IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0037/023/011
Case No: 2025577

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Cyanamid of Great Britain

Fareham Road, **Gosport, Hants**, **PO13 0AS**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Methotrexate Injection 50 mg/2ml

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **10/11/2006** until **12/12/2008**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Methotrexate Injection 50 mg/2ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains methotrexate sodium equivalent to 50 mg methotrexate, which is equivalent to 25 mg/ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.

A clear, yellowish solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Methotrexate is indicated in the treatment of neoplastic disease.

4.2 Posology and method of administration

Routes of administration: Methotrexate Injection may be given by intramuscular, intravenous (bolus injection or infusion), intrathecal, and intra-arterial routes of administration.

Dosage:

Adults and Children: Dosages are based on the patient's bodyweight or surface area except in the case of intrathecal administration when a maximum dose of 15mg is recommended. Doses should be reduced in cases of haematological deficiency and hepatic or renal impairment. Larger doses (greater than 100mg) are usually given by intravenous infusion over periods not exceeding 24 hours. Part of the dose may be given as an initial rapid intravenous infusion.

Methotrexate has been used with beneficial effects in a wide variety of neoplastic diseases, alone and in combination with other cytotoxic agents, hormones, radiotherapy or surgery. Dosage schedules therefore vary considerably, depending on the clinical use, particularly when intermittent high-dose regimes are followed by the administration of calcium leucovorin (calcium folinate) to rescue normal cells from toxic effects.

Examples of doses of methotrexate that have been used for particular indications are given below.

Choriocarcinoma and other trophoblastic tumours: Non-metastatic gestational trophoblastic neoplasms have been treated successfully with 0.25-1mg/kg up to a maximum of 60mg intramuscularly every 48 hours for four doses, followed by calcium leucovorin rescue. This course of treatment is repeated at seven day intervals until levels of urinary chorionic gonadotrophin hormone return to normal. Not less than four courses of treatment are usually necessary. Patients with complications, such as extensive metastases, may be treated with methotrexate in combination with other cytotoxic drugs.

Methotrexate has also been used in similar doses for the treatment of hydatidiform mole and chorio-adenoma destruens.

Leukaemia in children: In acute lymphocytic leukaemia remissions are usually best induced with a combination of corticosteroids and other cytotoxic agents.

Methotrexate 15mg/m^2, given parenterally or orally once weekly, in combination with other drugs appears to be the treatment of choice for maintenance of drug-induced remissions.

Meningeal leukaemia in children: Doses up to 15mg, intrathecally, at weekly intervals, until the cerebrospinal fluid (CSF) appears normal (usually two to three weeks), have been found useful for the treatment of meningeal leukaemia.

Although intravenous doses of the order of 50mg/m^2 of methotrexate do not appreciably penetrate the CSF, larger doses of the order of 500mg/m^2 or greater do produce cytotoxic levels of methotrexate in the CSF. This type of therapy has been used in short courses, followed by administration of calcium leucovorin, as initial maintenance therapy to prevent leukaemic invasion of the central nervous system in children with poor prognosis lymphocytic leukaemia.

Lymphoma: Non-Hodgkin's lymphoma, e.g. childhood lymphosarcoma has recently been treated with 3-30mg/kg (approximately 90-900mg/m^2) of methotrexate given by intravenous injection and infusion followed by administration of calcium leucovorin with the higher doses. Some cases of Burkitt's lymphoma, when treated in the early stages with courses of 15mg/m^2 daily orally for five days, have shown prolonged remissions. Combination chemotherapy is also commonly used in all stages of the disease.

Breast cancer: Methotrexate, in intravenous doses of 10-60mg/m^2, is commonly included in cyclical combination regimes with other cytotoxic drugs in the treatment of advanced breast cancer. Similar regimes have also been used as adjuvant therapy in early cases following mastectomy and/or radiotherapy.

Osteogenic sarcoma: The use of methotrexate alone and in cyclical combination regimes has recently been introduced as an adjuvant therapy to the primary treatment of osteogenic sarcoma by amputation with or without prosthetic bone replacement. This has involved the use of intravenous infusions of 20-300mg/kg (approximately 600-9,000mg/m^2) of methotrexate followed by calcium leucovorin rescue. Methotrexate has also been used as the sole treatment in metastatic cases of osteogenic sarcoma.

Bronchogenic carcinoma: Intravenous infusions of 20-100mg/m^2 of methotrexate have been included in cyclical combination regimes for the treatment of advanced tumours. High doses with calcium leucovorin rescue have also been employed as the sole treatment.

Head and neck cancer: Intravenous infusions of 240-1,080mg/m^2 with calcium leucovorin rescue have been used both as pre-operative adjuvant therapy and in the treatment of advanced tumours. Intra-arterial infusions of methotrexate have been used in the treatment of head and neck cancers.

Bladder carcinoma: Intravenous injections or infusions of methotrexate in doses up to 100mg every one or two weeks have been used in the treatment of bladder carcinoma with promising results, varying from only symptomatic relief to complete though unsustained regressions. The use of high doses of methotrexate with calcium leucovorin rescue is currently being evaluated.

Elderly: Due to diminished hepatic and renal function and decreased folate stores, methotrexate should be used with extreme caution in elderly patients, a reduction in dosage should be considered and these patients should be closely monitored for early signs of toxicity.

Folate Supplementation: In patients with rheumatoid arthritis, including polyarticular-course, juvenile rheumatoid arthritis, or psoriasis, folic acid or folinic acid may reduce methotrexate toxicities such as gastrointestinal symptoms, stomatitis, alopecia, and elevated liver enzymes. See also section 4.5 Interaction with other medicaments.

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

4.3 Contraindications

Profound impairment of renal or hepatic function or haematological impairment.

Alcoholism, liver disease including alcoholic liver disease, fibrosis, cirrhosis, recent or active hepatitis; active infectious disease; and overt or laboratory evidence of immunodeficiency syndrome(s).

Pre-existing blood dyscrasias, such as bone marrow hypoplasia, anaemia, leucopenia or thrombocytopenia. Methotrexate is contra-indicated in pregnant patients. Because of the potential for serious adverse reactions from methotrexate in breast fed infants, breast feeding is contra-indicated in women taking methotrexate.

Patients with a known allergic hypersensitivity to methotrexate, or any of the excipients in the formulation should not receive methotrexate.

Diluents containing preservatives must not be used for intrathecal or high dose methotrexate therapy.

4.4 Special warnings and precautions for use

Deaths have been reported with the use of methotrexate in the treatment of malignancy, therefore it should only be used in life threatening neoplastic diseases.

Methotrexate should be used with extreme caution in patients with haematological depression, renal impairment, peptic ulcer, ulcerative colitis, ulcerative stomatitis, diarrhoea, debility and in young children and the elderly.

Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anaemia, and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high doses) and nonsteroidal anti-inflammatory drugs (NSAIDs).

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

Patients with pleural effusions or ascites should have these drained if appropriate before treatment, and their plasma methotrexate levels monitored, or treatment should be withdrawn. The reason being that methotrexate exits slowly from third party compartments (e.g. pleural effusions, ascites). This results in a prolonged terminal half-life and unexpected toxicity.

Symptoms of gastrointestinal toxicity, usually first manifested by diarrhoea and ulcerative stomatitis, indicate interruption of therapy otherwise haemorrhagic enteritis and death from intestinal perforation may occur.

If vomiting resulting in dehydration happens, methotrexate should be discontinued until recovery occurs.

Methotrexate has some immunosuppressive activity and therefore the immunological response to concurrent vaccination may be decreased. In addition, concomitant use of a live vaccine could cause a severe antigenic reaction and is therefore not generally recommended. There have been reports of disseminated vaccinia infections after smallpox immunisation in patients receiving methotrexate therapy.

Like other cytotoxic drugs, methotrexate may induce ‘tumour lysis syndrome’ in patients with rapidly growing tumours. Appropriate supportive and pharmacologic measures may prevent or alleviate this condition.

Severe, occasionally fatal, skin reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis (Lyell’s syndrome) and erythema multiforme have been reported within days of administering single or multiple doses of methotrexate.

Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation. Skin ulceration in psoriatic patients and rarely painful erosion of psoratic plaques have been reported. The recall phenomenon has been reported in both radiation and solar damage skin.

Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported.

Pneumonia (in some case leading to respiratory failure) may occur. 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 pneumonia should be considered.

Pulmonary signs and symptoms, e.g. a dry non-productive cough, fever, cough, chest pain, dyspnoea, hypoxemia and an infiltrate on chest x-ray, or a non-specific pneumonitis may also be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Pulmonary lesions can occur at all dosages.

Methotrexate induced lung disease, including acute or chronic interstitial pneumonitis may occur at any time during thearpy and has been reported at low doses. It is not always fully reversible and fatalities have been reported. Infection, including pneumonia, needs to be excluded.

Patients should be monitored for pulmonary signs and symptoms 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 (especially a dry, non-productive cough) 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.

Methotrexate should only be used by clinicians who are familiar with the various characteristics of the drug and its mode of action. 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. Patients undergoing therapy should be subject to appropriate supervision every 2-3 months so that signs of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay. Renal function and full blood counts should be closely monitored before, during and after treatment.

It is essential that the following laboratory tests are included regularly (every 2-3 months) in the clinical evaluation and monitoring of patients receiving methotrexate: complete haematological analysis, urinalysis, renal function tests, liver function tests and, when high doses are administered, determination of plasma levels of methotrexate.

It is necessary to monitor patients on methotrexate closely. Methotrexate has the potential for serious toxicity. Toxic effects may be related in frequency and severity to dose or frequency of administration, but has been seen at all doses and can occur at any time during therapy. Most adverse reactions are reversible if detected early. When such reactions do occur, the dosage should be reduced or discontinued and appropriate corrective measures should be taken. If methotrexate therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the drug, and with increased alertness as to possible recurrence of toxicity.

Methotrexate causes hepatotoxicity, liver fibrosis, and cirrhosis, but generally after prolonged use. Particular attention should be given 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. Treatment should not be instituted or should be discontinued if any abnormality of liver functions tests, or liver biopsy, is present or develops during therapy. Such abnormalities should return to normal within two weeks after which treatment may be recommenced at the discretion of the physician.

Acutely, liver enzyme elevations are frequently seen. These are usually transient and asymptomatic, and do not appear predictive of subsequent hepatic disease. Persistent liver abnormalities and/or decrease of serum albumin may be indicators of serious liver toxicity. Liver biopsy after sustained use often shows histological changes, and fibrosis and cirrhosis have been reported.

Methotrexate can suppress haematopoiesis and cause anaemia, aplastic anaemia, pancytopenia, leucopenia, neutropenia and/or thrombocytopenia. Haematopoietic suppression caused by methotrexate may occur abruptly and with apparently

safe dosages. Methotrexate should be used in caution, if at all in patients with malignancy and pre-existing haematopoietic impairment. In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit outweighs the risk of severe myelosuppression. Any profound drop in white-cell or platelet counts should result in immediate withdrawal of the drug and appropriate supportive therapy. Patients should be advised to report all signs and symptoms suggestive of infection.

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.

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 Diamox* (500mg orally four times a day) is recommended as a preventive measure.

Malignant lymphomas may occur in patients receiving low-dose methotrexate, in which case therapy must be discontinued. Failure of the lymphoma to show signs of spontaneous regression requires the initiation of cytotoxic therapy.

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

The use of methotrexate high-dose regimens recommended for osteosarcoma requires meticulous care. High dosage regimens for other neoplastic diseases are investigational and a therapeutic advantage has not been established.

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

Folate deficiency states may increase methotrexate toxicity.

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

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

Symptomatic patients were commonly noted to have leucoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies. Chronic leucoencephalopathy has also been reported in patients who received repeated doses of high-dose methotrexate with leucovorin rescue even without cranial irradiation. Discontinuation of methotrexate does not always result in complete recovery.

A transient acute neurologic syndrome has been observed in patients treated with high dosage regimens. Manifestations of this neurologic syndrome may include behavioural abnormalities, focal sensorimotor signs including transient blindness or vision loss, and abnormal reflexes. The exact cause is unknown.

After the intrathecal use of methotrexate, the central nervous system toxicity that may occur can be classified as follows: acute chemical arachnoiditis manifested by eg, headache, back pain, nuchal rigidity, and fever; sub-acute myelopathy characterized by eg, paraparesis/paraplegia associated with involvement with one or more spinal nerve roots; chronic leucoencephalopathy manifested by eg, confusion, irritability, somnolence, ataxia, dementia, seizures, and coma. This central nervous system toxicity can be progressive and even fatal. There is evidence that the combined use of cranial radiation and intrathecal methotrexate increases the incidence of leucoencephalopathy. Signs of neurotoxicity (meningeal irritation, transient or permanent paresis, encephalopathy) should be monitored following intrathecal administration of methotrexate.

Intrathecal and intravenous administration of methotrexate may also result in acute encephalitis and acute encephalopathy with fatal outcome.

There have been reports of patients with periventricular CNS lymphoma who developed cerebral herniation with the administration of intrathecal methotrexate.

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.

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, sulphonamides, phenylbutazone, diuretics, hypoglycaemics, phenytoin and other diphenylhydantoins, tetracyclines, chloramphenicol, p-aminobenzoic acid, and the acidic non-steroidal anti-inflammatory drugs, so causing a potential for increased toxicity when used concurrently. Concomitant use of other drugs with nephrotoxic potential should generally be avoided unless considered justified, in which case the patient should be closely 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 and other potential hepatotoxic agents (e.g. alcohol, leflunomide, azathioprine, sulfasalazine, retinoids) should generally be avoided, unless clinically justified, in which case the patient should be closely monitored for possible increased risk of hepatotoxicity.

Enhancement of nephrotoxicity may be seen when high-dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent (e.g.cisplatin).

Renal tubular transport is also diminished by probenecid, penicillins, sulphonamides and omeprazole, which may result in potentially toxic methotrexate levels. The use of methotrexate with these drugs should be carefully monitored. Haematologic and gastrointestinal toxicity have been observed in combination with high dose methotrexate.

Nonsteroidal anti-inflammatory drugs (NSAIDs) should not be administered prior to, or concomitantly with, the high dose of methotrexate such as used in the treatment of osteosarcoma. Concomitant administration of 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 is also advised when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and thereby may enhance its toxicity. It is recommended that methotrexate dosage be carefully controlled during treatment with NSAIDs.

Methotrexate increases the plasma levels of mercaptopurine. Combinations of methotrexate and mercaptopurine may therefore require dose adjustment.

Methotrexate in combination with leflunomide may increase the risk of pancytopenia.

Concomitant administration of folate antagonists, such as co-trimoxazole, have been reported to cause acute megaloblastic pancytopenia in rare instances. Methotrexate should be used with caution in patients taking drugs known to have an antifolate potential including nitrous oxide and trimethoprim.

Vitamin preparations containing folic acid or its derivatives may alter response to methotrexate. Folate deficiency states may increase methotrexate toxicity. High doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Existing data suggests that etretinate is formed from acitretin after ingestion of alcoholic beverages. However, the formation of etretinate without concurrent alcohol intake cannot be excluded. Serum levels of methotrexate may be

increased by etretinate; severe hepatitis has been reported following concurrent use.

Oral antibiotics, such as tretacycline, chloramphenicol, and non-absorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of methotrexate by bacteria.

Trimethoprim/sufamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by decreased tubular secretion and/or additive antifolate effect.

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

4.6 Pregnancy and lactation

Methotrexate can cause foetal death, embryotoxicity, abortion or teratogenic effects when administered to a pregnant woman. Therefore it is not recommended in women of child-bearing potential unless the benefits can be expected to outweigh the considered risks. Methotrexate is contraindicated in pregnant patients with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the foetus.

Women of childbearing potential should not be started on methotrexate until pregnancy is excluded and should be fully counselled on the serious risk to the foetus should they become pregnant while undergoing the treatment,. Pregnancy should be avoided if either partner is receiving methotrexate. If this drug is used during pregnancy for antineoplastic indications, or if the patient becomes pregnant while taking this drug, the patient should be appraised of the potential hazard to the foetus.

Methotrexate affects spermatogenesis and oogenesis during the period of its administration which may result in decreased fertility. To date, this effect appears to be reversible on discontinuing therapy. The optimal time interval between the cessation of methotrexate treatment of either partner and pregnancy has not be clearly established. Published literature recommendation for time intervals vary from 3 months to one year. Patients receiving methotrexate and their partners should be advised appropriately.

Methotrexate has been detected in human breast milk and is contra-indicated during breastfeeding.

4.7 Effects on ability to drive and use machines

Methotrexate can cause dizziness and fatigue, which may affect the ability to drive or operate machinery.

4.8 Undesirable effects

In general, the incidence and severity of acute side effects are related to dose and frequency of administration. Other relevant sections should be consulted when looking for information about adverse reactions with methotrexate.
The most frequently reported adverse reactions include ulcerative stomatitis, leucopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness, and decreased resisitance to infection.
Other adverse reactions that have been reported 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.
Adverse reactions are listed in the Table in CIOMS frequency categories:

Very common >10%
Common: >1% and <10%
Uncommon:>0.1% and <1%
Rare: >0.01% and <0.1%
Very rare: <0.01%

Infections and infestations

Uncommon	Opportunistic infections, including fatal infections
Rare	Sepsis
Frequency undetermined	Infections, including pneumonia, Pneumocystis carinii pneumonia,nocardiosis, histoplasmosis, cryptococcosis, herpes zoster, H.simplex hepatitis, disseminated H.simplex, fatal sepsis, cytomegalovirus infection, including cytomegaloviral pneumonia

Neoplasms benign and malignant (including cysts and polyps)

Uncommon	Lymphoma, including reversible lymphoma
Very rare	Tumour lysis syndrome (*parenteral only*)

Blood and lymphatic system disorders

Uncommon	Anaemia, suppressed haematopoiesis, thrombocytopenia
Very rare	Aplastic anaemia
Frequency undetermined	Lymphadenopathy and lymphoproliferative disorders (including reversible), pancytopenia, neutropenia, agranulocytosis, eosinophilia, abnormal (usually 'megaloblastic') red cell morphology, bone marrow depression, leucopenia, haemorrhage

Immune system disorders

Uncommon	Anaphylactoid reactions
Very rare	Hypogammaglobulinemia

Metabolism and nutrition disorders

Rare	Diabetes
Frequency undetermind	Other metabolic changes

Psychiatric disorders

Rare	Mood alteration, transient cognitive dysfunction

Nervous system disorders

Uncommon	Convulsions (*parenteral only*), encephalopathy/leucoencephalopathy (*parenteral only*), headaches, hemiparesis
Rare	Drowsiness, paresis, speech impairment, including dysarthria and aphasia
Very rare	Unusual cranial sensations, mood alteration
Frequency undetermined	Transient subtle cognitive dysfunction, neurotoxicity, meningeal irritation, leucoencephalopathy and/or microangiopathic calcifications on diagnostic imaging studies, transient acute neurologic syndrome, behavioural abnormalities, focal sensorimotor signs, abnormal reflexes.

Eye disorders

Rare	Blurred vision, serious visual changes of unknown etiology
Very rare	Conjunctivitis, transient blindness/vision loss
Frequency undetermined	Eye irritation

Cardiac disorders

Rare	Hypotension
Very rare	Pericardial effusion, pericarditis

Vascular disorders

Rare	Thromboembolic events (including thrombophlebitis, arterial thrombosis, cerebral thrombosis, deep vein thrombosis, pulmonary embolism, retinal vein thrombosis)
Very rare	Vasculitis

Respiratory, throacic and mediastinal disorders

Uncommon	Acute or chronic interstitial pneumonitis, including fatalities (see section 4.4. 'Special warnings and preacations for use')
Rare	Pharyngitis, respiratory (pulmonary) fibrosis
Very rare	Chronic obstructive pulmonary disease
Frequency Undetermined	Alveolitis, acute pulmonary oedema, respiratory failure, chronic interstitial pulmonary disease, pleuritic pain and pleural thickening syndrome.

Gastrointestinal disorders

Uncommon	Anorexia, diarrhoea, stomatitis, vomiting, pancreatitis
Rare	Enteritis, gastrointestinal ulceration and bleeding, gingivitis, melena
Very rare	Haematemesis
Frequency Undetermined	Mucositis

Hepatobiliary disorders

Uncommon	Liver enzymes elevations
Rare	Acute hepatitis, chronic fibrosis and cirrhosis, hepatotoxicty
Very rare	Decrease in serum albumin
Frequency Undetermined	Hepatic failure or death, acute liver atrophy, necrosis, fatty metamorphosis

Skin and subcutaneous tissue disorders

Uncommon	Alopecia, Steven-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome)
Rare	Acne, ecchymosis, erythema multiforme, erythematous rashes, nodulosis, painful erosion of psoriatic plaques, photosensitivity, pigmentary changes, pruritus, skin ulceration, urticaria
Very rare	Furunculosis, telangiectasia
Frequency undetermined	Recall phenomenon in radiation and solar damaged skin

Musculoskeletal and connective tissue disorders

Rare	Arthralgia/myalgia, osteoporosis, stress fractures

Renal and urinary disorders

Uncommon	Severe nephropathy, renal failure
Rare	Dysuria
Very rare	Azotemia, cystitis, haematuria
Frequency undetermined	Proteinuria, uraemia

Pregnancy, puerperium and perinatal conditions

Uncommon	Foetal defects
Rare	Abortion
Frequency undetermined	Foetal death, embryotoxicity

Reproductive system and breast disorders

Rare	Menstrual dysfunction
Very rare	Defective oogenesis/spermatogenesis, impotence, infertility, loss of libido, transient oligospermia, vaginal discharge
Frequency undetermined	Vaginitis, vaginal ulcers, amenorrhoea

General disorders and administration site conditions

Very rare	Sudden death

4.9 Overdose

In postmarketing experience, overdose with methotrexate has generally occurred with oral and intrathecal administration, although intravenous overdosage has also been reported.

Symptoms of intrathecal overdose are generally CNS symptoms, including headache, nausea and vomiting, seizure or convulsion, and acute toxic encephalopathy. In some cases, no symptoms were reported. There have been reports of death following intrathecal overdose. In these cases, cerebellar herniation associated with increased intracranial pressure, and acute toxic encephalopathy have also been reported.

Calcium leucovorin is the antidote for neutralising the immediate toxic effects of methotrexate on the haematopoietic system. It may be administered orally, intramuscularly, or by an intravenous bolus injection or infusion. In cases of accidental overdosage, a dose of calcium leucovorin equal to or higher than the offending dose of methotrexate should be administered within one hour and dosing continued until the serum levels of methotrexate are below 10^{-7}M. Other supporting therapy such as a blood transfusion and renal dialysis may be required. Calcium leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

In cases of massive overdose, hydration and urinary alkalisation may be necessary to prevent precipitation of methotrexate and/or its metabolites in the renal tubules. Neither haemodialysis nor peritoneal dialysis has been shown to improve methotrexate elimination. Effective clearance of methotrexate has been reported with acute, intermittent haemodialysis using a high flux dialyser.

Following intrathecal overdose, CSF drainage may remove up to 95% of the dose if commenced within 15 minutes of administration, although this falls to 20% after 2 hours. For intrathecal doses over 100mg ventriculolumbar perfusion should accompany CSF drainage. In addition, high dose systemic leucovorin or alkaline diuresis may be required.

There are published case reports of intravenous and intrathecal carboxypeptidase G2 treatment to hasten clearance of methotrexate in cases of overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents and immunosuppressants
ATC code: L01 BA01

Methotrexate, a derivative of folic acid, belongs to the class of cytotoxic agents known as antimetabolites. It acts principally during the 'S' phase of cell division, by the competitive inhibition of the enzyme dihydrofolate reductase, thus preventing the reduction of dihydrofolate to tetrahydrofolate, a necessary step in the process of DNA synthesis and cellular replication.

5.2 Pharmacokinetic properties

Methotrexate distributes rapidly following a bolus intravenous injection; its disappearance from the plasma compartment is triphasic:
$t_{1/2}$ (alpha) = 0.25-0.7 hour; $t_{1/2}$ (beta) = 2.0-3.5 hours; $t_{1/2}$ (gamma) = 10-15 hours. The initial plasma half-life value is often obscured because methotrexate is infused over 2 to 12 hour periods.

Methotrexate metabolites account for less than 10% of the total dose if the drug is given intravenously at 30mg/m^2. The two major metabolites are 2,4-diamino-N^{10}-methylpteroic acid (DAMPA) and 7-hydroxy-methotrexate (7-OH MTX). Both metabolites are biologically inactive. The 7-OH MTX in the kidney tubules may contribute to nephrotoxicity especially with high-dose therapy.

Under conditions of normal renal function, drug clearance from plasma is 103ml/min/m^2. Young children are able to tolerate considerably more systemic methotrexate, presumably because of improved renal clearance.

Methotrexate is concentrated in the liver and bile, and can reach bile:plasma ratios as high as 200:1. However, the actual amount of methotrexate excreted by this route has been reported to be only 6.3% because most biliary methotrexate is reabsorbed from the GI tract.

With intrathecal administration, the slow rate of release of methotrexate from the CSF is rate controlling, therefore the elimination from the body is delayed. $t_{1/2}$ (beta) for methotrexate following intrathecal administration is 5.2-7.8 hours. The terminal elimination phase is greatly prolonged ($t_{1/2}$ (gamma) = 52-78 hours).

Methotrexate is distributed mainly in the extracellular spaces but a proportion penetrates cell membranes and is strongly bound to dihydrofolate reductase. About 50% is bound to plasma proteins. Bound methotrexate may be retained in the body for many months.

5.3 Preclinical safety data

Acute toxicity of methotrexate was studied in mice. Following intravenous administration, the LD_{50} was 64.8 mg/kg for CF1-C mice and 350 mg/kg for Swiss Albino mice.

Repeated-dose toxicity studies were conducted in rhesus monkeys via the intravenous route at doses of 5, 6, or 7 mg/kg twice weekly for 7 to 26 doses. However, deaths occurred in monkeys receiving seven doses of 35.0 mg/kg (Day 24). Pharmacotoxic signs observed during this period were emesis, diarrhoea, slight weight loss, and loss of appetite. Analysis of biochemical and haematologic results revealed changes in BUN, elevated SGPT and SGOT, and slight to moderate decreases in cell volume, haemoglobin, erythrocyte, and total leucocyte counts.

Methotrexate has been shown to seriously interfere with embryogenesis and cause embryolethality in several animal species.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide
Sodium chloride
Hydrochloric acid
Water for injection

6.2 Incompatibilities

It is inadvisable to mix fluorouracil and methotrexate.

Other drugs should not be mixed with methotrexate in the same infusion container.

6.3 Shelf Life

Not more than 2 years from the date of manufacture.

Parenteral methotrexate preparations do not contain an antimicrobial preservative.

Injection:
The product should be used immediately after opening.

Infusion:
Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C.
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 2-8°C, unless dilution with the following intravenous infusion fluids: 0.9% sodium chloride; glucose; sodium chloride (Ringers Injection); compound sodium lactate (Lactated Ringers Injection) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.
Keep vial in the outer carton.

6.5 Nature and contents of container

Type I Ph. Eur. clear glass vial with grey butyl rubber stopper, aluminium ring seal and plastic ‘flip off’ cover. Supplied in boxes of 1 vial of 2 ml.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only.
Discard any unused contents.

Infusion:

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 2-8°C, unless dilution with the following intravenous infusion fluids: 0.9% sodium chloride; glucose; sodium chloride and glucose; compound sodium chloride (Ringers Injection); compound sodium lactate (Lactated Ringers Injection) has taken place in controlled and validated aseptic conditions.

Handling of Cytotoxic drugs:

Individuals who have contact with anti-cancer drugs or work in areas where drugs are used may be exposed to these agents in air or through direct contact with contaminated objects. Potential health effects may be reduced by adherence to institutional procedures, published guidelines and local regulations for preparation, administration, transportation and disposal of hazardous drugs.

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 leucovorin cover should be given. Cytotoxic preparations should not be handled by pregnant staff. 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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Fareham Rd
Gosport
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United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 37/23/11

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10 DATE OF REVISION OF THE TEXT

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