Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Methotrexate Clonmel 25mg/ml Solution for Injection in Pre-filled Syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 25 mg methotrexate.

1 pre-filled syringe of 0.3 ml solution for injection contains 7.5 mg methotrexate.
1 pre-filled syringe of 0.4 ml solution for injection contains 10 mg methotrexate.
1 pre-filled syringe of 0.6 ml solution for injection contains 15 mg methotrexate.
1 pre-filled syringe of 0.8 ml solution for injection contains 20 mg methotrexate.
1 pre-filled syringe of 1.0 ml solution for injection contains 25 mg methotrexate.

The medicinal product contains maximum 5.21 mg per ml sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

The medicinal product is a clear, yellowish solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Active rheumatoid arthritis in adult patients.

- Polyarthritic forms of severe, active juvenile idiopathic arthritis (JIA), when the response to non-steroidal anti-inflammatory drugs (NSAIDs) has been inadequate.

- 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

Posology

Methotrexate should only be prescribed by physicians who are familiar with the various characteristics of the medicinal product and its mode of action. The administration should routinely be done by health professionals. If the clinical situation permits the treating physician can, in selected cases, delegate the administration to the patient her/himself. In these cases, detailed administration instructions from the physician are obligate.

Important warning with reference to methotrexate dosage
Methotrexate Clonmel for the therapy of <u>rheumatic or skin diseases must only be used once weekly</u>.
Faulty dosing may lead to serious adverse effects which can be fatal. Please read section 4.2 of this SmPC very carefully.

Methotrexate Clonmel is injected <u>once weekly!</u> Patients have to be clearly informed that Methotrexate Clonmel must be administered once weekly! It is recommended to specify a certain day of the week as “day for injection”.

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

Dosage in patients with rheumatoid arthritis
The recommended initial dose is 7.5 mg of methotrexate once weekly, administered either subcutaneously or intramuscularly (see below under “Method and duration of administration”).

Depending on the individual activity of the disease and tolerability by the patient, the dose may be increased gradually by 2.5 mg per week.
A weekly dose of 25 mg should not be exceeded. However, doses exceeding 20 mg/week can be associated with significant increase in toxicity, especially bone marrow suppression. Response to treatment can be expected after approximately 4-8 weeks.

Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Dosage in patients with severe forms of psoriasis and psoriatic arthritis
It is recommended that a test dose of 5 - 10 mg should be administered parenterally, one week prior to therapy to detect idiosyncratic adverse reactions.
The recommended initial dose is 7.5 mg of methotrexate once weekly, administered either subcutaneously or intramuscularly.
The dose should be increased as necessary but should not exceed a maximum weekly dose of 30 mg of methotrexate.

Response to treatment can generally be expected after approximately 2 - 6 weeks. Upon achieving the therapeutically desired result, the dose should be reduced gradually to the lowest possible effective maintenance dose.

Duration of treatment

The overall duration of the treatment is decided by the physician.

Methotrexate Clonmel treatment of rheumatoid arthritis, juvenile idiopathic arthritis, severe psoriasis vulgaris and psoriatic arthritis represents long-term treatment.

Rheumatoid arthritis
Treatment response in patients with rheumatoid arthritis can be expected after 4 - 8 weeks. Symptoms may return after treatment discontinuation.

Severe forms of psoriasis vulgaris and psoriatic arthritis
Response to treatment can generally be expected after 2 - 6 weeks. Depending on the clinical picture and the changes of laboratory parameters, the therapy is then continued or discontinued.

Dosage in patients with renal impairment
Methotrexate should be used with caution in patients with impaired renal function. The dose should be adjusted as follows:

Creatinine clearance (ml/min)
> 50: 100% of dose
20 - 50: 50% of dose
< 20: Methotrexate must not be used

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. If bilirubin is > 5 mg/dl (85.5 µmol/l), methotrexate is contraindicated (see section 4.3).

Paediatric population

Dosage in children and adolescents with polyarthritic forms of juvenile idiopathic arthritis
The recommended dose is 10 - 15 mg/m² body surface area (BSA)/week. In therapy-refractory cases the weekly dosage may be increased up to 20 mg/m² body surface area/week. However, an increased monitoring frequency is indicated if the dose is increased.

Patients with JIA should always be referred to a rheumatology unit specialising in the treatment of children/adolescents.

The use in children below 3 years of age is not recommended as insufficient data on efficacy and safety are available for this population (see section 4.4).

Method of administration

For subcutaneous and intramuscular use.
For single use only. This medicinal product has to be used immediately after opening. Any unused solution should be discarded!

Special note
If changing the oral application to parenteral administration a reduction of the dose may be required due to the variable bioavailability of methotrexate after oral administration.

Folic acid or folinic acid supplementation may be considered according to current treatment guidelines.

Any contact of methotrexate with skin and mucosa is to be avoided! In case of contamination, the affected parts are to be rinsed immediately with plenty of water!
See section 6.6.

The medicinal product should be inspected visually prior to use. The solution should only be used if it is clear, free from particles and if the container is undamaged.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1,
- Liver insufficiency (see section 4.2),
- Alcohol abuse,
- Renal insufficiency (creatinine clearance less than 20 ml/min, see section 4.2),
- Pre-existing blood dyscrasia, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia,
- Serious, acute or chronic infections, such as tuberculosis and HIV, ulcers of the oral cavity and known active gastrointestinal ulcer disease,
- Pregnancy, breast-feeding (see section 4.6),
- Concurrent vaccination with live vaccines.

4.4 Special warnings and precautions for use

Patients must be clearly informed, that Methotrexate Clonmel must be administered **once a week**, not every day.

Patients undergoing therapy should be subject to appropriate supervision so that signs of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay. Therefore, methotrexate should only be administered by, or under the supervision of, physicians whose knowledge and experience includes the use of antimetabolite therapy. Because of the possibility of severe or even fatal toxic reactions, the patient should be fully informed of the risks involved and the recommended safety measures. However, doses exceeding 20 mg/week can be associated with significant increase in toxicity, especially bone marrow suppression.

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 male and female patients of childbearing potential (see section 4.6).
Men treated with methotrexate are recommended not to father a child during treatment and at least 6 months thereafter. 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.

Recommended examinations and safety measures:

Before beginning methotrexate therapy or re-instituting methotrexate therapy after a rest period:
Complete blood count with differential blood count and platelets, liver enzymes, bilirubin, serum albumin, chest x-ray and renal function tests. If clinically indicated, tuberculosis and hepatitis should be excluded.

During therapy (at least once a month during the first six months and every three months thereafter):
An increased monitoring frequency should be considered also when the dose is increased.

1. Examination of the mouth and throat for mucosal changes.

2. Complete blood count with differential blood count and platelets. Haemopoietic suppression caused by methotrexate may occur abruptly and with apparently safe dosages. Any profound drop in white cell or platelet counts indicate immediate withdrawal of the medicinal product and appropriate supportive therapy. Patients should be advised to report all signs and symptoms suggestive of infection. Patients simultaneously taking haematotoxic medicinal products (e.g. leflunomide) should be monitored closely with blood count and platelets.

3. 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. There is no evidence to support use of a liver biopsy to monitor hepatic toxicity in rheumatological indications.

For psoriasis patients the need of a liver biopsy prior to and during therapy is controversial. Further research is needed to establish whether serial liver chemistry tests or propeptide of type III collagen can detect hepatotoxicity sufficiently. The evaluation should be performed case by case and differentiate between patients with no risk factors and patients with risk factors such as excessive prior alcohol consumption, persistent elevation of liver enzymes, history of liver disease, family history of inheritable liver disease, diabetes mellitus, obesity, and history of significant exposure to hepatotoxic active substances or chemicals, and prolonged methotrexate treatment or cumulative doses of 1.5 g or more.

Monitoring of liver 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 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 minimised (see section 4.5). Closer monitoring of liver enzymes should be exercised in patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide). This is also required during simultaneous administration of haematotoxic medicinal products (e.g. leflunomide).

4. Renal function should be monitored by renal function tests and urinalysis (see also 4.2 and 4.3):

As methotrexate is eliminated mainly by renal route, increased serum concentrations are to be expected in the case of renal insufficiency, which may result in severe undesirable effects.

Where renal function may be compromised (e.g. in the elderly), monitoring should take place more frequently. This

applies in particular, when medicinal products are administered concomitantly, which affect the elimination of methotrexate, cause kidney damage (e.g. non-steroidal anti-inflammatory medicinal products) or which can potentially lead to impairment of blood formation. Dehydration may also intensify the toxicity of methotrexate.

5. Respiratory system: 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 (including chest x-ray) should be made to exclude infection. If methotrexate induced lung disease is suspected, treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted.

Pulmonary symptoms require a quick diagnosis and discontinuation of methotrexate therapy. Pneumonitis can occur at all dosages.

6. Methotrexate may, due to its effect on the immune system, impair the response to vaccination and affect the results of immunological tests. Particular caution is also needed in the presence of inactive, chronic infections (e.g. herpes zoster, tuberculosis, hepatitis B or C) due to possible activation. Concurrent vaccination using live vaccines should not be carried out.

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.

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

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

Vitamin preparations or other products containing folic acid, folinic acid or their derivatives may decrease the effectiveness of methotrexate.

7. Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety are available for this population (see section 4.2).

Radiation induced dermatitis and sun-burn can reappear under methotrexate therapy (recall-reaction). Psoriatic lesions can exacerbate during UV-irradiation and simultaneous administration of methotrexate.

The absence of pregnancy should be confirmed before Methotrexate Clonmel is administered. Methotrexate causes embryotoxicity, abortion and foetal defects in humans. Methotrexate affects spermatogenesis and oogenesis during the period of its administration which may result in decreased fertility. These effects appear to be reversible on discontinuing therapy. Effective contraception in men and women should be performed during treatment and for at least six months thereafter. The possible risks of effects on reproduction should be discussed with patients of childbearing potential and their partners should be advised appropriately (see section 4.6).

This medicinal product contains less than 1 mmol sodium (23 mg) per pre-filled syringe, i.e. essentially ‘sodium- free’.

4.5 Interaction with other medicinal products and other forms of interaction

In animal experiments non-steroidal anti-inflammatory drugs (NSAIDs) including salicylic acid caused reduction of tubular methotrexate secretion and consequently increased its toxic effects. However, in clinical studies, where NSAIDs and salicylic acid were given as concomitant medication to patients with rheumatoid arthritis, no increase of adverse reactions was observed. Treatment of rheumatoid arthritis with such medicinal product s can be continued during methotrexate therapy but only under close medical supervision.

Regular alcohol consumption and administration of additional hepatotoxic medicinal products increase the probability of hepatotoxic effects of methotrexate.
Patients taking potentially hepatotoxic medicinal products during methotrexate therapy (e.g. leflunomide, azathioprine, sulphasalazine, and retinoids) should be closely monitored for possibly increased hepatotoxicity. Alcohol consumption should be avoided during treatment with methotrexate.

Be aware of pharmacokinetic interactions between methotrexate, anticonvulsant medicinal products (reduced methotrexate blood levels), and 5- fluorouracil (increased t½ of 5-fluorouracil).

Salicylates, phenylbutazone, phenytoin, barbiturates, tranquillisers, oral contraceptives, tetracyclines, amidopyrine derivatives, sulfonamides and p-aminobenzoic acid displace methotrexate from serum albumin binding and thus increase bioavailability (indirect dose increase).

Probenecid and mild organic acids may also reduce tubular methotrexate secretion, and thus cause indirect dose elevations, too.

Antibiotics such as penicillines, glycopeptides, sulfonamides, ciprofloxacin, and cefalotin can, in individual cases, reduce the renal clearance of methotrexate, so that increased serum concentrations of methotrexate with simultaneous haematological and gastro-intestinal toxicity may occur.

Oral antibiotics like tetracyclines, chloramphenicol and non-absorbable broad-spectrum antibiotics may reduce intestinal methotrexate absorption or interfere with enterohepatic circulation by inhibition of the intestinal flora or suppression of the bacterial metabolism.

Under (pre-)treatment with substances that may have adverse reactions affecting the bone marrow (e.g. sulfonamides, trimethoprim/sulfamethoxazole, chloramphenicol, pyrimethamine), the risk of pronounced haematopoietic disorders during methotrexate therapy must be considered.

Concomitant administration of medicinal products that cause folate deficiency (e.g. sulfonamides, trimethoprim/sulfamethoxazole) may lead to increased methotrexate toxicity. Therefore, particular caution must be exercised in patients with existing folic acid deficiency. On the other hand, concomitant administration of folinic acid containing medicinal products or of vitamin preparations, which contain folic acid or derivatives, may impair methotrexate efficacy.

Under concomitant administration of methotrexate and other basic treatments (e.g. gold compounds, penicillamine, hydroxychloroquine, sulphasalazine, azathioprine, cyclosporine), increased toxic effects of methotrexate are generally not to be expected.

Concomitant administration of proton-pump inhibitors like omeprazole or pantoprazole can lead to interactions: Concomitant administration of methotrexate and omeprazole has led to delayed renal elimination of methotrexate. In combination with pantoprazole inhibited renal elimination of the metabolite 7-hydroxymethotrexate, resulting in myalgia and shivering, was reported in one case.

Though the combination of methotrexate and sulfasalazine may enhance methotrexate efficacy by sulfasalazine related inhibition of folic acid synthesis, and thus may lead to an increased risk of side effects, these were only observed in single patients within several trials.

Methotrexate may reduce theophylline clearance. Therefore, theophylline blood levels should be monitored under concomitant methotrexate administration.

Excessive consumption of caffeine- or theophylline-containing beverages (coffee, caffeine-containing beverages, black tea) should be avoided during methotrexate therapy, since the efficacy of methotrexate may be reduced due to possible interaction between methotrexate and methylxanthines at adenosine receptors.

The combined use of methotrexate and leflunomide may increase the risk for pancytopenia. Methotrexate leads to increased plasma levels of mercaptopurines. Therefore, the combination of these may require dosage adjustment.

Particularly in the case of orthopaedic surgery where susceptibility to infection is high, a combination of methotrexate with immune-modulating agents must be used with caution.

Delayed methotrexate clearance should be considered in combination with other cytostatic agents.

On account of its possible effect on the immune system, methotrexate can falsify vaccinal and test results (immunological procedures to record the immune reaction). During methotrexate therapy concurrent vaccination with live vaccines must not be carried out (see section 4.3).

4.6 Fertility, pregnancy and lactation

Pregnancy:
Methotrexate is contraindicated during pregnancy (see section 4.3). In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (see section 5.3). Methotrexate has been shown to have a teratogenic effect in humans; it has been reported to cause foetal death and/or congenital abnormalities. Exposure of a limited number of pregnant women (42) resulted in an increased incidence (1:14) of malformations (cranial, cardiovascular and extremity related). When methotrexate was discontinued prior to conception, normal pregnancies have been reported.

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

Contraception in males and females:
Women must not get pregnant during methotrexate therapy and patients of a sexually mature age (women and men) must use effective contraception during treatment with Methotrexate Clonmel and at least 6 months thereafter (see section 4.4). 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 can be genotoxic, all women who wish to become pregnant are advised to consult a genetic councelling centre, if possible, already prior to therapy, and men should seek advice about the possibility of sperm preservation before starting therapy.

Breast-feeding:
As methotrexate passes into breast milk and may cause toxicity in nursing infants, treatment is contraindicated during the lactation period (see section 4.3). If use during the lactation period should become necessary, breast-feeding is to be stopped prior to treatment.

Fertility:
As methotrexate can be genotoxic, all women who wish to become pregnant are advised to consult a genetic councelling centre, if possible, already prior to therapy, and men should seek advice about the possibility of sperm preservation before starting therapy.

4.7 Effects on ability to drive and use machines

Central nervous symptoms such as tiredness and dizziness can occur during treatment, therefore in isolated cases methotrexate can have minor or moderate influence on the ability to drive and use machines.

4.8 Undesirable effects

Occurrence and severity of undesirable effects depend on dosage level and frequency of methotrexate administration. However, as severe adverse reactions may occur even at lower doses, it is indispensable that the doctor monitors patients regularly at short intervals. Most undesirable effects are reversible if recognised early. If such adverse reactions occur, dosage should be reduced or therapy be interrupted and appropriate countermeasures should be taken (see section 4.9). Methotrexate therapy should only be resumed with caution, under close assessment of the necessity for treatment and with increased alertness for possible reoccurrence of toxicity.

Frequencies in this table are defined using the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1,000 to <1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000
Not known	cannot be estimated from the available data

The following adverse reactions may occur:

After intramuscular methotrexate administration, local adverse reactions (burning sensation) or damage (formation of sterile abscess, destruction of fatty tissue) may occasionally occur at the injection site.
Subcutaneous methotrexate application indicates a good local tolerability. Up to now, only mild skin reactions have been observed, and their number decreases during treatment.

Within each system organ class, the adverse reactions have been ranked under the headings of frequency, most frequent reactions first.

System organ class	
Infections and infestations	*Very rare* sepsis, opportunistic infections (may be fatal in some cases), infections caused by the cytomegaly virus
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*Uncommon* individual cases of lymphoma, which abated in a number of cases once methotrexate treatment had been discontinued. In a recent study, it was not possible to establish that methotrexate therapy increases the incidence of lymphomas.
Blood and lymphatic system disorders	*Common* leukocytopenia, thrombocytopenia, anaemia *Uncommon* pancytopenia, agranulocytosis, haematopoietic disorders *Rare* megaloblastic anaemia *Very rare* severe courses of bone marrow depression, aplastic anaemia, lymphadenopathy, lymphoproliferative disorders (partly reversible), eosinophilia and neutropenia
Immune system disorders	*Very rare* immunosuppression, hypogammaglobulinaemia
Psychiatric disorders	*Very rare* insomnia
Nervous system disorders	*Common* headache, fatigue, drowsiness *Uncommon* vertigo, confusion, depression, seizures *Rare* severely impaired vision, mood alterations, *Very rare* pain, muscular asthenia or paraesthesia of the extremities, changes in sense of taste (metallic taste), meningism (paralysis, vomiting),

	acute aseptic meningitis
Eye disorders	*Rare*
	visual disturbances
	Very rare
	conjunctivitis, retinopathy
Cardiac disorders	*Rare*
	pericarditis, pericardial effusion, pericardial tamponade
Vascular disorders	*Rare*
	hypotension, thromboembolic events (including arterial and cerebral thrombosis, thrombophlebitis, deep vein thrombosis, retinal vein thrombosis, pulmonary embolism)
Respiratory, thoracic and mediastinal disorders	*Common*
	Pulmonary complications due to interstitial alveolitis/ pneumonitis and related deaths (independent of dose and duration of methotrexate treatment). Typical symptoms may be: general illness, dry, irritating cough, shortness of breath progressing to rest dyspnoea, chest pain, fever. If such complications are suspected, Methotrexate Clonmel treatment must be discontinued immediately and infections (including pneumonia) must be excluded.
	Uncommon
	pulmonary fibrosis
	Rare
	pharyngitis, apnoea, bronchial asthma
	Very rare
	pneumocystis carinii pneumonia, shortness of breath, chronic obstructive pulmonary disease, pleural effusion Infections including pneumonia have also been observed.
Gastrointestinal disorders	*Very common*
	loss of appetite, nausea, vomiting, abdominal pain, inflammation and ulcerations of the mucous membrane of mouth and throat (especially during the first 24 - 48 hours after administration of Methotrexate Clonmel, stomatitis, dyspepsia
	Common
	diarrhoea (especially during the first 24 - 48 hours after administration of Methotrexate Clonmel
	Uncommon
	gastrointestinal ulcers and bleeding
	Rare
	enteritis, melaena, gingivitis, malabsorption
	Very rare
	haematemesis, toxic megacolon
Hepatobiliary disorders	*Very common*
	increase in liver-related enzymes (ALAT, ASAT, alkaline phosphatase and bilirubin)
	Uncommon
	development of liver fattening, fibrosis and cirrhosis (occurs frequently despite regularly monitored normal values of liver enzymes), diabetic metabolism, drop of serum albumin

	Rare acute hepatitis, hepatotoxicity *Very rare* reactivation of chronic hepatitis, acute liver degeneration Furthermore, herpes simplex hepatitis and liver insufficiency have been observed (also see the notes regarding liver biopsy in section 4.4).
Skin and subcutaneous tissue disorders	*Common* exanthema, erythema, itching *Uncommon* urticaria, photosensibility, enhanced pigmentation of the skin, hair loss, increase of rheumatic nodules, herpes zoster, painful lesions of psoriatic plaque; severe toxic reactions: vasculitis, herpetiform eruption of the skin, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) *Rare* increased pigmentary changes of nails, acne, petechiae, ecchymoses, erythema multiforme, cutaneous erythematous eruptions *Very rare* acute paronychia, furunculosis, telangiectasia, allergic vasculitis, hidradenitis Furthermore, nocardiosis, histoplasma and cryptococcus mycosis and disseminated herpes simplex have been reported.
Musculoskeletal and connective tissue disorders	*Uncommon* arthralgia, myalgia, osteoporosis *Rare* stress fracture
Renal and urinary disorders	*Uncommon* inflammation and ulceration of the urinary bladder (possibly with haematuria), dysuria *Rare* renal failure, oliguria, anuria, azotaemia *Very rare* proteinuria
Reproductive system and breast disorders	*Uncommon* inflammation and ulceration of the vagina *Very rare* loss of libido, impotence, oligospermia, impaired menstruation, vaginal discharge, infertility
General disorders and administration site conditions	*Uncommon* severe allergic reactions progressing to anaphylactic shock *Very rare* fever, impaired wound healing

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

a) Symptoms of overdose

Toxicity of methotrexate mainly affects the haematopoietic and gastrointestinal systems. Symptoms include leukocytopenia, thrombocytopenia, anaemia, pancytopenia, neutropenia, bone marrow depression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration and gastrointestinal bleeding. Some patients showed no signs of overdose. There are reports of death due to sepsis, septic shock, renal failure and aplastic anaemia.

b) Therapeutic measures in case of overdose

Calcium folinate is the specific antidote for neutralising the toxic undesirable effects of methotrexate. In cases of accidental overdose, a dose of calcium folinate equal to or higher than the offending dose of methotrexate should be administered intravenously or intramuscularly within one hour and dosing continued until the serum levels of methotrexate are below 10^{-7} mol/l.

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

In patients with rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriasis arthritis or psoriasis vulgaris, administration of folic or folinic acid may reduce methotrexate toxicity (gastrointestinal symptoms, inflammation of oral mucosa, hair loss and increase of liver enzymes), see section 4.5.
Prior to using folic acid products, monitoring of vitamin B_{12} levels is recommended, since folic acid may mask an existing vitamin B_{12} deficiency, particularly in adults over 50 years of age.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, antimetabolites, folic acid analogues

ATC code: L01BA01

Methotrexate is a folic acid antagonist which belongs to the class of cytotoxic agents known as antimetabolites. It acts by the competitive inhibition of the enzyme dihydrofolate reductase and thus inhibits DNA and RNA synthesis. It has not yet been clarified, as to whether the efficacy of methotrexate, in the management of psoriasis, psoriatic arthritis, and rheumatoid arthritis is due to an anti-inflammatory or immunosuppressive effect and to which extent a methotrexate-induced increase in extracellular adenosine concentration at inflamed sites contributes to these effects.

5.2 Pharmacokinetic properties

After oral application, methotrexate is absorbed from the gastrointestinal tract. When administered in low doses (7.5 mg/m² to 80 mg/m² body surface area), methotrexate has a mean bioavailability of approximately 70 %, although considerable interindividual and intraindividual deviations are possible (25 – 100 %). Plasma peak concentrations are attained within 1 – 2 hours. Subcutaneous, intravenous, and intramuscular administration demonstrated similar bioavailability.
Approximately 50 % of methotrexate is bound to serum proteins. Upon being distributed into body tissues, high concentrations particularly in liver, kidneys and spleen in form of polyglutamates can be found, which can be retained for weeks or months. When administered in small doses, methotrexate passes into the liquor in minimal amounts; under high doses (300 mg/kg body weight), concentrations between 4 and 7 µg/ml have been measured in the liquor.
Average terminal half-life is 6 - 7 hours and demonstrates considerable variation (3 - 17 hours). Half-life may be prolonged to 4 times the normal length in patients with third spaces (pleural effusion, ascites).
Approximately 10 % of the administered methotrexate is metabolised intrahepatically. The major metabolite is 7-

hydroxymethotrexate.

Excretion takes place, mainly in unchanged form, primarily renal via glomerular filtration and active secretion in the proximal tubulus. Approx. 5 - 20% of methotrexate and 1 - 5% of 7-hydroxymethotrexate are eliminated via the bile. Pronounced enterohepatic blood flow exists.

In case of renal insufficiency, elimination is delayed significantly. Impaired elimination in presence of hepatic insufficiency is not known.

Methotrexate passes the placental barrier in rats and monkeys.

5.3 Preclinical safety data

Chronic toxicity
Chronic toxicity studies in mice, rats and dogs showed toxic effects in the form of gastrointestinal lesions, myelosuppression and hepatotoxicity.

Mutagenic and carcinogenic potential
Long-term studies in rats, mice and hamsters did not show any evidence of a tumourigenic potential of methotrexate. Methotrexate induces gene and chromosome mutations both *in vitro* and *in vivo*. A mutagenic effect is suspected in humans.

Reproductive toxicology
Teratogenic effects have been identified in four species (rats, mice, rabbits, cats). In rhesus monkeys, no malformations comparable to humans occurred.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide (for pH-adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.
Do not refrigerate or freeze.
Keep the pre-filled syringes in the outer carton in order to protect from light.

6.5 Nature and contents of container

Methotrexate Clonmel is available in pre-filled syringes of colourless glass (type I) of 1 ml capacity with a plunger stopper of chlorobutyl rubber (type I) and attached injection needle and needle shield.

0.3 ml pre-filled syringe, in packs of 1.
0.4 ml pre-filled syringe, in packs of 1.

0.6 ml pre-filled syringe, in packs of 1.
0.8 ml pre-filled syringe, in packs of 1.
1.0 ml pre-filled syringe, in packs of 1.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling and disposal must be consistent with that of other cytotoxic preparations in accordance with local requirements. Pregnant health care professionals should not handle and/or administer Methotrexate Clonmel.

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

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/262/001

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