# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Methotrexate 100 mg/ml Injection BP

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml contains methotrexate 100mg (1000mg in 10ml)
For excipients, see 6.1

## 3 PHARMACEUTICAL FORM

Solution for injection
The solution is a clear yellow solution free from particles.

## 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 injection may be given by the intramuscular, intravenous or intra-arterial routes.
**Note: Methotrexate injection 1000mg/10ml and 5000mg/50ml presentations are hypertonic and therefore are not suitable for intrathecal use.**

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.

**Antineoplastic Chemotherapy**

Methotrexate is active parenterally. Methotrexate injection may be given by the intramuscular, intravenous or intra-arterial routes. 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.

Note: Methotrexate injection 1000mg/10ml and 5000mg/50ml presentation are hypertonic and therefore are not suitable for intrathecal use.

**Choriocarcinoma and Similar Trophoblastic Diseases**

Methotrexate is administered intramuscularly in doses of 15–30mg daily for a five 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 40mg/m2 intravenously on the first and eighth days.

**Leukaemia**

Acute granulocytic leukaemia is rare in children but common in adults and it is not particularly sensitive to methotrexate but responds to other combination chemotherapy agents.
Methotrexate is not generally a drug of choice for induction of remission of lymphoblastic leukaemia. After a remission is attained, methotrexate in a maintenance dosage of 20–30mg/m2 by I.M. injection has been administered twice weekly. Twice weekly doses appear to be more effective than daily drug administration.
Alternatively, 2.5mg/kg has been administered I.V. 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 cases of acute lymphoblastic leukaemia and some cases of acute myeloblastic leukaemia. Methotrexate may be given in a prophylactic regimen in all cases of acute lymphoblastic leukaemia. Methotrexate is administered by intrathecal injection in doses of 200–500 microgram/kg body weight. The administration is at intervals of two to five days and is usually until clearance of blasts in the CSF. At this point one additional dose is advised. Alternatively, methotrexate 12mg/m2 can be given once weekly for two weeks, and then once monthly. Large doses may cause convulsions and untoward side effects, may commonly neurological in character, occur as with any intrathecal injection.
Note: Methotrexate injection 1000mg/10ml and 5000mg/50ml presentation are hypertonic and therefore are not suitable for intrathecal use.

**Lymphomas**

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 seven to ten day rest periods, and in stage 3 combined drug therapy is given with methotrexate in doses of 0.625mg to 2.5mg/kg daily. Hodgkin's Disease does not usually respond to methotrexate but can have a substantial response to the use of other combination chemotherapy agents.

**Mycosis Fungoides**

Therapy with methotrexate appears to produce clinical remissions in one half of the cases treated adjusted according to the patient‘s response and haematological monitoring. Methotrexate has been given intramuscularly in doses of 50mg once weekly or 25mg twice weekly.

**Psoriasis Chemotherapy**

Cases of severe uncontrolled psoriasis, unresponsive to conventional therapy, have responded to weekly single, I.M. or I.V. doses of 10–25mg per week, 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 5–10mg.
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 two to four 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.

*Renal Impairment* (see 4.4. Special warnings and precautions for use).
Reduce dose in patients with renal impairment.

## 4.3 Contraindications

Significantly impaired renal function.
Significantly impaired hepatic function
Pre-existing blood dyscrasias, such as significant marrow hypoplasia, leukopenia, thrombocytopenia or anaemia.
Methotrexate is contraindicated in pregnancy.
Because of the potential for serious adverse reactions from methotrexate in breast fed infants, breast feeding is contra-indicated in women taking methotrexate; additionally, for non-oncological indications.
Patients with a known allergic hypersensitivity to methotrexate or any of the other ingredients should not receive methotrexate.

## 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.
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, and 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. Since changes may occur without previous signs of gastrointestinal or haematological toxicity, it is imperative that hepatic function be determined prior to initiation of treatment and monitored regularly throughout therapy. If substantial hepatic function abnormalities develop, methotrexate dosing should be suspended for at least two weeks. Special caution is indicated in the presence of pre-existing liver damage or impaired hepatic function. Concomitant use of other drugs with hepatotoxic potential (including alcohol) should be avoided.
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. Renal function should be closely monitored before, during and after treatment. Caution should be exercised if significant renal impairment is disclosed. Reduce dose of methotrexate in patients with renal impairment. High doses may cause the precipitation of methotrexate or its metabolites in the renal tubules. A high fluid throughput and alkalinisation of the urine to pH 6.5 – 7.0, by oral or intravenous administration of sodium bicarbonate (5 x 625mg tablets every three hours) or acetazolamide (500mg orally four times a day) is recommended as a preventative measure. Methotrexate is excreted primarily by the kidneys. Its use in the presence of impaired renal function may result in accumulation of toxic amounts or even additional renal damage.
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 six 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.
8. Potentially fatal opportunistic infections, including Pneumocystis carinii pneumonia may occur with methotrexate therapy. When a patient presents with pulmonary symptoms the possibility of Pneumocystis carinii should be considered.
9. Pleural effusions and ascites should be drained prior to initiation of methotrexate therapy.
10. 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), (see 4.5 Interactions with other Medicaments and other forms of Interaction).
11. Concomitant administration of folate antagonists such as trimethoprim/sulphamethoxazole has been reported to cause an acute megaloblastic pancytopenia in rare instances.
12. Systemic toxicity may occur following intrathecal administration. Blood counts should be monitored closely.
13. A chest X-ray is recommended prior to initiation of methotrexate therapy.
14. If acute methotrexate toxicity occurs, patients may require folinic acid.
15. **Fertility**

    Methotrexate has been reported to cause impairment of fertility, oligospermia, menstrual dysfunction and amenorrhoea in humans during and for a short period after the discontinuation of treatment, affecting spermatogenesis and oogenesis during the period of its administration - effects that appear to be reversible on discontinuing therapy.

16. **Teratogenicity – Reproductive risk**
    Methotrexate methotrexate causes embryotoxicity, abortion and foetal malformations in humans. Therefore, the possible effects on reproduction, pregnancy loss and congenital malformations should be discussed with female patients of childbearing age (see section 4.6). In non-oncologic indications, 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.

<u>Photosensitivity</u>

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking methotrexate (see section 4.8). Exposure to intense sunlight or to UV rays should be avoided. Patients should use a sun-protection product with a high protection factor.

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.

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.

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. In addition, methotrexate causes embryotoxicity, abortion and foetal defects in humans. Therefore the possible risk of effects on reproduction should be discussed with patients of childbearing potential (see ‚Warnings‘).

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. Pretreatment and periodic haematological studies are essential to the use of methotrexate in chemotherapy because of its common adverse 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.
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 treatmen

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.

After absorption, methotrexate is bound in part to serum albumin 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 (see 4.5 Interactions with other Medicaments and other forms of Interaction). 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 judgment 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.

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) 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.

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 be restarted.

## 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 (see 4.4. Special warnings and precautions for use).
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 (see 4.4. Special warnings and precautions for use). 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 any problems being observed.
Renal tubular transport is also diminished by probenecid and penicillins; use of these with methotrexate should be carefully monitored.
Severe bone marrow depression has been reported following the concurrent use of methotrexate and co-trimoxazole or trimethoprim. Concurrent use should probably be avoided.
Methotrexate-induced stomatitis and other toxic effects may be increased by the use of nitrous oxide.

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.

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 case of intrathecal administration increased severe, unpredictable neurotoxicity with intrathecal administration. Whilst this effect can be reduced by administering calcium folinate, the concomitant use of nitrous oxide and methotrexate should be avoided.

## 4.6 Fertility, pregnancy and lactation

Abortion, foetal death, and/or congenital anomalies have occurred in pregnant women receiving methotrexate, especially during the first trimester of pregnancy.
Methotrexate is contraindicated in the management of psoriasis or rheumatoid arthritis in pregnant women. Women of childbearing potential should not receive Methotrexate until pregnancy is excluded. For the management of psoriasis or rheumatoid arthritis, methotrexate therapy in women should be started immediately following a menstrual period and appropriate measures should be taken in men or women to avoid conception during and for at least six months following cessation of methotrexate therapy.
Both men and women receiving methotrexate should be informed of the potential risk of adverse effects on reproduction.

**Women of childbearing potential/Contraception in males and 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 6 months after cessation of methotrexate. Men should not donate semen during therapy or for 6 months following discontinuation of methotrexate.

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

**Fertility**
Methotrexate affects spermatogenesis and oogenesis and may decrease fertility. In humans, methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea. 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).

## 4.7 Effects on ability to drive and use machines

Methotrexate is not known to affect ability to drive or use machines.

## 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. 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 disseminated Herpes Simplex and cytomegalovirus infection, including cytomegaloviral pneumonia. 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:

<u>General disorders and administration site conditions</u>
Not known: Injection site necrosis

<u>Skin and subcutaneous tissue disorders</u>*:*

Stevens-Johnson syndrome, epidermal necrolysis, erythematous rashes, pruritus, urticaria, photosensitivity, 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. Photosensitivity, Skin exfoliation / dermatitis exfoliative has also been reported (not known frequency).

<u>Blood and lymphatic system disorders:</u>
Bone marrow depression, leukopenia, thrombocytopenia, pancytopenia, anaemia, hypogammaglobulinaemia, haemorrhage from various sites, septicaemia.
Lymphoproliferative disorders (see “description” below), *very rare*
Description of selected adverse reactions Lymphoma/Lymphoproliferative disorders: there have been reports of individual cases of lymphoma and other lymphoproliferative disorders which subsided in a number of cases once treatment with methotrexate had been discontinued

<u>Musculoskeletal and connective tissue:</u>
Osteonecrosis of jaw (secondary to lymphoproliferative disorders), *frequency unknown*

<u>Alimentary System:</u>
Gingivitis, pharyngitis, stomatitis, anorexia, vomiting, diarrhoea, haematemesis, melaena, gastrointestinal ulceration and bleeding, 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, 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, and nephropathy have also been reported.

Pulmonary System:
Infrequently an acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported.
Acute pulmonary oedema has also been reported after intrathecal use.
Pulmonary fibrosis is rare. A syndrome consisting of pleuritic pain and pleural thickening has been reported following high doses.
Central Nervous System:
Headaches, drowsiness, blurred vision, aphasia, hemiparesis and convulsions have occurred possibly related to haemorrhage or to complications from intra-arterial catheterization. Convulsion, paresis, Guillain-Barré 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, abnormal (usually ‘megaloblastic’) red cell morphology and even sudden death have been reported.

There is the potential for Non-Hodgkin’s lymphoma to develop through the use of methotrexate.

There have been reports of leukoencephalopathy following intravenous methotrexate in high doses, or low doses following cranial-spinal radiation.
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.
Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. (see Section 4.4 Special warnings and precautions for use)

### 4.9 Overdose

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 75mg within 12 hours, followed by 12mg intramuscularly every six hours for four doses. Where average doses of methotrexate appear to have an adverse effect, 6–12mg of calcium folinate may be given intramuscularly every six hours for four 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 four 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 of the drug in the management of rheumatoid arthritis is not known, although suggested mechanisms have included immunosuppressive and/or anti-inflammatory effect.

### 5.2 Pharmacokinetic properties

Peak serum concentrations are achieved within 0.5–2 hours following I.V. / I.M. or intra-arterial administration.

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.

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 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those included in other sections.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium hydroxide
Water for injections

### 6.2 Incompatibilities

Immediate precipitation or turbidity results when combined with certain concentrations of droperidol, heparin sodium, metoclopramide hydrochloride or ranitidine hydrochloride in the syringe.
As with all parenteral solutions, incompatibility of the additive medications with the solution must be addressed before addition. In the absence of compatibility studies, this solution must not be mixed with other medicinal products, except sodium chloride solution 0.9% and glucose solution 5% (see Section 6.4, Special precautions for storage).

### 6.3 Shelf life

Two years
After dilution (see section 6.4. and 6.6.): 24 hours.
Any unused solution should be discarded immediately after use.

### 6.4 Special precautions for storage

Do not store above 25°C. Store in the original container.
After dilution (see section 6.6.):
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C for solutions with a final concentration of methotrexate 5mg/ml or 20mg/ml after dilution of the methotrexate 100mg/ml with one of the following solutions:
• sodium chloride solution 0.9%;
• glucose solution 5%

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 normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

### 6.5 Nature and contents of container

Colourless vials of hydrolytic type I glass, packed in a carton.
Vials are closed with a rubber stopper with an aluminium crimp cap with flip-off.
Packs of 1 vial containing 1000mg/10ml of methotrexate.

### 6.6 Special precautions for disposal

Cytotoxic drugs should only be handled by trained personnel in a designated area. The work surface should be covered with disposable plastic-backed absorbent paper. Protective gloves and goggles should be worn to avoid the drug accidentally coming into contact with the skin or eyes. Methotrexate is not a vesicant and should not cause harm if it comes into contact with the skin. It should of course be washed off with water immediately. Any transient stinging may be treated with bland cream. If there is any danger of systemic absorption of significant quantities of methotrexate, by any route, calcium folinate cover should be given.
Cytotoxic preparations should not be handled by pregnant staff.
Adequate care should be taken in the disposal of any unwanted product, syringes and containers. Any spillage or waste material may be disposed of by incineration. We do not make any specific recommendations with regard to the temperature of the incinerator.

## 7 MARKETING AUTHORISATION HOLDER

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A-4866 Unterach
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## 8 MARKETING AUTHORISATION NUMBER(S)

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## 10 DATE OF REVISION OF THE TEXT

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