NEW ZEALAND DATA SHEET-METHOBLASTIN® PFS

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 lactation

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

1. PRODUCT NAME

METHOBLASTIN® PFS 25 mg/mL, solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of METHOBLASTIN® PFS contains 25 mg of methotrexate as methotrexate sodium, 4.90 mg of sodium chloride, approximately 5 mg of sodium hydroxide and water for injections to a total volume of 1 mL. The volume of injection is sufficient to permit administration of the nominal volume declared on the label.

It is a sterile, clear, yellow brown solution of Methotrexate sodium in water for injections, practically free from visible particles. Sodium chloride is included for isotonicity. Sodium hydroxide is included for pH adjustment. METHOBLASTIN® PFS contains no anti-microbial preservative.

METHOBLASTIN® PFS has a pH of 7.5 to 9.0.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

METHOBLASTIN® PFS is a solution for subcutaneous injection, available in a pre-filled syringe.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Psoriasis chemotherapy (see WARNING box)

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

Rheumatoid arthritis chemotherapy (see WARNING box)

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

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

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

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

4.2 Dose and method of administration

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

Dose

Psoriasis chemotherapy

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

Assessment of renal function, liver function and blood elements should be made by history, physical examination and laboratory tests (such as haemogram, urinalysis, serum creatinine, liver function studies and liver biopsy if indicated) before beginning methotrexate, periodically during methotrexate therapy and before reinstituting methotrexate therapy after a rest period.

Appropriate steps should be taken to avoid conception for at least 12 weeks following methotrexate therapy.

The dosing schedule should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects. Complete blood count with platelets should be evaluated seven to ten days later.

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

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

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

The dosage may be gradually adjusted to achieve optimal clinical response, but not to exceed the maximum stated. After optimal response has been achieved, each dosage schedule should be reduced to the lowest possible dose with the largest possible rest period. Conventional topical therapy should be resumed as soon as possible.

Rheumatoid arthritis chemotherapy

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

Assessment of haematological, hepatic, renal and pulmonary function should be made by history, physical examination and laboratory tests before beginning, periodically during and before reinstituting methotrexate therapy. Appropriate steps should be taken in men and women to avoid conception during methotrexate therapy.

Both the doctor 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.

The dosing schedule should be continually tailored to the individual patient. An initial test dose may be given prior to the regular dosing schedule to detect any extreme sensitivity to adverse effects. Complete blood count with platelets should be evaluated seven to ten days later.

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

Weekly single dose schedule: Weekly dose of 7.5 to 25 mg administered subcutaneously is recommended, depending on response and tolerability. The recommended initial dose is 7.5 mg of methotrexate once weekly, administered subcutaneously. Depending on the individual activity of the disease and tolerability by the patient, the initial dose may be increased gradually by 2.5 mg per week. An alternative methotrexate product may be administered instead of

METHOBLASTIN® PFS if doses of 12.5 mg, 17.5 mg or 22.5 mg are necessary during dose titration. A weekly dose of 25 mg should not be exceeded. Dosage should not ordinarily exceed 20 mg/week due to significant increase in toxicity, especially bone marrow suppression.

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

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

Special populations

Methotrexate elimination is reduced in patients with a third distribution space (ascites, pleural effusions). Such patients require especially careful monitoring for toxicity, and require dose reduction or, in some cases, discontinuation of methotrexate administration (see Section 5.2 Pharmacokinetic properties and Section 4.4 Special warnings and precautions for use).

Assessment of renal function, liver function and blood elements should be made by history, physical examination and laboratory tests (such as haemogram, urinalysis, serum creatinine, liver function studies and liver biopsy if indicated) before beginning methotrexate, periodically during methotrexate therapy and before reinstituting methotrexate therapy after a rest period. Additional monitoring may also be required when changing from oral to parental routes of administration. Appropriate steps should be taken to avoid conception for at least 12 weeks following methotrexate therapy.

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

If changing the oral application to parental administration a reduction of the dose may be required due to the variable bioavailability of methotrexate after oral administration. Folic acid supplementation may be considered according to the current treatment guidelines.

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

Use in Elderly

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

Paediatric population

METHOBLASTIN® PFS is not recommended for use in paediatric patients.

Method of Administration

METHOBLASTIN® PFS is for subcutaneous use in one patient on one occasion only.

METHOBLASTIN® PFS should only be prescribed by physicians who are familiar with the various characteristics of the medicinal product and its mode of action. If the clinical situation

permits the treating physician can delegate subcutaneous administration to the patient or caregiver. METHOBLASTIN® PFS in injected once weekly.

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

Instructions for handling:

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

- personnel should be trained in good handling technique
- pregnant staff should be excluded from working with this drug
- personnel handling injectable methotrexate should wear appropriate personal protective equipment such as disposable gloves
- a designated area should be assigned for preparation , with the work surface protected by disposable, plastic-backed, absorbent paper
- all items used for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high temperature incineration
- accidental contact with the skin or eyes should be treated immediately by copious lavage with water or sodium bicarbonate solution; medical attention should be sought.

METHOBLASTIN® PFS does not contain any preservative, is for single use only and should be discarded after use in a sharps container.

Instructions to patients

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

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

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

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

It must be explicitly emphasised to the patient that the recommended dose is taken once a week in rheumatoid arthritis and psoriasis, and that mistaken daily use of the recommended dose has led to fatal toxicity. It is advisable to determine an appropriate fixed day of the week for the injection. Patients should be cautioned not to change the dosage or the schedule of administration without medical consultation.

Patients should subcutaneously inject the solution in the side of the upper thigh or the abdomen, except around the navel. However, obese patients (i.e. patients with a body weight of more than 100 kg) should inject METHOBLASTIN® PFS solely in the upper thighs (not in the abdomen).

Appropriate instruction for a subcutaneous self-injection or injection by a caregiver should be provided. If a patient or caregiver is to administer METHOBLASTIN® PFS:

a) The physical and cognitive ability of the patient or caregiver should be assessed.

b) The patient or caregiver's ability to administer METHOBLASTIN® PFS should be assessed.

c) Patients or caregivers administering METHOBLASTIN® PFS should be advised to wear disposable gloves.

d) The patient or caregiver should be instructed in correct subcutaneous injection techniques.

e) The initial subcutaneous injection should be performed under the supervision of an appropriately qualified health care professional.

f) Patients or caregivers should be advised of rotating sites of injection with each dose, to minimize the likelihood of injection site reactions.

g) Patients or caregivers should be instructed on managing spills of the solution.

h) Patients or caregivers should be instructed in the correct technique and importance of proper disposal of the pre-filled syringe and be cautioned against reuse of the pre-filled syringe.

4.3 Contraindications

Methotrexate is contraindicated in patients with 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 in those with pre-existing blood dyscrasias such as bone marrow hypoplasia, leucopenia, thrombocytopenia or anaemia.

Methotrexate is contraindicated in patients with overt or laboratory evidence of immunodeficiency syndrome(s).

Breast feeding is contraindicated in women taking methotrexate.

Methotrexate is contraindicated 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.

Methotrexate is contraindicated in patients with a known hypersensitivity to it or to any of the excipients.

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 (see WARNING box)

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 interaction).

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 warning and precautions for use).

4.5 Interaction with other medicines and other forms of interaction

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

Pregnancy - (Category D)

Methotrexate has caused foetal death and/or congenital abnormalities; therefore, it is not recommended in women of childbearing potential unless there is appropriate medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant psoriatic or rheumatoid arthritis patients should not receive methotrexate. Women of childbearing potential

should not be started on methotrexate until pregnancy is excluded and should be fully counselled on the serious risk to the foetus should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate, during and for at least 12 weeks after cessation of therapy.

Breastfeeding

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.

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.

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

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 of suspected adverse reactions

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.

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 Undersirable effects.

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

Concomitant hydration and alkalinisation of the urine with sodium bicarbonate is recommended to prevent precipitation of methotrexate or its metabolite in the renal tubules. Patients undergoing methotrexate therapy should be advised to increase fluid intake. Neither standard haemodialysis nor peritoneal dialysis have been shown to significantly improve methotrexate elimination. Some clearance of methotrexate may be obtained by haemodialysis if the patient is totally anuric and no other therapeutic options are available. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high-flux dialyzer.

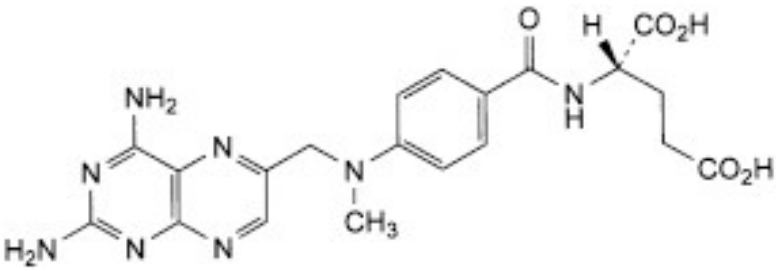
Patients who experience delayed early methotrexate elimination are likely to develop non reversible oliguric renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinisation, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved. If necessary, acute, intermittent haemodialysis with a high-flux dialyzer may also be beneficial in these patients.

For advice on the management of overdose please contact the National Poisons Centre on 0800 764 766 in New Zealand.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The structural formula is represented below.



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

Molecular weight: 454.4

CAS Number: 59-05-2

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

In patients with rheumatoid arthritis, effects of methotrexate on articular swelling and tenderness can be seen as early as three to six weeks. Although methotrexate clearly

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

Clinical efficacy and safety

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 $\geq$ 4, who have never been treated with MTX before and who were familiar with subcutaneous self- administration through confirmed practice phase were included into this trial.

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

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

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

Time to initial ACR20 response was evaluated using Kaplan-Meier methods. No difference was seen between the two treatment groups. In both arms the median number of weeks to reach an ACR20 response for the first time was 6 weeks. A low rate of withdrawal was observed in both groups with approximately 10% of the patients. Less patients discontinued study for insufficient clinical response in the SC group than in the oral group (1.1% vs 2.1%) but more patients withdrew from the study due to adverse events in the SC group (9.6% vs 5.3%).

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

Methotrexate at low doses (<25 mg/m^2) is well absorbed from the gastrointestinal tract; at larger doses absorption may become erratic and incomplete. Absorption is significantly higher after intramuscular and subcutaneous administration with no differences between both routes. Peak serum levels may be achieved within 0.25 and 1 hour following intramuscular (IM) administration and 0.25 to 1.5 hours following subcutaneous (SC) administration. Peak serum levels may be achieved within 1 to 4 hours following oral administration, and within 0.5 to 2 hours following intravenous (IV) or intramuscular (IM) administration.

Distribution

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

Biotransformation

Methotrexate does not appear to be appreciably metabolised.

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

Elimination

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

MC-MTX.7/PH

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

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

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

Parameter	MTX s.c. (test)	MTX i.m. (reference)	Geometric mean ratio s.c./i.m. (%)	90% CI (%)
Tmax h	1 (1.7)	0.5 (1.7)		
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
Cmax (µg/L)	221.76 (1.39)	381.28 (1.37)	58.16	47.61 - 71.06
AUC = area under the plasma concentration time curve; 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 Cmax was also similar (44.84 µg/L for SC and 52.85 µg/L for IM administration).

MC-MTX.9/PH

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

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

Treatment	50 mg/mL (test)	10 mg/mL (reference)	50 mg/mL (test)	10 mg/mL (reference)
Route of administration	SC	SC	IM	IM
Number of subjects	12	12	12	12

AUC [µg*h/L]	1451.713 (1.13)	1488.010 (1.11)	1169.934 (1.17)	1273.756 (1.22)
Point estimate test/reference (90% CI)	97.56 (89.90 - 105.88)		91.85 (84.63 - 99.68)	
Cmax [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; Cmax = 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 Cmax and slightly lower AUC when given by i.m. injection compared to s.c. injection. This difference in the AUC after IM administration of the 10 mg/mL and 50 mg/mL is not expected to have any clinical consequence. The differences between the i.m. and s.c. routes for the two injection concentrations in the cross study arm comparisons are similar, suggesting there are population differences contributing to this finding.

Studies comparing Oral with Parenteral Administration

Four published studies in adult patients with RA have compared oral MTX 7.5-30 mg/week with equivalent doses administered by either IM or SC injection. The mean bioavailability in 15 adult patients with RA after oral MTX 30 mg/week, as demonstrated by Hoekstra et al (2004), was 0.64 (range 0.21-0.96) which was statistically significantly different to the SC administration of the same dose. Seideman et al (1993) reported the AUC in nine patients where IM and oral doses met bioequivalence criteria (90% CI 92-121% for the AUC ratio). In the study of 21 RA patients conducted by Hamilton et al (1997) the 24-hour AUC was significantly lower with oral versus IM therapy at a mean MTX dose of 17 mg/week (p=0.027), but this was not seen at the lower 7.5 mg weekly dose of MTX. Auvinet et al (1992) observed a 10 mg/week oral dose that was 60% bioavailable relative to the same SC dose involving 8 adult patients with RA, which is consistent with the results reported by Hamilton and Hoekstra. Another study by Herman et al (1989) reported oral bioavailability of a 10 mg dose as 70% compared with the same dose given by IM injection in a study involving 41 RA patients. Overall, the published data indicates that a lower AUC is seen with oral therapy versus parenteral administration for doses of MTX as low as 10 mg, consistently when the dose is >15 mg. (See Section 4.2 Dose and method of administration.)

5.3 Preclinical safety data

Genotoxicity

Methotrexate has been reported to cause chromosome damage. The risk of genetic abnormalities may persist after discontinuing methotrexate therapy. Thus, it is advised that both men and women avoid intercourse leading to conception for an indefinite period (at least 12

weeks) after discontinuing methotrexate to ensure the re-establishment of normal germinal cells.

Carcinogenicity

Methotrexate is considered to be carcinogenic. However, extensive epidemiologic studies are required to determine its carcinogenicity potential.

6. PHARMACEUTICAL PARTICUALRS

6.1 List of excipients

Sodium chloride

Sodium hydroxide

Water for injection

6.2 Incompatibilities

Methotrexate has been reported to be incompatible with cytarabine, fluorouracil and prednisolone.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25ºC. Protect from light.

6.5 Nature and contents of container

METHOBLASTIN® PFS is available in the following presentations.

Presentation	**Container closure details**	**Pack size**
7.5 mg/0.3mL	glass syringe barrel, plastic backstop	1, 4, 6, 12 and 24 syringes
10 mg/0.4mL	glass syringe barrel, plastic backstop	1, 4, 6, 12 and 24 syringes
15 mg/0.6mL	glass syringe barrel, plastic backstop	1, 4, 6, 12 and 24 syringes
20 mg/0.8mL	glass syringe barrel, plastic backstop	1, 4, 6, 12 and 24 syringes
25 mg/ 1 mL	glass syringe barrel, plastic backstop	1, 4, 6, 12 and 24 syringes

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements

7. MEDICINE SCHEDULE

Prescription only medicine

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand, 1140

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

26 June 2020

10. DATE OF REVISION OF THE TEXT

27 July 2020

Summary table of changes

Section changed	Summary of new information
4.4	Signal pulmonary alveolar haemorrhage added.
4.8	Signal pulmonary alveolar haemorrhage added.