Public Assessment Report

Decentralised Procedure

METHOTREXATE 10 MG TABLETS

Procedure No: UK/H/3935/001/DC

UK Licence No: PL 20117/0172

MORNINGSIDE HEALTHCARE LIMITED
LAY SUMMARY

On 12 November 2010, Ireland and the UK agreed to grant a Marketing Authorisation to Morningside Healthcare Limited for the medicinal product Methotrexate 10 mg Tablets (PL 20117/0172; UK/H/3935/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 17 December 2010.

Methotrexate 10 mg Tablets is a Prescription-Only Medicine (POM) used to treat:
- active rheumatoid arthritis
- severe psoriasis, especially plaque-type
- psoriatic arthritis in adult patients who have tried other treatments, but their illness has not improved.

The active substance is methotrexate, which is an antimetabolite and immunosuppressant (medicine which affects the reproduction of the body’s cells and reduces the activity of the immune system).

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Methotrexate 10 mg Tablets outweigh the risks, hence a Marketing Authorisation has been granted.
## TABLE OF CONTENTS

Module 1: Information about initial procedure  Page 4

Module 2: Summary of Product Characteristics  Page 5

Module 3: Product Information Leaflets  Page 15

Module 4: Labelling  Page 17

Module 5: Scientific Discussion  Page 19

1 Introduction
2 Quality aspects
3 Non-clinical aspects
4 Clinical aspects
5 Overall conclusions

Module 6  Steps taken after initial procedure  Page 26
## Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Methotrexate 10 mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Morningside Healthcare Ltd, 115 Narborough Road Leicester, LE3 0PA, UK</td>
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</tr>
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Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Methotrexate 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg methotrexate.
Excipients: 50 mg lactose (as lactose monohydrate).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

Yellow coloured, capsule shaped bi-convex tablets with central break line on one side and plain on other side.

The break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
- Active rheumatoid arthritis in adult patients.
- Severe forms of psoriasis vulgaris, particularly of the plaque type, which cannot be sufficiently treated with conventional therapy such as phototherapy, PUVA, and retinoids, and severe psoriatic arthritis.

4.2 Posology and method of administration
For doses not realisable/practicable with this strength another strength of this medicinal product is available.

Rheumatoid arthritis
The usual dose is 7.5 - 15 mg once weekly. The planned weekly dose may be administered in three divided doses over 36 hours. The schedule may be adjusted gradually to achieve an optimal response but should not exceed a total weekly dose of 20 mg. Thereafter the dose should be reduced to the lowest possible effective dose which in most cases is achieved within 6 weeks.

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 7.5–15 mg taken once weekly.

The planned weekly dose administered as three divided doses over 24 hours. As necessary, the total weekly dose can be increased up to 25 mg. Thereafter the dose should be reduced to the lowest effective dose according to therapeutic response which in most cases is achieved within 4 to 8 weeks.

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 elderly
Methotrexate should be used with extreme caution in elderly patients, a dose reduction should be considered due to reduced liver and kidney function as well as lower folate reserves which occurs with increased age.

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.
4.3 Contraindications

- Significantly impaired hepatic function
- Significantly impaired renal function
- Pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopaenia, thrombocytopaenia, or significant anaemia
- Alcoholism
- Severe acute or chronic infections and immunodeficiency syndrome
- Pregnancy and breast-feeding (see also section 4.6).
- Hypersensitivity to methotrexate or to any of the excipients

During methotrexate therapy concurrent vaccination with live vaccines must not be carried out.

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 (disease-modifying antirheumatic drug, 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 constant supervision.

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

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

For 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 patient should be informed clearly that in the treatment of psoriasis and rheumatoid arthritis the administration is in most cases once weekly and that wrong daily administration can result in severe toxic reactions.

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.

Methotrexate may be hepatotoxic, particularly at high doses 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.

Liver function tests: Particular attention should be given to the appearance of liver toxicity. Treatment should not be instituted or should be discontinued if any abnormality of liver function 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.

Check of liver-related enzymes in serum: Temporary increases in transaminases to twice or three times of the upper limit of normal have been reported by patients at a frequency of 13 - 20%. In the case of a
constant increase in liver-related enzymes, a reduction of the dose or discontinuation of therapy should be taken into consideration.

Due to its potentially toxic effect on the liver, additional hepatotoxic medicinal products should not be taken during treatment with methotrexate unless clearly necessary and the consumption of alcohol should be avoided or greatly reduced (see section 4.5).

Closer monitoring of liver enzymes should be exercised in Patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide). The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide).

There is no evidence to support use of a liver biopsy to monitor hepatic toxicity in rheumatological indications. In case of longer-term treatment of severe forms of psoriasis with methotrexate, liver biopsies should be performed on account of the hepatotoxic potential.

It has proven useful to differentiate between patients with normal and elevated risk of hepatotoxicity.

a) Patients without risk factors
According to current medical standard of knowledge, liver biopsy is not necessary before a cumulative dose of 1.0-1.5 g is reached.

b) Patients with risk factors
These primarily include
- anamnestic alcohol abuse
- persistent increase in liver enzymes
- anamnestic hepatopathy including chronic hepatitis B or C
- familial anamnesis with hereditary hepatopathy and secondarily (with possibly lower relevance):
  - diabetes mellitus
  - adiposity
  - anamnestic exposure to hepatotoxic medicines or chemicals.

Liver biopsy is recommended for these patients during or shortly after initiation of therapy with methotrexate. Since a small percentage of patients discontinues therapy for various reasons after 2-4 months, the first biopsy can be delayed to a time after this initial phase. It should be performed when longer-term therapy can be assumed.

Repeated liver biopsies are recommended after a cumulative dose of 1.0-1.5 g is achieved.
No liver biopsy is necessary in the following cases:
- elderly patients
- patients with an acute disease
- patients with contraindication for liver biopsy (e.g. cardiac instability, altered blood coagulation parameters)
- patients with poor expectancy of life

More frequent check-ups may become necessary:
- during the initial phase of treatment
- when the dose is increased
- during episodes of a higher risk of elevated methotrexate blood levels (e.g. dehydration, impaired renal function, additional or elevated dose of medicines administered concomitantly, such as non-steroidal anti-inflammatory drugs).

Methotrexate has been shown to be teratogenic; it has caused foetal death and/o 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 must not receive methotrexate (see section 4.6).

Renal function should be closely monitored before, during and after treatment.

Caution should be exercised if significant renal impairment is disclosed. The dose of methotrexate in patients with renal impairment should be reduced. 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.

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

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.

Methotrexate has some immunosuppressive activity and immunological responses to concurrent vaccination may be decreased. Vaccination with live vaccines should be avoided during therapy.

The immunosuppressive effect of methotrexate should be taken into account when immune responses of patients are important or essential. Special attention should be paid in cases of inactive chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) because of their potential activation.

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

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).

In the treatment of rheumatoid arthritis, treatment with acetylsalicylic acid and nonsteroidal anti-inflammatory drugs (NSAID) as well as small-dose steroids can be continued. One has to take into consideration, however, that coadministration of NSAIDs and methotrexate may involve an increased risk of toxicity. The steroid dose can be reduced gradually in patients who exhibit therapeutic response to methotrexate therapy.

Interaction between methotrexate and other antirheumatic agents, such as gold, penicillamine, hydroxychloroquine, sulphasalazine or other cytotoxic agents, have not been studied comprehensively, and coadministration may involve an increased frequency of adverse reactions. Rest and physiotherapy can be continued as previously.

Concomitant administration of folate antagonists such as trimethoprim / sulphamethoxazole has been reported to cause an acute megaloblastic pancytopenia in rare instances. If acute methotrexate toxicity occurs, patients may require folinic acid.

Precautions
Before beginning methotrexate therapy or reinstituting methotrexate after a rest period, assessment of renal function, liver function and a bone marrow function 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.

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 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 section 4.6).

Patients undergoing therapy should be subject to appropriate supervision so that signs or symptoms of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay. Pre-treatment and periodic haematological studies are essential for the safe use of methotrexate in chemotherapy because of its common effect of haematopoietic suppression. This may occur without
warning when a patient is on an apparently safe dose, and any profound drop in blood cell count indicates immediate stopping of the drug and appropriate therapy.

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

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

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

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

Methotrexate should be used with extreme caution in the presence of infection, peptic ulcer, ulcerative colitis, debility, and in extreme youth and old age. If profound leukopaenia 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.

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

**4.5 Interaction with other medicinal products and other forms of interaction**

After absorption methotrexate binds partly to serum albumin. Certain medical products (e.g. salicylates, sulfonamides and phenytoin) decrease this binding. In such instances the toxicity of methotrexate may increase when coadministered. Since probenecid and weak organic acids, such as "loop-diuretics" as well as pyrazols, reduce tubular secretion, great caution should be exercised when these medical products are coadministered with methotrexate.

Penicillins can decrease the renal clearance of methotrexate and haematological and gastrointestinal toxicity has been observed in combination with high- and low-dose methotrexate.

Oral antibiotics, such as tetracycline, 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.

Coadministration of other, potentially nephro- and hepatotoxic agents (e.g. sulphasalazine, leflunomide and alcohol) with methotrexate should be avoided. Special caution should be exercised when observing patients receiving methotrexate therapy in combination with azathioprine or retinoids.

Methotrexate in combination with leflunomide can increase the risk for pancytopenia.

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

NSAIDs should not be administered before or concurrently with high-dose methotrexate. Concomitant use of some NSAIDs and high-dose methotrexate has been reported to increase and prolong the serum methotrexate concentration in serum and to increase gastrointestinal and haematological toxicity. When using smaller doses of methotrexate, these medicinal products have been found in animals to decrease the tubular secretion of methotrexate and possibly to increase its toxicity. In addition to methotrexate, patients with rheumatoid arthritis have generally been treated, however, with NSAIDs with no problems. It should be noted, however, that the doses of methotrexate used in the treatment of rheumatoid arthritis (7.5 – 15 mg/week) are slightly lower than those used for psoriasis and that higher doses can result in unexpected toxicity.
Vitamin preparations containing folic acid or its derivatives may change the response to methotrexate.

Trimethoprim/sulfamethoxazole has been reported in rare cases to increase bone marrow suppression in patients treated with methotrexate, presumably because of the increased antifolate effect. Bone marrow suppression and reduced folate concentrations have been reported when triamterene and methotrexate were coadministered.

There is evidence that coadministration of methotrexate and omeprazole prolongs the elimination of methotrexate via the kidneys. Coadministration of proton pump inhibitors, such as omeprazole or pantoprazole, can cause interactions.

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

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

Vaccination with a live vaccine in patients receiving chemotherapeutic agents may result in severe and fatal infections. Concomitant use with a live vaccine is not recommended.

Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug or risk of toxicity enhancement or lose of efficacy of the cytotoxic drug due to increased hepatic metabolism by phenytoin.

Cyclosporine may potentiate methotrexate efficacy and toxicity. There is a risk of excessive immunosuppression with risk of lymphoproliferation when the combination is used.

4.6 Pregnancy and lactation

Pregnancy
Use of methotrexate is contraindicated throughout pregnancy (see section 4.3), since there is evidence of a teratogenic risk in humans (craniofacial, cardiovascular and extremal malformations) and in several animal species (see section 5.3).

In women of child-bearing age, any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g. pregnancy test, prior to initiating therapy.

Women must not become pregnant during and at least 6 months after treatment with methotrexate and must therefore practise an effective form or contraception.

If, nevertheless, pregnancy occurs during this period, medical advice should be given regarding the risk of harmful effects on the child associated with treatment.

As methotrexate may be genotoxic, women who wish to become pregnant are advised to consult a genetic counselling centre, if possible, already prior to therapy.

Lactation
As methotrexate passes into breast milk and may cause toxicity in nursing infants, treatment is contraindicated during the lactation period (see section 4.3). Breastfeeding is therefore to be stopped prior to treatment.

Male fertility
Methotrexate may be genotoxic. Men treated with methotrexate are therefore recommended not to father a child during treatment and up to 6 months afterwards. Since treatment with methotrexate can lead to severe and possibly irreversible disorders in spermatogenesis, men should seek advice about the possibility of sperm preservation before starting 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.

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 may have minor or moderate influence on the ability to drive and use machines.

### 4.8 Undesirable effects

Generally the frequency and severity of adverse reactions are dependent of the size of the dose, the dosing frequency, the method of administration and the duration of exposure.

If adverse reactions occur, the dose should be reduced or therapy discontinued and necessary corrective therapeutic measures undertaken, such as administration of calcium folinate (see sections 4.2 and 4.4).

The most common adverse reactions of methotrexate are bone marrow suppression and mucosal damage which manifest as ulcerative stomatitis, leukopaenia, nausea and other gastrointestinal disorders. These adverse reactions are generally reversible and corrected in about two weeks after the single dose of methotrexate has been reduced or dose interval increased and/or calcium folinate is used. Other frequently occurring adverse reactions include e.g. malaise, abnormal fatigue, chills and fever, dizziness and reduced immunity to infections.

Methotrexate causes adverse reactions most at high and frequently repeated doses, e.g. in the treatment of cancer diseases. Adverse reactions reported on methotrexate are given below according to organ systems.

The frequencies of the adverse reactions are classified as follows: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000), not known (cannot be estimated from the available data).

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<td>Hypotension</td>
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<td>Vomiting</td>
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<td>Diarrhoea</td>
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<td>Hepatotoxicity</td>
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<tr>
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<td></td>
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1 Can be reversible (see 4.4).
2 See section 4.4.
3 Gastrointestinal severe adverse reactions require often dose reduction.

Ulcerative stomatitis and diarrhoea require discontinuation of methotrexate therapy because of the risk of ulcerative enteritis and fatal intestinal perforation.

The following adverse reactions have also been reported, but their frequency is not known: pancytopenia, sepsis resulting in death, miscarriage, fetal damages, increased risk of toxic reactions (soft tissue necrosis, osteonecrosis) during radiotherapy, eosinophilia, alveolitis.

The psoriatic lesions may get worse from simultaneous exposure to methotrexate and ultraviolet radiation.
4.9 Overdose
The toxicity of methotrexate affects mainly the haematopoietic organs. Calcium folinate neutralises effectively the immediate haematopoietic toxic effects of methotrexate. Parenteral calcium folinate therapy should be started within one hour after the administration of methotrexate. The dose of calcium folinate should be at least as high as the dose of methotrexate received by the patient.

Massive overdose requires hydration and alkalinisation of the urine to prevent precipitation of methotrexate and/or its metabolites in the renal tubules. Haemodialysis or peritoneal dialysis has not been found to affect the elimination of methotrexate. Instead, effective clearance of methotrexate has been achieved in a study by intermittent haemodialysis using a so-called “high-flux” dialysator.

Observation of serum methotrexate concentrations is relevant in determining the right dose of calcium folinate and the duration of the therapy.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antimetabolites
ATC code L01BA01

Methotrexate (4-amino-10-methylfolic acid) is a folic acid antagonist which inhibits the reduction of folic acid and increase of tissue cells. Methotrexate enters the cell through an active transport mechanism of reduced folates. As a result of polyglutamation of methotrexate caused by the folylpolyglutamate enzyme, the duration of the cytotoxic effect of the drug substance in the cell increases. Methotrexate is a phase-specific substance the main action of which is directed to the S-phase of cell mitosis. It acts generally most effectively on actively increasing tissues, such as malignant cells, bone marrow, fetal cells, skin epithelium, oral and intestinal mucosa as well as urinary bladder cells. As the proliferation of malignant cells is higher than that of most normal cells, methotrexate can slow down the proliferation of malignant cells without causing, however, irreversible damage to normal tissue.

Calcium folinate is a folinic acid which is used to protect normal cells from the toxic effects of methotrexate. Calcium folinate enters the cell through a specific transport mechanism, is converted in the cell into active folates and reverses the inhibition of the precursor synthesis caused by the DNA and RNA.

5.2 Pharmacokinetic properties
The effect of orally administered methotrexate seems to be dependent on the size of the dose. Peak concentrations in serum are reached within 1–2 hours. Generally a dose of methotrexate of 30 mg/m² or less is absorbed rapidly and completely. The bioavailability of orally administered methotrexate is high (80–100%) at doses of 30 mg/m² or less. Saturation of the absorption starts at doses above 30 mg/m² and absorption at doses exceeding 80 mg/m² is incomplete.

About half of the absorbed methotrexate binds reversibly to serum protein, but is readily distributed in tissues. The elimination follows a triphasic pattern. Excretion takes place mainly via the kidneys. Approximately 41% of the dose is excreted unchanged in the urine within the first six hours, 90% within 24 hours. A minor part of the dose is excreted in the bile of which there is pronounced enterohepatic circulation.

The half-life is approximately 3–10 hours following low dose treatment and 8–15 hours following high dose treatment. If the renal function is impaired, the concentration of methotrexate in serum and in tissues may increase rapidly.

5.3 Preclinical safety data
Chronic toxicity studies in mice, rats and dogs showed toxic effects in the form of gastrointestinal lesions, myelosuppression and hepatotoxicity. Animal studies show that methotrexate impairs fertility, and is embryo- and foetotoxic. Teratogenic effects have been identified in four species (rats, mice, rabbits, cats). In rhesus monkeys no malformations occurred. Methotrexate is mutagenic in vivo and in vitro. There is evidence that methotrexate causes chromosomal aberrations in animal cells and in human bone marrow cells, but the clinical significance of these findings has not been established. Rodent carcinogenicity studies do not indicate an increased incidence of tumours.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Dibasic Calcium Phosphate (Anhydrous)
Lactose Monohydrate
Sodium starch glycolate
Cellulose, microcrystalline
Purified Talc
Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
36 months

6.4 Special precautions for storage
Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container
Amber colour PVC /Aluminium blister- Blister packs of 7, 10, 14, 16, 20, 24, 28, 30, 56, 60, 84, 90, 100 and 112 film coated tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER
Morningside Healthcare Ltd
115 Narborough Road
Leicester
LE3 0PA
United Kingdom

8 MARKETING AUTHORITY NUMBER(S)
PL 20117/0172

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITY
17/12/2010

10 DATE OF REVISION OF THE TEXT
17/12/2010
Module 3

PAR Methotrexate 10 mg Tablets

Package Leaflet - Information for the User

Methotrexate 10mg Tablets (Methotrexate)

Read all of this leaflet carefully before you start taking this medicine

- Please read the package leaflet carefully before you start taking this medicine.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others.
- It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious or if you notice any side effects not listed on this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Methotrexate Tablets are and what they are used for
2. Before you take Methotrexate Tablets
3. How to take Methotrexate Tablets
4. Possible side effects
5. How to store Methotrexate Tablets
6. Further information

1. WHAT METHOTREXATE TABLETS ARE AND WHAT IT IS USED FOR

The active substance of Methotrexate tablets, methotrexate, is an antineoplastic and immunosuppressant medicine which affects the reproduction of the body's cells and reduces the activity of the immune system.

Methotrexate is used to treat:
- active rheumatoid arthritis
- severe psoriasis, especially plaque-type
- psoriatic arthritis in adult patients who have tried other treatments but their illness has not improved.

Your doctor will be able to explain how Methotrexate Tablets might help in your particular condition.

2. BEFORE YOU TAKE METHOTREXATE TABLETS

Do not take Methotrexate, if any of the following apply to you:
- You have significant liver disease (your doctor decides the severity of your disease).
- You have significant kidney disease (your doctor decides the severity of your disease).
- You have or have had a bone marrow disease or serious blood disorders.
- You are allergic (hypersensitive) to methotrexate or any of the other ingredients of Methotrexate Tablets.
- You are pregnant or breastfeeding (see also section "Pregnancy and breastfeeding").
- You have severe acute or chronic infections or immunodeficiency syndrome.
- You suffer from alcoholism.

Take special care with Methotrexate

Please tell your doctor or pharmacist any of the following apply to you:
- You have diabetes mellitus treated with insulin.
- You have or had any vaccinations recently or are due to have any.
- You are using any other medicines or vitamins (Please see section "Taking other medicines").
- You have infections.
- You have ulcerations in your stomach or bowel (gastric ulcer or ulcerative colitis).
- You are in poor general condition.
- You have or have had any liver or kidney disease.

Methotrexate temporarily affects sperm and egg production. You and your partner should avoid conception (becoming pregnant or fathering children) if currently receiving methotrexate and for at least six months after your treatment with methotrexate has stopped. See also section "Pregnancy and breastfeeding".

Before treatment is started your doctor may carry out blood tests, and also to check how well your kidneys and liver are working. You may also have a chest X-ray. Further tests may be done during and after treatment. Do not miss appointments for blood tests.

Taking other medicines

Other concurrent medication may affect the efficacy and safety of this medicine. Methotrexate may also affect the efficacy and safety of other medicines.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription and herbal or natural medicinal products. Remember to tell your doctor about your treatment with Methotrexate, if you are prescribed another medicine while the treatment is still ongoing. It is especially important to tell your doctor if you are using:
- certain antibiotics (such as penicillins, sulphamides, trimethoprim/sulfamethoxazole, tetracycline and chloramphenicol),
- agents that may be harmful to kidneys and liver (e.g. sulfonamides and sulfonanilides [medicines for psychiatric diseases], vitamin A and its derivatives, alcohol),
- anticonvulsant agents (e.g. carbamazepine, phenytoin),
- phenytoin (medicine often used to treat epilepsy),
- aspirin or similar medicines known as salicylates,
- non-steroidal anti-inflammatory medicines (medicines taken for pain relief) e.g. ibuprofen and naproxen,
- medicines taken to help control menorrhagia e.g. aspirinpirine,
- oral contraceptives or hormone replacement treatment used to stop the production of stomach acid,
- diuretics, immunosuppressant tablets,
- probenecid (medicine used to treat gout),
- tetracycline (medicine used to treat inflammatory diseases),
- cyclosporine (an agent that can suppress or prevent the immune response).

Tell your physician about use of Methotrexate during your next visits.

Taking Methotrexate Tablets with food and drink

Alcohol should be avoided during methotrexate therapy.

Pregnancy and breastfeeding

Pregnancy

Do not use Methotrexate during pregnancy or if you are trying to become pregnant. Methotrexate can cause birth defects, harm unborn babies or cause miscarriages and so it is very important that it is not given to pregnant patients or patients planning to become pregnant. Therefore, in women of childbearing age any possibility of pregnancy must be excluded with appropriate measures, e.g. a pregnancy test, before starting treatment. You must avoid becoming pregnant whilst taking methotrexate and for at least 6 months after treatment is stopped. Therefore you must use reliable contraception during this whole period (see also section "Take special care with Methotrexate").

If you do become pregnant during treatment, you should be offered advice regarding the risks and harmful effects on the child before treatment.

If you wish to become pregnant you should consult a genetic information centre before the planned start of treatment, because methotrexate may be genotoxic, which means that the medicine may cause genetic mutations.

Breastfeeding

Do not breastfeed during treatment, because methotrexate passes into breast milk. If your attending doctor considers treatment with methotrexate absolutely necessary during the lactation period, you must stop breastfeeding.

Male fertility

Methotrexate may be genotoxic. This means that the medicine may cause genetic mutation. Methotrexate can affect sperm and egg production with the potential to cause birth defects. Therefore, you must avoid fathering a child whilst taking methotrexate and for at least 6 months after treatment is stopped. Since treatment with methotrexate may lead to infertility, it might be advisable for male patients to look into the possibility of sperm preservation before starting treatment (see also section "Take special care with Methotrexate").

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

You can feel fatigue and dizziness during methotrexate treatment. Do not drive or use machines if you have such symptoms.

Important information about some of the ingredients of Methotrexate

These tablets contain lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.
PAR Methotrexate 10 mg Tablets

UK/H/3935/001/DC

2. HOW TO TAKE METHOTREXATE

Always take Methotrexate exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Patients with rheumatoid arthritis or psoriasis will usually take their tablets orally once a week on the same day each week.

- Do not take tablets more often than your doctor has told you to.
- Do not double up if you miss a dose.

The tablets are not intended to be swallowed whole, and should not be divided into smaller amounts.

3. Doseage for rheumatoid arthritis, psoriasis and psoriatic arthritis:

- Adults: The usual dose is 7.5 to 15 mg by mouth once weekly. This should be adjusted according to your response to treatment and side effects.

- Elderly: The doctor may adjust your dose depending on how well your kidneys and liver work.


Methotrexate tablets of a lower strength are available and your doctor may prescribe these together with 15mg tablet to ensure get the correct dose.

If you take more Methotrexate tablets than you should:

If you take more of the medicine than you should, contact a pharmacist or nearest hospital casualty department immediately. Take your medicine package with you if you go to see a doctor or hospital.

An overdose of methotrexate can lead to serious toxic reactions. Overdose symptoms may include easy bruising or bleeding, unusual weakness, mouth sores, nausea, vomiting, black or bloody stool, coughing up blood or vomit that looks like coffee grounds, and decreased urination. See also section 4.

Take your medicine package with you if you go to see a doctor or hospital.

If you forget to take Methotrexate Tablets:

Take the forgotten dose as soon as you remember if this is within 3 hours. However, if you have missed a dose by more than two days, please contact your doctor or pharmacist.

If you have further questions on the use of this product, ask your doctor or pharmacist.

If you stop taking Methotrexate Tablets:

Do not stop taking the tablets unless your doctor tells you to. If you have any further questions on how to take this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Methotrexate Tablets can cause side effects, although not everybody gets them. In general, the incidence and severity of adverse reactions of methotrexate are related to dose and frequency of administration. Most adverse reactions are reversible if detected early.

Most of the effects listed below will only be seen in patients who are receiving high doses of methotrexate to treat cancer. They are not seen as often and are not as severe at the doses used in the treatment of psoriasis or rheumatoid arthritis.

Common side effects (occurs in more than 100 patients and less than 10% of patients):
- Decreased resistance to infections, leukopenia (decreased number of white blood cells), nausea, vomiting, diarrhea, unusual fatigue, headache, dizziness, loss of appetite, a red rash, hair loss, stomatitis (sores of the mouth and lips) and increase in liver enzymes.

Uncommon side effects (occurs in more than 100 patients and less than 1% of patients):
- A reduction in bone marrow activity manifested by thrombocytopenia (reduction in blood platelets, which increase risk of bleeding or bruising) and other abnormalities developing in the blood; anemia (reduction in red blood cells, which can make the skin pale and cause weakness or breathlessness); redness; swelling; allergic reaction which causes difficulty in breathing or dizziness, severe blistering of the skin, severe skin rashes, itching, kidney dysfunction, vaginal ulceration.

Only detected by your doctor.

Rare side effects (occurs in more than 1 of 10,000 patients and less than 1 of 1000 patients):
- Depression, confusion, muscle weakness on one side of the body, diabetes mellitus, low blood pressure, thrombocytopenia (breakdown of blood clots), diarrhea or vomiting, inflammation of gums, pyrexia or small intestine, gastritis, intestinal ulceration and bleeding, liver damage (hepatic toxicity, periporal fibrosis, hepatic cirrhosis, acute hepatitis), skin reactions (acne, skin degeneration, varicosities, very itchy rash consisting of a number of raised pale bumpy warts surrounded by red skin), sensitivity to light, arthralgia (joint pain), itching, pink-red nodules, symmetrically arranged and sternum on the extremities), burning in skin psoriatic lesions, skin ulcers, absence of skin microsoma, herpes Zoster (a painful skin rash with blisters), sciatica (tenderness, pain or discomfort in the lower back), swelling of the joints or tongue, fever.

If you notice any of the following, please contact your doctor or pharmacist immediately:
- Unusual bleeding (including vomiting blood) or bruising.
- Severe diarrhoea.
- Ulcers in mouth.
- Black or tarry stools.
- Blood in the urine or stools.
- Tiny red spots on the skin.
- An allergic reaction such as skin rash or swelling of your lips or tongue.
- Yellowing of the skin (jaundice).
- Pain or difficulty in passing urine.
- A dry cough due to pain or difficulty in breathing or shortness of breath.
- Feeling cold, including shaking.
- Loss of consciousness.
- Blurred or decreased vision.

5. HOW TO STORE METHOTREXATE TABLETS

Keep out of the reach of children and out of sight.
- Keep the blister in the outer carton in order to protect from light.
- Do not use methotrexate tablets after the expiry date that is stated on the carton. The expiry date refers to the last day of that month.

Medicines should not be disposed of via waste, into the household waste or household waste.
- Ask your pharmacist how to dispose of medicines no longer required.
- These measures will help to protect the environment.

6. FURTHER INFORMATION

What Methotrexate Tablets contain:
Each tablet contains 15mg of the active ingredient methotrexate.

The other ingredients are Dibasic calcium phosphate (anhydrous), lactose monohydrate, sodium starch glycolate, cellulose microcrystalline, purified talc and magnesium stearate.

What Methotrexate Tablets looks like and contents of the pack:
Methotrexate Tablets are yellow coloured, capsule shaped, bi-convex tablets with control break lines on one side and plain on the other side.

Methotrexate 10 mg Tablets are available in blister packs of 7, 14, 16, 20, 24, 28, 30, 55, 60, 84, 90, 100 and 112 tablets.

Not all pack sizes may be marked.

Marketing Authorisation Holder:
Morningside Healthcare Ltd
115 North Road
Leicester, LE3 0HR
United Kingdom

Authorised manufacturer responsible for batch release in the EEA:
Morningside Pharmaceutica Ltd
5 Penfold Way, Loughborough, LE11 5GW
United Kingdom

This leaflet was last approved in November 2018.
Module 4
Labelling

Carton:

Methotrexate 10 mg Tablets

Each tablet contains Methotrexate 10mg. Also contains lactose monohydrate.

Dosage: To be taken as directed by doctor.

Check dose and frequency - methotrexate is usually taken once a week.

For oral use.

Read the package leaflet before use.

Keep out of the reach and sight of children.

Keep the blister in the outer carton in order to protect from light.

Dispensing label to be affixed here.

Methotrexate 10 mg Tablets

Methotrexate #10 mg Tablets
Carton:

Blister:
Module 5
Scientific discussion during initial procedure

1 INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Methotrexate 10 mg Tablets (PL 20117/00172; UK/H/3935/001/DC) could be approved. This application was submitted by the decentralised procedure, with the UK as Reference Member State (RMS) and Ireland as Concerned Member State (CMS).

The product is a prescription-only medicine for the treatment of:

- active rheumatoid arthritis in adult patients.
- severe forms of psoriasis vulgaris, particularly of the plaque type, which cannot be sufficiently treated with conventional therapy, such as phototherapy, psoralen and ultraviolet A radiation (PUVA), and retinoids, and severe psoriatic arthritis.

This is an application made according to Article 10.1 of 2001/83/EC, as amended, claiming to be a generic medicinal product of Methotrexate 2.5mg Tablets which was an originally granted licence in 1989 to Goldshield Pharmaceuticals, UK. The product used in the bioequivalence study was Maxtrex 10 mg Tablets,( Pharmacia Limited, UK)

Methotrexate is a folic acid antagonist which inhibits the reduction of folic acid and increase of tissue cells. Methotrexate enters the cell through an active transport mechanism of reduced folates. As a result of polyglutamation of methotrexate caused by the foltlypolyglutamylate enzyme, the duration of the cytotoxic effect of the drug substance in the cell increases. Methotrexate is a phase-specific substance the main action of which is directed to the S-phase of cell mitosis. It acts generally most effectively on actively increasing tissues, such as malignant cells, bone marrow, fetal cells, skin epithelium, oral and intestinal mucosa as well as urinary bladder cells. As the proliferation of malignant cells is higher than that of most normal cells, methotrexate can slow down the proliferation of malignant cells without causing, however, irreversible damage to normal tissue.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practise (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product

The RMS and CMS considered that the application could be approved with the end of procedure (Day 210) on 12 November 2010. After a subsequent national phase, the licence was granted in the UK on 17 December 2010.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Methotrexate 10 mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Antimetabolites, folic acid analogues (L01BA01)</td>
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<td>Pharmaceutical form and strength(s)</td>
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<td>UK/H/3935/001/DC</td>
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<td>Member State concerned</td>
<td>Ireland</td>
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<td>Marketing Authorisation Number(s)</td>
<td>PL 20117/0172</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Morningside Healthcare Ltd, 115 Narborough Road, Leicester LE3 0PA, UK</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Methotrexate

Chemical name: \(\text{L-(+)}\text{−N−(p-(2,4-\text{Diamino-6-pteridinyl})methyl)methylamino)}\)-benzoyl) glutamic acid.

\((2S)-2-[[4-[[2,4-\text{Diaminopteridin-6yl}methyl][methyl][methylamino][benzoyl][amino]\text{Pentanedioic acid}}

Structure:

Molecular formula: \(\text{C}_{20}\text{H}_{22}\text{N}_{8}\text{O}_{5}\)
Molecular mass: 454.54

Appearance: Methotrexate is a yellow or orange, crystalline, hygroscopic powder, practically insoluble in water, ethanol and in methylene chloride. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides and carbonates.

Methotrexate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance methotrexate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients dibasic calcium phosphate (anhydrous), lactose monohydrate, sodium starch glycolate, microcrystalline cellulose, purified talc and magnesium stearate

All excipients comply with their respective European Pharmacopoeia monograph. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as milk for human consumption. No genetically modified organisms (GMO) have been used in the preparation of these products.
Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious tablets, containing 10 mg methotrexate that could be considered a generic medicinal product of Methotrexate 2.5mg Tablets (Goldshield Pharmaceuticals, UK).

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of all strengths of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System
The finished product is packaged in amber colour polvinylchloride/aluminium blisters in pack sizes of 7, 10, 14, 16, 20, 24, 28, 30, 56, 60, 84, 90, 100 and 112 film-coated tablets.

It has been stated that not all pack sizes may be marketed, however, the Marketing Authorisation Holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 36 months with the special storage conditions ‘Keep the blister in the outer carton in order to protect from light’.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.
MAA form
The MAA form is pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of methotrexate are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment. As this product is intended for generic substitution with other products already on the market, it is not considered to increase the environmental risk. Thus, the applicant’s justification is accepted.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of this application, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, single-dose, four-cohort, two-treatment, two-period, two-sequence, crossover study to compare the pharmacokinetics of the test product Methotrexate 10 mg Tablets versus the reference product Maxtrex 10 mg Tablets (Pharmacia Limited, UK) in patients suffering from psoriasis under fasted conditions.

All volunteers were dosed in a fasted state in two treatment periods. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 48 hours post dose. The washout period between treatment periods was at least 5 days.

The pharmacokinetic results for methotrexate for the test product versus the reference product are presented below (log-transformed values; arithmetic mean):

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} ng/ml/h</th>
<th>AUC_{0-∞} (ng.h/ml)</th>
<th>C_{max} ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (mean)</td>
<td>616.1694</td>
<td>649.2756</td>
<td>143.2245</td>
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<tr>
<td>Reference (mean)</td>
<td>620.5333</td>
<td>657.6389</td>
<td>146.8425</td>
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<tr>
<td><em>Ratio (90% CI)</em></td>
<td>99.30 (91.21-108.10)</td>
<td>98.73 (90.44-107.77)</td>
<td>97.54 (90.00-105.70)</td>
</tr>
</tbody>
</table>

*ln-transformed values
The 90% confidence intervals for AUC and $C_{\text{max}}$ were within the predefined acceptance range for methotrexate. Thus, bioequivalence was demonstrated between the test product and the UK reference product.

**Pharmacodynamics**  
No new pharmacodynamic data were submitted and none were required for this application.

**Efficacy**  
No new efficacy data were submitted and none were required for this application.

**Safety**  
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**  
The SmPC, PIL and labels are medically acceptable. The SmPC is consistent with that for the originator product. The PIL is consistent with the SmPC and in-line current guidelines. The labelling is in-line with current guidelines.

**Clinical Expert Report**  
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Pharmacovigilance System and Risk Management Plan**  
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for this application.

**Conclusion**  
There are no objections to the approval of these products from a clinical viewpoint.

**IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**

**QUALITY**  
The important quality characteristics of Methotrexate 10 mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

**NON-CLINICAL**  
No new non-clinical data were submitted and none are required for an application of this type.

**EFFICACY**  
Bioequivalence has been demonstrated between the applicant’s Methotrexate 10 mg Tablets and its respective reference product (Maxtrex 10 mg Tablets)
No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate.

**BENEFIT-RISK ASSESSMENT**

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s product and the originator product are interchangeable. Extensive clinical experience with methotrexate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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