METHOTREXATE 25 MG/ML SOLUTION FOR INJECTION

(Methotrexate)

PL 18727/0015

UKPAR

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The MHRA granted Fresenius Kabi Oncology Plc a Marketing Authorisation (licence) for the medicinal product Methotrexate 25 mg/ml Solution for Injection on 22 November 2011. This product is a prescription-only medicine (POM).

Methotrexate 25 mg/ml Solution for Injection is an antimetabolite medicine (medicine which affects the growth of body cells) and immunosuppressant (medicine which reduces the activity of the immune system).

Methotrexate is used in large doses (on its own or in combination with other medicines) to treat certain types of cancer. In smaller doses it can be used to treat severe psoriasis (a skin disease with thickened patches of inflamed red skin, often covered by silvery scales), when it has not responded to other treatment.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Methotrexate 25 mg/ml Solution for Injection outweigh the risks and a Marketing Authorisation was granted.
METHOTREXATE 25 MG/ML SOLUTION FOR INJECTION

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Fresenius Kabi Oncology Plc, a Marketing Authorisation for the medicinal product Methotrexate 25 mg/ml Solution for Injection (PL 18727/0015) on 22 November 2011. This product is a prescription-only medicine (POM).

Methotrexate 25 mg/ml Solution for Injection is used for the following indications:
- severe, generalised psoriasis vulgaris resistant to therapy, including psoriatic arthritis
- acute lymphocytic leukaemias (ALL)
- non-Hodgkin's lymphomas
- cancer of the ovary
- head and neck cancer
- breast cancer
- choriocarcinoma and similar trophoblastic diseases
- cancer of the cervix
- bronchogenic carcinoma
- osteosarcoma
- mycosis fungoides
- cancer of the bladder

This is an abridged application submitted under Article 10(1) of Directive 2001/83/EC as amended, cross-referring to Methotrexate Injection 25 mg/ml (Cyanamid of Great Britain Ltd, UK), which has been authorised in the EEA since 27 September 1990.

Methotrexate is an antimetabolite antineoplastic agent that inhibits folate metabolism due to its effects on dihydrofolate reductase and thus diminishes reduced folate pools, which are essential cofactors, particularly for DNA synthesis, but also for purine and protein synthesis. Furthermore, the drug has immunosuppressive and anti-inflammatory effects.

No new non-clinical data have been submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

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

No new or unexpected safety concerns were raised during the assessment of this application and it was therefore judged that the benefits of taking Methotrexate 25 mg/ml Solution for Injection outweigh the risks and a Marketing Authorisation was granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE
INN: Methotrexate.
Structure:

\[
\begin{align*}
\text{Molecular formula:} & \quad \text{C}_{20}\text{H}_{22}\text{N}_8\text{O}_5 \\
\text{Molecular weight:} & \quad 454.4 \\
\text{Appearance:} & \quad \text{Methotrexate is a yellow or orange, crystalline hydroscopic powder. It is practically insoluble in water, ethanol and methylene chloride. It dissolves in dilute mineral acids and dilute solutions of alkali hydroxides and carbonates.}
\end{align*}
\]

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.

MEDICINAL PRODUCT
Other ingredients
Other ingredients consist of the pharmaceutical excipients, sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and Water for Injections.

Appropriate justification for the inclusion of each excipient has been provided.

All of the excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical development
The aim of the development programme was to formulate a safe, efficacious, stable solution for injection that could be considered a generic medicinal product of Methotrexate Injection 25 mg/ml (Cyanamid of Great Britain Ltd, UK).

Suitable pharmaceutical development data have been provided for this application.

Comparable impurity profiles have been provided for the proposed and an existing generic formulation which is acceptable as the licence for the originator product Methotrexate Injection 25 mg/ml (Cyanamid of Great Britain Ltd, UK) was cancelled in 2006.
Manufacture
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale and has shown satisfactory results.

Finished product specification
The finished product specifications are satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The finished product is packaged in 20 mm neck, clear colourless Type I tubular glass vials (50 ml) stoppered with 20 mm Flurotec rubber closures, with aluminium flip-off over seals, containing 1 g/40 ml methotrexate and is available in a pack size of 1 vial.

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
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with the storage conditions ‘This medicinal product should not be used after the expiry date. For single use only. Discard any unused solution immediately and safely after initial use.

After dilution, chemical and physical in-use stability has been demonstrated in glucose (5 %) and sodium chloride (0.9 %) solutions for 24 hours at room temperature and 30 days at 2 °C to 8 °C without special light protection.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Bioequivalence/Bioavailability
A bioequivalence study has not been submitted and is not required to support an application of this type.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are satisfactory.
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 (Marketing Authorisation Application) Form**
The MAA form is satisfactory.

**Expert Report**
A quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
It is recommended that a marketing authorisation is granted for this application.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
No new non-clinical data were submitted, which is acceptable given that the proposed product is a generic medicinal product of an originator product that has been licensed for over 10 years.

NON-CLINICAL EXPERT REPORT
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for the non-submission of an Environmental Risk Assessment. As this product is intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
It is recommended that a marketing authorisation is granted for this application.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

Pharmacokinetics
In accordance with the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), a bioequivalence study is not required if the product is to be administered as an aqueous intravenous solution and contains the same active substance in the same concentration as the currently licensed product.

EFFICACY
No new efficacy data have been submitted and none are required for an application of this type.

SAFETY
No new safety data have been submitted and none are required for this application.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPC, PIL and labelling are acceptable. The SmPC is consistent with that for the respective originator product. The PIL is consistent with the SmPC and is in line with current guidance. The labelling is in line with current guidance.

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.

Suitable justification has been provided for not submitting a Risk Management Plan for this product.

CONCLUSION
There are no objections to the approval of this product from a clinical viewpoint.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Methotrexate 25 mg/ml Solution for Injection 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 have been submitted and none are required for applications of this type.

EFFICACY
No new data have been submitted and none are required for an application of this type.

SAFETY
No new or unexpected safety concerns arose from this application.

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

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with methotrexate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is therefore considered to be positive.
METHOTREXATE 25 MG/ML SOLUTION FOR INJECTION

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STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation application on 07 April 2008.

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 15 April 2008.

3 Following assessment of the application the MHRA requested further information on 04 July 2008.

4 The applicant responded to the MHRA’s requests, providing further information on 13 February 2009.

5 The application was determined on 22 November 2011.
METHOTREXATE 25 MG/ML SOLUTION FOR INJECTION

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STEPS TAKEN AFTER ASSESSMENT

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


SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Methotrexate 25 mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml of solution for injection contains 25 mg of methotrexate.

Each vial of 40 ml of solution contains 1 g methotrexate

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection

Vials containing a clear yellowish solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Methotrexate 25 mg/ml solution for injection may be used for the following indications:

- Severe, generalised psoriasis vulgaris resistant to therapy, including psoriatic arthritis.
- Acute lymphocytic leukaemias (ALL).
- Non-Hodgkin's lymphomas.
- Cancer of the ovary.
- Head and neck cancer.
- Breast cancer.
- Choriocarcinoma and similar trophoblastic diseases.
- Cancer of the cervix.
- Bronchogenic carcinoma.
- Osteosarcoma.
- Mycosis fungoides.
- Cancer of the bladder.

4.2 Posology and method of administration
Note: Methotrexate 25 mg/ml solution for injection (1 g/40 ml) is hypertonic presentation and therefore not suitable for intrathecal and intraventricular use.

Since methotrexate is predominately eliminated renally, in patients with impaired creatinine clearance, delayed elimination is to be expected, which can lead to severe side effects. In patients with impaired renal function, the dose regimens must be adjusted according to the creatinine clearance and serum methotrexate concentrations. Renal function can be adversely affected by the application of methotrexate.

Doses are usually based on the patient’s body weight or body surface area. Total doses greater than 100 mg are usually given by intravenous infusion.

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 (e.g., 5 times 625 mg tablets every three hours) or acetazolamide (e.g., 500 mg orally four times a day) is recommended as a preventive measure.

Before beginning combination therapy involving high-dose methotrexate the leukocyte and thrombocyte count should exceed the respective minimum values (leukocytes 1,000 to 1,500/µl, thrombocytes 50,000 to 100,000/µl). When applying high-dose methotrexate therapy, the serum methotrexate concentration must be checked at regular intervals. The sampling times and the maximum values for toxic serum methotrexate concentrations which require measures such as an increase in the calcium folinate dose or the intravenous fluid supply can be taken from the individual therapy protocols. As a prophylactic measure against nephrotoxic effects, when conducting a course
of therapy involving high-dose methotrexate an intravenous fluid supply and alkalisation of the urine is necessary. Urine flow and the pH value of the urine should be monitored during the methotrexate infusion. Calcium folinate rescue therapy should be performed after high-dose treatment with methotrexate.

Methotrexate 25 mg/ml solution for injection may be further diluted with an appropriate preservative-free medium such as glucose solution (5 %) or sodium chloride solution (0.9 %) or glucose and sodium chloride solution.

Methotrexate 25 mg/ml solution for injection should only be applied by physicians with experience in antimetabolite chemotherapy and the other indication ranges. It is useful to separate the treatment with methotrexate according to the following regimen.

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose therapy</td>
<td>Single dose under 100 mg/m²</td>
</tr>
<tr>
<td>Medium-dose therapy</td>
<td>Single dose between 100 mg/m² and 1,000 mg/m²</td>
</tr>
<tr>
<td>High-dose therapy</td>
<td>Single dose above 1,000 mg/m²</td>
</tr>
</tbody>
</table>

For methotrexate doses exceeding approx. 100 mg/m² as a single dose, the methotrexate treatment must be followed by application of calcium folinate (see calcium folinate rescue).

The application and dosage recommendations for the administration of methotrexate (low-dose therapy, mostly as part of polychemotherapy) for different indications varies considerably. Some common dosages and therapy protocols, which have proved to be efficacious in the therapy of the disorder in each case, are given below. Furthermore, several different polychemotherapies involving methotrexate have proved efficacious for the various indications for high-dose methotrexate therapy. None of these therapy protocols can currently be described as standard therapy. Since the application and dosage recommendations for therapy with methotrexate at high and low dosages vary, only the most commonly used guidelines are given, and should be considered as examples. High-dose methotrexate therapy should only be carried out if the creatinine concentration is within the normal range. If there is evidence to indicate impairment of renal function (e.g., marked side effects from prior therapy with methotrexate or impairment of urine flow), the creatinine clearance must be determined. Current published protocols should be consulted for dosages and the method and sequence of administration.

**Adults and children**

**Severe generalised psoriasis vulgaris resistant to therapy, including psoriatic arthritis**

Psoriatic arthritis: The recommended initial dosage is 7.5 mg methotrexate once weekly intravenously or intramuscularly. According to the activity of the disease, the initial dose can be increased step by step with 2.5 mg methotrexate. A weekly dose of 20 mg methotrexate should not be exceeded. After reaching the desired therapy results, the dosage should be decreased step by step to the lowest effective maintenance dose if possible.

Psoriasis: The recommended initial dosage is 5-10 mg and maximum dose 25 mg methotrexate once weekly intravenously or intramuscularly. The initial dosage can be increased step by step until an optimal therapy result is reached but a weekly dose of 25 mg should not be exceeded. After reaching the desired therapy results, the dosage should be decreased step by step to the lowest effective maintenance dose if possible.

**Acute lymphocytic leukaemias (ALL)**

In low doses, methotrexate is applied within the scope of complex therapy protocols for maintaining remission in children and adults with acute lymphocytic leukaemias. Normal single doses lie within the range of 20-40 mg/m² methotrexate. The maintenance dose for ALL is 15-30 mg/m² once or twice weekly.

**Non-Hodgkin's lymphomas**
Stages I or II of Burkitt’s lymphoma have been treated with methotrexate (orally). Stage III lymphomas and lymphosarcomas may respond to methotrexate given in doses of 0.625-2.5 mg/kg bw daily as part of polychemotherapy, and 90-900 mg/m² as an intravenous infusion, followed by administration of calcium folinate.

In Non-Hodgkin's lymphomas in children, methotrexate is applied according to the phase of the disease and the histological type within the scope of various polychemotherapies at the appropriate doses. Dosage range for therapy with methotrexate at medium or high dosage: single doses from 300-5,000 mg/m² as an intravenous infusion.

Cancer of the ovary

Single doses of 40-1,000 mg/m² have been reported. One reported polychemotherapy (low-dose methotrexate) regimen includes methotrexate (40 mg/m² intravenously on Days 1 and 8), altretam (150 mg/day orally for 14 days), cyclophosphamide (150 mg/day orally for 14 days), and 5-fluorouracil (600 mg/m² intravenously on Days 1 and 8), repetition every 28 days. High-dose regimens include 1,000 mg/m² as an intravenous infusion every 4 weeks.

Head and neck cancer

Intravenous infusions of 240-1,080 mg/m² with calcium folinate rescue have been used both as preoperative adjuvant therapy and in the treatment of advanced tumours. Intra-arterial infusions of methotrexate have also been used.

Breast cancer

Prolonged cyclic combination with cyclophosphamide, methotrexate and fluorouracil has given good results when used as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary lymph nodes. The dose of methotrexate is 40 mg/m² intravenously on the first and eighth days of the cycle. Methotrexate, in intravenous doses of 10-60 mg/m², is also commonly included in cyclic combination regimes with other cytotoxic drugs in the treatment of advanced breast cancer.

Choriocarcinoma and similar trophoblastic diseases (e.g., hydatidiform mole and chorioadenoma destruens)

15-30 mg/m² intramuscularly for five days. Usually such courses may be repeated 3 to 5 times as required, with rest periods of one or more weeks interposed between the courses, until any manifesting toxic symptoms subside.

Cancer of the cervix

5 mg/m² intravenously for five days (single doses of 3-20 mg/m² are reported). One reported polychemotherapy regimen includes methotrexate (30 mg/m² intravenously on Days 1, 15, and 22), vinblastine (3 mg/m² intravenously on Days 2, 15, and 22), doxorubicin (30 mg/m² intravenously on Day 2), and cisplatin (70 mg/m² intravenously on Day 2), repetition every 28 days.

Bronchogenic carcinoma

Intravenous infusions of 20-100 mg/m² of methotrexate has been included in cyclical combination regimens for the treatment of advanced tumours. High doses with calcium folinate rescue have also been employed as the sole treatment.

Osteosarcoma

Effective adjuvant chemotherapy requires the administration of several cytotoxic chemotherapeutic drugs. Methotrexate is used in high doses (8,000-12,000 mg/m²) once weekly. Calcium folinate rescue is necessary. Methotrexate has also been used as the sole treatment in metastatic cases of osteosarcoma.

Mycosis fungoides
50 mg once weekly or 25 mg 2 times weekly intramuscularly. Dose levels of the drug and adjustment of dose regimen by reduction or cessation of the drug are guided by patient response and haematologic monitoring.

**Cancer of the bladder**

Intravenous injections or infusions of methotrexate in doses of up to 100 mg every one or two weeks have been used in the treatment of bladder cancer with promising results, varying from symptomatic relief only to complete though unsustained regression.

**Elderly**

Methotrexate should be used with extreme caution in elderly patients. A reduction in dosage should be considered.

Methotrexate can be applied in the form of an intravenous, intramuscular, or intra-arterial injection, as well as an intravenous infusion. Within the scope of therapy with high doses, methotrexate is administered as a continuous intravenous infusion (glucose, isotonic saline). The duration of treatment is determined by the attending physician, taking the therapy protocol and individual therapy situation into consideration.

### 4.3 Contraindications

Methotrexate 25 mg/ml solution for injection is contraindicated in patients with hypersensitivity to methotrexate, pronounced renal and hepatic insufficiency, pronounced functional impairment of the haematopoietic system such as anaemia, leucopenia, and/or thrombocytopenia (e.g., following prior radio- or chemotherapy), bone marrow suppression, active infections, overt or laboratory evidence of immunodeficiency syndrome(s), and in pregnant or breast feeding patients.

### 4.4 Special warnings and precautions for use

Strict monitoring is necessary in patients with pulmonary dysfunction. Especially strict monitoring of the patient is indicated following prior radiotherapy (especially of the pelvis), functional impairment of the haematopoietic system (e.g., following prior radio- or chemotherapy), impaired general condition as well as advanced age and in very young children.

A chest X-ray has to be performed as a routine examination prior to administration of methotrexate. In addition, before administration of methotrexate, the following check-up examinations and safety precautions are recommended. Renal and hepatic function tests have to exclude the possibility of renal insufficiency or liver damage. Furthermore, a complete blood picture has to be taken. Urinalysis should be performed as part of the prior and follow-up examinations. During therapy, the following examinations have to be performed:

| Monitoring of the serum concentration of methotrexate as a factor of the dosage for the therapy protocol used. |
| Regular check-ups of the oral cavity and the pharynx for changes in the mucus membranes. Ulceration mainly precedes a decrease in the number of leukocytes and/or thrombocytes. |
| Regular leucocyte and thrombocyte counts have to be taken. |
| A complete blood picture has to be taken regularly. |
| Regular testing of hepatic and renal function, especially in the case of high-dose methotrexate therapy should be performed. Creatinine, urea, and electrolytes have to be checked on days 2 and 3 to identify any threatening impairment of methotrexate elimination at an early stage. |
| In the case of long-term therapy, if deemed necessary, bone marrow biopsies have to be taken. |
Preparations for a possible blood transfusion should be made.

Laboratory analysis should be repeated at least every 2 months in the course of treatment with methotrexate.

Liver biopsy should be considered after cumulative doses of methotrexate >1.5 g, if hepatic impairment is suspected.

In addition, skin and mucus membrane contact with methotrexate should be avoided.

In the case of high-dose methotrexate therapy as well as inadvertently administered overdosage with methotrexate, calcium folinate is indicated to diminish the toxicity and counteract the effects of methotrexate.

Methotrexate should be used with extreme caution in patients with ulcers of the mouth, peptic ulcer, ulcerative colitis, ascites, and/or pleural effusion. Patients with pleural effusions or ascites should have these drained before treatment, or treatment should be withdrawn.

Special care is also required in the treatment of patients with mild to moderate renal or hepatic impairment, and in patients with diarrhoea.

Concomitant use of other medicinal products with nephrotoxic and hepatotoxic potential (incl. alcohol) should be avoided.

Concomitant use of NSAIDs (non-steroidal anti-inflammatory drugs) and cotrimoxazole (trimethoprim) should be avoided (see also section 4.5).

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.

When methotrexate is combined with radiotherapy soft tissue necrosis and osteonecrosis may occur.

Necessary actions have to be taken in case of a drop in white cell count or platelet count (i.e. immediate withdrawal of methotrexate), liver function abnormalities (suspension of therapy for at least two weeks), renal impairment (adjustment of dose), diarrhoea and ulcerative stomatitis (interruption of therapy).

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 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.

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

Salicylates, amidopyrine derivatives, phenylbutazone, diphenylhydantoin (phenytoin) barbiturates, tranquillisers, tetracyclines, sulphonamides, doxorubicin, probenecid, and p-aminobenzoic acid, antidiabetic agents and diuretics displace methotrexate bound to the plasma protein and can increase its toxicity.

Penicillins (e.g., amoxicillin, carbenicillin, mezlocillin) can reduce the renal clearance of methotrexate in some cases, so that increased serum concentrations of methotrexate with concomitant haematological and gastrointestinal toxicity can occur.

Non-steroidal anti-inflammatory agents (e.g., indomethacin, ibuprofen) should not be administered prior to or concomitantly with high-dose methotrexate therapy used for the treatment of osteosarcoma, for example. Concomitant administration of some non-steroidal anti-inflammatory
agents with methotrexate has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe haematological and gastrointestinal toxicity.

Salicylate, non-steroidal anti-inflammatory agents, p-aminohippuric acid, probenecid, penicillin, and sulphonamide can reduce the tubular secretion of methotrexate and, especially within the low-dose range of methotrexate, increase its toxicity.

In the case of pre-treatment with medicinal products exhibiting myelosuppressive or immunosuppressive effects (e.g., cytostatics, sulphonamides, chloramphenicol, di-phenylhydantoin, amidopyrine derivatives), it is possible to observe enhancement of bone marrow toxicity and immunosuppression.

Sequential use of methotrexate and 5-fluorouracil may result in synergistic enhancement of cytotoxic effects.

In the presence of an existing folic acid deficiency, the toxicity of methotrexate is increased, the efficacy of therapy can be impaired by tetrahydrofolic acid preparations. Vitamin preparations containing folic acid may alter the response to methotrexate (“over-rescue”).

The application of pyrimethamine and cotrimoxazole (trimethoprime) in combination with methotrexate can cause acute megaloblastic pancytopenia, probably due to additive inhibition of the dihydrofoleric acid reductase.

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

Cholestyramine can increase the nonrenal elimination of methotrexate by interrupting the enterohepatic circulation.

The application of procarbazine during high-dose methotrexate therapy increases the risk of impairment of renal function.

Patients receiving concomitant therapy with methotrexate and acitretin or other retinoids should be monitored closely for any possible increased risk of hepatotoxicity.

In patients receiving methotrexate therapy, treated for a cutaneous herpes zoster with adrenocortical steroids, in isolated cases, disseminated herpes zoster manifested.

Concomitant application of methotrexate and theophylline can reduce theophylline clearance.

Care should be taken when erythrocyte concentrates are administered concomitantly with methotrexate. In patients infused with methotrexate over 24 hours and who subsequently received blood transfusions, increased toxicity was observed, caused by prolonged high serum concentrations of methotrexate.

The use of nitrous oxide-based anaesthetics intensifies the effect of methotrexate on folic acid metabolism and leads to severe unpredictable myelosuppression and stomatitis. This can be reduced by the administration of calcium folinate.

Concomitant application of L-asparaginase is antagonistic towards the effects of methotrexate.

Concomitant use of other medicinal products with nephrotoxic and hepatotoxic potential (incl. alcohol) should be avoided.

4.6 **Fertility, pregnancy and lactation**

Methotrexate is a human teratogen which causes a variety of malformations. It causes chromosomal aberrations in bone marrow cells in humans. Methotrexate must not be administered during pregnancy as the drug can cause foetal death and congenital abnormalities. Women must not become pregnant during treatment with methotrexate. The drug may only be used in the event of the potential benefit outweighing the risk to the foetus.
Conception during and for up to six months after methotrexate therapy should be avoided.

Methotrexate can cause genetic damage. Although patients who had previously received methotrexate have conceived and born normal children, both men and women should avoid conception during and immediately following methotrexate therapy so that normal reproduction of germinal cells may be re-established.

Since methotrexate is excreted in the breast milk, treatment must not be carried out during lactation, or breast feeding should be stopped, to avoid serious adverse drug reactions in breast-fed infants.

Fertility may be (temporarily) decreased as a result of methotrexate therapy due to defective oogenesis / spermatogenesis, transient oligosperma, or menstrual dysfunction.

4.7 Effects on ability to drive and use machines
Not known.

4.8 Undesirable effects

General remarks
The most common undesirable effects are ulcerative stomatitis, leucopenia, nausea, and abdominal discomfort.

With respect to treatment of rheumatoid arthritis with methotrexate adverse reactions with DMARDs frequently occur and may be life-threatening. All patients require careful monitoring to avoid severe toxicity. Patients who relapse during treatment with one DMARD may gain benefit when a different one is substituted. Treatment with more than one DMARD in various regimens is being tried but there is little evidence available to assess benefit. A meta-analysis of 5 different combinations of DMARDs demonstrated that although efficacy might be greater than single DMARDs, toxicity was also increased.

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.

The major toxic effects of methotrexate refer to normal, rapidly proliferating tissues, particularly the bone marrow and lining of the gastrointestinal tract. Myelosuppression and mucositis are the predominant dose-limiting toxic effects of methotrexate. The severity of these reactions depends on the dose, mode and duration of application of methotrexate. Mucositis generally appears about 3 to 7 days after methotrexate application, leucopenia and thrombocytopenia follow a few days later. In patients with unimpaired elimination mechanisms, myelosuppression and mucositis are generally reversible within 14 to 28 days. Concomitant treatment and the underlying disease make it very difficult to attribute an observed side effect specifically to methotrexate.

Haematological effects
Myelosuppression and leucopenia, thrombocytopenia, anaemia up to pancytopenia, hypogammaglobulinaemia, eosinophilia, haemorrhages, haematoma, and septicaemia, and abnormal (megaloblastic) red cell morphology have been reported.

Gastrointestinal disturbances
Therapy with methotrexate may cause inflammation of the oral and pharyngeal mucus membranes, e.g., gingivitis, glossitis, pharyngitis, stomatitis, enteritis as well as ulcerations. Furthermore, anorexia, nausea, vomiting, diarrhoea, haemorrhagic gastroenteritis, melaena, pancreatitis and ulceration accompanied by bleeding and susceptibility to perforation, malabsorption, and toxic megacolon, haematemesis have been reported.
When stomatitis or diarrhoea occur, therapy with methotrexate should be discontinued due to the danger of haemorrhagic enteritis or perforation or dehydration. The drug must be used with caution in patients with peptic ulcer disease or ulcerative colitis.

**Urogenital tract**

Therapy with methotrexate at high doses especially can lead to renal failure with oliguria / anuria and an increase in the creatinine concentration.

In addition, impairment of renal function, azotaemia, cystitis, haematuria, defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, infertility, abortion, and foetal defects, dysuria, vaginitis and vaginal ulcers may occur.

**Hepatotoxicity**

Acute hepatotoxicity caused by methotrexate may manifest as elevations in liver enzymes (transaminases, alkaline phosphatase) and bilirubin. In addition, after long-term methotrexate therapy hepatotoxicity may occur and manifest as hepatic (periportal) fibrosis, cirrhosis, hepatitis, acute hepatic necrosis, fatty degeneration of the liver or other histologic changes in the liver which may sometimes be fatal.

**Respiratory effects**

Upper respiratory infection has been reported. Pulmonary toxicity, which can progress rapidly and is potentially fatal, can be observed in patients treated with methotrexate. Severe reactions such as acute or chronic interstitial pneumonitis (nonspecific / interstitial accompanied by eosinophilia) and pulmonary fibrosis (rare) may occur even at low dosages of 7.5 mg per week.

Acute pulmonary oedema and the development of a “syndrome consisting of pleuritic pain and pleural thinking” following high doses have been reported.

**Dermatologic reactions and integumentary appendages**

Severe, occasionally fatal, cutaneous or sensitivity reactions (e.g., toxic epidermal 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.

Furthermore, exanthema, erythema, pruritus, urticaria, folliculitis, photosensitivity, pigmentary changes, telangectasia, acne, furunculosis, petechia, ecchymosis, (acute desquamative) dermatitis, and an increase in rheumatic nodules have been reported. Alopecia occurs occasionally (reversible after several months). With concomitant UV therapy psoriatic lesions can worsen. Hyperpigmentation of the nails, acute paronychia and onycholysis can occur. Radiation dermatitis and sunburn may be “recalled” by the use of methotrexate.

**Effects following intrathecal administration**

After intrathecal administration of methotrexate, acute chemical arachnoiditis (manifested as headache, back pain, nuchal rigidity, and/or fever), subacute myelopathy (manifested as paraparesis, paraplegia), Guillian-Barré syndrome, chronic leukoencephalopathy (which may be progressive or even fatal) and increased CSF pressure may occur. The leukoencephalopathy may manifest as ventricular enlargement, confusion, tremor, irritability, somnolence, ataxia, dementia, nausea, vomiting, fever, and occasionally seizures or coma, spasticity and death.

**Central nervous system effects and sensory organs**

After high-dose parenteral application with or without prior cranial radiotherapy leukoencephalopathy may also occur as well as a significant intellectual deficit. Discontinuance of methotrexate did not always result in a complete recovery.
Furthermore, headache, drowsiness, aphasia, hemiparesis, paresis, convulsions, vertigo, vomiting, psychoses, pain, myasthenia, paraesthesia and cerebral oedema, may occur. After low doses of methotrexate subtle cognitive dysfunction, mood alterations, or unusual cranial sensations have occasionally been reported.

Ophthalmic reactions (sometime severe) include periorbital oedema, blepharitis, conjunctivitis, epiphora, photophobia, and impairment of vision.

**Other side effects**

Other rare reactions related to or attributed to the use of methotrexate can be anaphylactic reactions, nodulosis, loss of libido / impotence, chills, fever without any detectable pathogen, immunosuppression, decreased resistance to infection, abnormal tissue cell changes, metabolic disorders, hyperuricaemia (due to cell destruction and hepatic and renal damage), diabetes, osteoporosis, including aseptic necrosis of the femoral head, arthralgia, myalgia, malaise and undue fatigue, gynaecomastia, tinnitus, sweating, in rare cases pericarditis, pericardial effusion, hypotension, thromboembolic complications (e.g. thrombophlebitis, pulmonary embolism, arterial, cerebral, deep vein or retinal vein thrombosis), pericardial tamponade, and even sudden death.

There have been reports on the manifestation of lymphomas which were, in some cases, reversible after discontinuing methotrexate therapy. In a recent study, no increased incidence in the manifestation of lymphomas during the course of methotrexate treatment could be detected. Furthermore, the potential of methotrexate to produce other cancers in humans has been evaluated in several studies, but the results do not confirm a cancerogenic risk.

Sometimes fatal opportunistic infections (pneumocystis carinii pneumonia, norcardiosis, histoplasmosis, cryptococcosis, herpes zoster, herpes simplex hepatitis, disseminated herpes simplex) have been reported.

Due to the immunosuppressive action of methotrexate, the drug should be used with extreme caution in patients with an active infection or in the presence of debility and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. Immunisation may be ineffective during methotrexate therapy and immunisation with live virus vaccines is generally not recommended. Hypogammaglobulinaemia has been reported. There have been reports of disseminated vaccinia infections. Cytostatics can reduce antibody formation following an influenza vaccination.

In rare cases, following intrathecal administration, a tumour lysis syndrome has been observed.

It has been suggested that children with Down's syndrome are less able to tolerate methotrexate therapy.

In cases of acute lymphocytic leukaemia, methotrexate can cause pain in the left epigastric region (inflammation of the episplenic region due to destruction of the leukaemic cells).

Furthermore, osteopathy may occur. Several authors reported this effect in patients (adults and children) treated with methotrexate for, acute lymphocytic leukaemia, osteosarcoma.

**4.9 Overdose**

In the case of high-dose methotrexate therapy as well as inadvertently administered overdosage with methotrexate, calcium folinate is indicated to diminish the toxicity and counteract the effects of methotrexate. As there are no generally valid standard recommendations for the dosage and mode of application of calcium folinate as an antidote to massive-dose methotrexate therapy at higher dosage, the following dose recommendations are given as examples. Dosage guidelines are presented below. In cases of massive overdosage with methotrexate, hydration and alkaline diuresis may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Neither haemodialysis nor peritoneal dialysis have been shown to improve methotrexate elimination.

Calcium folinate dosage regimens vary depending upon the dose of methotrexate administered. In general, it should be administered at a dosage of 15 mg (approximately 10 mg/m²) every 6 hours for
10 doses either parenterally by intramuscular injection, bolus intravenous injection or intravenous infusion. Where overdosage of methotrexate is suspected, the dose should be equal to or higher than the offending dose of methotrexate and should be administered within the first hour. The following dose recommendations are given as examples.

<table>
<thead>
<tr>
<th>Serum Methotrexate Level 24-30 Hours</th>
<th>Dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1.5 x 10^{-6} mol/l to 1 x 10^{-8} mol/l</td>
<td>10-15 mg/m^2 every 6 hours</td>
<td>48 hours</td>
</tr>
<tr>
<td>1.5 to 5.0 x 10^{-8} mol/l</td>
<td>30 mg/m^2 every 6 hours</td>
<td>until level is less than 5 x 10^{-8} mol/l</td>
</tr>
<tr>
<td>More than 5.0 x 10^{-8} mol/l</td>
<td>60-100 mg/m^2 every 6 hours</td>
<td>until level is less than 5 x 10^{-8} mol/l</td>
</tr>
</tbody>
</table>

Intrathecal overdosage (exceeding 100 mg) results in severe neurotoxicity, which occurs as prompt burning or numbness in the lower extremities, stupor, agitation, seizures, and/or respiratory insufficiency, and in some cases brain damage or fatal necrotising leucoencephalopathy. Intensive systemic support, high-dose systemic calcium folinate, alkaline diuresis, and rapid CSF drainage and ventriculolumbar perfusion are necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
ATC-Code: L01 BA 01 (Antineoplastic and immunosuppressive drugs, cytostatics, antimetabolites).

Methotrexate is an antimetabolite antineoplastic agent that inhibits folate metabolism due to its effects on dihydrofolate reductase and thus diminishes reduced folate pools, which are essential cofactors, particularly for DNA synthesis, but also for purine and protein synthesis. Furthermore, the drug has immunosuppressive and anti-inflammatory effects.

5.2 Pharmacokinetic properties
Methotrexate is completely available systemically after intravenous, intramuscular or intrathecal administration. Peak serum concentrations are reached within 0.5 to 2 hours following intravenous or intramuscular administration. Conventional doses of methotrexate of 25-100 mg/m^2 result in peak plasma concentrations of 1-10 x 10^{-6} M. High-dose infusion regimens using 1,500 mg/m^2 or greater yield peak levels of 1-10 x 10^{-4} M.

The drug is actively transported across cell membranes and is bound as polyglutamate conjugates. The drug is widely distributed into body tissues with the highest concentrations in the kidneys, gallbladder, spleen, liver, skin, colon and small intestine. The drug may remain in the body for several months, particularly in the liver. As the drug penetrates ascitic fluid and effusions, these spaces may act as depots.

After intravenous administration the initial volume of distribution is approximately 0.18 l/kg (18% of the body weight) and the steady-state volume of distribution is approximately 0.4 to 0.8 l/kg, which correspond to 40% to 80% of the body weight.

The drug undergoes hepatic and intracellular metabolism to polyglutamated forms, which can be converted back to methotrexate by hydrolase enzymes. Small amounts of these active metabolites may be converted to 7-hydroxymethotrexate. The accumulation of this metabolite may become substantial following the administration of high doses. The clearance of methotrexate from the serum
is reported to be triphasic and the terminal elimination half-life is within a range of 3-10 hours for patients receiving methotrexate for psoriasis or who have received low-dose methotrexate antineoplastic therapy. In patients receiving high-dose methotrexate, the elimination half-life is within the range between 8 and 15 hours. The drug is eliminated primarily in the urine by glomerular filtration and active tubular secretion. After intravenous administration about 80-90% is excreted within the urine as unchanged drug within 24 hours. Biliary excretion is limited to about 10% and small amounts (up to 10%) can also be detected in the faeces (enterohepatic circulation). The clearance rates of methotrexate vary widely and are generally decreased at higher dosages and dependent on the route of administration. Drug clearance from plasma under conditions of normal renal function is 103 ml/min/m².

Delayed drug clearance has been reported to be one of the major reasons for methotrexate toxicity. Excretion is impaired and accumulation occurs more rapidly in patients with impaired renal function, pleural effusions, or those with other “third-space” compartments (e.g., ascites).

Approximately 50% of the drug is bound to serum proteins and laboratory studies demonstrate that the drug may be displaced from plasma albumin by various compounds, including sulphonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate crosses the placental barrier and is distributed into breast milk. The drug does not reach therapeutic concentrations in the cerebrospinal fluid (CSF) after parenteral administration of low doses. High CSF concentrations can be attained after intrathecal administration. After the administration of extremely high doses (15,000 to 30,000 mg/m²) CSF concentrations can be attained, which correspond to CSF concentrations after intrathecal administration. Following intrathecal application there is a significant passage into the systemic circulation. Intrathecal administration is associated with delayed elimination of methotrexate from the body due to slow release from the CSF (terminal elimination half-life 52-78 hours).

5.3 Preclinical safety data
There are no preclinical data of relevance to the prescriber other than those already provided in other sections of this SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium chloride
Sodium hydroxide (For pH adjustment)
Hydrochloric acid (For pH adjustment)
Water for injections

6.2 Incompatibilities
Incompatibility data are available for the following drugs and the product may not be mixed with these: chlorpromazine hydrochloride, cytarabine, droperidol, fluorouracil, fludarabine, heparin sodium, idarubicine, metoclopramide hydrochloride, prednisolone sodium phosphate, promethazine, and ranitidine hydrochloride. The product is incompatible with strong oxidants and strong acids.

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6.

6.3 Shelf life
The shelf-life is 2 years.

This medicinal product should not be used after the expiry date.

For single use only. Discard any unused solution immediately and safely after initial use.

After dilution – Chemical and physical in-use stability has been demonstrated in glucose (5%) and sodium chloride (0.9%) solutions for 24 hours at room temperature and 30 days at 2 °C to 8 °C without special light protection.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
Do not store above 25 °C. Do not freeze. Keep the vial in the outer carton in order to protect from light.

After dilution – see 6.3.

6.5 Nature and contents of container
20 mm neck, clear colorless Type I tubular glass vials (50 ml) stoppered with 20 mm Flurotec rubber closures, with aluminium flip-off over seal, containing 1 g/40 ml methotrexate. Methotrexate Solution for Injection is presented in packs of 1 vial.

6.6 Special precautions for disposal
Methotrexate 25 mg/ml solution for injection may be further diluted with 5% glucose solution, or 0.9% sodium chloride solution, or 5% glucose and 0.9% sodium chloride solution.

With respect to the handling the following general recommendations should be considered: The product should be used and administered only by trained personnel; the mixing of the solutions should take place in designated areas, designed to protect personnel and the environment (e.g. safety cabins); protective clothing should be worn (including gloves, eye protection, and masks if necessary).

The product is for single use only; discard any unused solution immediately after initial use. Waste should be disposed of carefully in suitable separate containers, clearly labelled as to their contents (as the patient’s body fluids and excreta may also contain appreciable amounts of antineoplastic agents and it has been suggested that they, and material such as bed linen contaminated with them, should also be treated as hazardous waste). Any unused product or waste should be disposed of in accordance with local requirements by incineration, for example. Chemical destruction methods (oxidation with e.g., potassium permanganate and sulphuric acid or aqueous alkaline potassium permanganate or sodium hypochlorite) have also been used.

Adequate procedures should be in place for accidental contamination due to spillage; staff exposure to antineoplastic agents should be recorded and monitored.

If a cytotoxic drug should contaminate the skin it should be washed off immediately using copious amounts of running water for at least ten minutes, for example. If eyes are sprayed with cytotoxic material they should be rinsed immediately with copious amounts of water and bathed with sterile sodium chloride solution for at least ten minutes, for example.

Pregnant staff should avoid handling antineoplastic agents.

7 MARKETING AUTHORISATION HOLDER
Fresenius Kabi Oncology Plc.
Lion Court, Farnham Road
Bordon, Hampshire GU35 0NF
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)
PL 18727/0015

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/11/2011

10 DATE OF REVISION OF THE TEXT
22/11/2011
Module 3

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

METOTREXATE 25 MG/Ml SOLUTION FOR INJECTION (METHOTREXATE)

Read all of this leaflet carefully before you are given Methotrexate 25 mg/ml Solution for Injection

- Keep this leaflet. You may need to read it again.
- If you have any further questions, 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 gets worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Methotrexate 25 mg/ml Solution for Injection is and what it is used for
2. Before you receive Methotrexate 25 mg/ml Solution for Injection
3. How Methotrexate 25 mg/ml Solution for Injection is given
4. Possible side effects
5. How to store Methotrexate 25 mg/ml Solution for Injection
6. Further Information

1. WHAT METHOTREXATE 25 MG/Ml SOLUTION FOR INJECTION IS AND WHAT IT IS USED FOR

Methotrexate Injection is an immunosuppressive medicine (medicine which affects the growth of body cells) and an antimetabolite (medicine which reduces the activity of the immune system).

Methotrexate is used in large doses (in its own or in combination with other medicines) to treat certain types of cancer. In smaller doses it can be used to treat severe psoriasis (a skin disease with thickened patches of inflamed red skin, often covered by scaly scales), when it is not responding to other treatments.

2. BEFORE YOU ARE GIVEN METHOTREXATE 25 MG/ML SOLUTION FOR INJECTION

You should not be given methotrexate if:
- you have shown signs of hypersensitivity (severe allergy) to methotrexate or any of the other ingredients on previous occasions
- you have a significant liver problem including liver disease, fibrosis, recent or active hepatitis (inflammation of the liver)
- you have a significant kidney problem
- you have a blood disorder which may be characterised by leucocytes, white cells, neutrophils (granulocytes), platelets (thrombocytes), red cells, blood platelet levels which may be low.
- you are pregnant, or trying to become pregnant, or your partner is trying to become pregnant
- you are breast-feeding

Check with your doctor if any of the above apply to you as methotrexate treatment may not be appropriate.

Special care should be taken:
- if you have a stomach ulcer or ulcers of the colon (inflammation of the stomach or the colon)
- if you have a medical condition which causes a build up of fluid in the lining of your lungs or in your abdomen (the fluid will need to be drained before methotrexate treatment is started)
- if you are to have radiotherapy (risk of loss of bone and bone damage may be increased)
- if you are to have any vaccinations (methotrexate can reduce the effect of vaccines)
- if you suffer from alcoholism
- if you have an infectious disease
- if you have a problem with your ammonia system
- if you are suffering from diarrhoea
- if you are weak or fatigued

Taking 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:
  - pain-killers such as paracetamol and ibuprofen
  - anti-inflammatory drugs (NSAIDs), medications against "rheumatism", e.g. indomethacin, ibuprofen
  - analgesics (medications used against pain and other symptoms) e.g. paracetamol, aspirin, ibuprofen, ketoprofen, codeine, paracetamol, dextropropoxyphene, salsalate
  - antibiotics (including from foods of animal origin) and some medicines (e.g. phenytoin), barbiturates and tricyclics (antidepressants)
  - hormones (including oral contraceptives), anticoagulants, antihistamines, antidepressants, anticoagulants, antihypertensive agents or saccharin.

Driving and using machines:
- Do not drive or use machines:
  - if you feel drowsy
  - if it impairs your ability to drive or use machines

3. HOW METHOTREXATE 25 MG/Ml SOLUTION FOR INJECTION IS GIVEN

Methotrexate will be given to you under the supervision of a doctor experienced in its use. Methotrexate will usually be given to you by a nurse or doctor as an injection either, into a vein (intravenously), or into the fatty tissue (subcutaneously).

The dose of methotrexate given to you will depend on the condition being treated, your medical condition, your age, your body weight or body surface area (square metre), how well your kidneys are working and the way that you will be given the drug.

The amount of methotrexate you are given will also depend on the condition being treated and whether methotrexate is being given at all or with one of several medicines. Your doctor will decide on the correct amount of Methotrexate Injection which you should receive.

Before treatment is started, your doctor may carry out blood tests to check the levels of cells in your blood, and also to check how well your kidneys and liver are working. You may have tests before, during and after your treatment to ensure that Methotrexate is working properly and your kidneys are getting rid of the drug that is not needed. You may also have a chest X-ray. Further tests may also be done during and after treatment. Do not miss appointments for these tests.

As this medicine will be given to you while you are in hospital, it is unlikely that you will be given too much or too little, however, tell your doctor or pharmacist if you have any concerns.

4. POSSIBLE SIDE EFFECTS

Like all medicines, methotrexate can cause side effects although not everybody gets them.

Methotrexate is a very toxic medicine which has the potential for serious, sometimes fatal toxicity. During treatment you should watch for any side effects and report them to the doctor.

Methotrexate may affect some of the other cells in your body as well as the cancer cells and you will probably suffer from some side effects. Side effects increase with a higher dose of methotrexate.

Pregnancy and breast-feeding:
- Ask your doctor or pharmacist for advice before taking any medicine.
- Tell your doctor at once if you think you have become pregnant.
- Methotrexate can harm unborn babies. You should not receive methotrexate if you are pregnant or trying to become pregnant or your partner is trying to become pregnant.
- Methotrexate should not be given to you if you are breast-feeding, because methotrexate passes into the mother’s breast milk and can cause side-effects in breast-feeding infants.
- Avoid becoming pregnant or fasting children for at least six months after stopping your treatment with methotrexate due to the temporary-effect of methotrexate on sperm and egg production.

MHRA PAR – Methotrexate 25 mg/ml Solution for Injection (PL 18727/0015)  25 -
The most common side effects are nausea, a painful or swollen abdomen, sweating or irritation of the mouth and lips, and leucopenia and thrombocytopenia (a blood disorder that may be characterized by fever or chills) and sore throat or ulcers in your mouth or throat.

Unwanted effects of Methotrexate 25 mg/ml Solution for Injection are:

- Blood function changes - e.g. your vulnerability for infections may increase, you may suffer from unusual bleeding or bruising and you may observe signs of anaemia (tiredness, weakness, difficulties in breathing), palpebral lymph nodes.
- Gastrointestinal: disorders of the mouth, stomach and intestine like nausea (unusual measure inflammation, e.g. inflammation of the gums, tongue, throat, mouth, intestines as well as ulcers), loss of appetite, feeling sick, vomiting, diarrhoea, unusual bleeding from the mouth, stomach and intestines, inflammation of the pancreas, increased risk of perforation, melaena (red to black stools), abdominal pain (disturbances of appetite with consequences such as body weight loss & malnutrition), and tummy ache (severe complication with massive dilation of the colon and severe pain).
- Kidney and urinary function: renal failure (loss of urine or no urine), impairment of renal function, inflammation of the urinary bladder, blood in the urine, reduced or finally functioning of the kidneys, the leak in dermal function (periods may become less frequent or even stop completely or irregularly), uric acid, electrolyte imbalances of the foetus and pain or difficulty in passing urine, inflammation & infection at the renal tubular organ.
- Liver and gall function: damage to the liver such as fibrosis (increase in the connective tissue formation), cirrhosis (hardening of the liver with hardening and sclerosis of the liver tissue) and cholangitis (inflammation of the bile), acute liver cell death, fatty degeneration of the liver or other histologic changes in the liver, marked changes (laboratory investigations and elevations in liver enzymes (transaminases, alkaline phosphatase) & bilirubin).
- Respiratory function: damage to the lungs such as inflammation and fibrosis (increase in the connective tissue), the pulmonary toxicity may manifest as fever, cough (especially dry and productive), difficulties or increase in the frequency of breathing, chest pain, hypoxemia (low oxygen in the blood).
- Dermatologic (skin) reaction: adverse reactions of the skin such as formation of blisters, becoming red and inflamed, loss/ detaching of skin tissue, vasculitis (inflammation of blood vessels), extensive herpesiform skin eruptions (erythematous, urticarial plaques), rash, itching, nettle rash, inflammatory skin eruptions, phototoxicity (pigment changes (discoloration) of the skin), telangiectasia (expansion of small superficial blood vessels in the skin), acne, formation of boils, pustule or small flat bleeding, loss of hair, weakening of poxiness (with concurrent UV therapy), increased coloration or inflammation or detachment of the nails, tender infections and inflammation around the base of nail, a "reef" of radiation dermatitis (inflammation of the skin) and sunburn.
- Nervous system: leucoencephalopathy (inflammation of the brain), manifested by vertebrobasilar encephalopathy (expansion of fluid spaces inside the brain), confusion, shaking, irritability, sleepiness, ataxia (disturbance of balance and co-ordination), dizziness, feeling sick, fever, and occasionally convulsions, significant intellectual deficit, headache, drowsiness, speech disorder, involuntary yelping or affective one or both sides of the body, tics, dizziness, vomiting, mental deterioration, pain, muscle weakness, weakness of the tongue, touch and variable sensitization, subtle cognitive dysfunction (slower tempo, difficulty attention, mood swings, unusual sensations in the hands, and even death, central oedema (swelling of the brain), eye migration disorders.
- Eye migration disorders of the eyes like swelling inflammation of the eyelids, conjunctivae (inflammation of the eye conjunctive), unusual formation of tears, photophobia, and impairment of vision.
- Other side effects: allergic reactions, haemorrhagic nodules (formation of nodules under the skin), loss of interest in sex / impotence, chills, fever without any detectable cause, decreased resistance to infection, upper respiratory tract infection, abnormal tissue cell changes, metabolic disorder, hypercalcemia (increased blood levels ofraised levels of uric acid, possibly leading to gout), diabetes, osteoporosis and other bone disorders, including severe loss of the femoral head (loss of bone tissue in the hip joint), pain in the joints, muscle pain, malaise and reduced fatigue as growth of the brain glands, in the lungs, the joint, swelling, vagal discomfort, in rare cases pericarditis (inflammation of the outer lining of the heart), periocular effusion and tamponade (collections of fluid and blood, respectively, in the space between the outer lining of the heart and the heart muscle), low blood pressure, complications resulting from the formation of blood clots in veins and arteries, tumour brain syndrome (overall failure due to massive destruction of rapidly growing tumour cells) and even sudden death.
- In cases of acute lymphocytic leukaemia, Methotrexate can cause pain in the left epigastric region (the area overlying the stomach, below the left lower border of the rib cage), inflammation of the space above the spleen due to destruction of the leukaemic cells.
- Other possible complications from administration into the central nervous system include Guillain-Barré syndrome (inflammation of the central nervous system), nerve paralysis, and cerebellar dysfunction, myelitis, encephalitis, meningitis (inflammation of one of the membranes surrounding the spinal cord) manifested as headache, back pain, neck stiffness, and/or fever, vertebrobasilar myelopathy (disorder affecting the spinal cord) manifested as complete or incomplete palsy of the lower limbs (spina bifida) or paralysis) following intrathecal administration.
- Methotrexate can reduce your resistance to infection (opportunistic infections). If you think you have an infection, sore throat, fever, chills or aches you should contact your doctor.
- Sometimes fatal opportunistic infections (granulomatous brain, pneumonia, neoplasia, histoplasmosis, cryptococcosis, herpes zoster, herpes simplex, pneumoconiosis) have been reported.
- It has been suggested that children with Down’s syndrome are less able to tolerate methotrexate therapy.

Osteomyelitis may occur with Methotrexate therapy in patients (adults and children) for treatment of acute lymphocytic leukaemia, osteosarcoma.

There have been reports on the manifestation of lymphomas which were, in some cases, reversible after discontinuing methotrexate therapy. The potential of Methotrexate to produce other cancers in humans has been evaluated in several studies, but the results do not confirm a carcinogenic risk.

If you notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

If you experience any other unexpected effects, which you think may be due to receiving this injection, inform your doctor.

5. HOW TO STORE METHOTREXATE 25 mg/ml SOLUTION FOR INJECTION

Keep Methotrexate 25 mg/ml Solution for Injection out of the reach and sight of children. The vials should not be stored above 25°C. Do not freeze. Keep out in outer carton in order to protect from light.

The medicine should not be used after the expiry date (e.g. Expiry) printed on the vial and carton. The expiry date refers to the last day of the month.

Medicines should not be disposed of via wastewater 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 25 mg/ml Solution for Injection contains:

The active substance is Methotrexate. Each 1 ml of solution contains 25 mg of methotrexate.

The other ingredients are sodium chloride, sodium hydroxide, hydrochloric acid and water for injection.

What Methotrexate 25 mg/ml Solution for Injection looks like and contains of the pack:

This medicine is a yellowish solution for injection, presented in glass containers called vials. Each vial of 40 ml of solution contains 1 g methotrexate. The vials contain 25 mg of methotrexate (as methotrexate sodium formed in situ) per ml (millilitre). Methotrexate 25 mg/ml Solution for Injection is available in 1g in 40 ml and 50 ml vials.

Marketing Authorisation Holder and Manufacturer:

Freecell Kabi Oy, Uusiokatu 10, 00600 Helsinki, Finland

United Kingdom

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MHRA PAR – Methotrexate 25 mg/ml Solution for Injection (PL 18727/0015) 26 -
CARTON:

Methotrexate 25 mg/ml Solution for Injection

CONCENTRATION:
Each vial of 40 ml of solution contains 1 g methotrexate.
1 ml of solution for injection contains 25 mg of methotrexate.
Also contains sodium chloride, sodium hydroxide, hydrochloric acid and water for injections.

SPECIAL WARNINGS
Single use only.
Read the leaflet for further information.
Use as directed by the physician.
Do not store above 25 °C. Do not freeze.
Keep vial in the outer carton in order to protect from light.
Discard any unused solution. For appropriate disposal, refer to the package leaflet.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

VIAL LABEL:

Methotrexate 25 mg/ml Solution for Injection

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