether these medications may decrease the efficacy of methotrexate in treating arthritis. Because vitamin preparations containing folic acid or folinic acid may decrease the effectiveness or alter the responses to methotrexate these should not be given to patients taking methotrexate for conditions other than arthritis, including in the treatment of neoplastic disease.

NSAIDs should not be administered prior to or concomitantly with high doses of methotrexate. NSAIDs elevate and prolong serum methotrexate levels, resulting in deaths from severe haematologic and gastrointestinal toxicity. These unexpectedly severe toxicities have been

reported with concomitant administration of methotrexate and aspirin, other salicylates, azapropazone, diclofenac, indomethacin and ketoprofen. Naproxen has been reported not to affect the pharmacokinetics of methotrexate but a fatal interaction has been reported.

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 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 rheumatoid arthritis (7.5 to 15 mg/week) are somewhat lower than those used in psoriasis and the 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 may increase the methotrexate plasma half-life and thereby increase blood levels.

A potential interaction may exist between methotrexate and proton pump inhibitors (e.g. omeprazole, pantoprazole).

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

Methotrexate in combination with leflunomide may also increase the risk of pancytopenia and interstitial pneumonitis.

Methotrexate is often used in combination with other cytotoxic drugs. Additive toxicity may be expected in chemotherapy regimens which combine drugs with similar pharmacologic effects and special monitoring should be performed with regard to bone marrow depression, renal, gastrointestinal and pulmonary toxicity. The dosage of methotrexate should be adjusted if it is used in combination with other chemotherapeutic agents with overlapping toxicities.

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.

The use of nitrous oxide anaesthesia potentiates the effect of methotrexate on folate metabolism, yielding severe, unpredictable myelosuppression and stomatitis. This effect can be reduced by the use of calcium folinate.

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

An increased risk of hepatotoxicity has been reported when methotrexate and etretinate are given concurrently (see Section 4.3 Contraindications).

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

monitored for possible increased risk of hepatotoxicity. Methotrexate in combination with leflunomide may also increase the risk of pancytopenia.

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

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

The administration of asparaginase has been reported to antagonise the effects of methotrexate.

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).

Care should be exercised whenever packed red blood cells and methotrexate are given concurrently. Patients receiving 24 hour methotrexate infusion and subsequent transfusions have showed enhanced toxicity probably resulting from prolonged serum methotrexate concentrations.

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

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 hydromethotrexate, possibly leading to methotrexate toxicities.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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.

Use in pregnancy

Category D

Methotrexate is contraindicated during pregnancy. In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester. Methotrexate has been shown to be teratogenic to humans; it has been reported to cause fetal death and/or congenital abnormalities. Exposure of a limited number of pregnant women (42) resulted in an increased incidence (1:14) of malformations (cranial, cardiovascular and extremital). If methotrexate is discontinued prior to conception, normal pregnancies have been reported.

In women of child-bearing age, any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. a pregnancy test, prior to initiating therapy. Women must not get pregnant during methotrexate therapy and patients of a sexually mature age (women and men) must use effective contraception during treatment with Methotrexate Sandoz® and at least 6 months thereafter (see Section 4.4 Special warnings and precautions for use). If, nevertheless, pregnancy occurs during this period, medical advice should be given regarding the risk of harmful effects on the child associated with treatment.

As methotrexate can be genotoxic, all women who wish to become pregnant are advised to consult a genetic counselling centre, if possible, already prior to therapy, and men should seek advice about the possibility of sperm preservation before starting therapy.

Use in lactation

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

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8. UNDESIRABLE EFFECTS

Occurrence and severity of undesirable effects depend on dosage level and frequency of Methotrexate Sandoz® administration. However, as severe adverse reactions may occur even at lower doses, it is indispensable that the doctor monitors patients regularly at short intervals.

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.

Ulcerative stomatitis, leucopenia, nausea and abdominal distress are the most common adverse effects. Others reported include malaise, undue fatigue, chills and fever, dizziness, drowsiness, tinnitus, blurred vision, eye discomfort and decreased resistance to infection. The incidence and severity of side effects generally appear to be dose- and frequency-related. Adverse effects 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 in patients with neoplastic and non-neoplastic diseases.

Blood and lymphatic system: bone marrow depression, leucopenia, 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 proliferative 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). Pulmonary alveolar haemorrhage has been reported for methotrexate used in rheumatologic and related indications.

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 carinii 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 and tumour lysis syndrome 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 and even sudden death, have been reported.

Radiation dermatitis and sunburn may be "recalled". A few cases of anaphylactoid reactions have been reported.***Reporting suspected adverse effects***

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9. OVERDOSE

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

Signs and symptoms

Symptoms commonly reported following overdose include those symptoms and signs reported at pharmacological doses, particularly haematological and gastrointestinal reactions. For example, leucopenia, thrombocytopenia, anaemia, pancytopenia, bone marrow suppression, mucositis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In some cases, no symptoms were reported. There have been reports of death following overdose. In these cases, events such as sepsis or septic shock, renal failure, and aplastic anaemia were also reported.

Symptoms following injectable overdosage would be expected to produce effects, which are an extension of the pharmacological effects. The toxic reactions expected would include those listed under Section 4.8 Undesirable effects.

Management

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 National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group

Pharmacotherapeutic group: Other immunosuppressants; Folic acid analogues. ATC-code: L01BA01.

Mechanism of action

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, e.g. malignant cells, 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 epithelialcells 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.

Clinical trials

Rheumatoid Arthritis

Subcutaneous use

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 ≥ 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%).

Methotrexate 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.

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 randomised 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.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

After oral application, methotrexate is absorbed from the gastrointestinal tract.

Distribution

When administered in low doses (7.5 mg/m^2 to 80 mg/m^2 body surface area), methotrexate has a mean bioavailability of approximately 70%, although considerable inter- and intra-subject variations are possible (25-100%). Plasma peak concentrations are attained within 1-2 hours. Subcutaneous, intravenous and intramuscular administration demonstrated similar bioavailability.

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

Approximately 50% of methotrexate is bound to serum proteins. Upon being distributed into body tissues, high concentrations particularly in liver, kidneys and spleen in form of polyglutamates can be found, which can be retained for weeks or months. When administered in small doses, methotrexate passes into the liquor in minimal amounts; under high doses (300 mg/kg body weight), concentrations between 4 and 7 µg/mL have been measured in the liquor. Average terminal half-life is 6-7 hours and demonstrates considerable variation (3-17 hours). Half-life may be prolonged to 4 times the normal length in patients with third spaces (pleural effusion, ascites). Approximately 10% of the administered methotrexate is metabolised intra-hepatically. The major metabolite is 7-hydroxymethotrexate.

Excretion

Excretion takes place, mainly in unchanged form, primarily renal via glomerular filtration and active secretion in the proximal tubulus. Approx. 5-20% of methotrexate and 1-5% of 7-hydroxymethotrexate are eliminated via the bile. Pronounced entero-hepatic blood flow exists.

Special patient considerations

Methotrexate passes the placental barrier in rats and monkeys.

Renal Impairment

In case of renal insufficiency, elimination is delayed significantly. Impaired elimination in presence of hepatic insufficiency is not known.

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 C_{max} for SC administration is approximately 60% of that seen following IM injection of MTX.

Table 1. 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 (%)**
T_{max} h	1 (1.7)	0.5 (1.7)		
AUC0-t (µg*h/L)	1020.79 (1.23)	1043.33 (1.18)	97.84	91.07 – 105.11
AUC0-∞ (µg*h/L)	1058.89 (1.22)	1088.86 (1.18)	97.25	91.00 – 103.92
C_{max} (µg/L)	221.76 (1.39)	381.28 (1.37)	58.16	47.61 - 71.06
AUC = area under the plasma concentration time curve; C_{max} = 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 C_{max} 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 C_{max} 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.

Table 2. 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)

Treatment	50 mg/mL (test)	10 mg/mL (reference)	50 mg/mL (test)	10 mg/mL (reference)
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.

5.3. PRECLINICAL SAFETY DATA

Chronic toxicity

Chronic toxicity studies in mice, rats and dogs showed toxic effects in the form of gastrointestinal lesions, myelosuppression and hepatotoxicity.

Mutagenic and carcinogenic potential

Long-term studies in rats, mice and hamsters did not show any evidence of a tumorigenic potential of methotrexate. Methotrexate induces gene and chromosome mutations both in vitro and in vivo. A mutagenic effect is suspected in humans.

Reproductive toxicology

Teratogenic effects have been identified in four species (rats, mice, rabbits, cats). In rhesus monkeys, no malformations comparable to humans occurred.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Sodium chloride

Sodium hydroxide for pH adjustment

Water for injections

6.2. INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3. SHELF LIFE

2 years

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store in the original package in order to protect from light.

Do not store above 25°C

6.5. NATURE AND CONTENTS OF CONTAINER

Methotrexate Sandoz® [7.5 mg, 10 mg, 12.5 mg, 15 mg & 17.5 mg] is available in pre-filled syringes with a capacity of 1.25 mL of colourless glass (type I according Ph.Eur), an elastomeric tip cap and an elastomeric plunger stopper.

Methotrexate Sandoz® [20 mg, 22.5 mg, 25 mg, 27.5 mg & 30 mg] is available in pre-filled syringes with a capacity of 2.25 mL of colourless glass (type I according Ph.Eur), an elastomeric tip cap and an elastomeric plunger stopper.

Methotrexate Sandoz® [40 mg] is available in pre-filled syringes with a capacity of 3.0 mL of colourless glass (type I according Ph.Eur), an elastomeric tip cap and an elastomeric plunger stopper.

Each box contains 1, 4, 5, 6 or 12 pre-filled syringes with 1 mL, 1.25mL, 1.5 mLand 2.0 mL solution for injection, single-use injection needles and alcohol pads.

Not all pack sizes may be marketed.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

Administration Precautions:

Handling and disposal must be consistent with that of other cytotoxic preparations in accordance with local requirements. Pregnant health care personnel should not handle and/or administer Methotrexate Sandoz®.

Reconstitution/Preparation Administration:

For single use only. Any unused solution should be discarded.

Procedure for proper disposal:

Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Novartis New Zealand Limited
PO Box 99102, Newmarket,
Auckland 1149

Telephone: 0800 354 335

9. DATE OF FIRST APPROVAL

08 Dec 2011

10. DATE OF REVISION OF THE TEXT

05/12/2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Minor editorial changes made throughout.
Boxed Warning	Addition of boxed warning.
4.3	Updated contraindications.
4.4	Updated precautions and warnings.
4.5	Updated interactions with other medicines and other forms of interactions
4.6	Updated fertility and lactation information.
4.7	Updated effects on ability to drive and use machines information.
4.8	Updated adverse events information.
4.9	Updated overdosage information.
5.1	Updated mechanism of action and inclusion of clinical trials information.
5.2	Updated pharmacokinetic information.