NEW ZEALAND DATA SHEET

WARNINGS

Methotrexate may cause significant toxicities which may be fatal including haematological, hepatic, renal, pulmonary, gastrointestinal, dermatological, and immune-related. See section 4.4.

The importance of once weekly dosing should be emphasized. Mistaken daily use may cause serious and sometimes life-threatening or fatal toxicity.

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.

Important warning about the dosage of methotrexate

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”.

Dosage errors in the use of methotrexate can results in serious adverse reactions, including death. Please read this section of the product information carefully.

Prescribers should advise the patient of the dosing regimen for their awareness and obtain at least verbal indication from the patient that they have understood the dosing regimen.

Pharmacists should clearly indicate the dosing regimen on the dispensing label at the point of dispensing and obtain at least a verbal indication from the patient that they have understood the dosing regimen.

General

The patient should be fully informed of the risks involved and should be under constant supervision of the physician.

Methotrexate should be started at a low dose and gradually increased to achieve the optimal clinical response, taking into consideration potential toxicities. All schedules should be continually tailored to the individual patient.

Doses exceeding 20 mg/week can be associated with significant increase in toxicity. Use of such doses should be carefully considered by the physician taking into account the risks and benefits.

Once the optimal clinical response has been achieved, the dosage should be gradually reduced to the lowest possible effective maintenance dose.

Patients should be monitored regularly for treatment response and toxicity and treatment tailored accordingly.

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 25 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 is excreted to a significant extent by the kidneys, and therefore should be used with caution in patients with impaired renal function (see sections 4.3 and 4.4). Dose adjustment may be needed to prevent the accumulation of the medicine. The dose should be adjusted as follows:

Creatinine clearance (mL/min)	**Dose**
> 60	100%
30 – 59	50%
< 30	Contraindicated

Further adjustment may be needed depending on the individual patient.

A lower initial dose and a more gradual dose increase is also recommended in renal impairment. Renal function should be closely monitored.Patients with hepatic impairment

Methotrexate is contraindicated in patients with significantly impaired hepatic function including alcoholism (see section 4.3).

Methotrexate should be administered with great caution to patients with hepatic impairment. Dose adjustment may be needed. See also section 4.4.

If bilirubin is >5 mg/dl (85.5 µmol/l), methotrexate is contraindicated.

Patients who have low albumin levels, such as those with poor nutritional status, may be at greater risk of toxicity.

Use in children

Use in children < 3 years of age for polyarthritic forms of severe, active juvenile idiopathic arthritis (JIA) is not recommended as insufficient data on efficacy and safety are available for this population.

Except in children over 3 years for polyarthritic forms of severe, active juvenile idiopathic arthritis (JIA), methotrexate is not recommended in paediatric patients.

Use in elderly

Due to diminished hepatic and renal functions as well as decreased folate states in elderly patients, lower doses should be considered, and these patients should be closely monitored (see section 4.4).

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 (see Section 6.1 List of excipients),
- alcoholism or hepatic disorders including alcoholic liver disease, severe hepatic impairment or other chronic liver disease,
- severe renal impairment (creatinine clearance less than 30 mL/min),
- pre-existing blood dyscrasias, such as bone marrow hypoplasia, bone marrow depression, leukopenia, thrombocytopenia, or significant anaemia,
- poor nutritional status,
- serious, acute or chronic infections such as tuberculosis, HIV or with overt or laboratory evidence of immunodeficiency syndromes,
- patients with peptic ulcer disease or ulcerative colitis and ulcers of the oral cavity,
- concurrent vaccination with live vaccines.

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.

Methotrexate is contraindicated in pregnancy and breast-feeding.

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

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Weekly dosing

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

Both the physician and the pharmacist should emphasise to the patient the importance of the weekly dosing regimen treatment, as mistaken daily use may cause serious and sometimes life-threatening or fatal toxicity.

General

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 of the possibility of fatal or severe toxic reactions the patient should be fully informed by the doctor of the risks involved before commencing methotrexate treatment, and should remain under the physician's constant supervision.

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.

When considering the use of methotrexate, 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 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.

Fertility

Methotrexate has been reported to cause impairment of fertility, oligospermia, menstrual dysfunction and amenorrhoea in humans, during and for a short time after cessation of therapy, affecting spermatogenesis and oogenesis during the period of its administration.

The risk of effects on reproduction should be discussed with both male and female patients prior to initiating methotrexate (see section 4.6).

Pregnancy

Methotrexate causes embryotoxicity, abortion and foetal malformations in humans. Therefore, the possible effects on reproduction, pregnancy loss and congenital malformations should be discussed with female patients of childbearing age prior to initiating methotrexate (see section 4.6).

Pregnancy should be avoided if either partner is receiving methotrexate, during and after cessation of therapy. Reliable contraception is recommended during and for at least three months after the end of the treatment for males. For females, reliable contraception is recommended during and for at least six months after end of the treatment. The optimal time interval between the cessation of methotrexate treatment of either partner and pregnancy, has not been clearly established.

See section 4.6.

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.

Evaluate for personal and family history of liver disease, personal history of alcohol use or gastrointestinal ulcerative conditions.

In women of childbearing age, rule out pregnancy.

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.

During therapy

Monitoring

Monitor full blood count, liver function and renal function tests, and signs and symptoms of possible toxicity.

Full blood count, renal and liver functions tests should generally be taken weekly until therapy is stabilised, thereafter every 1 – 3 months throughout treatment. Local guidelines should be followed.

More frequent monitoring may be necessary during the initial phase of treatment, when the dose is increased and during episodes of a higher risk of elevated methotrexate blood levels (e.g., dehydration, impaired renal function, additional or elevated dose of medicines administered concomitantly, such as NSAIDs). Closer monitoring is also necessary especially in patients taking other hepatotoxic or haematotoxic or renal toxic medicinal products (see section 4.5), and also in elderly patients.

Patients should also be monitored often for signs and symptoms of methotrexate toxicity as outlined in organ system toxicity below.

Most adverse reactions are reversible if detected early. When adverse reactions do occur, the dose should be reduced or the medicine discontinued, and appropriate corrective measures taken.

Folic acid or folinic acid may reduce methotrexate toxicities such as gastrointestinal symptoms, stomatitis, alopecia, and elevated liver enzymes. Folic acid or folinic acid supplementation may be considered according to current treatment guidelines.

If acute methotrexate toxicity occurs, which may occur at any dose, patients may require folinic acid. It is important to determine any increase in methotrexate levels within 48 hours of therapy, for treatment with folinic acid, otherwise irreversible methotrexate toxicity may occur. See also section 4.9.

Folinic acid deficiency

Folinic acid deficiency states may increase methotrexate toxicity.

Before taking a folate supplement, it is advisable to check B12 levels, particularly in adults over the age of 50, since folate administration can mask symptoms of B12 deficiency.

Hepatotoxic or haematotoxic DMARDs (disease-modifying antirheumatic drugs)

Concomitant use of hepatotoxic or haematotoxic DMARDs (disease-modifying antirheumatic drugs, e.g., leflunomide) is not advisable.

Organ system toxicity

Haematologic

Methotrexate may produce marked depression of bone marrow, anaemia, aplastic anaemia, pancytopenia, leucopenia, neutropenia, thrombocytopenia and bleeding. Clinical sequelae such as fever, sore throat, flu-like symptoms, infections, abnormal bruising and haemorrhage from various sites and septicaemia may be expected. Patients should be encouraged to report signs and symptoms of these if occur.

Methotrexate should not be used in patients with pre-existing haematopoietic impairment (see section 4.3).

Pretreatment and periodic haematologic studies are essential to the use of methotrexate in chemotherapy because of the common effect of haematopoietic suppression. This may occur abruptly and on apparent safe dosage, and any profound drop in blood cell count indicates immediate stoppage of the drug and appropriate therapy.

If profound leucopenia occurs during therapy, bacterial infection may occur or become a threat. Cessation of the drug and appropriate antibiotic therapy is usually indicated. In severe bone marrow depression, blood or platelet transfusions may be necessary.

Concomitant administration of folate antagonists such as trimethoprim/sulfamethoxazole has been reported to cause an acute megaloblastic pancytopenia in rare instances (see section 4.5).

Megaloblastic anaemia has also been reported, mainly in elderly patients receiving long-term weekly methotrexate therapy.

Hepatic

Methotrexate is contraindicated in severe hepatic impairment, particularly if alcohol related (see section 4.3). Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function.

Methotrexate may cause acute and chronic hepatotoxicity, particularly at high dosage or with prolonged therapy, including liver atrophy, necrosis, hepatic cirrhosis, acute hepatitis, fatty changes and periportal fibrosis. Transient and asymptomatic elevations of liver enzymes are frequently seen after methotrexate administration and are usually not a reason for modification of methotrexate therapy or predictive of subsequent hepatic disease.

Persistent abnormalities in liver function tests, and/or significant decreases in serum albumin, and/or symptoms/signs of liver toxicity may be indicators of serious liver toxicity and require evaluation.

Chronic (fibrosis and cirrhosis) liver toxicity is potentially fatal and may occur following prolonged (2 years or longer) treatment and high cumulative drug doses of at least 1.5 grams in non-oncological indications.

Particular attention should be given to the appearance of liver toxicity, since changes may occur without previous signs of gastrointestinal or haematologic toxicity. It is imperative that liver function be determined prior to initiation of treatment and monitored regularly throughout therapy.

Methotrexate has caused reactivation of hepatitis B infection or worsening of hepatitis C infections, in some cases resulting in death. Some cases of hepatitis B reactivation have occurred after discontinuation of methotrexate. Clinical and laboratory evaluation should be performed to evaluate pre-existing liver disease in patients with prior hepatitis B or C infections. Based on these evaluations, treatment with methotrexate may not be appropriate for some patients.

The primary risk factors for severe liver damage, due to methotrexate hepatotoxicity, include: previous liver disease, repeatedly abnormal liver function tests, alcohol consumption/abuse, hepatopathy (including chronic hepatitis B or C), and a family history of hepatopathy. Secondarily risk factors (with possibly lower relevance) for methotrexate hepatotoxicity include diabetes mellitus (in patients treated with insulin), obesity and exposure to hepatotoxic medicines or chemicals. Additional hepatotoxic medicinal products should not be taken during the treatment of methotrexate unless clearly necessary and with close monitoring and the consumption of alcohol should be avoided (see section 4.5).

In studies in psoriatic patients, hepatotoxicity appeared to be correlated not only to the cumulative dose of the drug but also to the presence of concurrent conditions such as alcoholism, obesity, diabetes, advanced age and arsenical compounds.

Treatment should not be instituted or should be discontinued if any abnormalities of liver function tests, or liver biopsy, are present or develop during therapy. Such abnormalities should return to normal within two weeks after which treatment may be recommenced at the discretion of the physician. Temporary increases in transaminases to 2 – 3 x ULN have been reported by patients. In the case of a constant increase in liver-related enzyme, a reduction of the dose or discontinuation of therapy should be considered. Methotrexate should be discontinued if no other reasons for the elevations are found, and the elevations remain above the normal limits.

The need for liver biopsy should be evaluated on an individual basis and national recommendations should be followed.

Renal

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 is recommended.

As methotrexate is eliminated mainly be 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 and use of lower doses are recommended in renal impairment (see section 4.2). If serum creatinine is increased, drug dosage should be reduced or discontinued until renal function is improved or restored.

Methotrexate is contraindicated in patients with severe renal impairment (see section 4.3).

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 drugs) or which can potentially lead to impairment of blood formation. Dehydration may also intensify the toxicity of methotrexate.

Pulmonary

Methotrexate has been associated with pulmonary toxicity, which is potentially fatal. It may occur at any time throughout treatment, and at any dose. Particular caution is required in patients with impaired pulmonary function.

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, 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. Pulmonary diseases induced by methotrexate were not always completely reversible.

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.

Patients should be closely monitored for pulmonary signs and symptoms at each follow-up visit and be informed of the risk of pneumonitis. Patients should be advised to contact their doctor immediately should they develop persistent cough, dyspnoea, fever or if they experience symptoms of spitting or coughing up blood.

Pulmonary function tests may be useful if lung disease (e.g., interstitial pneumonitis) is suspected, especially if baseline measurements are available.

Methotrexate should be discontinued from patients with pulmonary symptoms and a thorough investigation undertaken to exclude infection and tumours, including a chest x-ray. The possibility of *Pneumocystis jirovecii* pneumonia should be taken into account.

If methotrexate induced lung disease is suspected, treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted. Methotrexate-induced pulmonary toxicity may not be fully reversible.

Infection or immunological states

Methotrexate therapy has immunosuppressive activity which can potentially lead to serious or even fatal infections.

Methotrexate is contraindicated in active serious infections and in patients with overt or laboratory evidence of immunodeficiency syndromes (see section 4.3).

Potentially fatal opportunistic infections especially *Pneumocystis jirovecii* pneumonia may occur with methotrexate therapy. This factor must be taken into consideration in evaluating the use of the drug where immune responses in a patient may be important or essential.

Pneumonia (in some cases leading to respiratory failure) may occur. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis jirovecii* pneumonia should be considered.

Special attention should be paid in cases of inactive chronic infections (e.g., herpes zoster, TB, hepatitis B or C) because of their potential for re-activation. These may occur after treatment has been discontinued.

Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients receiving methotrexate, mostly in combination with other immunosuppressive medication. PML can be fatal and should be considered in the differential diagnosis in immunosuppressed patients with new onset or worsening neurological symptoms.

Signs/symptoms of infection should be carefully observed. Patients should be advised to report all symptoms or signs suggestive of infection.

Immunisation

Methotrexate may, due to its effect on the immune system, impair the response to vaccination and affect the result of immunological tests.

Vaccination using live vaccines must not be carried out under methotrexate therapy.

There have been reports of disseminated vaccinia infections after smallpox immunisation in patients receiving methotrexate therapy (see section 4.5).

Gastrointestinal

Vomiting, diarrhoea and ulcerative stomatitis are frequent toxic effects and require interruption of therapy; otherwise haemorrhagic enteritis and death from intestinal perforation may occur. In rare cases the effect of methotrexate on the intestinal mucosa has led to malabsorption or toxic megacolon.

Examine the oral cavity and throat for mucosal change. Encourage patients to report any potential signs for gastrointestinal toxicity such as signs of stomatitis or diarrhoea and vomiting.

If vomiting, diarrhoea, stomatitis or other suggestive symptoms occur, interruption of treatment is generally required until symptoms cease and supportive therapy (including preventing dehydration) should be instituted until recovery occurs.

Gastrointestinal disorders frequently require dosage adjustment.

Conditions leading to dehydration such as emesis, diarrhoea or stomatitis, can increase the toxicity of methotrexate due to elevated levels of the active substance.

Skin

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.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Skin ulceration has been reported in psoriatic patients. Radiation dermatitis and sunburn may be "recalled" by the use of methotrexate.

Patients receiving immunosuppressive therapy, including methotrexate, are at an increased risk of developing skin cancer (melanoma and non-melanoma). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Periodic skin examination is recommended for all patients who are at increased risk for skin cancer and exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Patients receiving methotrexate should avoid excessive unprotected exposure to sun or sunlamps because of possible photosensitivity reactions and increased risk of skin cancer (nonmelanoma and melanoma).

Neurotoxicity

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.

Other

Malignant lymphomas may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued. These lymphomas may regress following withdrawal of methotrexate without requiring treatment. Failure of the lymphoma to show signs of spontaneous regression requires initiation of cytotoxic therapy.

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

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 Section 4.3 Contraindications).

Leflunomide

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

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 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 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 (generally 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 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 (e.g. 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 cytotoxic-induced 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.

Nitrous oxide anaesthesia

The use of nitrous oxide anaesthesia potentiates the effect of methotrexate on folate metabolism, yielding severe, unpredictable myelosuppression and stomatitis. Whilst this effect can be reduced by administering folinic acid, avoid concomitant use of nitrous oxide in patients receiving methotrexate.

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-sulfamethoxazole, 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 methotrexate is administered simultaneously with other antirheumatic medicinal products (e.g. gold compounds, penicillamine, hydroxychloroquine, sulfasalazine, azathioprine).

Ciclosporin

Ciclosporin may potentiate methotrexate efficacy and toxicity. There is an increased risk of renal dysfunction. In addition, there is a biological plausibility of excessive immunosuppression and its associated complications.

Sulfasalazine

Although the combination of methotrexate and sulfasalazine can case increase in efficacy of methotrexate and as a result more undesirable effects due to the inhibition of folic acid synthesis through sulfasalazine, such as 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.

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

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.

Sodium Valproate

Some case reports describe a significant decrease in valproate serum levels after methotrexate administration, with occurrence of seizures. Prescribers should monitor clinical response (seizure control or mood control) and consider monitoring valproate serum levels as appropriate.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Methotrexate may cause impairment of fertility, defective oogenesis and spermatogenesis, oligospermia, menstrual dysfunction and amenorrhoea in humans, during and for a short period after cessation of therapy.

In men and women of fertile age, steps should be taken to avoid conception during methotrexate therapy.

Men undergoing methotrexate therapy should use contraception, and not father a child, during and for three months after treatment because methotrexate may be genotoxic and has caused increased number of abnormal and immobile spermatozoa in clinical studies. Men should not donate semen during therapy or for three months following discontinuation of methotrexate.

The possible risks of effects on reproduction should be discussed with patients of childbearing potential.

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 embryotoxicity, abortion, intrauterine growth restriction, 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.

Methotrexate is not recommended in women of childbearing potential unless there is appropriate medical evidence that benefits are expected to outweigh the considered risks.

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.

Both male and female patients should be fully counselled on the serious risk to the fetus should they become pregnant while undergoing treatment and counselled regarding pregnancy prevention and planning.

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 after therapy has ceased for women, and 3 months after therapy has ceased for men. The optimal time interval between the cessation of methotrexate treatment of either partner, and pregnancy, has not been clearly established). If, nevertheless, pregnancy occurs during this period, medical advice should be given regarding the risk of harmful effects on the child associated with treatment and appropriate examinations should be performed.

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

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

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.

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, leucopenia, nausea and abdominal distress as the most common adverse effects. 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 effects have been reported for the various systems:

Skin and subcutaneous tissue disorders: 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. Skin exfoliation/dermatitis exfoliative reactions have been reported.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia, osteoporosis, stress fracture, osteonecrosis of jaw (secondary to lymphoproliferative disorders).

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 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, 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.

Respiratory, thoracic and mediastinal disorders: interstitial pneumonitis, interstitial fibrosis, reversible eosinophilic pulmonary infiltrates, respiratory fibrosis, respiratory failure, chronic interstitial obstructive pulmonary disease, alveolitis, epistaxis, pulmonary alveolar haemorrhage, 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).

Nervous system disorders: headaches, tiredness, drowsiness, dizziness, pain, muscular asthenia or paraesthesia/hypoaesthesia, changes in sense of taste (metallic taste), meningism, acute aseptic meningitis, paralysis, encephalopathy/ leukoencephalopathy, 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 reactivation of inactive chronic infections, 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.

General disorders and administration site conditions: Fever, wound-healing impairment, local damage (formation of sterile abscess, lipodystrophy) of injection site following intramuscular or subcutaneous administration, asthenia, injection site necrosis, oedema.

Neoplasms benign, malignant, and unspecified: There have been reports of individual cases of lymphoma and other lymphoproliferative disorders which subsided in a number of cases once treatment with methotrexate had been discontinued.

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, proteinuria, nodulosis, 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 of 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://pophealth.my.site.com/carmreportnz/s/.

4.9. OVERDOSE

Cases of overdose (sometimes fatal) due to erroneous daily intake instead of weekly intake of oral methotrexate have been reported (see section 4.4).

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

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.

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.

Management

Calcium folinate (leucovorin calcium) is a potent agent for neutralising the immediate toxic effects of methotrexate on the haematopoietic system. After an inadvertent overdosage of methotrexate, calcium folinate should be given as soon as possible and preferably started within 1 hour after the administration of methotrexate. As the time interval between methotrexate administration and folinic acid initiation increases, the effectiveness of folinic acid in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is

essential in determining the optimal dose and duration of treatment with folinic acid. Refer to the calcium folinate data sheet for dosing and administration information.

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

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.

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

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)
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

Sandoz New Zealand Limited
12 Madden Street
Auckland 1010
New Zealand

Telephone: 0800 726 369

9. DATE OF FIRST APPROVAL

08 Dec 2011

10. DATE OF REVISION OF THE TEXT

11 September 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Minor editorial changes made throughout
Boxed Warning	Boxed warning text content revised
4.2	Maximum weekly dose for use in psoriasis reduced to 25 mg/week Additional dosing information and warnings for special populations included Recommended limits of use of Methotrexate in renal impairment revised
4.3	'Severe hepatic impairment' and 'bone marrow depression' added to existing contraindications
4.4	Layout of information revised to group information on organ toxicity together for clarity Additional warnings for use in 'Fertility' and 'Pregnancy' included Monitoring and organ toxicity information revised 'Folinic acid deficiency' and 'Hepatotoxic or haematotoxic DMARDs (disease-modifying antirheumatic drugs)' added
4.5	Additional information relating to ciclosporin drug interaction included Additional information relating to leflunomide drug interaction included Interaction information revised in line with Medsafe request
4.6	Fertility and pregnancy information revised Fertility and pregnancy recommendations for men undergoing methotrexate therapy added
4.8	Additional safety information included Adverse reaction reporting URL updated
4.9	Dosing and administration information of calcium folinate revised