SUMMARY OF PRODUCT CHRACTERISTICS

1. Name of the medicinal product

Methotrexate "Ebewe" 2.5mg Tablets

2. Qualitative and quantitative composition

Methotrexate 2.5mg

For the full list of excipients, see section 6.1

Patient safety information Card

The marketing of Methotrexate "Ebewe" 2.5mg Tablets is subject to a risk management plan (RMP), which includes a 'Patient safety information card'. The 'Patient safety information card' emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

HCP Guide

This product is marketed with a Healthcare Professional Guide providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

3. Pharmaceutical form

Tablet

Methotrexate 2.5mg Tablets are light yellow tablets; may contain yellow to red sprinkles

4. Clinical particulars

4.1. Therapeutic indications

The treatment of acute lymphoblastic leukaemia and Burkitt's lymphoma. The treatment of severe cases of uncontrolled psoriasis, unresponsive to conventional therapy.

The treatment of adults with severe, active, classical or definite rheumatoid arthritis who are unresponsive or intolerant to conventional therapy**.**

4.2. Posology and method of administration

Posology

Dosages are based on the patient's body weight or surface area. Doses should be reduced in cases of haematological deficiency and hepatic or renal impairment.

This medicine should only be taken once a week.

Important warning about the dosage of Methotrexate "Ebewe" 2.5 mg tablets:

For the treatment of psoriasis, rheumatoid arthritis and for some of the hematological indications (as prescribed by the physician according to the treatment protocol), Methotrexate "Ebewe" 2.5 mg tablets must only be taken once a week.
Methotrexate "Ebewe" 2.5 mg tablets should not be taken daily. Daily dosage intake of Methotrexate "Ebewe" 2.5 mg tablets can result in serious adverse reactions and severe complications, including death. Please read this section of the summary of product characteristics very carefully.
Choose the most convenient day of the week to take Methotrexate "Ebewe" 2.5mg tablets. In order to remember on which day Methotrexate "Ebewe" 2.5mg tablets are taken, you should keep a tracking sheet.

Methotrexate should only be prescribed by physicians with expertise in the use of methotrexate and a full understanding of the risks of methotrexate therapy.

The prescriber should ensure that patients or their carers will be able to comply with the once weekly regimen.

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

Acute Lymphoblastic Leukaemia:

Paediatric population

In acute lymphoblastic leukaemia remissions are usually best induced with a combination of corticosteroids and other cytotoxic agents.

Methotrexate 15mg/m^2, given orally once weekly, in combination with other drugs, appears to be the treatment of choice for maintenance of drug-induced remissions.

Burkitt's Lymphoma:

Paediatric population

Some cases of Burkitt's lymphoma, when treated in the early stages with courses of 15mg/m^2 daily orally for five days, have shown prolonged remissions. Combination chemotherapy is also commonly used in all stages of the disease.

Psoriasis:

Adults

It is recommended that a test dose of 5-10mg should be administered, one week prior to therapy to detect idiosyncratic adverse reactions.

In most cases of severe uncontrolled psoriasis, unresponsive to conventional therapy, 10-25mg orally once a week and adjusted by the patient's response is recommended.

The use of methotrexate in psoriasis may permit the return to conventional topical therapy which should be encouraged.

Rheumatoid arthritis:

Adults

It is recommended that a test dose of 5-10mg should be administered, one week prior to therapy to detect idiosyncratic adverse reactions.

In adults with severe, acute, classical or definite rheumatoid arthritis who are unresponsive or intolerant to conventional therapy, 7.5mg orally once weekly. The schedule may be adjusted gradually to achieve an optimal response but should not exceed a total weekly dose of 20mg. Once response has been achieved, the schedule should be reduced to the lowest possible effective dose.

Elderly

Methotrexate should be used with extreme caution in elderly patients; a reduction in dosage should be considered (see 4.4).

Paediatric population

Safety and effectiveness in children have not been established, other than in cancer chemotherapy.

Method of administration

For oral administration.

4.3. Contraindications

Methotrexate is contra-indicated in the presence of severe/significant renal or significant hepatic impairment. Liver disease including fibrosis, cirrhosis, recent or active hepatitis; serious, acute or chronic active infectious disease such as tuberculosis and HIV; stomatitis and ulcers of the gastrointestinal tract; alcohol abuse; concomitant use with a live vaccine; and overt or laboratory evidence of immunodeficiency syndrome(s). Serious cases of anemia, leucopenia, or thrombocytopenia. Methotrexate should not be used concomitantly with drugs with antifolate properties. Methotrexate is teratogenic and should not be given during pregnancy or to mothers who are breast-feeding (see section 4.6).

Patients with a known allergic hypersensitivity to methotrexate or any of the excipients should not receive methotrexate.

4.4. Special warnings and precautions for use

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

The prescriber should make sure patients understand that Methotrexate should only be taken once a week.

Patients should be instructed on the importance of adhering to the once-weekly intakes.

Warnings:

Methotrexate should be used with extreme caution in patients with hematological depression, renal impairment, peptic ulcer, ulcerative colitis, ulcerative stomatitis, diarrhea, debility and in young children and the elderly. (See 4.2).

Patients with pleural effusions or ascites should have these drained if appropriate before treatment or treatment should be withdrawn. A chest x-ray is recommended prior to initiation of methotrexate therapy or treatment should be withdrawn.

Conditions leading to dehydration such as emesis, diarrhea, stomatitis, can increase the toxicity of methotrexate due to elevated agent levels. In these cases, use of methotrexate should be interrupted until the symptoms cease.

It is important to identify patients with possibly elevated methotrexate levels within 48 hours after therapy, as otherwise methotrexate toxicity may be irreversible.

Symptoms of gastro-intestinal toxicity, usually first manifested by stomatitis, indicate that therapy should be interrupted otherwise hemorrhagic enteritis and death from intestinal perforation may occur.

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

Particular caution should be exercised in the presence of inactive, chronic infections (e.g., herpes zoster, tuberculosis, hepatitis B or C), due to possible activation.

Methotrexate has some immunosuppressive activity and therefore the immunological response to concurrent vaccination may be decreased. In addition, concomitant use of a live vaccine could cause a severe antigenic reaction.

Potentially fatal opportunistic infections, including Pneumocystis carinii pneumonia may occur with methotrexate therapy. When a patient presents with pulmonary symptoms the possibility of Pneumocystis carinii should be considered.

Acute or chronic interstitial pneumonitis, often associated with blood eosinophilia, may occur and deaths have been reported. Symptoms typically include dyspnea, 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 contract their doctor immediately should they develop persistent cough or dyspnea.

In addition, pulmonary alveolar hemorrhage has been reported with methotrexate used in rheumatologic and related indications. This event may also be associated with vasculitis and other comorbidities. Prompt investigations should be considered when pulmonary alveolar hemorrhage is suspected to confirm the diagnosis.

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

Special caution is required in patients with impaired pulmonary function.

Fertility

Methotrexate has been reported to cause impairment of fertility, oligospermia, menstrual dysfunction and amenorrhea in humans during and for a short period after the discontinuation of treatment, affecting spermatogenesis and oogenesis during the period of its administration - effects that appear to be reversible on discontinuing therapy.

Teratogenicity – Reproductive risk

Methotrexate causes embryotoxicity, abortion and fetal malformations in humans. Therefore, the possible effects on reproduction, pregnancy loss and congenital malformations should be discussed with female patients of childbearing age (see section 4.6). In non-oncologic indications, the absence of pregnancy must be confirmed before Methotrexate is used. If women of a sexually mature age are treated, effective contraception must be used during treatment and for at least six months after.

For contraception advice for men see section 4.6.

Precautions:

Methotrexate should only be used by clinicians who are familiar with the various characteristics of the drug and its mode of action. Before beginning methotrexate therapy or reinstituting methotrexate after a rest period, a chest x-ray, assessment of renal function, liver function and blood elements should be

made by history, physical examination and laboratory tests. This will include a routine examination of lymph nodes and patients should report any unusual swelling to the doctor.

Patients undergoing therapy should be subject to appropriate supervision every 2-3 months so that signs of possible toxic effects or adverse reactions may be detected and evaluated with minimal delay. Renal function and full blood counts should be closely monitored before, during and after treatment.

Patients receiving low-dose methotrexate should:

Have a full blood count and renal and liver function tests before starting treatment. These should be repeated weekly until therapy is stabilised It is essential that the following laboratory tests are included regularly (every 2-3 months) in the clinical evaluation and monitoring of patients receiving methotrexate: complete hematological analysis, urinalysis, renal function tests, liver function tests and, when high doses are administered, determination of plasma levels of methotrexate.

Patients should report all symptoms and signs suggestive of infection, especially sore throat.

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

Liver function tests

Treatment should not be initiated or should be discontinued if there are persistent or significant abnormalities in liver function tests, other non-invasive investigations of hepatic fibrosis, or liver biopsies.

Temporary increases in transaminases to two or three times the upper limit of normal have been reported in patients at a frequency of 13-20 %. Persistent elevation of liver enzymes and/or decrease in serum albumin may be indicative for severe hepatotoxicity. In the event of a persistent increase in liver enzymes, consideration should be given to reducing the dose or discontinuing therapy.

Histological changes, fibrosis and more rarely liver cirrhosis may not be preceded by abnormal liver function tests. There are instances in cirrhosis where transaminases are normal. Therefore, non-invasive diagnostic methods for monitoring of liver condition should be considered, in addition to liver function tests. Liver biopsy should be considered on an individual basis taking into account the patient's comorbidities, medical history and the risks related to biopsy. Risk factors for hepatotoxicity include excessive prior alcohol consumption, persistent elevation of liver enzymes, history of liver disease, family history of hereditary liver disorders, diabetes mellitus, obesity and previous contact with hepatotoxic drugs or chemicals and prolonged methotrexate treatment.

Additional hepatotoxic medicinal products should not be given during treatment with methotrexate unless clearly necessary. Alcohol consumption should be avoided (see sections 4.3 and 4.5). Closer monitoring of liver enzymes should be undertaken in patients concomitantly taking other hepatotoxic medicinal products.

Increased caution should be exercised in patients with insulin-dependent diabetes mellitus, as during methotrexate therapy, liver cirrhosis developed in isolated cases without any elevation of transaminases.

Pleuropulmonary manifestations of rheumatoid arthritis have been reported in the literature. In patients with rheumatoid arthritis, the physician should be specifically alerted to the potential for methotrexate induced adverse effects in the pulmonary system. Patients should be advised to contact their physicians immediately should they develop a cough or dyspnoea (see 4.8).

Haematopoietic suppression caused by methotrexate may occur abruptly and with apparently safe dosages. Any profound drop in white-cell or platelet counts indicates immediate withdrawal of the drug and appropriate supportive therapy (see 4.8). Patients should be advised to report all signs and symptoms suggestive of infection.

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

Renal lesions may develop if the urinary flow is impeded and urinary pH is low, especially if large doses have been administered.

Reduce dose of methotrexate in patients with renal impairment.

In the presence of risk factors, such as – even borderline – impaired renal function, concomitant administration of non-steroidal anti-inflammatories is not recommended. Dehydration may also potentiate the toxicity of methotrexate.

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 (5x 625mgtablets every three hours) or acetazolamide (500mg orally four times a day) is recommended as a preventive measure.

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 given concomitantly with radiotherapy may increase the risk of soft tissue necrosis and osteonecrosis.

In paediatric population, radiation induced dermatitis and sunburn can reappear under methotrexate therapy(recall-reaction).

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

Photosensitivity

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking methotrexate (see section 4.8). Exposure to intense sunlight or to UV rays should be avoided. Patients should use adequate sun- protection to protect themselves from intense sunlight.

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

Methotrexate is immunosuppressive and may therefore reduce immunological response to concurrent vaccination. Severe antigenic reactions may occur if a live vaccine is given concurrently.

Methotrexate is extensively protein bound and may displace or be displaced by other acidic drugs. The concurrent administration of agents such as p-aminobenzoic acid, chloramphenicol, penicillins, ciprofloxacin, diphenylhydantoins, phenytoin, 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. Concomitant use of other drugs with nephrotoxic or hepatotoxic potential (including alcohol) should generally be avoided, unless considered clinically justified, in which case the patient should be closely monitored.

Administration of additional haemotoxic medicinal products (e.g., metamizole) increase the probability of severe haemotoxic effects of methotrexate. Concurrent administration of metamizole and methotrexate can increase the haematotoxic effect of methotrexate, especially in elderly patients. Therefore, coadministration should be avoided.

Renal tubular transport is also diminished by probenecid and penicillins; use of methotrexate with these drugs should be carefully monitored.

NSAIDs should not be administered prior to, or concomitantly with, high dose methotrexate as fatal methotrexate toxicity has been reported. Caution is also advised when NSAIDs and salicylates are administered concomitantly with lower doses of methotrexate. These drugs have been reported to reduce the tubular secretion of methotrexate in an animal model and thereby may enhance its toxicity. It is recommended that methotrexate dosage be carefully controlled during treatment with aspirin, ibuprofen or indomethacin (NSAIDs).

Concomitant administration of folate antagonists, such as co-trimoxazole, trimethoprim and nitrous oxide should be avoided.

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

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

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

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

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

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

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

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

Anaesthetics on nitric oxide base potentiate the effect of methotrexate on the folic acid metabolism and lead to severe unpredictable myelosuppression and stomatitis. This can be reduced by administering calcium folinate.

Colestyramine can increase the non-renal elimination of methotrexate by interrupting the enterohepatic circulation.

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

Radiotherapy during use of methotrexate can increase the risk of soft tissue or bone necrosis

On account of its possible effect on the immune system, methotrexate can falsify vaccinal and test results (immunological procedures to record the immune reaction). During methotrexate therapy concurrent vaccination with live vaccines must not be carried out (see section 4.3 and 4.4).

Existing data suggest that etretinate is formed from acitretin after ingestion of alcoholic beverages. However, the formation of etretinate without concurrent alcohol intake cannot be excluded. Serum levels of methotrexate may be increased by etretinate, and severe hepatitis has been reported following concurrent use.

The use of nitrous oxide potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe, unpredictable myelosuppression and stomatitis and in case of intrathecal administration increased severe, unpredictable neurotoxicity. Whilst this effect can be reduced by administering calcium folinate, the concomitant use of nitrous oxide and methotrexate should be avoided**.**

4.6. Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women must not get pregnant during methotrexate therapy, and effective contraception must be used during treatment with methotrexate and at least 6 months thereafter (see section 4.4). Prior to initiating therapy, women of childbearing potential must be informed of the risk of malformations associated with methotrexate and any existing pregnancy must be excluded with certainty by taking appropriate measures, e.g., a pregnancy test. During treatment pregnancy tests should be repeated as clinically required (e.g., after any gap of contraception). Female patients of reproductive potential must be counselled regarding pregnancy prevention and planning.

Contraception in males

It is not known if methotrexate is present in semen. Methotrexate has been shown to be genotoxic in animal studies, such that the risk of genotoxic effects on sperm cells cannot completely be excluded. Limited clinical evidence does not indicate an increased risk of malformations or miscarriage following paternal exposure to low-dose methotrexate (less than 30 mg/week). For higher doses, there is insufficient data to estimate the risks of malformations or miscarriage following paternal exposure.

As precautionary measures, sexually active male patients or their female partners are recommended to use reliable contraception during treatment of the male patient and for at least 6 months after cessation of methotrexate. Men should not donate semen during therapy or for 6 months following discontinuation of methotrexate.

Pregnancy

Methotrexate is contraindicated during pregnancy in non-oncological indications (see section 4.3). If pregnancy occurs during treatment with methotrexate and up to six months thereafter, medical advice should be given regarding the risk of harmful effects on the child associated with treatment and ultrasonography examinations should be performed to confirm normal foetal development. In animal studies, methotrexate has shown reproductive toxicity, especially during the first trimester (see section 5.3). Methotrexate has been shown to be teratogenic to humans; it has been reported to cause foetal death, miscarriages and/or congenital abnormalities (e.g., craniofacial, cardiovascular, central nervous system and extremity-related).

Methotrexate is a powerful human teratogen, with an increased risk of spontaneous abortions, intrauterine growth restriction and congenital malformations in case of exposure during pregnancy.

• Spontaneous abortions have been reported in 42.5% of pregnant women exposed to low-dose methotrexate treatment (less than 30 mg/week), compared to a reported rate of 22.5% in disease-matched patients treated with drugs other than methotrexate.

• Major birth defects occurred in 6.6% of live births in women exposed to low-dose methotrexate treatment (less than 30mg/week) during pregnancy, compared to approximately 4% of live births in in disease-matched patients treated with drugs other than methotrexate.

Insufficient data is available for methotrexate exposure during pregnancy higher than 30 mg/week, but higher rates of spontaneous abortions and congenital malformations are expected, in particular at doses commonly used in oncologic indications

When methotrexate was discontinued prior to conception, normal pregnancies have been reported.

When used in oncological indications, methotrexate should not be administered during pregnancy in particular during the first trimester of pregnancy. In each individual case the benefit of treatment must be weighed up against the possible risk to the foetus. If the drug is used during pregnancy or if the patient becomes pregnant while taking methotrexate, the patient should be informed of the potential risk to the foetus.

Breast-feeding

Because of the potential for serious adverse reactions from methotrexate in breast fed infants, breast feeding is contra-indicated in women taking methotrexate. If use during the lactation period should become necessary, breast-feeding is to be stopped prior to treatment.

Fertility

Methotrexate affects spermatogenesis and oogenesis and may decrease fertility. In humans, methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhoea. These effects appear to be reversible after discontinuation of therapy in most cases. In oncologic indications, women who are planning to become pregnant are advised to consult a genetic counselling center, if possible, prior to therapy and men should seek advice about the possibility of sperm preservation before starting therapy as methotrexate can be genotoxic at higher doses (see section4.4).

4.7. Effects on ability to drive and use machines

CNS symptoms, such as fatigue and confusion, can occur during treatment. Methotrexate has minor or moderate influence on the ability to drive and use machines.

4.8. Undesirable effects

Occurrence and severity of undesirable effects depend on dose level and frequency of Methotrexate administration. However, as severe adverse reactions may occur even at lower doses, it is indispensable that the doctor monitors patients regularly at short intervals.

Most undesirable effects are reversible if recognised early. If such adverse reactions occur, dose should be reduced or therapy be interrupted and appropriate countermeasures should be taken (see section 4.9). Methotrexate therapy should only be resumed with caution, under close assessment of the necessity for treatment and with increased alertness for possible reoccurrence of toxicity.

Frequencies in this table are defined using the following convention:

very common (≥ 1/10) common (≥ 1/100 < 1/10), uncommon (≥ 1/1,000 < 1/100), rare (≥ 1/10,000 < 1/1,000), very rare(< 1/10,000) , not known (cannot be estimated from the available data).
Further details are given in the following table. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness

The following adverse reactions may occur:

	Very common	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations					Sepsis, opportunistic infections (may be fatal in some cases), infections caused by the cytomegaly virus. Furthermore, nocardiosis, histoplasma and cryptococcus mycosis and disseminated herpes simplex have been reported	
Cardiac disorders				Pericarditis, pericardial effusion, pericardial tamponade		
Blood and lymphatic system disorders		Leukocytopenia thrombocytopenia, anaemia	Pancytopenia, agranulocytosi, haematopoietic disorders	Megaloblastic anaemia	Severe courses of bone marrow depression, aplastic anaemia. Lymphadenopathy, lymphoproliferative disorders (partly reversible see “description” below), eosinophilia and neutropenia. First signs for these life-threatening complications maybe: fever, sore throat, ulcerations of oral mucosa, flu-like complaints, strong exhaustion, dermatorrhagia. Use of methotrexate should be interrupted immediately if the number of blood cells significantly declines	
Immune system disorders			Allergic reactions, anaphylactic shock		Immunosuppression Hypogamma-globulinaemia Allergic vasculitis	
Metabolism and nutrition disorders			Diabetes mellitus			
Psychiatric disorders			Depression	Mood fluctuations	Insomnia	
Nervous system disorders		Headache, fatigue, drowsiness	Vertigo, confusion, seizures		Pain, muscular asthenia or paresthesia of the extremities, changes in sense of taste (metallic taste), acute aseptic meningitis	Leukoen-cephalopathy, Aphasia, paresis, hemiparesis

					with meningism (paralysis, vomiting)	
Eye disorders				Servere visual disturbances	Conjunctivitis, retinopathy	
Ear and labyrinth disorders						
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			Individual cases of lymphoma, which abated in a number of cases once methotrexate treatment had been discontinued. In a recent study, it was not possible to establish that methotrexate therapy increases the incidence of lymphomas			
Vascular disorders			Vasculitis (as severe toxic symptom)	Hypotension, thromboemboli c events (including arterial and cerebral thrombosis, thrombophlebit is, deep vein thrombosis, retinal vein thrombosis, pulmonary embolism).		
Respirator, thoracic and mediastinal disorders		Pulmonary complications due to interstitial alveolitis/pneum onitis and related deaths (independent of dose and duration of methotrexate treatment). Typical symptoms may be: general illness; dry,irritating cough; shortness of breath progressing to rest dyspnoea, chest pain, fever. If such complications are suspected, Methotrexate treatment must be discontinued	Pulmonary fibrosis	Pharyngitis, apnoea, bronchial asthma-like reactions with cough, dyspnoe and pathological findings in the lung function test	Pneumocystis carinii pneumonia and other pulmonary infections, chronic Obstructive pulmonary disease. Pleural effusion	Epistaxis Pulmonary alveolar haemorrhage* *(has been reported for methotrexate used in rheumatologic and related indications)

		immediately and infections (including pneumonia) must be excluded.				
Gastrointestinal disorders	Loss of appetite, nausea, vomiting, abdominal pain, inflammation and ulcerations of the mucous membrane of mouth and throat (especially during the first 24-48 hours after administration of Methotrexate). Stomatitis, dyspepsia	Diarrhoea (especially during the first 24-48 hours after administration of Methotrexate).	Gastrointestinal ulcers and bleeding.	Enteritis, melaena Gingivitis, malabsorption	Haematemesis, toxic megacolon	
Hepato-biliary disorders	Increase in liver-related enzymes (ALAT [GPT], ASAT [GOT], alkaline phosphatase and bilirubin).		Development of liver fattening, fibrosis and cirrhosis (occurs frequently despite regularly monitored, normal values of liver enzymes); drop of serum albumin.	Acute hepatitis and hepatotoxicity	Reactivation of chronic hepatitis, acute liver degeneration, hepatic failure Furthermore, herpes simplex hepatitis and liver insufficiency have been observed (also see the notes regarding liver biopsy in section4.4).	

Skin and subcutaneous tissue disorders		Exanthema, erythema, itching	Urticaria, photosensitivity, enhanced pigmentation of the skin, hair loss, disturbed wound healing, increase of rheumatic nodules, herpes zoster, skin ulceration in psoriatic patients, painful lesions of psoriatic plaque (Psoriatic lesions can exacerbate due to UV radiation during concomitant treatment with methotrexate (also see section 4.4); severe toxic reactions: vasculitis, herpetiform eruption of the skin, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome)	Increased pigmentary changes of nails, onycholysis, acne, petechiae, ecchymoses, erythema multiforme, cutaneous erythematous eruptions.	Acute paronychia, furunculosis, telangiectasia Hidradenitis, photosensitivity	Skin exfoliation /dermatitis exfoliative
Musculoskeletal system, connective tissue and bone disorders			Arthralgia, myalgia, osteoporosis	Stress fracture		Osteonecrosis of jaw (secondary to lymphoproliferative disorders)
Renal and urinary disorders			Inflammation and ulceration of the urinary bladder (possibly with haematuria), dysuria.	Renal failure, oliguria, anuria, azotaemia	Proteinuria	Nephropathy
General disorders and administration site conditions			After intramuscular use of methotrexate, local adverse reactions (burning sensation) or damage (sterile formation of abscess, destruction of fatty tissue) can occur at the site of injection.		Fever, Subcutaneous administration of methotrexate shows good local tolerance. Only mild local skin reactions, the number of which decreased in the course of treatment, have been observed so far.	
Investigations						

Reproductive system and breast disorders			Inflammation and ulceration of the vagina	Oligospermia, menstruation disorders	Loss of libido, impotence, vaginal discharge, infertility Gynaecomastia	

The appearance and degree of severity of undesirable effects depends on the dosage level and the frequency of administration. However, as severe undesirable effects can occur even at lower doses, it is indispensable that patients are monitored regularly by the doctor at short intervals.
When methotrexate is given by the intramuscular route, local undesirable effects (burning sensation) or damage (formation of sterile abscess, destruction of fatty tissue) at the site of injection can occur commonly. Subcutaneous application of methotrexate is locally well tolerated. Only mild local skin reactions were observed, decreasing during therapy.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9. Overdose

Calcium folinate is the antidote for neutralising the immediate toxic effects of methotrexate on the haematopoietic system. It may be administered orally, intramuscularly, or by an intravenous bolus injection or infusion. In cases of accidental overdosage, a dose of calcium folinate equal to or higher than the offending dose of methotrexate should be administered within one hour and dosing continued until the serum levels of methotrexate are below 10-7M. Other supporting therapy such as a blood transfusion and renal dialysis may be required.

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

Cases of overdose have been reported, sometimes fatal, due to erroneous daily intake instead of weekly intake of oral methotrexate.

In these cases, symptoms that have been commonly reported are haematological and gastrointestinal reactions. E.g leukocytopenia, thrombocytopenia, anaemia, pancytopenia, neutropenia, bone marrow depression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration and gastrointestinal bleeding

Some patients showed no signs of overdose.

There are reports of death due to sepsis, septic shock, renal failure and aplastic anaemia.

5. Pharmacological properties

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomoduling agents, antineoplastic agents, antimetabolites, folic acid analogues, ATC code: L01BA01

Methotrexate, a derivative of folic acid, belongs to the class of cytotoxic agents known as antimetabolites. It acts principally during the 'S' phase of cell division, by the competitive inhibition of the enzyme dihydrofolate reductase, thus preventing the reduction of dihydrofolate to tetrahydrofolate, a necessary step in the process of DNA synthesis and cellular replication. Actively proliferating tissues such as malignant cells, bone marrow, foetal cells, buccal and intestinal mucosa, and cells of the urinary bladder are generally more sensitive to the effects of methotrexate. When cellular proliferation in malignant tissues is greater than in most normal tissues, methotrexate may impair malignant growth without irreversible damage to normal tissues.

The mechanism of action in rheumatoid arthritis is unknown; it may affect immune function. Clarification of the effect of methotrexate on immune activity and its relation to rheumatoid immunopathogenesis await further investigation.

In psoriasis, the rate of production of epithelial cells in the skin is greatly increased over normal skin. This differential in proliferation rates is the basis for the use of methotrexate to control the psoriatic process.

5.2. Pharmacokinetic properties

In doses of 0.1mg (of methotrexate) per kg, methotrexate is completely absorbed from the G.I. tract; larger oral doses may be incompletely absorbed. Serum concentrations following oral administration of methotrexate may be slightly lower than those following I.V. injection.

Methotrexate is actively transported across cell membranes. The drug is widely distributed into body tissues with highest concentrations in the kidneys, gall bladder, spleen, liver and skin. Methotrexate is retained for several weeks in the kidneys and for months in the liver. Sustained serum concentrations and tissue accumulation may result from repeated daily doses. Methotrexate crosses the placental barrier and is distributed into breast milk. Approximately 50% of the drug in the blood is bound to serum proteins.

Following oral doses of 0.06mg/kg or more, the drug had a serum half-life of 2-4 hours, but the serum half-life was reported to be increased to 8-10 hours when oral doses of 0.037mg/kg were given.

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

5.3. Preclinical safety data

<u>Chronic toxicity</u>

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

<u>Mutagenic and carcinogenic potential</u>

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

Reproductive toxicology

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

6. Pharmaceutical particulars

6.1. List of excipients

lactose monohydrate, maize starch, microcrystalline cellulose, magnesium stearate, colloidal silicone dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packging materials.

6.4 Special precautions for storage

Do not store above 25ºC

Keep out the reach and sight of children.

6.5 Nature and contents of container

Each bottle contains 50 tablets in white polypropylene tablet containers sealed with a white low density polyethylene stopper equipped with lamellar retainers and three sealing lamellas.

Blister pack contains 10 or 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Cytotoxic drugs should only be handled by trained personnel in a designated area. The work surface should be covered with disposable plastic-backed absorbent paper. Protective gloves and goggles should be worn to avoid the drug accidentally coming into contact with the skin or eyes. Methotrexate is not a vesicant and should not cause harm if it comes into contact with the skin. It should of course be washed off with water immediately. Any transient stinging may be treated with bland cream. If there is any danger of systemic absorption of significant quantities of methotrexate, by any route, calcium folinate cover should be given.

Cytotoxic preparations should not be handled by pregnant staff.

Adequate care should be taken in the disposal of any unwanted product and containers. Any waste material may be disposed of by incineration. We do not make any specific recommendations with regard to the temperature of the incinerator.

7. Marketing authorization holder

Sandoz Pharmaceuticals Israel Ltd., P.O.Box 9015, Tel Aviv, Israel

8. Marketing authorization number

129-29-30819-00

9. Date of revision of the text

Revised in June 2026

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