PRODUCT SUMMARY

1. TRADE NAME OF THE MEDICINAL PRODUCT

Methotrexate 100 mg/ml Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 100 mg methotrexate (sodium salt formed in situ).

Each vial of 10 ml of solution contains 1 g methotrexate (sodium salt formed in situ).
Each vial of 50 ml of solution contains 5 g methotrexate (sodium salt formed in situ).

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection.

Vials containing a clear yellow/orange 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

Adults and children

Antineoplastic Chemotherapy

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

**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/m² 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 3.3 mg/m² daily, and prednisolone 40-60 mg/m² daily for 4-6 weeks has been used. After a remission is attained, methotrexate in a maintenance dosage of 20-30 mg/m² orally or by I.M. 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 I.V. every 14 days.

**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.

**Psoriasis Chemotherapy**

Cases of severe uncontrolled psoriasis, unresponsive to conventional therapy, have responded to weekly single, oral, I.M. or I.V. 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.

An alternative dosage schedule consists of 2.5 to 5 mg of methotrexate administered orally at 12 hour intervals for 3 doses each week or at 8-hour intervals for 4 doses each week; weekly dosages should not exceed 30 mg.

A daily oral dosage schedule of 2 to 5 mg administered orally for 5 days followed by a rest period of at least 2 days may also be used. The daily dose should not exceed 6.25 mg.

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**

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.

Patients with a known allergic hypersensitivity to methotrexate 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.

Methotrexate 100mg/ml Injection (1 g in 10 ml and 5 g in 50 ml) is hypertonic and it should not be given by the intrathecal route of administration. Furthermore, use of this preparation via intrathecal route may lead to accidental overdosage and significant neurotoxicity.

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 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.

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 perportal 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 2 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 625 mg tablets every three hours) or acetazolamide (500 mg 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 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. A chest X-ray is recommended prior to initiation of methotrexate therapy.

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

13. 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.

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 risks 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 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 biopsy may be considered after cumulative doses >1.5 g have been given, if hepatic impairment is suspected.

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.

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 anaesthesia potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe unpredictable myelosuppression, stomatitis and neurotoxicity. Severe neurotoxicity has particularly been reported with intrathecal administration of methotrexate following nitrous oxide anaesthesia.

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. 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 6 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 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.

Defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, and infertility have been reported in patients receiving Methotrexate.

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.

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, exfoliative dermatitis, epidermal necrolysis. Erythematous rashes, pruritus, urticaria, dermatitis, 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.

Blood: Bone marrow depression, leukopenia, thrombocytopenia, anaemia, hypogammaglobulinaemia, haemorrhage from various sites, septicemia.

Alimentary System: Gingivitis, pharyngitis, stomatitis, mucositis, 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 Special warnings and special precautions for use). 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.

**Central Nervous System:** Headaches, drowsiness, blurred vision, aphasia, cognitive disorder, hemi-paraesises and convulsions have occurred possibly related to haemorrhage or to complications from intraarterial catheterization.

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.

**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

**Psychiatric disorders:** Mood altered

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

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.

### 4.9. Overdose

Calcium Folinate (Calcium Leucovorin) is a potent agent for neutralising 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 6 hours for 4 doses. Where average doses of Methotrexate appear to have an adverse effect 6-12mg 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 tetrahydrofolatic 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 Preclinical safety data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Hydroxide and Water for Injections.

6.2 Incompatibilities

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

6.3 Shelf-life

As packaged for sale – 30 months.

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-
Do not store above 25°C. Do not freeze. Keep container in the outer carton.

After dilution – see 6.3.

6.5. Nature and contents of container

1g/10 ml – Conventional, or Onco-Tain® 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.

5g/50 ml – Conventional, or Onco-Tain® 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.

Not all presentations and pack sizes 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 Faulding administration device.

7 MARKETING AUTHORISATION HOLDER

Hospira UK Limited
Horizon
Honey Lane
Hurley
Maidenhead
SL6 6RJ
UK

8. MARKETING AUTHORISATION NUMBER

PL 04515/0038

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION
13th March 1987 / 7th June 1994

10 DATE OF REVISION OF THE TEXT

04/07/2017