SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Methotrexate Injection 25mg/ml.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 25 mg methotrexate (sodium salt formed *in situ*)

Each vial of 2 ml of solution contains 50 mg methotrexate (sodium salt formed *in situ*)
Each vial of 10 ml of solution contains 250 mg methotrexate (sodium salt formed *in situ*)
Each vial of 20 ml of solution contains 500 mg methotrexate (sodium salt formed *in situ*)
Each vial of 40 ml of solution contains 1 g methotrexate (sodium salt formed *in situ*)

Excipient with known effect
Methotrexate 500 mg/20 ml contains 41.1 mg sodium per vial
Methotrexate 1 g/40 ml contains 82.2 mg sodium per vial

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Vials containing a clear yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Methotrexate is indicated in the treatment of neoplastic disease, such as trophoblastic neoplasms and leukaemia, and the symptomatic treatment of severe recalcitrant disabling psoriasis which is not adequately responsive to other forms of therapy.

4.2 Posology and method of administration

Methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy.

The prescriber should ensure that patients or their carers will be able to comply with the once weekly regimen.

Important warning about the dosage of Methotrexate

In the treatment of psoriasis, Methotrexate **must only be used once a week.** Dosage errors in the use of Methotrexate can result in serious adverse reactions, including death. Please read this section of the summary of product characteristics very carefully.

Adults and children

Antineoplastic Chemotherapy

Methotrexate is active orally and parenterally. Methotrexate Injection may be given by the intramuscular, intravenous, intraarterial or intrathecal routes.

Note: Only the 50 mg/2 ml presentation should be used for the intrathecal route of administration to prevent accidental overdose.

Dosage is related to the patient's body weight or surface area. Methotrexate has been used with beneficial effect in a wide variety of neoplastic diseases, alone and in combination with other cytotoxic agents.

Choriocarcinoma and Similar Trophoblastic Diseases

Methotrexate is administered orally or intramuscularly in doses of 15-30 mg daily for a 5 day course. Such courses may be repeated 3-5 times as required, with rest periods of one or more weeks interposed between courses until any manifesting toxic symptoms subside.

The effectiveness of therapy can be evaluated by 24 hours quantitative analysis of urinary chorionic gonadotrophin hormone (HCG). Combination therapy with other cytotoxic drugs, has also been reported as useful.

Hydatidiform mole may precede or be followed by choriocarcinoma, and methotrexate has been used in similar doses for the treatment of hydatidiform mole and chorioadenoma destruens.

Breast Carcinoma

Prolonged cyclic combination with cyclophosphamide, methotrexate and fluorouracil has given good results when used as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary lymph nodes. Methotrexate dosage was 40 mg/m^2 intravenously on the first and eighth days.

Leukaemia

Acute granulocytic leukaemia is rare in children but common in adults and this form of leukaemia responds poorly to chemotherapy.

Methotrexate is not generally a drug of choice for induction of remission of lymphoblastic leukaemia. Oral methotrexate dosage 3.3 mg/m^2 daily, and prednisolone 40-60 mg/m^2 daily for 4-6 weeks has been used. After a remission is attained, methotrexate in a maintenance dosage of 20-30 mg/m^2 orally or by intramuscular

injection has been administered twice weekly. Twice weekly doses appear to be more effective than daily drug administration. Alternatively, 2.5 mg/kg has been administered intravenously every 14 days.

Meningeal Leukaemia

Some patients with leukaemia are subject to leukaemic invasions of the central nervous system and the CSF should be examined in all leukaemia patients.

Passage of methotrexate from blood to the cerebrospinal fluid is minimal and for adequate therapy the drug should be administered intrathecally. Methotrexate may be given in a prophylactic regimen in all cases of lymphocytic leukaemia. The dose of intrathecal Methotrexate is constant regardless of age or body surface area in patients over the age of 3 years of age, the maximum intrathecal dose should be 12 mg in such patients. Patients under the age of 3 years should be treated in accordance with combination chemotherapy protocols. The administration is at weekly intervals and is usually repeated until the cell count of cerebrospinal fluid returns to normal. At this point one additional dose is advised. Large doses may cause convulsions and untoward side effects may occur as with any intrathecal injection, and are commonly neurological in character.

Note: Only the 50 mg/2 ml presentation should be used for the intrathecal route of administration to prevent accidental overdose.

Lymphomas

In Burkitt's Tumour, stages 1-2, methotrexate has prolonged remissions in some cases. Recommended dosage is 10-25 mg per day orally for 4 to 8 days. In stage 3, methotrexate is commonly given concomitantly with other antitumour agents. Treatment in all stages usually consists of several courses of the drug interposed with 7 to 10 day rest periods, and in stage 3 they respond to combined drug therapy with methotrexate given in doses of 0.625 mg to 2.5 mg/kg daily. Hodgkin's disease responds poorly to methotrexate and to most types of chemotherapy.

Mycosis Fungoides

Therapy with methotrexate appears to produce clinical remissions in one half of the cases treated. Recommended dosage is usually 2.5 to 10 mg daily by mouth for weeks or months and dosage should be adjusted according to the patient's response and haematological monitoring. Methotrexate has also been given intramuscularly in doses of 50 mg once weekly or 25 mg twice weekly.

Use in patients with renal impairment – dose adjustments

Methotrexate is excreted to a significant extent by the kidneys, and therefore should be used with caution in patients with impaired renal function (see sections 4.3 and 4.4). The health care provider may need to adjust the dose to prevent accumulation of drug. The table below provided recommended starting doses in renally impaired patients; dosing may need further adjustment due to wide intersubject pK variability.

Table 1 a. Dose adjustments for methotrexate doses <100 mg/m^2 in patients with renal impairment

Creatinine Clearance (ml/min)	% of dose to Administer
>60	100
30-59	50
<30	Methotrexate must not be administered.

Table 1 b. Dose adjustments for methotrexate doses >100 mg/m^2 in patients with renal impairment

Creatinine Clearance (ml/min)	% of dose to Administer
>80	100
= ~80	75
= ~60	63
<60	Methotrexate must not be administered.

Psoriasis Chemotherapy

Cases of severe uncontrolled psoriasis, unresponsive to conventional therapy, have responded to weekly single, oral, intramuscular or intravenous doses of 10-25 mg per week, and adjusted according to the patient's response. An initial test dose one week prior to initiation of therapy is recommended to detect any idiosyncrasy. A suggested dose range is 5-10 mg.

The prescriber should specify the day of intake on the prescription.

The patient should be fully informed of the risks involved and the clinician should pay particular attention to the appearance of liver toxicity by carrying out liver function tests before starting methotrexate treatment, and repeating these at 2 to 4 month intervals during therapy. The aim of therapy should be to reduce the dose to the lowest possible level with the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy which should be encouraged.

Use in the elderly
Methotrexate should be used with extreme caution in elderly patients. A reduction in dosage should be considered.

4.3 Contraindications

Methotrexate is contraindicated in:

Patients with significantly impaired renal function (creatinine clearance less than 30 ml/min) for methotrexate doses <100 mg/m2, and moderate renal impairment (creatinine clearance less than 60 ml/min) for methotrexate doses >100 mg/m2 (see section 4.2).

Patients with significantly impaired hepatic function

Patients with pre-existing blood dyscrasias, such as significant marrow hypoplasia, leukopenia, thrombocytopenia or anaemia.

Patients with active infections.

Patients with overt or laboratory evidence of immunodeficiency syndrome(s).

Methotrexate is contraindicated in pregnancy (see section 4.6).

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, breast feeding is contraindicated in women taking methotrexate (see section 4.6).

Patients with a known hypersensitivity to methotrexate or any of the other excipients listed in 6.1..

4.4 Special warnings and precautions for use

WARNINGS

Methotrexate must be used only by physicians experienced in antimetabolite chemotherapy.

Because of the possibility of fatal or severe toxic reactions, the patient should be fully informed by the physician of the risks involved and be under his constant supervision.

The prescriber should specify the day of intake on the prescription. The prescriber should make sure patients understand that methotrexate should only be taken once a week. Patients should be instructed on the importance of adhering to the once-weekly intakes.

Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Symptoms typically include dyspnoea, cough (especially a dry non-productive cough), thoracic pain, and fever for which patients should be monitored at each follow-up visit. Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop persistent cough or dyspnoea.

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.

Methotrexate should be withdrawn from patients with pulmonary symptoms and a

thorough investigation should be made to exclude infection. If methotrexate induced lung disease is suspected treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted.

When a patient presents with pulmonary symptoms, the possibility of *Pneumocystis carinii* pneumonia should be considered.

Methotrexate has the potential for serious, sometimes fatal toxicity. The toxic effects may be related in frequency and severity to the dose or frequency of administration but have been seen at all doses. Because the toxic reactions can occur at any time during therapy, the patients have to be observed closely and must be informed of early signs and symptoms of toxicity.

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

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 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 drug interaction studies of methotrexate with ranitidine have been conducted.

Deaths have been reported with the use of methotrexate in the treatment of psoriasis.

In the treatment of psoriasis, methotrexate should be restricted to severe recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established by biopsy and/or after dermatological consultation.

1. Full blood counts should be closely monitored before, during and after treatment. If a clinically significant drop in white-cell or platelet count develops, methotrexate should be withdrawn immediately. Patients should be advised to report all symptoms or signs suggestive of infection.

2. Methotrexate may be hepatotoxic, particularly at high dosage or with prolonged therapy. Liver atrophy, necrosis, cirrhosis, fatty changes, and periportal fibrosis have been reported.

Liver function tests: Treatment should not be initiated or should be discontinued if there are persistent or significant abnormalities in liver function tests, other non-invasive investigations of hepatic fibrosis, or liver biopsies.

Temporary increases in transaminases to two or three times the upper limit of normal have been reported in patients at a frequency of 13-20 %. Persistent elevation of liver enzymes and/or decrease in serum albumin may be indicative for severe hepatotoxicity. In the event of a persistent increase in liver enzymes, consideration should be given to reducing the dose or discontinuing therapy.

Histological changes, fibrosis and more rarely liver cirrhosis may not be preceded by abnormal liver function tests. There are instances in cirrhosis where transaminases are normal. Therefore, non-invasive diagnostic methods for monitoring of liver condition should be considered, in addition to liver function tests. Liver biopsy should be considered on an individual basis taking into account the patient's comorbidities, medical history and the risks related to biopsy. Risk factors for hepatotoxicity include excessive prior alcohol consumption, persistent elevation of liver enzymes, history of liver disease, family history of hereditary liver disorders, diabetes mellitus, obesity and previous contact with hepatotoxic drugs or chemicals and prolonged methotrexate treatment.

Additional hepatotoxic medicinal products should not be given during treatment with methotrexate unless clearly necessary. Alcohol consumption should be avoided (see sections 4.3 and 4.5). Closer monitoring of liver enzymes should be undertaken in patients concomitantly taking other hepatotoxic medicinal products.

Increased caution should be exercised in patients with insulin-dependent diabetes mellitus, as during methotrexate therapy, liver cirrhosis developed in isolated cases without any elevation of transaminases.

3. Methotrexate has been shown to be teratogenic; it has caused foetal death and/or congenital anomalies. 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 patients should not receive methotrexate.

4. Methotrexate therapy in patients with impaired renal function should be undertaken with extreme caution because impairment of renal function will decrease methotrexate elimination.

Renal function should be monitored by renal function tests and urinalyses. If serum creatinine levels are increased, the dose should be reduced. If creatinine clearance is less than 30 ml/min, treatment with methotrexate should not be given. If creatinine clearance is less than 60 ml/min, methotrexate doses >100 mg/m2 not be given (see section 4.2 and 4.3).

Treatment with methotrexate doses of >100 mg/m2 should not be initiated at urinary pH values of less than 7.0. Alkalinisation of the urine must be tested by repeated pH monitoring (value greater than or equal to 6.8) for at least the first 24 hours after the administration of methotrexate is started.

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

As methotrexate is eliminated mainly via the kidneys, increased concentrations are to be expected in the presence of renal impairment, which may result in severe adverse reactions.

If there is the possibility of renal impairment (e.g. in elderly subjects), monitoring should take place at shorter intervals. This applies in particular when medicinal products that affect the elimination of methotrexate, or that cause kidney damage (e.g. NSAIDs) or that can potentially lead to impairment of haematopoiesis, are administered concomitantly.

If risk factors such as renal function disorders, including mild renal impairment, are present, combined administration with NSAIDs is not recommended. Dehydration may also intensify the toxicity of methotrexate.

Concomitant use of proton pump inhibitors (PPIs) and high dose methotrexate should be avoided, especially in patients with renal impairment.

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

6. Methotrexate affects gametogenesis during the period of its administration and may result in decreased fertility which is thought to be reversible on discontinuation of therapy. Conception should be avoided during the period of methotrexate administration and for at least 6 months thereafter. Patients and their partners should be advised to this effect.

7. Methotrexate has some immunosuppressive activity and immunological responses to concurrent vaccination may be decreased. The immunosuppressive effect of methotrexate should be taken into account when immune responses of patients are important or essential. Immunisation with live virus vaccines is generally not recommended.

8. Pleural effusions and ascites should be drained prior to initiation of methotrexate therapy.

9. Deaths have been reported with the use of methotrexate. Serious adverse reactions including deaths have been reported with concomitant administration of methotrexate (usually in high doses) along with some non-steroidal anti-inflammatory drugs (NSAIDs).

10. Concomitant administration of folate antagonists such as trimethoprim/sulphamethoxazole has been reported to cause an acute megaloblastic pancytopenia in rare instances.

11. Systemic toxicity may occur following intrathecal administration. Blood counts should be monitored closely.

12. A chest X-ray is recommended prior to initiation of methotrexate therapy.

13. If acute methotrexate toxicity occurs, patients may require folinic acid.

14. Severe, occasionally fatal, cutaneous or sensitivity reactions (e.g., toxic epidermic necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, erythema multiforme, vasculitis and extensive herpetiform skin eruptions) may occur after the administration of methotrexate and recovery ensured mostly after discontinuation of the therapy.

PRECAUTIONS

Methotrexate has a high potential toxicity, usually dose related, and should be used only by physicians experienced in antimetabolite chemotherapy, in patients under their constant supervision. The physician should be familiar with the various characteristics of the drug and its established clinical usage.

Before beginning methotrexate therapy or reinstituting methotrexate after a rest period, assessment of renal function, liver function and blood elements should be made by history, physical examination and laboratory tests.

It should be noted that intrathecal doses are transported into the cardiovascular system and may give rise to systemic toxicity. Systemic toxicity of methotrexate may also be enhanced in patients with renal dysfunction, ascites, or other effusions due to prolongation of serum half-life.

In rare cases, following intrathecal administration, a tumour lysis syndrome has been observed.

Carcinogenesis, mutagenesis, and impairment of fertility: Animal carcinogenicity studies have demonstrated methotrexate to be free of carcinogenic potential. Although methotrexate has been reported to cause chromosomal damage to animal somatic cells and bone marrow cells in humans, these effects are transient and reversible. In patients treated with methotrexate, evidence is insufficient to permit conclusive evaluation of any increased risk of neoplasia.

Fertility and reproduction
Fertility
Methotrexate has been reported to cause impairment of fertility, oligospermia, menstrual dysfunction and amenorrhoea in humans, during and for a short period after cessation of therapy, affecting spermatogenesis and oogenesis during the period of its administration - effects that appear to be reversible on discontinuing therapy. In addition, methotrexate causes embryotoxicity, abortion and foetal defects in humans.

Teratogenicity – Reproductive risk: Methotrexate causes embryotoxicity, abortion and foetal malformations in humans. Therefore, the possible risks of effects on reproduction, pregnancy loss and congenital malformations should be discussed with female patients of childbearing potential (see section 4.6), the absence of pregnancy must be confirmed before Methotrexate is used. If women of a sexually mature age are treated, effective contraception must be used during treatment and for at least six months after.

For contraception advice for men see section 4.6.

Patients undergoing therapy should be subject to appropriate supervision so that signs or symptoms of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay. Pre-treatment and periodic haematological studies are essential to the use of methotrexate in chemotherapy because of its common effect of haematopoietic suppression. This may occur abruptly and on apparent safe dosage, and any profound drop in blood cell count indicates immediate stopping of the drug and appropriate therapy. In patients with malignant disease who have pre-existing bone marrow aplasia, leukopenia, thrombocytopenia or anaemia, methotrexate should be used with caution, if at all.

In general, the following laboratory tests are recommended as part of essential clinical evaluation and appropriate monitoring of patients chosen for or receiving methotrexate therapy: complete haemogram; haematocrit; urinalysis; renal function tests; liver function tests and chest X-ray.

The purpose is to determine any existing organ dysfunction or system impairment. The tests should be performed prior to therapy, at appropriate periods during therapy and after termination of therapy.

Methotrexate is bound in part to serum albumin after absorption, and toxicity may be increased because of displacement by certain drugs such as salicylates, sulphonamides, phenytoin, and some antibacterials such as tetracycline, chloramphenicol and para-aminobenzoic acid. These drugs, especially salicylates and sulphonamides, whether antibacterial, hypoglycaemic or diuretic, should not be given concurrently until the significance of these findings is established.

Vitamin preparations containing folic acid or its derivatives may alter response to methotrexate.

Methotrexate should be used with extreme caution in the presence of infection, peptic ulcer, ulcerative colitis, debility, and in extreme youth and old age. If profound leukopenia occurs during therapy, bacterial infection may occur or become a threat. Cessation of the drug and appropriate antibiotic therapy is usually indicated. In severe bone marrow depression, blood or platelet transfusions may be necessary.

Since it is reported that methotrexate may have an immunosuppressive action, this factor must be taken into consideration in evaluating the use of the drug where immune responses in a patient may be important or essential.

In all instances where the use of methotrexate is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risks of toxic effects or adverse reactions. Most such adverse reactions are reversible if detected early. When such effects or reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to the clinical judgement of the physician. Reinstitution of methotrexate therapy should be carried out with caution, with adequate consideration of further need for the drug and alertness as to the possible recurrence of toxicity.

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

Photosensitivity: Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking methotrexate (see section 4.8). Exposure to intense sunlight or UV rays should be avoided unless medically indicated. Patients should use adequate sun-protection to protect themselves from intense sunlight.

Excipient information

Methotrexate 50 mg/2 ml and 250 mg/10 ml contain less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium free’.

Methotrexate 500 mg/20 ml contains 41.1 mg sodium per vial, equivalent to 2.06% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Methotrexate 1 g/40 ml contains 82.2 mg sodium per vial, equivalent to 4.11% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Methotrexate is extensively protein bound and may be displaced by certain drugs such as salicylates, hypoglycaemics, diuretics, sulphonamides, diphenylhydantoins, tetracyclines, chloramphenicol and p-aminobenzoic acid, and the acidic anti-inflammatory agents, so causing a potential for increased toxicity when used concurrently.

Concomitant use of other drugs with nephrotoxic or hepatotoxic potential (including alcohol) should be avoided.

Vitamin preparations containing folic acid or its derivatives may decrease the effectiveness of methotrexate.

Caution should be used when NSAIDs and salicylates are administered concomitantly with methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate and thereby may enhance its toxicity. Concomitant use of NSAIDs and salicylates has been associated with fatal methotrexate toxicity.

However, patients using constant dosage regimens of NSAIDs have received concurrent doses of methotrexate without problems observed.

Treatment with more than one DMARD in various regimens is being tried but there is little evidence available to assess benefit. A meta-analysis of 5 different combinations of DMARDs demonstrated that although efficacy might be greater than single DMARDs, toxicity was also increased.

Renal tubular transport is also diminished by probenecid and penicillins; use of these with methotrexate should be carefully monitored.

A potential interaction may exist between methotrexate and proton-pump inhibitors (e.g. omeprazole, pantoprazole). Omeprazole may inhibit methotrexate clearance resulting in potentially toxic methotrexate levels.

Severe bone marrow depression has been reported following the concurrent use of methotrexate and co-trimoxazole or trimethoprim. Concurrent use should probably be avoided.

The use of nitrous oxide potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe, unpredictable myelosuppression and stomatitis and in cases of intrathecal administration increased severe, unpredictable neurotoxicity. Whilst this effect can be reduced by administering calcium folinate, the concomitant use of nitrous oxide and methotrexate should be avoided.

Concurrent administration of metamizole and methotrexate can increase the haematotoxic effect of methotrexate, especially in elderly patients. Therefore, coadministration should be avoided.

An increased risk of hepatitis has been reported following the use of methotrexate and the acitretin metabolite, etretinate. Consequently, the concomitant use of methotrexate and acitretin should be avoided.

Methotrexate may increase the bioavailability of mercaptopurine by interference with first-pass metabolism.
Concomitant application of methotrexate and theophylline can reduce theophylline clearance.

4.6 Fertility, pregnancy and lactation

Pregnancy
Methotrexate is contraindicated during pregnancy in non-oncological indications (see section 4.3).

Both men and women receiving methotrexate should be informed of the potential risk of adverse effects on reproduction. Women of childbearing potential should be fully informed of the potential hazard to the foetus should they become pregnant during methotrexate therapy. In cancer chemotherapy, methotrexate should not be used in pregnant women or women of childbearing potential who might become pregnant unless the potential benefits to the mother outweigh the possible risks to the foetus.

If pregnancy occurs during treatment with methotrexate and up to six months thereafter, medical advice should be given regarding the risk of harmful effects on the child associated with treatment and ultrasonography examinations should be performed to confirm normal foetal development.

In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (see section 5.3). Methotrexate has been shown to be teratogenic to humans; it has been reported to cause foetal death, miscarriages and/or congenital abnormalities (e.g. craniofacial, cardiovascular, central nervous system and extremity-related).

Methotrexate is a powerful human teratogen, with an increased risk of spontaneous abortions, intrauterine growth restriction and congenital malformations in case of exposure during pregnancy.

• Spontaneous abortions have been reported in 42.5% of pregnant women exposed to low-dose methotrexate treatment (less than 30 mg/week), compared to a reported rate of 22.5% in disease-matched patients treated with drugs other than methotrexate.
• Major birth defects occurred in 6.6% of live births in women exposed to low-dose methotrexate treatment (less than 30 mg/week) during pregnancy, compared to approximately 4% of live births in in disease-matched patients treated with drugs other than methotrexate.

Insufficient data is available for methotrexate exposure during pregnancy higher than 30 mg/week, but higher rates of spontaneous abortions and congenital malformations are expected, in particular at doses commonly used in oncologic indications.

When methotrexate was discontinued prior to conception, normal pregnancies have been reported.

When used in oncological indications, methotrexate should not be administered during pregnancy in particular during the first trimester of pregnancy. In each individual case the benefit of treatment must be weighed up against the possible risk to the foetus. If the drug is used during pregnancy or if the patient becomes pregnant while taking methotrexate, the patient should be informed of the potential risk to the foetus.

Breast-Feeding
Methotrexate is distributed into breast milk. Because of the potential for serious adverse reactions to methotrexate in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.

Fertility
Methotrexate affects spermatogenesis and oogenesis and may decrease fertility. Methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea in humans. These effects appear to be reversible after discontinuation of therapy in most cases. In oncologic indications, women who are planning to become pregnant are advised to consult a genetic counselling centre, if possible, prior to

therapy and men should seek advice about the possibility of sperm preservation before starting therapy as methotrexate can be genotoxic at higher doses (see section 4.4).

Women of childbearing potential/Contraception in females
Women must not get pregnant during methotrexate therapy, and effective contraception must be used during treatment with methotrexate and at least 6 months thereafter (see section 4.4). Prior to initiating therapy, women of childbearing potential must be informed of the risk of malformations associated with methotrexate and any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. a pregnancy test. During treatment pregnancy tests should be repeated as clinically required (e.g. after any gap of contraception). Female patients of reproductive potential must be counselled regarding pregnancy prevention and planning.

Contraception in males
It is not known if methotrexate is present in semen. Methotrexate has been shown to be genotoxic in animal studies, such that the risk of genotoxic effects on sperm cells cannot completely be excluded. Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low-dose methotrexate (less than 30 mg/week). For higher doses, there is insufficient data to estimate the risks of malformations or miscarriage following paternal exposure.

As precautionary measures, sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 3 months after cessation of methotrexate. Men should not donate semen during therapy or for 3 months following discontinuation of methotrexate.

4.7. Effects on Ability to Drive and Use Machines

Not applicable

4.8 Undesirable effects

The most common adverse reactions include ulcerative stomatitis, leukopenia, nausea and abdominal distress. Although very rare, anaphylactic reactions to methotrexate have occurred. Others reported are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection. In general, the incidence and severity of side effects are considered to be dose-related. Adverse reactions as reported for the various systems are as follows:

Skin: Severe, occasionally fatal, dermatologic reactions including erythema multiforme, Stevens-Johnson syndrome, skin necrosis, epidermal necrolysis. Erythematous rashes, pruritus, urticaria, dermatitis, photosensitivity reactions (frequency uncommon), pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis. Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Skin ulceration in psoriatic patients and rarely painful erosion of psoriatic plaques have been reported. The recall phenomenon has been reported in both radiation and solar damaged skin. Skin exfoliation, dermatitis exfoliative (frequency not known).

Blood: Bone marrow depression, leukopenia, thrombocytopenia, anaemia hypogammaglobulinaemia, haemorrhage from various sites, septicaemia, lymphoproliferative disorders (frequency very rare).

Alimentary System: Gingivitis, pharyngitis, stomatitis, mucostitis, anorexia, vomiting, diarrhoea, haematemesis, melaena, gastrointestinal ulceration and bleeding, pancreatitis, enteritis, hepatic toxicity resulting in active liver atrophy, necrosis, fatty metamorphosis, periportal fibrosis, or hepatic cirrhosis. In rare cases the effect of methotrexate on the intestinal mucosa has led to malabsorption or toxic megacolon.

Hepatic: Hepatic toxicity resulting in significant elevations of liver enzymes, acute liver atrophy, necrosis, fatty metamorphosis, hepatitis, periportal fibrosis, or cirrhosis or death may occur, usually following chronic administration.

Urogenital System: Renal failure, azotaemia, cystitis, haematuria, defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, infertility, abortion, foetal defects, severe nephropathy. Vaginitis, vaginal ulcers, cystitis, haematuria and nephropathy have also been reported.

Pulmonary System: Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported (see section 4.4). Acute pulmonary oedema has also been reported after oral and intrathecal use. Pulmonary fibrosis is rare. A syndrome consisting of pleuritic pain and pleural thickening has been reported following high doses. Frequency Not Known: Pulmonary alveolar haemorrhage*.
*(has been reported for methotrexate used in rheumatologic and related indications).

Central Nervous System: Headaches, drowsiness, blurred vision, aphasia, cognitive disorder, hemiparesis and convulsions have occurred possibly related to haemorrhage or to complications from intraarterial catheterization. Convulsion, paresis, Guillain-Barre syndrome and increased cerebrospinal fluid pressure have followed intrathecal administration.

Other reactions related to, or attributed to the use of methotrexate such as pneumonitis, metabolic changes, precipitation of diabetes, osteoporotic effects, abnormal changes in tissue cells and even sudden death have been reported.

There have been reports of leukoencephalopathy following intravenous methotrexate in high doses, or low doses following cranial-spinal radiation.

Paraesthesia, hypoaesthesia (frequency very rare).

Cardiac disorders: Pericarditis, pericardial effusion.

Ear disorders: Tinnitus.

Eye disorders: Conjunctivitis.

Infections and infestations: Opportunistic infections (sometimes fatal e.g. fatal sepsis) have also been reported in patients receiving methotrexate therapy for neoplastic and non-neoplastic diseases, Pneumocystis carinii pneumonia being the most common. Other reported infections include, pneumonia, nocardiosis, histoplasmosis, cryptococcosis, Herpes Zoster, Herpes Simplex, hepatitis and cytomegalovirus infection, including cytomegaloviral pneumonia.

Musculoskeletal and connective tissue disorders: Arthralgia/myalgia, Osteonecrosis of jaw (secondary to lymphoproliferative disorders) – frequency unknown.

Psychiatric disorders: Mood altered.

Vascular disorder: Vasculitis, hypotension, thromboembolic events (e.g. thrombophlebitis, pulmonary embolism, arterial, cerebral, deep vein or retinal vein thrombosis).

General disorders and administration site conditions: Oedema, injection site reaction*, injection site necrosis* (frequency not known).
*(parenteral only).

Adverse reactions following intrathecal methotrexate are generally classified into three groups, acute, subacute, and chronic. The acute form is a chemical arachnoiditis manifested by headache, back or shoulder pain, nuchal rigidity, and fever. The subacute form may include paresis, usually transient, paraplegia, nerve palsies, and cerebellar dysfunction. The chronic form is a leukoencephalopathy manifested by irritability, confusion, ataxia, spasticity, occasionally convulsions, dementia, somnolence, coma, and rarely, death. There is evidence that the combined use of cranial radiation and intrathecal methotrexate increases the incidence of leukoencephalopathy.

Additional reactions related to or attributed to the use of methotrexate such as osteoporosis, abnormal (usually 'megaloblastic') red cell morphology, precipitation of diabetes, other metabolic changes, and sudden death have been reported.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Cases of overdose have been reported, sometimes fatal, due to erroneous daily intake instead of weekly intake of oral methotrexate. In these cases, symptoms that have been commonly reported are hematological and gastrointestinal reactions

Calcium folinate (calcium leucovorin) is a potent agent for neutralizing the immediate toxic effects of methotrexate on the haematopoietic system. Where large doses or overdoses are given, calcium folinate may be administered by intravenous infusion in doses up to 75 mg within 12 hours, followed by 12 mg intramuscularly every 6 hours for 4 doses. Where average doses of methotrexate appear to have an adverse effect 6-12 mg of calcium folinate may be given intramuscularly every 6 hours for 4 doses. In general, where overdosage is suspected, the dose of calcium folinate should be equal to or higher than, the offending dose of methotrexate and should be administered as soon as possible; preferably within the first hour and certainly within 4 hours after which it may not be effective.

Other supporting therapy such as blood transfusion and renal dialysis may be required. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high flux dialyser.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Methotrexate is an antimetabolite which acts principally by competitively inhibiting the enzyme, dihydrofolate reductase. In the process of DNA synthesis and cellular replication, folic acid must be reduced to tetrahydrofolic acid by this enzyme, and inhibition by Methotrexate interferes with tissue cell reproduction. Actively proliferating tissues such as malignant cells are generally more sensitive to this effect of Methotrexate. It also inhibits antibody synthesis.

Methotrexate also has immunosuppressive activity, in part possibly as a result of inhibition of lymphocyte multiplication. The mechanism(s) of action in the management of rheumatoid arthritis of the drug is not known, although suggested mechanisms have included immunosuppressive and/or anti-inflammatory effect.

5.2. Pharmacokinetic Properties

In doses of 0.1mg (of Methotrexate) per kg, Methotrexate is completely absorbed from the G.I. tract; larger oral doses may be incompletely absorbed. Peak serum concentrations are achieved within 0.5 - 2 hours following I.V. / I.M. or intra-arterial administration. Serum concentrations following oral administration of Methotrexate may be slightly lower than those following I.V. injection.

Methotrexate is actively transported across cell membranes. The drug is widely distributed into body tissues with highest concentrations in the kidneys, gall bladder, spleen, liver and skin. Methotrexate is retained for several weeks in the kidneys and for months in the liver. Sustained serum concentrations and tissue accumulation may result from repeated daily doses. Methotrexate crosses the placental barrier and is distributed into breast milk. Approximately 50% of the drug in the blood is bound to serum proteins.

In one study, Methotrexate had a serum half-life of 2-4 hours following I.M. administration. Following oral doses of 0.06mg/kg or more, the drug had a serum half-life of 2-4 hours, but the serum half-life was reported to be increased to 8-10 hours when oral doses of 0.037mg/kg were given.

Methotrexate does not appear to be appreciably metabolised. The drug is excreted primarily by the kidneys via glomerular filtration and active transport. Small amounts are excreted in the faeces, probably via the bile. Methotrexate has a biphasic excretion pattern. If Methotrexate excretion is impaired accumulation will occur more rapidly in patients with impaired renal function. In addition, simultaneous administration of other weak organic acids such as salicylates may suppress Methotrexate clearance.

5.3. Pre-clinical Safety Data

None

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sodium chloride, sodium hydroxide and Water for injections.

6.2 Incompatibilities

Immediate precipitation or turbidity results when combined with certain concentrations of Droperidol, Heparin Sodium, Metaclopramide Hydrochloride, Ranitidine Hydrochloride in syringe.

6.3 Shelf-Life

As packaged for sale – 2 years.

After dilution – Chemical and physical in-use stability has been demonstrated in dextrose 5% and sodium chloride 0.9% infusion solutions for 30 days at 4°C in PVC containers when protected from light.

From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special Precautions for Storage

As packaged for sale-

For the 50 mg/2 ml, 250 mg/10 ml and 500 mg/20 ml presentations: Do not store above 25°C. Do not freeze. Keep container in the outer carton.

For the 1 g/40 ml presentation: Store at 2°C – 8°C. Keep container in the outer carton.

After dilution – see 6.3.

6.5 Nature and Content of Container

50 mg/2 ml – Conventional or OncoTain® Type I glass vial with rubber stopper, aluminium seal and plastic ‘flip-off’ top. Packs containing 5 vials.

250 mg/10 ml – Conventional Type I glass vial with rubber stopper, aluminium seal and plastic ‘flip-off’ top. Packs containing 5 vials.

500 mg/20 ml – Conventional or OncoTain® Type I glass vial with rubber stopper, aluminium seal and plastic ‘flip-off’ top, or Onco-Vial Type I glass vials with rubber stopper. Packs containing 1 vial.

1 g/40 ml – Onco-Vial® Type I glass vial with rubber stopper. Packs containing 1 vial.

Not all presentations and pack sizes listed above may be marketed.

6.6 Instruction for Use, Handling and Disposal

Single use only. Discard any unused contents.

Onco-Vials® should be used with an appropriate Mayne administration device

7 MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

PL 04515/0015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 21/8/85
First Renewal of Authorisation: 31/10/90

10 DATE OF REVISION OF THE TEXT

18/10/2024