PRODUCT SUMMARY

1. NAME OF THE MEDICINAL PRODUCT

Methotrexate 10 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Methotrexate 10 mg per tablet.

Excipient with known effect:
Each tablet contains 38.5mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet for oral administration.

Scored yellow capsule shaped tablets marked ‘M10’ on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Severe forms of psoriasis vulgaris, particularly of the plaque type, which cannot be sufficiently treated with conventional therapy such as phototherapy and PUVA, and severe psoriatic arthritis.

- Active rheumatoid arthritis in adult patients.

4.2 Posology and method of administration

This medicine should be taken once a week.

Do not exceed the weekly dose of this medicine due to toxicity hazards in psoriasis and rheumatoid arthritis.
The prescriber may specify the day of intake on the prescription.

**Psoriasis**

Before starting treatment it is advisable to give the patient a test dose of 2.5-5.0 mg to exclude unexpected toxic effects. If, one week later, appropriate laboratory tests are normal, treatment may be initiated.

The usual dose is 5-25 mg taken once weekly, starting with a low dose and increasing as necessary. The planned weekly dose may be administered in three divided doses at 12 hour intervals over 24 hours.

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.

**Rheumatoid arthritis**

The usual dose is 7.5 – 15 mg once weekly. The planned weekly dose may be administered in three divided doses at 12 hour intervals over 24 hours. The schedule may be adjusted gradually to achieve an optimal response but should not exceed a total weekly dose of 20 mg.

**Patients with renal impairment**

Methotrexate should be used with caution in patients with impaired renal function.

The dose should be adjusted as follows:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>100 %</td>
</tr>
<tr>
<td>20-50</td>
<td>50 %</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>Methotrexate must not be used</td>
</tr>
</tbody>
</table>

**Patients with hepatic impairment**

Methotrexate should be administered with great caution, if at all, to patients with significant current or previous liver disease, especially if due to alcohol. Methotrexate is contraindicated if bilirubin values are > 5 mg/dl (85.5 μmol/l) (see section 4.3).

**Patients with pathological fluid accumulation**

Methotrexate elimination is reduced in patients with pathological fluid accumulation (third space fluids) such as ascites or pleural effusions that may lead to prolonged methotrexate plasma elimination half-life and unexpected toxicity. Pleural effusions and ascites should be drained prior to initiation of methotrexate treatment. Methotrexate dose should be reduced according to the serum methotrexate concentrations.

**Elderly**
Methotrexate should be used with extreme caution in elderly patients. Dose reduction should be considered due to reduced liver and kidney function as well as lower folate reserves which occur with increased age.

**Children**
Methotrexate is not recommended for children under 3 years as insufficient data on efficacy and safety is available for this population.

### 4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

Active infections;

Overt or laboratory evidence of immunodeficiency syndrome(s);

Renal insufficiency (creatinine clearance less than 20 ml/min, see section 4.2).

Liver insufficiency (see section 4.2)

Alcohol abuse

Pre-existing blood dyscrasias, such as significant marrow hypoplasia, leukopenia, thrombocytopenia or anaemia.

Methotrexate is contraindicated in pregnancy.

Due to the potential for serious adverse reactions from methotrexate in breast fed infants, breast feeding is contra-indicated in women taking methotrexate.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

### 4.4 Special warnings and precautions for use

**Warnings**

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

Concomitant administration of hepatotoxic or haematotoxic DMARDs (e.g. leflunomide) is not advisable.

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

The carton and bottle label will state: “Check dose and frequency – methotrexate is usually taken once a week.”
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.

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

Patients should be aware of importance of adhering to the once weekly intakes.

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 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 alkalisation 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. Immunization with live virus vaccines is generally not recommended.

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

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

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

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

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

13. If acute methotrexate toxicity occurs, patients may require folinic acid.
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. If any abnormality in liver function tests or liver biopsy is seen prior to initiation of treatment or develops during therapy, treatment with methotrexate should not be instituted, or should be discontinued. Should such abnormalities return to normal within two weeks, treatment may be recommenced at the discretion of the physician.

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.

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.

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 > 1.5g 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. Reinstatement 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

No interaction studies have been performed.

Methotrexate is extensively protein bound and may be displaced by certain drugs such as salicylates, hypoglycaemics, diuretics, sulphonamides, diphenylhydantoin, 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, myelotoxic or hepatotoxic potential such as leflunomide, azathioprine, sulphasalazine, retinoids and 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. It is recommended that methotrexate dosage be carefully controlled during treatment with NSAIDs.

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.

Methotrexate-induced stomatitis and other toxic effects may be increased by the use of nitrous oxide.

Existing data suggest 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 and severe hepatitis has been reported following concurrent use. Consequently, the concomitant use of methotrexate and acitretin should be avoided.

Methotrexate may increase the bioavailability of mercaptopurine by interference with first-pass metabolism.

Concomitant application of methotrexate and theophylline can reduce theophylline clearance.

4.6 Fertility, pregnancy and lactation

Pregnancy

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.

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

**Fertility**
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.

### 4.7 Effects on ability to drive and use machines

Central nervous system symptoms, such as fatigue and dizziness, can occur during treatment with methotrexate which have minor or moderate influence on the ability to drive and use machines.

### 4.8 Undesirable effects

The most common adverse reactions include ulcerative stomatitis, leukopenia, vasculitis, eye-irritation and loss of libido/impotence, 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, pigmented 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, melena, 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 and uraemia (usually in high doses), cystitis, haematuria, defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, infertility, abortion, foetal defects, severe nephropathy. Amenorrhoea (during and for a short period after cessation of therapy), 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, unusual cranial sensations, hemiparesis and convulsions have occurred possibly related to haemorrhage or to complications from intra-arterial catheterization. Convulsion, paresis, Guillain-Barre syndrome and increased cerebrospinal fluid pressure have followed intrathecal administration.

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

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

**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, disseminated Herpes Simplex, hepatitis and cytomegalovirus infection, including cytomegaloviral pneumonia.

**Musculoskeletal and connective tissue disorders:** Arthralgia/myalgia

**Psychiatric disorders:** Mood altered

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

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

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

A small number of cases of accelerated nodulosis have been reported in the literature it is unclear whether the development of accelerated nodulosis during methotrexate therapy is a drug-related side effect or is part of the natural history of the rheumatoid disease.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

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

Calcium folinate (Calcium Leucovorin) is a potent agent for neutralizing the immediate toxic effects of methotrexate on the haematopoietic system. It may be administered orally, intramuscularly or by an intravenous bolus injection or infusion. Where large doses or overdoses are given, calcium folinate may be administered by intravenous infusion in doses up to 75 mg within 12 hours, followed by 12 mg intramuscularly every 6 hours for 4 doses. Where average doses of methotrexate appear to have an adverse effect 6-12 mg of calcium folinate may be given intramuscularly every 6 hours for 4 doses. In general, where overdosage is suspected, the dose of calcium folinate should be equal to or higher than, the offending dose of methotrexate and should be administered as soon as possible, preferably within the first hour and dosing continued until the serum levels of methotrexate are below 10⁻⁷M.

Other supporting therapy such as blood transfusion and renal dialysis may be required. 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.

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic properties

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

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

5.2. Pharmacokinetic properties

In doses of 0.1 mg (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 0.06 mg/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 0.037 mg/kg were given.

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Other Constituents

Maize Starch
Lactose
Pre gelatinised Starch (Prejel PA5)
Polysorbate 80
Microcrystalline Cellulose (AVICEL 101)
Magnesium Stearate

There is no overage included in the formulation.

6.2 Incompatibilities

Not applicable

6.3. Shelf life

60 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5. Nature and content of container

White polyethylene bottle with high density polyethylene screw closure containing 100 tablets.

6.6. Instructions for use and handling, (and disposal)

Not applicable.
6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Hospira UK Limited
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW
UK

8. MARKETING AUTHORISATION NUMBER(S)

PL: 04515/0005.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24th April 2002.

10 DATE OF REVISION OF THE TEXT

06/04/2016