PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

Methotrexate 500 mg/20 mL Fresenius

Methotrexate 50 mg/2 mL Fresenius

Pharmaceutical form

Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL contains 25 mg Methotrexate

Methotrexate 500 mg/20 mL Fresenius: Each 20 mL contains 500 mg methotrexate

Methotrexate 50 mg/2 mL Fresenius: Each 2 mL vial contains 50 mg methotrexate

Sugar free

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Clear yellow coloured solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Lymphoblastic leukaemia in children and meningeal leukemia.
- Choriocarcinoma and related trophoblastic tumours of women.
- Women with non-metastatic trophoblastic disease, hydatidiform mole and chorioadenoma destruens.

- Carcinomas of the breast, tongue, pharynx and testes (in conjunction with chlorambucil and dactinomycin).
- Carcinoma of the lung and osteogenic sarcomas (high dose Methotrexate Fresenius with folinic acid rescue).
- Treatment of severe psoriasis (see section 4.3 and section 4.4).
- Prevention of graft-versus-host reactions that result from marrow transplantation.
- Dermatomyositis, rheumatoid arthritis (not adequately responding to other therapy), Wegner's granulomatosis and pityriasis rubra pilaris.

4.2 Posology and method of administration

Methotrexate Fresenius may be given by mouth, or by injection.

The dose of Methotrexate Fresenius, the dosage frequency, the total dose and combination with other cytostatic medicine and/or folinic acid are subject to frequent modification as scientific knowledge improves.

Lymphoblastic leukaemia: When used for induction, Methotrexate Fresenius in doses of 3,3 mg/m^2 in combination with prednisone 60 mg/m^2 given daily produced remission in 50 % of patients treated, usually within a period of 4 to 6 weeks. Methotrexate Fresenius alone or in combination with other medicines appears to be the medicine of choice for securing maintenance of medicine-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated, as follows: Methotrexate Fresenius is administered twice weekly either by mouth or intramuscularly in doses of 30 mg/m^2. It can also be given in doses of 2,5 mg/kg intravenously every 14 days. If and when relapse does occur, re-induction of remission can again usually be obtained by repeating the initial induction regime.

Meningeal leukaemia: Some patients with leukaemia are subject to leukaemic invasion of the central nervous system. This may manifest characteristic signs or symptoms or may

remain silent and be diagnosed only by examination of the cerebrospinal fluid which contains leukaemic cells in such cases. Therefore, the CSF should be examined in all leukaemic patients. Since passage of Methotrexate Fresenius from blood serum to the cerebrospinal fluid is minimal, for adequate therapy the medicine is administered intrathecally. A common approach is to treat such patients as may actually manifest leukaemic involvement by direct intrathecal instillation of Methotrexate Fresenius.

Intrathecal administration:

Administration is at intervals of 2 to 5 days and is usually repeated until the cell count of the cerebrospinal fluid returns to normal. At this point one additional dose is advised. Large doses may cause convulsions.

The following dosage regimen is based on age instead of body surface area:

Age (years)	Dose (mg)
<1	6
1	8
2	10
3 or older	12

Similar doses are given prophylactically to patients with lymphoblastic leukaemia, often in association with cranial irradiation. Methotrexate Fresenius in intravenous doses of about 500 mg per m^2, followed by folinic acid rescue, may also produce effective concentrations in the CSF.

Choriocarcinoma and similar trophoblastic diseases: Doses of 15 to 30 mg daily by mouth or intramuscularly for 5 days, at intervals of 1 to 2 weeks for 3 to 5 courses. Alternatively, 0,25 to 1 mg per kg body-weight up to a maximum of 60 mg has been given intramuscularly every 48 hours for 4 doses, followed by folinic acid rescue, and repeated at intervals of 7 days. Since hydatidiform mole may precede or be followed by

choriocarcinoma, prophylactic chemotherapy with Methotrexate Fresenius has been recommended.

Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate Fresenius administered in these disease states in doses similar to those recommended for choriocarcinoma.

Breast carcinoma: Prolonged cyclic combination chemotherapy with cyclophosphamide, Methotrexate Fresenius and fluorouracil can give good results when used as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary lymph nodes. Methotrexate Fresenius dosage of 40 mg/m^2 intravenously can be given on the first and eighth days. Combination chemotherapy may be necessary in patients with metastases. A range of doses of Methotrexate Fresenius can be used in the management of solid tumours. Very high doses can be given by intravenous infusion, followed by folinic acid, in patients with osteogenic sarcoma and carcinoma of the lung and of the head and neck.

Psoriasis: Methotrexate Fresenius has been given by mouth, intramuscularly, and intravenously in the treatment of psoriasis. Single weekly doses of 10 to 25 mg may be given by mouth or injection. Alternatively, 2,5 mg has been administered by mouth every 12 hours for 3 doses or every 8 hours for 4 doses each week or 2,5 mg may be given daily by mouth for 5 days out of 7.

High-dose therapy: High dose therapy should be used only by qualified specialists in suitable hospital setting.

METHOTREXATE FRESENIUS RESCUE SCHEDULES FOLLOWING TREATMENT WITH HIGHER DOSES OF METHOTREXATE FRESENIUS

CLINICAL SITUATION	LABORATORY FINDINGS	FOLINIC ACID DOSAGE AND DURATION
Normal Methotrexate Fresenius elimination.	Serum Methotrexate Fresenius level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0,2 micromolar at 72 hours.	15 mg PO, IM or IV every 6 hours for 60 hours (10 doses starting at 24 hours after start of Methotrexate Fresenius infusion).
Delayed Late Methotrexate Fresenius elimination.	Serum Methotrexate Fresenius level remaining above 0,2 micromolar at 72 hours, and more than 0,05 micromolar at 96 hours after administration.	Continue 15 mg PO, IM or IV every 6 hours, until Methotrexate Fresenius level is less than 0,05 micromolar.
Delayed Early Methotrexate Fresenius Elimination and/or Evidence of Acute Renal Injury.	Serum Methotrexate Fresenius level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR; a 100 % or greater increase in serum creatinine level at 24 hours after Methotrexate Fresenius administration (e.g., an increase from 0,5 mg/dL to a level of 1 mg/dL or more).	150 mg IV every 3 hours, until Methotrexate Fresenius level is less than 1 micromolar; then 15 mg IV every 3 hours, until Methotrexate Fresenius level is less than 0,05 micromolar.

GUIDELINES FOR ISOVORIN* METHOTREXATE RESCUE DOSAGE AND ADMINISTRATION

CLINICAL SITUATION	LABORATORY FINDINGS	LEVOFOLINIC ACID DOSAGE AND DURATION
Normal Methotrexate Fresenius elimination.	Serum Methotrexate Fresenius level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0,2 micromolar at 72 hours.	7,5 mg PO, IM or IV every 6 hours for 60 hours (10 doses starting at 24 hours after start of Methotrexate Fresenius infusion).
Delayed Late Methotrexate Fresenius elimination.	Serum Methotrexate Fresenius level remaining above 0,2 micromolar at 72 hours, and more than 0,05 micromolar at 96 hours after administration.	Continue 7,5 mg PO, IM or IV every 6 hours, until Methotrexate Fresenius level is less than 0,05 micromolar.
Delayed Early Methotrexate Fresenius Elimination and/or Evidence of Acute Renal Injury.	Serum Methotrexate Fresenius level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR; a 100 % or greater increase in serum creatinine level at 24 hours after Methotrexate Fresenius administration (e.g., an increase from 0,5 mg/dL to a level of 1 mg/dL or more).	75 mg IV every 3 hours, until Methotrexate Fresenius level is less than 1 micromolar; then 7,5 mg IV every 3 hours, until Methotrexate Fresenius level is less than 0,05 micromolar.

Mycosis fungoides: Therapy with Methotrexate Fresenius appears to produce clinical remissions in half of the cases treated. Dosage is usually 2,5 to 10 mg daily by mouth for weeks or months. Dose levels of medicine and adjustment of dose regime by reduction or cessation of medicine are guided by patient response and haematologic monitoring. Methotrexate Fresenius may also be given intramuscularly in doses of 50 mg once weekly or 25 mg twice weekly.

Rheumatoid arthritis: In case of intravenous or intramuscular administration of Methotrexate Fresenius, the starting dose in adults is 10 mg once weekly. If necessary, this dose can be increased in steps of 2,5 mg each until maximally a dose of 25 mg once weekly. Between the subsequent dose increases of each scheme there should be an interval of ca. 6 weeks.

It is possible to administer parenterally a week before the initiation of therapy a test dose of 5 – 10 mg of Methotrexate Fresenius to detect idiosyncratic reactions of the patient. In most patient's improvement of the clinical situation occurs after 4 – 6 weeks. After about 6 months a plateau in the response is reached, whereafter sometimes modification of the dose is necessary to maintain this optimal clinical result.

After discontinuation of therapy a flare-up of rheumatoid arthritis may occur. In case of oral administration of Methotrexate Fresenius, initially 2,5 mg to 5 mg every 12 hours for 3 doses once a week, the dosage being increased as necessary in increments of 2,5 mg per week up to a maximum of 20 mg per week or initially 10 mg once a week, the dosage being increased as necessary up to 20 mg per week.

4.3 Contraindications

- Patients with a known hypersensitivity to methotrexate or any of the excipients should not receive Methotrexate Fresenius.
- Methotrexate Fresenius is contraindicated in pregnancy and in lactation (see section 4.6).

- Methotrexate Fresenius is contraindicated in patients with psoriasis or rheumatoid arthritis with serious renal or liver disorders, bone marrow hypoplasia, leucopenia, thrombocytopenia, anaemia, and alcohol abuse.
- Safety and efficacy in children have not been established other than in cancer chemotherapy.

4.4 Special warnings and precautions for use

- Methotrexate Fresenius should be used only in life threatening neoplastic diseases, or in patients with psoriasis or rheumatoid arthritis with severe, recalcitrant, disabling disease which is not adequately responsive to other forms of therapy.
- Deaths have been reported with the use of methotrexate in the treatment of malignancy, psoriasis, and rheumatoid arthritis.
- Patients should be closely monitored for bone marrow, liver, lung and kidney toxicities.
- Patients should be informed by their physician of the risks involved and be under a physician's care throughout therapy.
- The use of Methotrexate Fresenius high-dose regimens recommended for osteosarcoma requires meticulous care. (see section 4.2) high-dose regimens for other neoplastic diseases are investigational and a therapeutic advantage has not been established.

Use caution when administering high-dose Methotrexate Fresenius to patients receiving proton pump inhibitor (PPI) therapy. Case reports and published population pharmacokinetic studies suggest that concomitant use of some PPIs, such as omeprazole, esomeprazole, and pantoprazole, with methotrexate (primarily at high dose), may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. In two of these cases, delayed methotrexate elimination was observed when high-dose methotrexate was co-administered with PPIs, but was not observed when methotrexate was co-administered with ranitidine. However, no formal medicines interaction studies of methotrexate with ranitidine have been conducted.

(see Section 4.5).

Methotrexate Fresenius has the potential for serious toxicity. Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients on Methotrexate Fresenius closely. Most adverse reactions are reversible if detected early. When such reactions do occur, Methotrexate Fresenius should be reduced in dosage or discontinued, and appropriate corrective measures should be taken. If necessary, this could include the use of leucovorin calcium and/or acute, intermittent hemodialysis with a high-flux dialyser (see section 4.9).

If Methotrexate Fresenius therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the medicines and increased alertness as to possible recurrence of toxicity.

The clinical pharmacology of methotrexate has not been well studied in older individuals. Due to diminished hepatic and renal function as well as decreased folate stores in this population, relatively low doses should be considered, and these patients should be closely monitored for early signs of toxicity.

Laboratory Tests

Patients undergoing Methotrexate Fresenius therapy should be closely monitored so that toxic effects are detected promptly. Baseline assessment should include a complete blood count with differential and platelet counts, hepatic enzymes, renal function tests and a chest X-ray.

During therapy of rheumatoid arthritis and psoriasis, monitoring of these parameters is recommended: haematology at least monthly, renal function and liver function every 1 to 2 months. More frequent monitoring is usually indicated during antineoplastic therapy. During initial or changing doses, or during periods of increased risk of elevated methotrexate blood

levels (e.g., dehydration), more frequent monitoring may also be indicated.

Transient liver function test abnormalities are observed frequently after Methotrexate Fresenius administration and are usually not cause for modification of Methotrexate Fresenius therapy.
Persistent liver function test abnormalities, and/or depression of serum albumin may be indicators of serious liver toxicity and require evaluation.

A relationship between abnormal liver function tests and fibrosis or cirrhosis of the liver has not been established for patients with psoriasis. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in the rheumatoid arthritis population.

Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.

Carcinogenicity, Mutagenicity

No controlled human data exist regarding the risk of neoplasia with methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain. Non-Hodgkin's lymphoma and other tumours have been reported in patients receiving low-dose oral methotrexate. However, there have been instances of malignant lymphoma arising during treatment with low-dose oral methotrexate, which have regressed completely following withdrawal of methotrexate, without requiring active antilymphoma treatment. Benefits should be weighed against the potential risk before using Methotrexate Fresenius alone or in combination with other medicines, especially in pediatric patients or young adults.

Paediatric population

Safety and effectiveness in pediatric patients have been established only in cancer chemotherapy. (see section 4.3)

Serious neurotoxicity, frequently manifested as generalised or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m^2). (see section 4.8)

Use in the elderly

Clinical studies of methotrexate did not include sufficient numbers of patients age 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious reflecting the greater frequency of decreased hepatic and renal function, decreased folate stores, concomitant disease or other drug therapy (i.e., that interfere with renal function, methotrexate or folate metabolism) in this population (See section 4.5). Since decline in renal function may be associated with increases in adverse events and serum creatinine measurements may overestimate renal function in the elderly, more accurate methods (i.e., creatinine clearance) should be considered. Serum methotrexate levels may also be helpful. Elderly patients should be closely monitored for early signs of hepatic, bone marrow and renal toxicity. In chronic use situations, certain toxicities may be reduced by folate supplementation. Post-marketing experience suggests that the occurrence of bone marrow suppression, thrombocytopenia, and pneumonitis may increase with age. See section 4.8.

Organ System Toxicity

Gastrointestinal: If vomiting, diarrhoea, or stomatitis occur, which may result in dehydration, Methotrexate Fresenius should be discontinued until recovery occurs. Methotrexate Fresenius should be used with extreme caution in the presence of peptic ulcer disease or

ulcerative colitis.

Hematologic: Methotrexate Fresenius can suppress hematopoiesis and cause anaemia, aplastic anaemia, pancytopenia, leukopenia, neutropenia, and/or thrombocytopenia. In patients with malignancy and preexisting hematopoietic impairment, the drug should be used with caution, if at all.

In psoriasis and rheumatoid arthritis, Methotrexate Fresenius should be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit warrants the risk of severe myelosuppression. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotic therapy.

Hepatic: Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally two years or more) and after a total dose of at least 1,5 grams. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes and advanced age. An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known. Special caution is indicated in the presence of preexisting liver damage or impaired hepatic function.

In psoriasis, liver function tests, including serum albumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis. These lesions may be detectable only by biopsy. The usual recommendation is to obtain a liver biopsy at 1) pretherapy or shortly after initiation of therapy (2 to 4 months), 2) a total cumulative dose of 1,5 grams, and 3) after each additional 1,0 to 1,5 grams. Moderate fibrosis or any cirrhosis normally leads to discontinuation of 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 pretherapy. Although these mild changes are usually not a reason to avoid or discontinue Methotrexate Fresenius therapy, the medicine should be used with caution.

In rheumatoid arthritis, age at first use of methotrexate and duration of therapy have been reported as risk factors for hepatotoxicity; other risk factors, similar to those observed in psoriasis, may be present in rheumatoid arthritis but have not been confirmed to date. Persistent abnormalities in liver function tests may precede appearance of fibrosis or cirrhosis in this population. 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.

Liver function tests should be performed at baseline at 4 to 8 week intervals in patients receiving Methotrexate Fresenius 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 Fresenius may be continued and the patient monitored as per 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).

Infection or Immunologic States: Methotrexate Fresenius should be used with extreme caution in the presence of active infection, in patients with overt or laboratory evidence of

immunodeficiency syndromes. Immunisation may be ineffective when given during Methotrexate Fresenius therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunizations in patients receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely. (See sections 4.5 and 4.8) Potentially fatal opportunistic infections, especially *Pneumocystis carinii* pneumonia, may occur with methotrexate therapy. When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered.

Neurologic: There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had craniospinal irradiation. Serious neurotoxicity, frequently manifested as generalized or focal seizures, has been reported with unexpectedly increased frequency among pediatric patients with acute lymphoblastic leukemia who were treated with intermediate-dose intravenous methotrexate (1 gm/m^2). Symptomatic patients were commonly noted to have leukoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies. Chronic leukoencephalopathy has also been reported in patients who received repeated doses of high-dose methotrexate with leucovorin rescue even without cranial irradiation. Discontinuation of Methotrexate Fresenius does not always result in complete recovery.

A transient acute neurologic syndrome has been observed in patients treated with high-dose regimens. Manifestations of this stroke-like encephalopathy may include confusion, hemiparesis, transient blindness, seizures and coma. The exact cause is unknown.

After the intrathecal use of Methotrexate Fresenius, the central nervous system toxicity which may occur can be classified as follows: acute chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity, and fever; sub-acute myelopathy characterized by paraparesis/paraplegia associated with involvement with one or more

spinal nerve roots; chronic leukoencephalopathy manifested by confusion, irritability, somnolence, ataxia, dementia, seizures and coma. This condition can be progressive and even fatal.

Pulmonary: Pulmonary symptoms (especially a dry nonproductive cough) or a non-specific pneumonitis occurring during Methotrexate Fresenius therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on chest X-ray; infection (including pneumonia) needs to be excluded. This lesion can occur at all dosages.

Renal: Methotrexate Fresenius may cause renal damage that may lead to acute renal failure. High doses of Methotrexate Fresenius used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinisation and measurement of serum methotrexate and creatinine levels are essential for safe administration.

Skin: 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.

Other precautions: Methotrexate Fresenius should be used with extreme caution in the presence of debility.

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

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Radiation dermatitis and sunburn may be "recalled" by the use of Methotrexate Fresenius.

Like other cytotoxic medicines, methotrexate may induce "tumor lysis syndrome" in patients with rapidly growing tumors. Appropriate supportive and pharmacologic measures may prevent or alleviate this complication

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

4.5 Interaction with other medicines and other forms of interaction

Nonsteroidal anti-inflammatory medicines should not be administered prior to or concomitantly with the high doses of Methotrexate Fresenius, such as used in the treatment of osteosarcoma. Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and gastrointestinal toxicity.

Caution should be used when NSAIDs and salicylates are administered concomitantly with lower doses of Methotrexate Fresenius. These medicines 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 has usually included concurrent use of constant 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 that larger doses could lead to unexpected toxicity.

The potential toxicity of Methotrexate Fresenius is increased with simultaneous use of NSAIDS when diuretics are also used. Methotrexate is partially bound to serum albumin, and toxicity may be increased because of displacement by certain medicines, such as salicylates, phenylbutazone, phenytoin, and sulfonamides. Renal tubular transport is also diminished by probenecid; use of Methotrexate Fresenius with this medicine should be carefully monitored.

In the treatment of patients with osteosarcoma, caution must be exercised if high-dose Methotrexate Fresenius is administered in combination with a potentially nephrotoxic chemotherapeutic medicine (e.g., cisplatin).

Methotrexate increases the plasma levels of mercaptopurine. The combination of Methotrexate Fresenius and mercaptopurine may therefore require dose adjustment.

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 medicine by bacteria.

Penicillins may reduce the renal clearance of methotrexate; increased serum concentrations of methotrexate with concomitant hematologic and gastrointestinal toxicity have been observed with high and low dose Methotrexate Fresenius. Use of Methotrexate Fresenius with penicillins should be carefully monitored.

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 Fresenius and other potential hepatotoxins (e.g., azathioprine, retinoids, sulfasalazine) should be closely monitored for possible increased risk of hepatotoxicity.

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

Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered Methotrexate Fresenius. Preliminary animal and human studies have shown that small quantities of intravenously administered. Leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1 to 3 orders of magnitude lower than the usual
methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered Methotrexate Fresenius.

Folate deficiency states may increase methotrexate toxicity. Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or an additive antifolate effect.

The use of nitrous oxide anesthesia potentiates the effect of methotrexate on folate-dependent metabolic pathways, resulting in the potential for increased toxicity such as stomatitis, myelosuppression, and neurotoxicity. Avoid concomitant nitrous oxide anesthesia in patients receiving Methotrexate Fresenius.
Administration of methotrexate (primarily at high dose) with proton pump inhibitors such as omeprazole or pantoprazole may elevate and prolong serum levels of methotrexate and its

metabolite hydroxymethotrexate as a result of delayed renal elimination of methotrexate (see Sections 4.4 and 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

Methotrexate Fresenius is contraindicated in pregnant women (see section 4.3) Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving Methotrexate Fresenius; during

and for a minimum of three months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients.

Breastfeeding

Methotrexate Fresenius in breastfed infants, it is contraindicated inlactation (See section 4.3).

Fertility

Methotrexate causes embryotoxicity, abortion, and foetal defects in humans. It has also been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy. (see section 4.8)

4.7 Effects on ability to drive and use machines

Dizziness blurred vision, transient blindness and fatigue, have been reported in some patients during treatment with Methotrexate Fresenius, and this should be borne in mind when considering a patient's ability to drive or operate machinery. (see section 4.8)

4.8 Undesirable effects

In general, the incidence and severity of acute side effects are related to dose and frequency of administration.

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress.

Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection. Other adverse reactions that have been observed with methotrexate are listed below by organ system. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to methotrexate difficult.

Frequent:

Gastrointestinal disorders: gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.

Frequent:

Blood and lymphatic system disorders: suppressed hematopoiesis, anaemia, aplastic anaemia, pancytopenia, leukopenia, neutropenia, thrombocytopenia, agranulocytosis, eosinophilia, lymphadenopathy and lymphoproliferative disorders (including reversible). Hypogammaglobulinemia has been reported rarely.

Cardiac disorders: pericarditis, pericardial effusion

Vascular disorders: hypotension, thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and

pulmonary embolus).

Less Frequent:

Nervous system disorders: headaches, drowsiness, blurred vision, transient blindness, speech impairment including dysarthria and aphasia, hemiparesis, paresis and convulsions have also occurred following administration of methotrexate. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration or unusual cranial sensations, leukoencephalopathy, or encephalopathy.

Less Frequent:

Hepato-biliary disorders: hepatotoxicity, acute hepatitis, chronic fibrosis and cirrhosis, hepatic failure, decrease in serum albumin, liver enzyme elevations.

Infections and Infestations: 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 opportunistic infection. There have also been reports of infections, pneumonia, Cytomegalovirus infection, including cytomegaloviral pneumonia, sepsis, fatal sepsis, nocardiosis; histoplasmosis, cryptococcosis, Herpes zoster, H. simplex hepatitis, and disseminated H. simplex.

Musculoskeletal and connective tissue disorders: stress fracture.

Eye disorders: conjunctivitis, serious visual changes of unknown etiology.

Less Frequent:

Respiratory, thoracic and mediastinal disorders: respiratory fibrosis, respiratory failure, alveolitis, interstitial pneumonitis deaths have been reported, and chronic interstitial

obstructive pulmonary disease has occasionally occurred.

Less Frequent:

Skin and subcutaneous tissue disorders: erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, skin necrosis, skin ulceration and exfoliative dermatitis.

Frequent:

Renal and urinary disorders: severe nephropathy or renal failure, azotemia, cystitis, hematuria, proteinuria.

Reproductive system and breast disorders: defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, foetal death, foetal defects.(see Section 4.6)

Frequency Unknown

Other rarer reactions related to or attributed to the use of methotrexate such as nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death, lymphoma, including reversible lymphomas, tumor lysis syndrome, soft tissue necrosis and osteonecrosis. 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 providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

Health care providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

Folinic acid neutralises the immediate toxic effect of Methotrexate Fresenius on the bone marrow and is given by mouth, intramuscularly, by intravenous bolus injection, or by infusion as calcium folinate. When overdosage is suspected, the dose of calcium folinate should be at least as high as that of Methotrexate Fresenius and should be administered within the first hour; further doses are given as required. When average doses of ABITREXATE have an adverse effect, the equivalent of 12 mg of folinic acid may be given intramuscularly every 6 hours for 4 doses. The majority of a dose is excreted unchanged in the urine within 24 hours. Bound Methotrexate Fresenius may be retained in the body for many months.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of medicine: A 26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic Agents

ATC code: L01BA01.

Mechanism of action

Methotrexate inhibits dihydrofolic acid reductase. Dihydrofolates must be reduced to tetrahydrofolates by this enzyme before they can be utilized as carriers of one-carbon groups in the synthesis of purine nucleotides and thymidylate. Therefore, methotrexate interferes with DNA synthesis, repair, and cellular replication. Actively proliferating tissues

such as malignant cells, bone marrow, foetal cells, buccal and intestinal mucosa, and cells of the urinary bladder are in general more sensitive to this effect of methotrexate. When cellular proliferation in malignant tissues is greater than in most normal tissues, methotrexate may impair malignant growth without irreversible damage to normal tissues.

The mechanism of action in rheumatoid arthritis is unknown; it may affect immune function. Two reports describe in vitro methotrexate inhibition of DNA precursor uptake by stimulated mononuclear cells, and another describes in animal polyarthritis partial correction by methotrexate of spleen cell hyporesponsiveness and suppressed IL 2 production. Other laboratories, however, have been unable to demonstrate similar effects. Clarification of methotrexate's effect on immune activity and its relation to rheumatoid immunopathogenesis await further studies.

In patients with rheumatoid arthritis, effects of methotrexate on articular swelling and tenderness can be seen as early as 3 to 6 weeks. Although methotrexate clearly ameliorates symptoms of inflammation (pain, swelling, stiffness), there is no evidence that it induces remission of rheumatoid arthritis nor has a beneficial effect been demonstrated on bone erosions and other radiologic changes which result in impaired joint use, functional disability, and deformity.

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

Methotrexate in high doses, followed by leucovorin rescue, is used as a part of the treatment of patients with non-metastatic osteosarcoma. The original rationale for high dose methotrexate therapy was based on the concept of selective rescue of normal tissues by leucovorin. Recent evidence

suggests that high dose methotrexate may also overcome methotrexate resistance caused by impaired active transport, decreased affinity of dihydrofolic acid reductase for methotrexate, increased levels of dihydrofolic acid reductase resulting from gene amplification, or decreased polyglutamation of methotrexate. The actual mechanism of action is unknown.

5.2 Pharmacokinetic properties

Absorption - In adults, oral absorption appears to be dose dependent. Peak serum levels are reached within one to two hours. At doses of 30 mg/m^2 or less, methotrexate is generally well absorbed with a mean bioavailability of about 60 %. The absorption of doses greater than 80 mg/m^2 is significantly less, possibly due to a saturation effect.

In leukemic pediatric patients, oral absorption of methotrexate also appears to be dose dependent and has been reported to vary widely (23 % to 95 %). A twenty-fold difference between highest and lowest peak levels (C_{max}: 0,11 to 2,3 micromolar after a 20 mg/m^2 dose) has been reported. Significant interindividual variability has also been noted in time to peak concentration (T^{max}: 0,67 to 4 hrs after a 15 mg/m^2 dose) and fraction of dose absorbed. The absorption of doses greater than 40 mg/m^2 has been reported to be significantly less than that of lower doses. Food has been shown to delay absorption and reduce peak concentration. Methotrexate is generally completely absorbed from parenteral routes of injection. After intramuscular injection, peak serum concentrations occur in 30 to 60 minutes. In pediatric patients receiving methotrexate for acute lymphocytic leukemia (6,3 to 30 mg/m^2), or for JRA (3,75 to 26,2 mg/m^2), the terminal half-life has been reported to range from 0,7 to 5,8 hours or 0,9 to 2,3 hours, respectively.

Distribution - After intravenous administration, the initial volume of distribution is approximately 0,18 L/kg (18 % of body weight) and steady-state volume of distribution is approximately 0,4 to 0,8 L/kg (40 to 80 % of body weight). Methotrexate competes with

reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50 % protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin. (see section 4.5)

Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally. High CSF concentrations of the medicine may be attained by intrathecal administration.

Metabolism - After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged medicines action of these active metabolites vary among different cells, tissues and tumors. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. Accumulation of this metabolite may become significant at the high doses used in osteogenic sarcoma. The aqueous solubility of 7-hydroxymethotrexate is 3-to-5-fold lower than the parent compound.

Half-Life - The terminal half-life reported for methotrexate is approximately three to ten hours for patients receiving treatment for psoriasis, or rheumatoid arthritis or low dose antineoplastic therapy (less than 30 mg/m). For patients receiving high doses of methotrexate, the terminal half-life is eight to 15 hours.

Excretion - Renal excretion is the primary route of elimination and is dependent upon

dosage and route of administration. With IV administration, 80 % to 90 % of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10 % or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7,5 and 30 mg. Impaired renal function, as well as concurrent use of mediciness such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels. Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.

Methotrexate clearance rates vary widely and are generally decreased at higher doses. Delayed medicines clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the medicines rather than the peak level achieved. When a patient has delayed medicines elimination due to compromised renal function, a third space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods.

The potential for toxicity from high dose regimens or delayed excretion is reduced by the administration of leucovorin calcium during the final phase of methotrexate plasma elimination. Pharmacokinetic monitoring of methotrexate serum concentrations may help identify those patients at high risk for methotrexate toxicity and aid in proper adjustments of leucovorin dosing.

Methotrexate has been detected in human breast milk. The highest breast milk to plasma concentration ratio reached was 0,08:1. (see section 4.6)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid; sodium chloride; sodium hydroxide and water for injection

6.2 Incompatibilities

Methotrexate sodium has been reported to be incompatible with cytarabine, fluorouracil, and prednisolone sodium phosphate; however, another study suggests it is compatible with fluorouracil. Furthermore, a mixture of methotrexate sodium with cytarabine and hydrocortisone sodium succinate in various infusion fluids have been reported to be visually compatible for at least 8 hours at 25 °C, although precipitation did occur on storage for several days.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

6.5 Nature and contents of container

Methotrexate 500 mg/20 mL Fresenius: 20 mL USP Type I, molded clear glass vials; grey bromobutyl rubber plug and aluminum flip off seals.

Methotrexate 50 mg/2 mL Fresenius: 5 mL USP Type I, molded clear glass vials; grey bromobutyl rubber plug and aluminium flip off seals.

Each vial may/may not be shrink wrapped.

6.6 Special precautions for disposal and other handling

Procedures for proper handling and disposal of anticancer medicines should be

considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Parenteral medicines products should be inspected visually for particulate matter and discoloration prior to administration.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Limited

Stand 7, Growthpoint Business Park

162 Tonetti Street

Midrand, 1685

Telephone number: (011) 545 0000

8. REGISTRATION NUMBER(S)

Methotrexate 500 mg/20 mL Fresenius: 49/26/0815

Methotrexate 50 mg/2 mL Fresenius: 49/26/0814

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 August 2020

10. DATE OF REVISION OF THE TEXT