Risk management plan (RMP)

Active substance(s) (INN or common name):	Methotrexate
Pharmaco-therapeutic group (ATC Code):	Immunosuppressants (L04AX03)
Name of Marketing Authorisation Holder or Applicant:	Cipla Europe NV
Number of medicinal products to which this RMP refers:	02
Product(s) concerned (brand name(s)):	1) Methotrexate 2.5 mg tablets 2) Methotrexate 10 mg tablets

Data lock point for this RMP	16-Jul-2014	Version number	02
Date of final sign off	10-Nov-2014		

Part I: Product(s) Overview

Administrative information on the RMP

Part	**Module/annex**	**Date last updated for submission (sign off date)**	***Version number of RMP when last submitted/ or** **Not Applicable**
Part II Safety Specification	SV Post authorisation experience Only required for updates to the RMP		Not Applicable
	SVIII Summary of the safety concerns	10-Nov-2014	02
Part III Pharmacovigilance Plan	Only needed if reference product has additional PhV activities		Not Applicable
Part IV Plan for post-authorisation efficacy studies	Only needed if reference product has imposed post-authorisation efficacy studies		Not Applicable
Part V Risk Minimisation Measures		10-Nov-2014	02
Part VI Summary of RMP		10-Nov-2014	02
Part VII Annexes	ANNEX 2 Current or proposed SmPC/PIL	10-Nov-2014	02
	ANNEX 3 Worldwide marketing status by country		Not Applicable
	ANNEX 5 Synopsis of pharmacoepidemiological study programme		Not Applicable
	ANNEX 6 Protocols for proposed and on-going studies in Part III		Not Applicable
	ANNEX 7 Specific adverse event follow-up		Not Applicable

Part	Module/annex	Date last updated for submission (sign off date)	*Version number of RMP when last submitted/ or Not Applicable
	forms		
	ANNEX 8 Protocols for studies in Part IV		Not Applicable
	ANNEX 9 Synopsis of newly available study reports in Parts III-IV		Not Applicable
	ANNEX 10 Details of proposed additional risk minimisation activities		Not Applicable
	ANNEX 11 Mock up examples		Not Applicable
	ANNEX 12 Other supporting data		Not Applicable

QPPV name Dr. Vineet Kacker

QPPV signature ……

Contact person for this RMP Mrs. Kiran Nair

E-mail address or telephone number of contact person: kiran.nair@cipla.com

Overview of versions:

Version number of last agreed RMP:

Version number	Not applicable
Agreed within	Not applicable

Current RMP versions under evaluation:

RMP Version number	Submitted on	Submitted within
Not applicable	Not applicable	Not applicable

For each product in the RMP

Invented name(s) in the European Economic Area (EEA)	Methotrexate 2.5mg tablets Methotrexate 10mg tablets
Authorisation procedure	Decentralised Procedure
Brief description of the product including: • chemical class • summary of mode of action • important information about its composition (e.g. origin of active substance of biological, relevant adjuvants or residues for vaccines	Pharmacotherapeutic group: Other immunosuppressants, ATC code: L04AX03 Methotrexate is a folic acid antagonist and its major site of action is the enzyme dihydrofolate reductase. Its main effect is inhibition of DNA synthesis but it also acts directly both on RNA and protein synthesis. Methotrexate is a phase specific substance, the main effect being directed during the S-phase of cell division. The inhibition of dihydrofolate reductase can be circumvented by the use of leucovorin (folinic acid; citrovorum factor) and protection of normal tissues can be carried out by properly timed administration of leucovorin calcium.
Indication(s) in the EEA Current (if applicable)	• Methotrexate is used in the treatment of active rheumatoid arthritis in adult patients.. • Methotrexate has also been used in the treatment of 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.
Proposed (if applicable)	None.
Posology and route of administration in the EEA Current (if applicable)	This medicine should be taken once a week. Do not exceed the weekly dose of this medicine due to toxicity hazards in psoriasis and rheumatoid arthritis. The prescriber may specify the day of intake on the prescription. <u>Rheumatoid arthritis</u> The usual dose is 7.5 - 15 mg once weekly. The planned weekly dose may be administered in three divided doses over 36 hours.

	The schedule may be adjusted gradually to achieve an optimal response but should not exceed a total weekly dose of 20 mg. Thereafter the dose should be reduced to the lowest possible effective dose which in most cases is achieved within 6 weeks. Psoriasis Before starting treatment it is advisable to give the patient a test dose of 2.5–5.0 mg to exclude unexpected toxic effects. If, one week later, appropriate laboratory tests are normal, treatment may be initiated. The usual dose is 7.5–15 mg taken once weekly. The planned weekly dose administered as three divided doses over 24 hours. As necessary, the total weekly dose can be increased up to 25 mg. Thereafter the dose should be reduced to the lowest effective dose according to therapeutic response which in most cases is achieved within 4 to 8 weeks. The patient should be fully informed of the risks involved and the clinician should pay particular attention to the appearance of liver toxicity by carrying out liver function tests before starting methotrexate treatment, and repeating these at 2 to 4 month intervals during therapy. The aim of therapy should be to reduce the dose to the lowest possible level with the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy which should be encouraged. Use in elderly patients: Methotrexate should be used with extreme caution in elderly patients, a dose reduction should be considered due to reduced liver and kidney function as well as lower folate reserves which occur with increased age. 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) Dose > 50 100 % 20 – 50 50 % < 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 Methotrexate is not recommended for children under 3 years as

	insufficient data on efficacy and safety is available for this population.
Proposed (if applicable)	None
Pharmaceutical form(s) and strengths Current (if applicable)	1) 2.5 mg tablet: yellow, circular, biconvex uncoated tablets with dimension of 4.50 mm ± 0.20 mm plain on both sides 2) 10 mg tablet: yellow coloured, capsule shaped, biconvex uncoated tablet with length of 10.00 mm ± 0.20 mm and breadth 5.00 mm ± 0.20 mm, with central breakline on one side and plain on other side. The breakline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
Proposed (if applicable)	None

Country and date of first authorisation worldwide	07-Jun-1994 <Unknown>
Country and date of first launch worldwide	<Unknown> <Unknown>
Country and date of first authorisation in the EEA	<Unknown>

Is the product subject to additional monitoring in the EU? Yes ☐ No ☑

Part II: Module SV - Post-authorisation experience

Not applicable

Part II: Module SVIII - Summary of the safety concerns

Table 1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Use in severe/significant renal impairment • Use in significant hepatic impairment • Immunodeficiency syndrome • Reduced immunological response to concurrent vaccination • Bone marrow depression and Haematopoietic suppression • Concomitant administration with drugs with antifolate properties (e.g. cotrimoxazole, trimethoprim and nitrous oxide) • concomitant administration with NSAIDs • concomitant administration with hepatic and nephrotoxic drugs • Teratogenic potential on use during pregnancy • Hypersensitivity including anaphylactic reactions • Pleuropulmonary manifestation of rheumatoid arthritis, chronic interstitial pneumonitis • Steven Johnson syndrome, epidermal necrolysis • Infertility • Eosinophilic pulmonary reactions and

Summary of safety concerns	
	treatment resistant interstitial fibrosis after long term treatment
Important potential risks	• Use in elderly population • Concomitant administration with Acitretin and vitamin preparations containing folic acid or its derivatives • Gastrointestinal toxicity including haemorrhagic enteritis and intestinal perforation • Malignant Lymphomas • Risk of soft tissue necrosis and osteonecrosis • Concurrent administration of agents such as p-aminobenzoic acid, chloramphenicol, diphenylhydantoins, acidic anti-inflammatory agents, salicylates, sulphonamides, tetracyclines, thiazide diuretics, probenicid or sulfinpyrazone or oral hypoglycaemics • Accidental overdose
Missing information	• Use in Paediatric population

Part III: Pharmacovigilance Plan

Not applicable

Part IV: Plans for post-authorisation efficacy studies

The marketing authorization holder has not planned any post-authorisation efficacy studies for Methotrexate.

Part V: Risk minimisation measures

V.1 Risk minimisation measures by safety concern

Safety concern	**Use in severe/significant renal impairment**
Objective(s) of the risk minimisation measures	To reduce the use of Methotrexate in severe/significant renal impairment
Routine risk minimisation measures	As per section 4.4 (Special warnings and precautions for use) and 4.3 (Contraindications) of SPC as well as section 2 of PIL (What you need to know before you take Methotrexate Tablets), methotrexate is contra indicated in severe/significant renal impairment. Renal function should be closely monitored before, during and after treatment. Reduce dose of methotrexate in patients with renal impairment.
Additional risk minimisation measure(s)	None

Safety concern	**Use in significant hepatic impairment**
Objective(s) of the risk minimisation measures	To reduce the use of Methotrexate in significant hepatic impairment
Routine risk minimisation measures	As per section 4.4 (Special warnings and precautions for use) and 4.3 (Contraindications) of SPC as well as section 2 of PIL (What you need to know before you take Methotrexate Tablets), methotrexate is contra indicated in significant hepatic impairment**.**
Additional risk minimisation measure(s)	None

Safety concern	**Immunodeficiency syndrome**
Objective(s) of the risk minimisation measures	To reduce the use of Methotrexate in Immunodeficiency syndrome
Routine risk minimisation measures	As per section 4.3 (Contraindications), section 4.4 (Special warnings and precautions for use) of SPC and Section 2 of PIL(What you need to know before you take Methotrexate Tablets) as well as section 4 (Possible side effects), Methotrexate is contra indicated in Immunodeficiency syndrome.

Safety concern	**Immunodeficiency syndrome**
	Methotrexate has some immunosuppressive activity and therefore the immunological response to concurrent vaccination may be decreased.
Additional risk minimisation measure(s)	None

Safety concern	**Reduced immunological response to concurrent vaccination**
Objective(s) of the risk minimisation measures	To minimize the Reduced immunological response to concurrent vaccination.
Routine risk minimisation measures	As per section 4.4 (Special warnings and precautions for use) of SPC and 4.5 (Interaction with other medicinal products and other forms of interaction) as well as section 2 of PIL (What you need to know before you take Methotrexate Tablets), Methotrexate may lead to reduced immunological response to concurrent vaccination. Concomitant use of a live vaccine could cause severe antigenic reaction.
Additional risk minimisation measure(s)	None

Safety concern	**Bone marrow depression and Haematopoietic suppression**
Objective(s) of the risk minimisation measures	To reduce the occurrence of Bone marrow depression and Haematopoietic suppression.
Routine risk minimisation measures	As per section (4.8) Undesirable effects of SPC and section 4 (Possible side effects) of PIL, methotrexate may lead to Bone marrow depression and Haematopoietic suppression. A rest period of at least two weeks is recommended between treatments, in order to allow the bone marrow to return to normal.
Additional risk minimisation measure(s)	None

Safety concern	**Concomitant administration with drugs with antifolate properties (e.g. cotrimoxazole, trimethoprim and nitrous oxide)**
Objective(s) of the risk minimisation measures	To minimize the Concomitant administration of Methotrexate with drugs with antifolate properties (e.g. cotrimoxazole, trimethoprim and nitrous oxide)
Routine risk minimisation measures	As per section, 4.5 (Interaction with other medicinal products and other forms of interaction) of SPC as well as section 2 (What you need to know before you take Methotrexate Tablets) of PIL, Concomitant administration of Methotrexate with drugs with antifolate properties (e.g. cotrimoxazole, trimethoprim and nitrous oxide) should be avoided.
Additional risk minimisation measure(s)	None

Safety concern	**Concomitant administration with NSAIDs**
Objective(s) of the risk minimisation measures	To reduce the Concomitant administration of Methotrexate with NSAIDs.
Routine risk minimisation measures	As per section 4.5 (Interaction with other medicinal products and other forms of interaction) of SPC and section 2 (What you need to know before you take Methotrexate Tablets) of PIL, concomitant administration of Methotrexate with NSAIDs is contra indicated.
Additional risk minimisation measure(s)	None

Safety concern	**Concomitant administration with hepatic and nephrotoxic drugs**
Objective(s) of the risk minimisation measures	To reduce the Concomitant administration of Methotrexate with hepatic and nephrotoxic drugs.
Routine risk minimisation measures	As per section 4.5 (Interaction with other medicinal products and other forms of interaction) of SPC and section 4.8 (Undesirable effects) and section 2 (What you need to know before you take Methotrexate Tablets) of PIL, Concomitant administration of Methotrexate with hepatic and nephrotoxic drugs is contra indicated.

Safety concern	**Concomitant administration with hepatic and nephrotoxic drugs**
	Hepatic toxicity resulting in significant elevations of liver enzymes, acute liver atrophy, necrosis, fatty metamorphosis, periportal fibrosis or cirrhosis or death may occur, usually following chronic administration.
Additional risk minimisation measure(s)	None

Safety concern	**Teratogenic potential on use during pregnancy**
Objective(s) of the risk minimisation measures	To reduce adverse events due to Teratogenic potential on use during pregnancy.
Routine risk minimisation measures	As per section 4.3 (Contraindications) and 4.4 (Special warnings and precautions for use) of SPC and section 2 (What you need to know before you take Methotrexate Tablets) of PIL, Methotrexate is teratogenic and should not be given during pregnancy or to mothers who are breast feeding. Methotrexate has been shown to be teratogenic; it has been reported to cause foetal death and/or congenital abnormalities.
Additional risk minimisation measure(s)	None

Safety concern	**Hypersensitivity including anaphylactic reactions**
Objective(s) of the risk minimisation measures	To reduce the risk of Hypersensitivity including anaphylactic reactions
Routine risk minimisation measures	The risk of Hypersensitivity including anaphylactic reactions with Methotrexate has been mentioned in section 4.3 (Contraindications) of SPC and section 4 (Possible side effects) of PIL.
Additional risk minimisation measure(s)	None

Safety concern	**Pleuropulmonary manifestation of rheumatoid arthritis, chronic interstitial pneumonitis**
Objective(s) of the risk minimisation measures	To reduce pleuropulmonary manifestation of rheumatoid arthritis, chronic interstitial

Safety concern	**Pleuropulmonary manifestation of rheumatoid arthritis, chronic interstitial pneumonitis**
	pneumonitis with the use of Methotrexate.
Routine risk minimisation measures	The risk of pleuropulmonary manifestation of rheumatoid arthritis, chronic interstitial pneumonitis is mentioned in sectioned 4.8 (Undesirable effects) of SPC and section 2 (What you need to know before you take Methotrexate) Tablets of PIL. In the treatment of rheumatoid arthritis, methotrexate induced lung disease is a potentially serious adverse drug reaction which may occur acutely at any time during therapy.
Additional risk minimisation measure(s)	None

Safety concern	**Steven Johnson syndrome, epidermal necrolysis**
Objective(s) of the risk minimisation measures	To reduce the risk of Steven Johnson syndrome and epidermal necrolysis with the use of Methotrexate.
Routine risk minimisation measures	The risk of Steven Johnson syndrome and epidermal necrolysis is mentioned in sectioned 4.8 (Undesirable effects) of SPC and section 4 (Possible side effects) of PIL.
Additional risk minimisation measure(s)	None

Safety concern	**Infertility**
Objective(s) of the risk minimisation measures	To reduce the risk of infertility with the use of methotrexate**.**
Routine risk minimisation measures	The risk of infertility is mentioned in section 4.6 (Fertility, pregnancy and lactation) and section 4.8 (Undesirable effects) of SPC and section 2 of PIL. Both men and women receiving methotrexate should be informed of the potential risk of adverse effects on reproduction. Defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, and infertility have been reported in patients receiving methotrexate

Safety concern	**Infertility**
Additional risk minimisation measure(s)	None

Safety concern	**Eosinophilic pulmonary reactions and treatment resistant interstitial fibrosis after long term treatment**
Objective(s) of the risk minimisation measures	To reduce the risk of Leucoencephalopathy with the use of methotrexate**.**
Routine risk minimisation measures	As per section 4.4 (Special warnings and precautions for use) of SPC. Reversible eosinophilic pulmonary reactions and treatment-resistant, interstitial fibrosis may occur, particularly after long-term treatment.
Additional risk minimisation measure(s)	None

Effectiveness of risk minimisation measures	
How effectiveness of risk minimisation measures for the safety concern will be measured	Not applicable
Criteria for judging the success of the proposed risk minimisation measures	Not applicable
Planned dates for assessment	Not applicable
Results of effectiveness measurement	Not applicable
Impact of risk minimisation	Not applicable
Comment	Not applicable

V.2 Risk minimisation measure failure (if applicable)

Not applicable

V.3 Summary table of risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Use in severe/significant renal impairment	As per section 4.4 (Special warnings and precautions for use) and 4.3 (Contraindications) of SPC as	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	well as section 2 of PIL (What you need to know before you take Methotrexate Tablets), methotrexate is contra indicated in severe/significant renal impairment. Renal function should be closely monitored before, during and after treatment. Reduce dose of methotrexate in patients with renal impairment.	
Use in significant hepatic impairment	As per section 4.4 (Special warnings and precautions for use) and 4.3 (Contraindications) of SPC as well as section 2 of PIL (What you need to know before you take Methotrexate Tablets), methotrexate is contra indicated in significant hepatic impairment.	None
Immunodeficiency syndrome	As per section 4.3 (Contraindications), section 4.4 (Special warnings and precautions for use) of SPC and Section 2 of PIL (What you need to know before you take Methotrexate Tablets) as well as section 4 (Possible side effects) of PIL, Methotrexate is contra indicated in Immunodeficiency syndrome.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Reduced immunological response to concurrent vaccination	As per section 4.4 (Special warnings and precautions for use) of SPC and 4.5 (Interaction with other medicinal products and other forms of interaction) as well as section 2 of PIL (What you need to know before you take Methotrexate Tablets), Methotrexate may lead to reduced immunological response to concurrent vaccination. Concomitant use of a live vaccine could cause severe antigenic reaction.	None
Bone marrow depression and Haematopoietic suppression	As per section (4.8) Undesirable effects of SPC and section 4 (Possible side effects) of PIL, methotrexate may lead to Bone marrow depression and Haematopoietic suppression. A rest period of at least two weeks is recommended between treatments, in order to allow the bone marrow to return to normal.	None
Concomitant administration with drugs with antifolate properties (e.g. cotrimoxazole, trimethoprim and nitrous oxide)	As per section, 4.5 (Interaction with other medicinal products and other forms of interaction) of SPC as well as section 2 (What you need to know before you take Methotrexate Tablets) of PIL, Concomitant administration of Methotrexate with drugs with antifolate properties (e.g. cotrimoxazole, trimethoprim and nitrous oxide) should be avoided.	None
concomitant administration with NSAIDs	As per section 4.5 (Interaction with other medicinal products and other forms of interaction) of SPC and section 2 (What you need to know before you take Methotrexate Tablets) of PIL, concomitant	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	administration of Methotrexate with NSAIDs is contra indicated.	
concomitant administration with hepatic and nephrotoxic drugs	As per section 4.5 (Interaction with other medicinal products and other forms of interaction) of SPC and section 4.8 (Undesirable effects) and section 2 (What you need to know before you take Methotrexate Tablets) of PIL, Concomitant administration of Methotrexate with hepatic and nephrotoxic drugs is contra indicated. Hepatic toxicity resulting in significant elevations of liver enzymes, acute liver atrophy, necrosis, fatty metamorphosis, periportal fibrosis or cirrhosis or death may occur, usually following chronic administration.	None
Teratogenic potential on use during pregnancy	As per section 4.3 (Contraindications) and 4.4 (Special warnings and precautions for use) of SPC and section 2 (What you need to know before you take Methotrexate Tablets) of PIL, Methotrexate is teratogenic and should not be given during pregnancy or to mothers who are breast feeding. Methotrexate has been shown to be teratogenic; it has been reported to cause foetal death and/or congenital abnormalities.	None
Hypersensitivity including anaphylactic reactions	The risk of Hypersensitivity including anaphylactic reactions with Methotrexate has been mentioned in section 4.3 (Contraindications) of SPC and section 4 (Possible side effects) of PIL.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Pleuropulmonary manifestation of rheumatoid arthritis, chronic interstitial pneumonitis	The risk of pleuropulmonary manifestation of rheumatoid arthritis, chronic interstitial pneumonitis is mentioned in sectioned 4.8 (Undesirable effects) of SPC and section 2 (What you need to know before you take Methotrexate Tablets) of PIL. In the treatment of rheumatoid arthritis, methotrexate induced lung disease is a potentially serious adverse drug reaction which may occur acutely at any time during therapy.	None
Steven Johnson syndrome, epidermal necrolysis	The risk of Steven Johnson syndrome and epidermal necrolysis is mentioned in sectioned 4.8 (Undesirable effects) of SPC and section 4 (4. Possible side effects) of PIL.	None
Infertility	The risk of infertility is mentioned in section 4.6 (Fertility, pregnancy and lactation) and section 4.8 (Undesirable effects) of SPC and section 2 of PIL. Both men and women receiving methotrexate should be informed of the potential risk of adverse effects on reproduction. Defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, and infertility have been reported in patients receiving methotrexate	None
Eosinophilic pulmonary reactions and treatment resistant interstitial fibrosis after long term treatment	As per section 4.4 (Special warnings and precautions for use) of SPC. Reversible eosinophilic pulmonary reactions and treatment-resistant, interstitial	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	fibrosis may occur, particularly after long-term treatment.	

Part VI: Summary of the risk management plan by product

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	• Use in severe/significant renal impairment • Use in significant hepatic impairment • Immunodeficiency syndrome • Reduced immunological response to concurrent vaccination • Bone marrow depression and Haematopoietic suppression • Concomitant administration with drugs with antifolate properties (e.g. cotrimoxazole, trimethoprim and nitrous oxide) • concomitant administration with NSAIDs • concomitant administration with hepatic and nephrotoxic drugs • Teratogenic potential on use during pregnancy • Hypersensitivity including anaphylactic reactions • Pleuropulmonary manifestation of rheumatoid arthritis, chronic interstitial

Summary of safety concerns	
	pneumonitis • Steven Johnson syndrome, epidermal necrolysis • InfertilityEosinophilic pulmonary reactions and treatment resistant interstitial fibrosis after long term treatment
Important potential risks	• Use in elderly population • Concomitant administration with Acitretin and vitamin preparations containing folic acid or its derivatives • Gastrointestinal toxicity including haemorrhagic enteritis and intestinal perforation • Malignant Lymphomas • Risk of soft tissue necrosis and osteonecrosis • Concurrent administration of agents such as p-aminobenzoic acid, chloramphenicol, diphenylhydantoins, acidic anti-inflammatory agents, salicylates, sulphonamides, tetracyclines, thiazide diuretics, probenicid or sulfinpyrazone or oral hypoglycaemics • Accidental overdose
Missing information	• Use in Paediatric population

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not Applicable

VI.1.3 Summary of Post authorisation efficacy development plan

Not Applicable

VI.1.4 Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Use in severe/significant renal impairment	As per section 4.4 (Special warnings and precautions for use) and 4.3 (Contraindications) of SPC as well as section 2 of PIL (What you need to know before you take Methotrexate Tablets), methotrexate is contra indicated in severe/significant renal impairment. Renal function should be closely monitored before, during and after treatment. Reduce dose of methotrexate in patients with renal impairment.	None
Use in significant hepatic impairment	As per section 4.4 (Special warnings and precautions for use) and 4.3 (Contraindications) of SPC as well as section 2 of PIL (What you need to know before you take Methotrexate Tablets), methotrexate is contra indicated in significant hepatic impairment.	None
Immunodeficiency syndrome	As per section 4.3 (Contraindications), section 4.4 (Special warnings and precautions for use) of SPC and Section 2 (What you need to know before you take Methotrexate Tablets) as well as section 4 (Possible side effects) of PIL, Methotrexate is contra indicated in Immunodeficiency syndrome.	None
Reduced immunological response to concurrent vaccination	As per section 4.4 (Special warnings and precautions for use) of SPC and 4.5 (Interaction with other medicinal products and other	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	forms of interaction) as well as section 2 of PIL (What you need to know before you take Methotrexate Tablets), Methotrexate may lead to reduced immunological response to concurrent vaccination. Concomitant use of a live vaccine could cause severe antigenic reaction.	
Bone marrow depression and Haematopoietic suppression	As per section (4.8) Undesirable effects of SPC and section 4 (Possible side effects) of PIL, methotrexate may lead to Bone marrow depression and Haematopoietic suppression. A rest period of at least two weeks is recommended between treatments, in order to allow the bone marrow to return to normal.	None
Concomitant administration with drugs with antifolate properties (e.g. cotrimoxazole, trimethoprim and nitrous oxide)	As per section, 4.5 (Interaction with other medicinal products and other forms of interaction) of SPC as well as section 2 (What you need to know before you take Methotrexate Tablets) of PIL, Concomitant administration of Methotrexate with drugs with antifolate properties (e.g. cotrimoxazole, trimethoprim and nitrous oxide) should be avoided.	None
concomitant administration with NSAIDs	As per section 4.5 (Interaction with other medicinal products and other forms of interaction) of SPC and section 2 (What you need to know before you take Methotrexate Tablets) of PIL, concomitant administration of Methotrexate with NSAIDs is contra indicated.	None
concomitant administration with hepatic and nephrotoxic	As per section 4.5 (Interaction with other medicinal products	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
drugs	and other forms of interaction) of SPC and section 4.8 (Undesirable effects) and section 2 (What you need to know before you take Methotrexate Tablets) of PIL, Concomitant administration of Methotrexate with hepatic and nephrotoxic drugs is contra indicated. Hepatic toxicity resulting in significant elevations of liver enzymes, acute liver atrophy, necrosis, fatty metamorphosis, periportal fibrosis or cirrhosis or death may occur, usually following chronic administration.	
Teratogenic potential on use during pregnancy	As per section 4.3 (Contraindications) and 4.4 (Special warnings and precautions for use) of SPC and section 2 (What you need to know before you take Methotrexate Tablets) of PIL, Methotrexate is teratogenic and should not be given during pregnancy or to mothers who are breast feeding. Methotrexate has been shown to be teratogenic; it has been reported to cause foetal death and/or congenital abnormalities.	None
Hypersensitivity including anaphylactic reactions	The risk of Hypersensitivity including anaphylactic reactions with Methotrexate has been mentioned in section 4.3 (Contraindications) of SPC and section 4 (Possible side effects) of PIL.	None
Pleuropulmonary manifestation of rheumatoid arthritis, chronic interstitial pneumonitis	The risk of pleuropulmonary manifestation of rheumatoid arthritis, chronic interstitial pneumonitis is mentioned in sectioned 4.8 (Undesirable effects) of SPC and section 2	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	(What you need to know before you take Methotrexate Tablets) of PIL. In the treatment of rheumatoid arthritis, methotrexate induced lung disease is a potentially serious adverse drug reaction which may occur acutely at any time during therapy.	
Steven Johnson syndrome, epidermal necrolysis	The risk of Steven Johnson syndrome and epidermal necrolysis is mentioned in sectioned 4.8 (Undesirable effects) of SPC and section 4 (4. Possible side effects) of PIL.	None
Infertility	The risk of infertility is mentioned in section 4.6 (Fertility, pregnancy and lactation) and section 4.8 (Undesirable effects) of SPC and section 2 of PIL. Both men and women receiving methotrexate should be informed of the potential risk of adverse effects on reproduction. Defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, and infertility have been reported in patients receiving methotrexate	None
Eosinophilic pulmonary reactions and treatment resistant interstitial fibrosis after long term treatment	As per section 4.4 (Special warnings and precautions for use) of SPC. Reversible eosinophilic pulmonary reactions and treatment-resistant, interstitial fibrosis may occur, particularly after long-term treatment.	None

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

1) **Rheumatoid arthritis :** Arthritis means inflammation of joints. Rheumatoid arthritis (RA) is a common form of arthritis. (There are various other causes of arthritis and RA is just one cause.) About 1 in 100 people develops RA at some stage in their life. It can happen to anyone. It is not an hereditary disease. It can develop at any age, but most commonly starts between the ages of 40 and 60. It is about three times more common in women than in men.Rheumatoid arthritis causes inflammation, pain, and swelling of joints. Persistent inflammation over time can damage affected joints. The severity can vary from mild to severe. Treatments include disease-modifying medicines to suppress inflammation, which can prevent or delay the progression of the disease, and medication to ease pain. The earlier treatment is started, the less joint damage is likely to occur. Surgery is needed in some cases.
.
2) **Psoriasis :** Psoriasis is a common condition where there is inflammation of the skin. It typically develops as patches (plaques) of red, scaly skin. Once you develop psoriasis it tends to come and go throughout life. In some people it is mild with a few small patches that develop and are barely noticeable. In others, there are many patches of varying size. In many people the severity is somewhere between these two extremes. Treatment with various creams or ointments can often clear or reduce patches of psoriasis. The worldwide prevalence of psoriasis is around 2%, but studies in developed countries have reported higher prevalence rates of on average about 4.6%.1 Nearly two thirds of people with psoriasis have a mild form of the disease, with less than 3% of the skin surface of the body affected, but others have more extensive involvement of the skin.

VI.2.2 Summary of treatment benefits

The applicant has not conducted any pivotal study for methotrexate. The results of recent clinical trials comparing methotrexate with several biologic agents have shown it to be the first-line therapy among the classic systemic treatments for psoriasis. Moreover, the incremental cost-effectiveness ratio for subcutaneous methotrexate has been shown to be superior to that of ciclosporin, adalimumab, and infliximab.

VI.2.3 Unknowns relating to treatment benefits

There is no information available regarding use in paediatric population.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Use in severe/significant kidney disease (renal impairment)	Methotrexate may cause adverse events if given in patients with severe/significant kidney disease (renal impairment).	As per section 4.4 (Special warnings and precautions for use) and 4.3 (Contraindications) of SPC as well as section 2 of PIL (What you need to know before you take Methotrexate Tablets), methotrexate should not be given in severe/significant kidney disease. kidney function should be closely monitored before, during and after treatment. The dose of Methotrexate should be decreased in patients with kidney disease.
Use in significant Liver diseases (hepatic impairment)	Methotrexate may cause adverse events if given in patients with Liver diseases (hepatic impairment).	As per section 4.4 (Special warnings and precautions for use) and 4.3 (Contraindications) of SPC as well as section 2 (What you need to know before you take Methotrexate Tablets), methotrexate should not be given in significant Liver diseases.
State in which the immune system's ability to fight infectious disease is compromised or entirely absent (Immunodeficiency syndrome)	Methotrexate should not be used in patients having State in which the immune system's ability to fight infectious disease is compromised or entirely absent (Immunodeficiency syndrome).	As per section 4.3 (Contraindications), section 4.4 (Special warnings and precautions for use) of SPC and Section 2 (What you need to know before you take Methotrexate Tablets) as well as section 4 (Possible side effects) of PIL, Methotrexate should not be given in a state in which the immune system's ability to fight infectious

Risk	What is known	Preventability
		disease is compromised or entirely absent.
Decrease a bodily defense reaction that recognizes an invading substance (immunological response) to concurrent administration of antigenic material (a vaccine) to stimulate an individual's immune system to develop adaptive immunity to a pathogen (vaccination)	Methotrexate reduces the activation or efficacy of the immune system. (immunosuppressive activity) and therefore a bodily defense reaction that recognizes an invading substance (immunological response) to concurrent vaccination may be decreased.	As per section 4.4 (Special warnings and precautions for use) of SPC and 4.5 (Interaction with other medicinal products and other forms of interaction) as well as section 2 (What you need to know before you take Methotrexate Tablets), Methotrexate should not be given along with vaccine, it could cause severe antigenic reaction.
Condition characterized by the decreased ability or inability of the bone marrow to produce blood cells (Bone marrow depression) and decreased formation of blood (Haematopoietic suppression).	Condition characterized by the decreased ability or inability of the bone marrow to produce blood cells (Bone marrow depression) is most frequently manifested by decreased white blood cells (leucopenia), decreased platelet (thrombocytopenia) (which are usually reversible) and decrease in the number of red blood cells or in their haemoglobin content (anaemia), or any combination may occur.	As per section 4.8 (Undesirable effects) of SPC and section 4 (Possible side effects) of PIL, methotrexate may lead to a condition characterized by the decreased ability or inability of the bone marrow to produce blood cells (Bone marrow depression) and decreased formation of blood (Haematopoietic suppression). A rest period of at least two weeks is advised between treatments, in order to allow the bone marrow to return to normal.
Concomitant administration with drugs with antifolate properties (e.g. cotrimoxazole, trimethoprim and nitrous oxide)	Methotrexate should not be used along with the drugs which impair the function of folic acids (antifolate properties). Methotrexate is a folic acid antagonist and its major site of action is the enzyme dihydrofolate reductase.	As per section, 4.5 (Interaction with other medicinal products and other forms of interaction) of SPC as well as section 2 (What you need to know before you take Methotrexate Tablets) of PIL, Methotrexate should not be used with the drugs which impair the function of folic acids (antifolate properties). (e.g. cotrimoxazole, trimethoprim and nitrous oxide) should be avoided.
Concomitant administration with NSAIDs	If Methotrexate is used with NSAIDs, it may lead to Methotrexate toxicity which	As per section 4.5 (Interaction with other medicinal products and other forms of interaction)

Risk	What is known	Preventability
	can cause death. Methotrexate dosage should be monitored if concomitant treatment with NSAIDs is started.	of SPC and section 2 (What you need to know before you take Methotrexate Tablets) of PIL, Methotrexate should not be used along with with NSAIDs. Methotrexate dosage should be monitored if concomitant treatment with NSAIDs is started, as it may lead to Methotrexate toxicity which can cause death.
Concomitant administration with drugs that harm liver and kidneys (hepatic and nephrotoxic drugs)	Methotrexate should not be taken along with the drugs which harm liver and kidneys (hepatic and nephrotoxic drugs)	As per section 4.5 (Interaction with other medicinal products and other forms of interaction) of SPC and section 4.8 (Undesirable effects) and section 2 (What you need to know before you take Methotrexate Tablets) of PIL, use of Methotrexate along with the drugs that harm liver and kidneys (hepatic and nephrotoxic drugs) is not advised. Liver toxicity (Hepatic toxicity) resulting in significant increase of liver enzymes, decreased size of liver (acute liver atrophy), death of liver cells (necrosis), accumulation of fat inside liver tissue cells (fatty metamorphosis), scarring near portal vein (periportal fibrosis) or of normal tissue with fibrous tissue and the loss of functional liver cells (cirrhosis) or death may occur, usually following long term use.
Malformation of an embryo or fetus (Teratogenic potential) on use during pregnancy	Methotrexate has been shown to cause malformation of an embryo or fetus.; it has been reported to cause death of unborn baby (foetal death) and/or birth defects (congenital abnormalities).	As per section 4.3 (Contraindications) and 4.4 (Special warnings and precautions for use) of SPC and section 2 (What you need to know before you take Methotrexate Tablets) of PIL, Methotrexate causes defects in

Risk	What is known	Preventability
		an embryo or unborn baby and should not be given during pregnancy or to mothers who are breast feeding.
Allergy (Hypersensitivity) including anaphylactic reactions)	Methotrexate can cause allergic reactions.	The risk of allergic reactions (Hypersensitivity including anaphylactic reactions) with Methotrexate has been mentioned in section 4.3 (Contraindications) of SPC and section 4 (Possible side effects) of PIL.
Lung disorders (Pleuropulmonary) by form of inflammation of joints that causes pain, swelling, stiffness and loss of function in joints (rheumatoid arthritis) and inflammation of lung (chronic interstitial pneumonitis)	In the treatment of inflammatory joint disease (rheumatoid arthritis), methotrexate induced lung disease is a potentially serious adverse drug reaction which may occur acutely at any time during therapy. It is not always fully reversible. Lung symptoms (especially a dry, non productive cough) may require stoppage of treatment and careful investigation.	The risk of lung disorders caused by rheumatoid arthritis and inflammation of lungs (chronic interstitial pneumonitis) is mentioned in sectioned 4.8 (Undesirable effects) of SPC and section 2 (What you need to know before you take Methotrexate Tablets of PIL).
Forms of a life-threatening skin condition, in which cell death causes the epidermis to separate from the dermis. (Steven Johnson syndrome, epidermal necrolysis)	Methotrexate may cause forms of a life-threatening skin condition, in which cell death causes the epidermis to separate from the dermis. Steven Johnson syndrome and epidermal necrolysis).	The risk of skin condition which puts patient in immediate risk of death, in which cell death causes the epidermis to separate from the dermis is mentioned in sectioned 4.8 (Undesirable effects) of SPC and section 4 (Possible side effects) of PIL.
infertility	. Methotrexate can affect sperm and egg production with the potential to cause birth defects. Therefore, patients must avoid fathering a child whilst taking methotrexate and for at least **6** months after treatment is stopped. Since treatment with methotrexate may lead to infertility, it might be advisable for male patients to look into the possibility of **sperm preservation** before starting treatment.	The risk of infertility is mentioned in section 4.6 (Fertility, pregnancy and lactation) and section 4.8 (Undesirable effects) of SPC and section 2 of PIL. Patients are advised to consult their doctor or pharmacist for advice before taking this medicine.

Risk	What is known	Preventability
Swelling (inflammation) of the lungs from an increase in eosinophils, a type of white blood cell (Eosinophilic pulmonary reactions) and treatment resistant scarring and thickening of the lung tissues (interstitial fibrosis) after long term treatment	Reversible Swelling (inflammation) of the lungs from an increase in eosinophils, a type of white blood cell (Eosinophilic pulmonary reactions) and treatment-resistant, scarring and thickening of the lung tissues (interstitial fibrosis) may occur, particularly after long-term treatment of methotrexate.	This risk has been mentioned in section 4.4 (Special warnings and precautions for use) of SPC.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Use in elderly population	Methotrexate should be used with extreme caution in elderly patients, a reduction in dosage should be considered. Elderly patients may need smaller doses of methotrexate.
Concomitant administration with Acitretin and vitamin preparations containing folic acid or its derivatives	Acitretin (a treatment for psoriasis) is converted to to eretinate. Methotrexate levels may be increased by eretinate and severe inflammation of liver (hepatitis) has been reported following concomitant use of Methotrexate with Acitretin and vitamin preparations containing folic acid or its derivatives.
Gastrointestinal toxicity including haemorrhagic enteritis and intestinal perforation	Particular care and possible stoppage of treatment are advised if inflammation of lips (stomatitis) or gastro intestinal toxicity occurs as inflammation of intestine causing bleeding (haemorrhagic enteritis) and formation of hole in intestine (intestinal perforation) may result.
Malignant Lymphomas	**Cancerous** cells that have the ability to spread in lymphatic system (Malignant lymphomas) may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued. Failure of the type of cancer that begins in immune system cells called lymphocytes (lymphoma) to show signs of spontaneous lessening of the severity of a disease (regression) requires the initiation of cytotoxic therapy.
Risk of soft tissue necrosis and osteonecrosis	Methotrexate given along with radiotherapy may increase the risk of soft tissue cell death (necrosis) and bone death (osteonecrosis).

Risk	What is known (Including reason why it is considered a potential risk)
Concurrent administration of agents such as p-aminobenzoic acid, chloramphenicol, diphenylhydantoins, acidic anti-inflammatory agents, salicylates, sulphonamides, tetracyclines, thiazide diuretics, probenicid or sulfinpyrazone or oral hypoglycaemics	The concurrent administration of agents such as p-aminobenzoic acid, chloramphenicol, diphenylhydantoins, acidic anti-inflammatory agents, salicylates, sulphonamides, tetracyclines, thiazide diuretics, probenicid, sulfinpyrazone or oral hypoglycaemics will decrease the methotrexate transport function of renal tubules, thereby reducing excretion and almost certainly increasing methotrexate toxicity.
Accidental overdose	Cases of overdose, sometimes leading to death, due to erroneous daily intake instead of weekly intake of oral methotrexate have been reported.

Missing information

Risk	What is known
Use in Paediatric population	There is no information available regarding use in paediatric population.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Methotrexate can be found in the Methotrexate's EPAR page

This medicine has no additional risk minimisation measures.***VI.2.6 Planned post authorisation development plan***

Not applicable

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable

Part VII: Annexes

Annex 1 – EudraVigilance Interface

Not applicable

Annex 2 - SmPC & Package Leaflet

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Methotrexate 2.5mg tablets

Methotrexate 10mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

2.5 mg tablet: each tablet contain methotrexate 2.5mg

Excipients with known effects

Each 2.5 mg tablet contain 12.50 mg lactose (as lactose monohydrate)

10 mg tablet: each tablet contain methotrexate 10mg

Excipients with known effects

Each 10 mg tablet contain 50 mg lactose (as lactose monohydrate)

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

2.5 mg tablet: yellow, circular, biconvex uncoated tablets with dimension of 4.50 mm ± 0.20 mm plain on both sides

10 mg tablet: yellow coloured, capsule shaped, biconvex uncoated tablet with length of 10.00 mm ± 0.20 mm and breadth 5.00 mm ± 0.20 mm, with central breakline on one side and plain on other side. The breakline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Active rheumatoid arthritis in adult patients.

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

4.2 Posology and method of administration

This medicine should be taken once a week. Do not exceed the weekly dose of this medicine due to toxicity hazards in psoriasis and rheumatoid arthritis. The prescriber may specify the day of intake on the prescription.

Rheumatoid arthritis

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

Psoriasis

Before starting treatment it is advisable to give the patient a test dose of 2.5–5.0 mg to exclude unexpected toxic effects. If, one week later, appropriate laboratory tests are normal, treatment may be initiated. The usual dose is 7.5–15 mg taken once weekly. The planned weekly dose administered as three divided doses over 24 hours. As necessary, the total weekly dose can be increased up to 25 mg. Thereafter the dose should be reduced to the lowest effective dose according to therapeutic response which in most cases is achieved within 4 to 8 weeks.

The patient should be fully informed of the risks involved and the clinician should pay particular attention to the appearance of liver toxicity by carrying out liver function tests before starting methotrexate treatment, and repeating these at 2 to 4 month intervals during therapy. The aim of therapy should be to reduce the dose to the lowest possible level with the longest possible rest period. The use of methotrexate may permit the return to conventional topical therapy which should be encouraged.

Use in elderly patients:

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

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)	Dose
> 50	100 %
20 – 50	50 %
< 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. Methotrexate is not recommended for children under 3 years as insufficient data on efficacy and safety is available for this population.

4.3 Contraindications

- Hypersensitivity to methotrexate or to any of the excipients listed in section 6.1
- Significantly impaired hepatic function
- Alcoholism
- Significantly impaired renal function
- Pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia
- Severe acute or chronic infections and immunodeficiency syndromes
-
- Pregnancy and breast-feeding (see section 4.6)
- During methotrexate therapy concurrent vaccination with live vaccines must not be carried out.

4.4 Special warnings and precautions for use

Warnings

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

Concomitant administration of hepatotoxic or haematotoxic DMARDs (disease-modifying antirheumatic drug, e.g. leflunomide) is not advisable.

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

Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Symptoms typically include dyspnoea, cough (especially a dry non-productive cough) and fever for which patients should be monitored at each follow-up visit. Patients should be informed of the risk of pneumonitis and advised to contact their doctor immediately should they develop persistent cough or dyspnoea.

Methotrexate should be withdrawn from patients with pulmonary symptoms and a thorough investigation undertaken to exclude infection. If methotrexate induced lung disease is suspected treatment with corticosteroids should be initiated and treatment with methotrexate should not be restarted.

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

For the treatment of psoriasis, methotrexate should be restricted to severe recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established by biopsy and/or after dermatological consultation.

The Patients should be informed clearly that in the treatment of psoriasis and rheumatoid arthritis the administration is in most cases once weekly. Patients should be aware of the importance of adhering to the once weekly intakes and that wrong daily administration can result in severe toxic reactions. The prescriber may specify the day of intake on the prescription.

Full blood counts should be closely monitored before, during and after treatment. If a clinically significant drop in white-cell or platelet count develops, methotrexate should be withdrawn immediately. Patients should be advised to report all symptoms or signs suggestive of infection.

Methotrexate may be hepatotoxic, particularly at high doses or with prolonged therapy. Liver atrophy, necrosis, cirrhosis, fatty changes, and periportal fibrosis have been reported. Since changes may occur without previous signs of gastrointestinal or haematological toxicity, it is imperative that hepatic function be determined prior to initiation of treatment and monitored regularly throughout therapy.

Liver function tests: Particular attention should be given to the appearance of liver toxicity. Treatment should not be instituted or should be discontinued if any abnormality of liver function tests, or liver biopsy, is present or develops during therapy. Such abnormalities should return to normal within two weeks after which treatment may be recommenced at the discretion of the physician.

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

Due to its potentially toxic effect on the liver, additional hepatotoxic medicinal products should not be taken during treatment with methotrexate unless clearly necessary and the consumption of alcohol should be avoided or greatly reduced (see section 4.5). Closer monitoring of liver enzymes should be exercised in Patients taking other hepatotoxic medicinal products concomitantly (e.g. leflunomide). The same should be taken into account with the simultaneous administration of haematotoxic medicinal products (e.g. leflunomide).

There is no evidence to support use of a liver biopsy to monitor hepatic toxicity in rheumatological indications. In case of longer-term treatment of severe forms of psoriasis

with methotrexate, liver biopsies should be performed on account of the hepatotoxic potential.

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

a) Patients without risk factors

According to current medical standard of knowledge, liver biopsy is not necessary before a cumulative dose of 1.0-1.5 g is reached.

b) Patients with risk factors

These primarily include:

- anamnestic alcohol abuse
- persistent increase in liver enzymes
- anamnestic hepatopathy including chronic hepatitis B or C
- familial anamnesis with hereditary hepatopathy

and secondarily (with possibly lower relevance):

- diabetes mellitus
- adiposity
- anamnestic exposure to hepatotoxic medicines or chemicals.

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

Repeated liver biopsies are recommended after a cumulative dose of 1.0-1.5 g is achieved.

No liver biopsy is necessary in the following cases:

- elderly patients
- patients with an acute disease
- patients with contraindication for liver biopsy (e.g. cardiac instability, altered blood coagulation parameters)
- patients with poor expectance of life.

More frequent check-ups may become necessary

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

Methotrexate has been shown to be teratogenic; it has caused foetal death and/or congenital anomalies. Therefore it is not recommended in women of childbearing potential unless there is appropriate medical evidence that the benefits can be expected to outweigh the considered risks. Pregnant psoriatic patients must not receive methotrexate (see section 4.6).

Renal function should be closely monitored before, during and after treatment. Caution should be exercised if significant renal impairment is disclosed. The dose of methotrexate in patients with renal impairment should be reduced. High doses may cause the precipitation of methotrexate or its metabolites in the renal tubules. A high fluid throughput and alkalinisation of the urine to pH 6.5 – 7.0, by oral or intravenous administration of sodium bicarbonate (5 x 625 mg tablets every three hours) or acetazolamide (500 mg orally four times a day) is recommended as a preventative measure. Methotrexate is excreted primarily by the kidneys. Its use in the presence of impaired renal function may result in accumulation of toxic amounts or even additional renal damage.

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

Methotrexate affects gametogenesis during the period of its administration and may result in decreased fertility which is thought to be reversible on discontinuation of therapy.

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

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

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

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

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

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

Interaction between methotrexate and other antirheumatic agents, such as gold, penicillamin, hydroxychloroquine, sulphasalazine or other cytotoxic agents, have not been studied comprehensively, and coadministration may involve an increased frequency of adverse reactions.

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

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

Precautions

Before beginning methotrexate therapy or reinstituting methotrexate after a rest period, assessment of renal function, liver function and a bone marrow function should be made by history, physical examination and laboratory tests.

Systemic toxicity of methotrexate may also be enhanced in patients with renal dysfunction, ascites, or other effusions due to prolongation of serum half-life.

Malignant lymphomas may occur in patients receiving low dose methotrexate, in which case therapy must be discontinued. Failure of the lymphoma to show signs of spontaneous regression requires the initiation of cytotoxic therapy.

Methotrexate has been reported to cause impairment of fertility, oligospermia, menstrual dysfunction and amenorrhoea in humans, during and for a short period after cessation of therapy. In addition, methotrexate causes embryotoxicity, abortion and foetal defects in humans. Therefore the possible risks of effects on reproduction should be discussed with patients of childbearing potential (see section 4.6).

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

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

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

Methotrexate is bound in part to serum albumin after absorption, and toxicity may be increased because of displacement by certain drugs such as salicylates, sulphonamides, phenytoin, and some antibacterials such as tetracycline, chloramphenicol and para-aminobenzoic acid. These drugs, especially salicylates and sulphonamides, whether

antibacterial, hypoglycaemic or diuretic, should not be given concurrently until the significance of these findings is established.

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

Methotrexate should be used with extreme caution in the presence of infection, peptic ulcer, ulcerative colitis, debility, and in extreme youth and old age. If profound leukopenia occurs during therapy, bacterial infection may occur or become a threat. Cessation of the drug and appropriate antibiotic therapy is usually indicated. In severe bone marrow depression, blood or platelet transfusions may be necessary.

The tablets contains lactose. Patient with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Oral antibiotics, such as tetracycline, chloramphenicol, and non-absorbable broad spectrum antibiotics, may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of methotrexate by bacteria.

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

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

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

NSAIDs should not be administered before or concurrently with high-dose methotrexate. Concomitant use of some NSAIDs and high-dose methotrexate has been reported to increase and prolong the serum methotrexate concentration in serum and to increase

gastrointestinal and haematological toxicity. When using smaller doses of methotrexate, these medicinal products have been found in animals to decrease the tubular secretion of methotrexate and possibly to increase its toxicity. In addition to methotrexate, patients with rheumatoid arthritis have generally been treated, however, with NSAIDs with no problems. It should be noted, however, that the doses of methotrexate used in the treatment of rheumatoid arthritis (7.5 - 15 mg/week) are slightly lower than those used for psoriasis and that higher doses can result in unexpected toxicity.

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

Trimethoprim/sulfamethoxazole has been reported in rare cases to increase bone marrow suppression in patients treated with methotrexate, presumably because of the increased antifolate effect.

Bone marrow suppression and reduced folate concentrations have been reported when triamterene and methotrexate were coadministered.

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

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

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

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

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

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

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

Breastfeeding

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

Fertility

Male fertility

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

Both men and women receiving methotrexate should be informed of the potential risk of adverse effects on reproduction. Women of childbearing potential should be fully informed of the potential hazard to the foetus should they become pregnant during methotrexate therapy.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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

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

The frequencies of the adverse reactions are classified as follows:
Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 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)

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Uncommon: Lymphoma [1]

Blood and lymphatic system disorders

Common: Leukopenia

Uncommon: Bone marrow depression, thrombocytopenia, anaemia.

Very rare: Hypogammaglobulinaemia.

Nervous system disorders

Common: Headache, dizziness, fatigue, paraesthesia in the extremities.

Rare: Hemiparesis.

Very rare: Irritation, dysarthria, aphasia, lethargy

Eye disorders

Very rare: Conjunctivitis, blurred vision.

Cardiac disorders

Very rare: Pericarditis, pericardial effusion.

Vascular disorders

Uncommon: Nosebleed

Rare: Hypotension, thromboembolism.

Very rare: Vasculitis.

Respiratory, thoracic and mediastinal disorders

Uncommon: Pneumonia, interstitial pneumonitis (con be fatal), interstitial fibrosis.

Rare: Dyspnoea, pharyngitis [2] .

Very rare: Pneumocystis carinii-pneumonia, chronic interstitial obstructive lung disease, pleuritis, dry cough.

Gastrointestinal disorders [3]

Common: Stomatitis, anorexia, nausea, vomiting, diarrhoea.

Rare: Gastrointestinal ulcerations and haemorrhage, gingivitis, enteritis.

Very rare: Haematemesis.

Hepatobiliary disorders

Common: Elevated transaminase concentrations.

Rare: Acute hepatitis, hepatotoxicity, periportal fibrosis, liver cirrhosis.

Skin and subcutaneous tissue disorders

Common: Erythematous rash, alopaecia.

Uncommon: Pruritus, Stevens-Johnson’s syndrome, toxic epidermal necrolysis.

Rare: Photohypersensitivity, depigmentation, acne, urticaria, erythema multiforme, painful damage to psoriatic lesion, skin ulceration.

Very rare: Ecchymoses, furunculosis, telangiectasia.

Musculoskeletal and connective tissue disorders

Rare: Arthralgia, myalgia, osteoporosis, increased rheumatic nodules.

Renal and urinary disorders

Uncommon: Renal insufficiency, nephropathy.

Very rare: Dysuria, azotaemia, cystitis, haematuria.

Reproductive system and breast disorders

Uncommon: Vaginal ulceration.

Rare: Decreased libido, impotence, menstrual disorders.

Very rare: Formation of defective oocytes or sperm cells, transient oligospermia, infertility, vaginal bleeding, gynaecomastia.

Infections and infestations

Common: Infections.

Uncommon: Opportunistic infections.

Rare: Herpes zoster, sepsis.

Immune system disorders

Uncommon: Anaphylactic-type reaction

Endocrine disorders

Rare: Diabetes mellitus.

Psychiatric disorders

Rare: Depression, confusion.

1. Can be reversible (see 4.4).
2. See section 4.4.
3. Gastrointestinal severe adverse reactions require often dose reduction. Ulcerative stomatitis and diarrhoea require discontinuation of methotrexate therapy because of the risk of ulcerative enteritis and fatal intestinal perforation.

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

The psoriatic lesions may get worse from simultaneous exposure to methotrexate and ultraviolet radiation.

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 national reporting systems listed in Appendix V.

4.9 Overdose

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

The toxicity of methotrexate affects mainly the haematopoietic organs. Calcium folinate neutralises effectively the immediate haematopoietic toxic effects of methotrexate. Parenteral calcium folinate therapy should be started within one hour after the administration of methotrexate. The dose of calcium folinate should be at least as high as the dose of methotrexate received by the patient.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other immunosuppressive agents, ATC code: L04AX03

Methotrexate (4-amino-10-methylfolic acid) is a folic acid antagonist which inhibits the reduction of folic acid and increase of tissue cells. Methotrexate enters the cell through an active transport mechanism of reduced folates. As a result of polyglutamation of methotrexate caused by the folylpolyglutamylate enzyme, the duration of the cytotoxic effect of the drug substance in the cell increases. Methotrexate is a phase-specific substance the main action of which is directed to the S-phase of cell mitosis. It acts generally most effectively on actively increasing tissues, such as malignant cells, bone marrow, fetal cells, skin epithelium, oral and intestinal mucosa as well as urinary bladder cells. As the proliferation of malignant cells is higher than that of most normal cells, methotrexate can

slow down the proliferation of malignant cells without causing, however, irreversible damage to normal tissue..

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

5.2 Pharmacokinetic properties

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

About half of the absorbed methotrexate binds reversibly to serum protein, but is readily distributed in tissues. The elimination follows a triphasic pattern. Excretion takes place mainly via the kidneys. Approximately 41% of the dose is excreted unchanged in the urine within the first six hours, 90% within 24 hours. A minor part of the dose is excreted in the bile of which there is pronounced enterohepatic circulation. The half-life is approximaltey 3–10 hours following low dose treatment and 8–15 hours following high dose treatment. If the renal function is impaired, the concentration of methotrexate in serum and in tissues may increase rapidly.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipient

Anhydrous calcium hydrogen phosphate,
Lactose monohydrate,
Sodium starch glycolate,
Microcrystalline cellulose,
Talc,

Magnesium stearate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Blister: keep the blister in the outer carton in order to protect from light.

HDPE container: store in original container in order to protect from light.

6.5 Nature and contents of container

2.5 mg tablets:

White high density polyethylene container with non CRC high density polyethylene cap with induction wad. Pack size: 25 or 100 tablets

Amber colour Polyvinylchloride (PVC)/Plain Aluminium blister foil. Pack size: 10, 24, 25, 28 30, 50 or 100 tablets

10 mg tablets:

White high density Polyethylene container with non CRC high density polyethylene cap with induction wad. Pack size: 25 or 100 tablets

Amber colour Polyvinylchloride (PVC)/Plain Aluminium blister foil. Pack size: 10, 25, 30, 50 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

For UK IE, MT:

Cipla (EU) Limited

Hillbrow House, Hillbrow Road,
Esher, Surrey, KT10 9NW,
United Kingdom.

For CZ, DK, EL, ES, HR, NO, PL, SE:

Cipla Europe NV
Uitbreidingstraat 80
2600 Antwerp
Belgium.

8 MARKETING AUTHORISATION NUMBER(S)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

PACKAGE LEAFLET: INFORMATION FOR THE USER

Package leaflet: Information for the user

Methotrexate 2.5 mg tablets
Methotrexate 10 mg tablets
methotrexate

▼Do not exceed the weekly dose of this medicine due to toxicity hazards.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Methotrexate Tablets are and what they are used for

Methotrexate Tablets contain the active ingredient methotrexate. Methotrexate is an antimetabolite and immunosuppressant (medicine which affects the reproduction of the body's cells and reduces the activity of the immune system) .

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

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

2. What you need to know before you take Methotrexate Tablets

Do not take Methotrexate Tablets:
- if you are allergic (hypersensitive) to methotrexate, or any of the other ingredients of this medicine (listed in section 6);
- if you are pregnant or breast-feeding (see section "Pregnancy, breast-feeding and fertility");
- if you have significant liver disease (your doctor decides the severity of your disease);
- if you have significant kidney disease(your doctor decides the severity of your disease);
- if you have or have had a bone marrow disease or serious blood disorders;
-
- if you have severe acute or chronic infections or immunodeficiency syndrome;
- if you suffer from alcoholism.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Methotrexate Tablets

if you suffer from or have suffered in the past from any of the following conditions;
- have or have had any liver or kidney disease;

- are using any medicines or vitamin products (see section “Other medicines and Methotrexate Tablets”);
- ;
- have ulcerations in your stomach or bowel (peptic ulcer or ulcerative colitis);
- are in poor general condition;
- ;
- have received any vaccinations recently or are you due to have any;
- have any symptoms or signs of infection;
- Diabetes mellitus treated with insulin.
- .

Methotrexate temporarily affects sperm and egg production. You and your partner should avoid conception (becoming pregnant or fathering children) if currently receiving methotrexate and for at least six months after your treatment with methotrexate has stopped. See section “Pregnancy, breast-feeding and fertility”.

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

Children and adolescents
Methotrexate tablets are not recommended in children and adolescents for rheumatoid arthritis and psoriasis.

Other medicines and Methotrexate Tablets
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines including medicines obtained without a prescription.

Some medicines can affect the way Methotrexate Tablets work, or Methotrexate Tablets can reduce the effectiveness of other medicines taken at the same time. These include:
- ;
- aspirin or similar medcines (known as salicylates);
- certain antibiotics (such as chloramphenicol, penicillin, sulphonamides, co-trimoxazole, trimethoprim and tetracyclines);
- diuretics, triamterene (water tablets);
-
- phenytoin (medicine often used to treat epilepsy);
- probenicid(medicine used to treat gout);
- folic acid (vitamin preparations);
-
- omeprazole or pantoprazole (medicine used to stop the production of stomach acid);
- agents that may be harmful to kidneys and liver [e.g. sulfasalazine and leflunomide (medicines for rheumatic disease), vitamin A and its derivatives, alcohol];
- anticancer agents (e.g. cisplatin, mercaptopurine);
- non-steroidal anti-inflammatory medicines (medicines taken for pain relief) e. g. ibuprofen and pyrazols;
- medicines taken to help control rheumatism e. g. azathioprine;

- theophylline (medicine used to treat respiratory diseases);
- cyclosporine (an agent that can suppress or prevent the immune response).

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

Methotrexate Tablets with food and alcohol
Alcohol should be avoided while taking methotrexate.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you might be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

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

If you do become pregnant during treatment, you should be offered advice regarding the risk of harmful effects on the child through treatment.

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

Breast-feeding

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

Fertility

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

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

Driving and using machines

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

Methotrexate Tablets contain lactose

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

3. How to take Methotrexate Tablets

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

- Take Methotrexate Tablets once a week.
- Patients with rheumatoid arthritis or psoriasis will usually take their tablets orally **once a week** on the same day each week.
- Do not take tablets more often than your doctor has told you to.
- **Daily administration can lead to serious toxic effects.**
- Take the tablets with a glass of water whilst sitting upright or standing.

Dosage for rheumatoid arthritis, psoriasis and psoriatic arthritis:
The recommended dose is 7.5 - 15 mg **orally**, **once weekly**.
This should be adjusted according to your response to treatment and side effects.

Use in children
Not recommended for use in children.

If you take more Methotrexate Tablets than you should
If you take (or someone else has taken) more of the medicine than you should, a physician or nearest hospital casualty department must be contacted immediately.

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

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

If you forget to take Methotrexate Tablets
If you forget to take a dose, take it as soon as you remember if this is within two days. However, if you have missed a dose by more than two days, please contact your doctor for advice. **Do not take a double dose to make up for a missed dose.**

If you stop taking Methotrexate Tablets
Do not stop taking Methotrexate Tablets unless your doctor tells you to. Should you need to stop taking Methotrexate Tablets, your doctor will have decided which is the best method for you.

If you have any further questions on how to take this product, ask your doctor or pharmacist.

4. Possible side effects

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

In general, the incidence and severity of adverse reactions of methotrexate are related to dose and frequency of administration. Most adverse reactions are reversible if detected early.

<u>If you notice any of the following, please contact your doctor immediately:</u>

- Unusual bleeding (including vomiting blood) or bruising
- severe diarrhoea
- ulcers in mouth
- an allergic reaction such as skin rash or swelling of your lips or tongue -
- fever
- yellowing of the skin (jaundice)
- pain or difficulty in passing urine
- thirst and/or frequent urination
- chest pain
- a dry cough and/or pain or difficulty in breathing or shortness of breath
- blurred or decreased vision.

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

•

Common (may affect up to 1 in 10 people)

- leukopenia (decrease number of white blood cells)*,
•
- nausea,
- vomiting,
- diarrhoea
- unusual fatigue,
- headache,
- dizziness,
- loss of appetite,
- erythematous rashes,
- stomatitis (soreness of the mouth and lips),

- increase of liver transaminases (enzymes)*,
- decreased resistance to infections,
- Tingling or numbness in the hands or feet
- alopecia.
  -

Uncommon (may affect up to 1 in 100 people)

- bone marrow depression manifested by thrombocytopenia and other abnormalities developing in the blood*,
- formation of excess fibrous connective tissue in an organ (fibrosis),
- inflammation of the lungs, which can cause shortness of breath and difficulty breathing,
- itchy skin ,
- anemia,
- nosebleed,
- skin condition that causes painful blisters and sores of the skin and mucous membranes, especially in the mouth (Stevens-Johnson syndrome)
- serious illness with blistering of the skin (Toxic epidermal necrolysis),
- anaphylactic reactions,
- kidney dysfunction,
- a cancer of the lymph nodes (or tissues),
- vaginal ulceration.

* Only detected by your doctor.

Rare (may affect up to 1 in 1,000 people)

-
- depression,
- confusion,
- hemiparesis (impairment of motor function affecting only one side of the body),
- diabetes mellitus,
- hypotension,
- thromboembolism,
- dyspnoea,
- gastrointestinal ulceration and bleeding,
- liver damage (hepatic toxicity, periportal fibrosis, hepatic cirrhosis, acute hepatitis),
- skin reactions (acne, skin depigmentation, urticaria, photosensitivity, erythema multiforme, burning in skin psoriatic lesions, skin ulcers),
- herpes zoster,
- decreased bone mineral density a type of bone disease (osteoporosis),
- increase in rheumatic nodules,
- pain in joint or muscles,
- menstrual disorders,
- impotence,
- decrease of libido.
-
-
-
-
-
- fatal whole-body inflammation (sepsis),
-

Very rare (may affect up to 1 in 10,000 people)

- immune deficiency (hypogammaglobulinaemia),
- irritation,
- difficulty in speaking (dysarthria),
- sleepiness, tiredness (lethargy),
-
-
- visual disturbance,
-
- redness and irritation of the thin membrane that covers the eye(conjunctivitis),
- fluid in the sac around the heart. May cause cardiac tamponade which is a life threatening condition where the heart is unable to pump correctly due to the external pressure. May require medical intervention to drain the fluid and remove the pressure,
- inflammation of blood vessels, often with skin rash (vasculitis),
- infection of lungs,dry cough,
-
- loss of sex drive,
-
- low sperm count,
-

- vaginal bleeding.
-

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. by reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Methotrexate Tablets

Keep this medicine out of the sight and reach of children.

This medicinal product does require any special temperature storage conditions.

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

Store in original container in order to protect from light.

Do not use Methotrexate Tablets after the expiry date which is stated on the label after EXP. The expiry date refers to last day of that month.

Do not throw any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Methotrexate Tablets contain

The active substance is methotrexate.

2.5 mg tablets: each tablet contains methotrexate 2.5 mg.

10 mg tablets: each tablet contains methotrexate 10 mg.

The other ingredients in 2.5 mg tablets and 10 mg tablets are: anhydrous calcium hydrogen phosphate, lactose monohydrate, sodium starch glycolate, microcrystalline cellulose, talc, magnesium stearate.

What Methotrexate Tablets look like and contents of the pack

Methotrexate 2.5 mg Tablets are yellow, circular, biconvex uncoated tablets with dimension of 4.50 mm ± 0.2 mm plain on both sides.
Methotrexate 2.5 mg Tablets are available in HDPE bottles containing 25 or 100 tablets and Blister pack containing 10, 24, 25, 28 30, 50 or 100 tablets.

Methotrexate 10 mg Tablets are yellow coloured, capsule shaped, biconvex uncoated tablet with length of 10 mm ± 0.2 mm and breadth 5 mm ± 0.2 mm, with central breakline on one side and plain on other side.
Methotrexate 10 mg Tablets are available in HDPE bottles containing 25 or 100 tablets and Blister pack containing 10, 25, 30, 50 or 100 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

For UK IE, MT:

Cipla (EU) Limited
Hillbrow House, Hillbrow Road,
Esher, Surrey, KT10 9NW,
United Kingdom.

For CZ, DK, EL, ES, HR, NO, PL, SE:

Cipla Europe NV
Uitbreidingstraat 80
2600 Antwerp
Belgium.
Manufacturer
Cipla (EU) Limited,
4th Floor
1 Kingdom street
London
W2 6BY
United Kingdom

S&D Pharma CZ
spol. s.r.o, Theodor 28
Pchery (Pharmos a.s. facility), 27308
Czech Republic
This leaflet was last revised in <{MM/YYYY}> <{month YYYY}>.

Annex 3 - Worldwide marketing authorisation by country (including EEA)

A3.1 Licensing status in the EEA

Country	Current licence status	Date of licence action	Date first marketed in country	Brand name(s)	Comments
Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

A3.2 Licensing status in the rest of the world

Country	Current licence status	Date of licence action	Date first marketed in country	Brand name(s)	Comments
Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

Annex 4 - Synopsis of on-going and completed clinical trial programme

Not applicable

Annex 5 - Synopsis of on-going and completed pharmacoepidemiological study programme

Not applicable

Annex 6 - Protocols for proposed and on-going studies in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in RMP part III

Not applicable

Annex 7 - Specific adverse event follow-up forms

Not applicable

Annex 8 - Protocols for proposed and on-going studies in RMP part IV

Not applicable

Annex 9 - Newly available study reports for RMP parts III & IV

Not applicable

Annex 10 - Details of proposed additional risk minimisation measures (if applicable)

Not applicable

Annex 11 - Mock-up of proposed additional risk minimisation measures (if applicable)

Not applicable

Annex 12 - Other supporting data (including referenced material)

1.Servicio de Dermatología, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, España. Electronic address: lpuig@santpau.cat, Methotrexate: New Therapeutic Approaches. Actas Dermosifiliogr. 2014 July - August;105(6):583-589.

2. Hoffmeister RT, Methotrexate therapy in rheumatoid arthritis: 15 years experience. Am J Med. 1983;75(6A):69.