SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Methotrexat “Ebewe” 100 mg/ml - concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 100 mg of methotrexate in an aqueous solution.

Excipients with known effect:
1 ml contains 17.62 mg of sodium hydroxide in aqueous solution.

The solution has a pH value of 7.0–8.5.

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Clear, yellow concentrate for solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antineoplastic chemotherapy: Treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole. Palliation of acute lymphocytic leukemia. In the treatment and prophylaxis of meningeal leukemia. Greatest effect has been observed in palliation of acute lymphoblastic (stem cell) leukemias in children. In combination with other anticancer agents, methotrexate may be used for the induction of remission, but is most commonly used in maintenance of induced remissions. Methotrexate may be used alone or in combination with other antineoplastics in the management of breast cancer, epidermoid cancers of the head and neck, lung cancer (particularly squamous cell and small cell types), bladder cancer and osteogenic cancer. Methotrexate is effective in the treatment of the advanced stages (III and IV, Peters’ Staging System) of lymphosarcoma, particularly in children, and in advanced cases of mycosis fungoides.

4.2 Posology and method of administration

Methotrexate should only be prescribed by doctors with experience in the use of methotrexate and who are fully familiar with the risks associated with a methotrexate treatment.

WARNINGS
The **dose must be carefully adjusted** to the body surface area if methotrexate is used to treat **tumour diseases**.
Cases of intoxication with fatal outcome have been reported after the administration of **incorrectly calculated** doses. The medical personnel and the patients must be comprehensively informed about the toxic effects.

Dose

Malignant tumors and hemoblastoses:
In polychemotherapy of malignant tumors and hemoblastoses the dosage of methotrexate has to be adjusted according to the indication, general condition and the blood counts of the patient. The administered dose in conventional low-dose MTX therapy (single dose lower than 100 mg/m^2), medium-dose MTX therapy (single dose 100 mg/m^2–1000 mg/m^2) and high-dose MTX therapy (single dose higher than 1000 mg/m^2) depends on the respective therapy protocol.

The following dosage instructions are only guidelines:
Conventional dose of methotrexate therapy – no calcium folinate rescue required:
15–20 mg/m^2 IV - twice weekly
30–50 mg/m^2 IV - once weekly
15 mg/m^2/day IV/IM - given at 2–3 weeks intervals

Intermediate dose of methotrexate therapy:
50–150 mg/m^2 IV injection; no calcium folinate rescue required, given at 2–3 weeks intervals
240 mg/m^2 IV infusion over 24 h; calcium folinate rescue required, given at 4–7 days intervals
500–1000 mg/m^2 IV infusion over 36–42 h; calcium folinate rescue required, given at 2–3 weeks intervals

High-dose methotrexate therapy – calcium folinate rescue required:
1–12 gm/m^2 IV over 1–6 hours, given at 1–3 weeks intervals

For intrathecal or intraventricular methotrexate therapy a maximum dose of 15 mg/m^2 is administered.
Intrathecal route of administration: 0.2–0.5 mg/kg or 8–12 mg/m^2 methotrexate is administered every 2–3 days, after disappearance of the symptoms at weekly intervals, and subsequently at monthly intervals until CSF findings return to normal. Prophylactic intrathecal instillation should be carried out every 6–8 weeks.

Method of administration

For intravenous, intramuscular, intra-arterial, intrathecal and intraventricular use after dilution.

Methotrexat "EBEWE" 500 mg, 1000 mg and 5000 mg – concentrate for infusion has to be diluted with standard solutions for infusions before administration according to therapy protocol and duration of infusion. Use 5% glucose solution or physiological saline solution.
Generally 1–2% methotrexate solution is administered (in osteosarcoma higher concentrations are described in the literature).
These methotrexate solutions for infusion are stable at room temperature over 24 hours when exposed to light or protected from light. If longer infusion period is required, the infusion bags/bottle should be changed.
Dosages higher than 100 mg/m^2 are generally administered as IV infusion.
Avoid contact with skin or mucosa.
For single use only!

4.3 Contraindications

- hypersensitivity to the active substance methotrexate or to any of the excipients listed in section 6.1

- severe, acute or chronic infections, such as tuberculosis and HIV
- stomatitis, gastrointestinal ulcers
- liver disease due to chronic alcohol abuse or other chronic liver diseases
- hepatic insufficiency
- severe renal impairment (creatinine clearance <30 ml/min) for methotrexate doses <100 mg/m^2, severe and moderate renal impairment (creatinine clearance <60 ml/min) for methotrexate doses >100 mg/m^2 (see section 4.4)
- disorders of the haemopoietic system (for example, after previous radio- or chemotherapy), such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia
- Immunodeficiency
- increased alcohol consumption
- pre-existing blood disorders
- breast-feeding (see section 4.6)
- pregnancy, unless a vital indication is present (see also section 4.6)
- concomitant vaccination with live vaccines

4.4 Special warnings and precautions for use

Methotrexate must be used only by doctors experienced in tumour therapy with sufficient experience in methotrexate treatment.
Incorrect use of methotrexate can cause severe undesirable effects, which may be fatal. Medical personnel and patients must be given clear instructions.

Toxicity
During the treatment with methotrexate, the patients must be closely monitored due to the possible severe toxic reactions (which may be fatal) so that any signs of toxicity can be quickly recognised.
The patients must be informed of the possible risks and benefits of methotrexate therapy (including the early signs and symptoms of toxicity). Furthermore, they must be instructed to see a doctor immediately if signs of toxicity become apparent and regarding the required monitoring of signs of toxicity, including regular lab tests.

Discontinuation of methotrexate does not always lead to a full regression of the undesirable effects that have occurred.

A prerequisite for treatment with methotrexate is that methotrexate serum levels can be determined.

The discharge of methotrexate from **pathological accumulations in body cavities** such as ascites or intrapleural effusions (called "third space") will be slow, which leads to a prolonged plasma elimination half-life period and unexpected toxicity. If at all possible, the fluid accumulations must be removed by puncture prior to methotrexate therapy.

Blood and lymphatic system
Methotrexate can suppress **haematopoiesis**, causing anaemia, aplastic anaemia, pancytopenia, leukopenia, neutropenia and/or thrombocytopenia.
First signs of these life-threatening complications may be: fever, sore throat, ulcerations of the oral mucosa, flu-like complaints, severe feeling of exhaustion, nosebleeds and skin haemorrhage.
Methotrexate therapy should only be continued in the treatment of neoplastic diseases if the potential benefits outweigh the risk of severe myelosuppression.

There are reports about **megaloblastic anaemias**, mainly during long-term therapy in older patients.

Methotrexate must not be used if a peptic ulcer or ulcerative colitis is present (see section 4.3).

With respect to **the condition after the treatment with medicinal products with cumulative myelotoxicity** and **radiotherapy involving the bone marrow**, attention must be paid to a limited bone-marrow reserve. This can lead to increased bone marrow susceptibility towards methotrexate therapy with increased suppression of the haematopoietic system. In longer-lasting methotrexate therapies, it may be necessary to carry out bone marrow biopsies.

In **acute lymphoblastic leukaemia**, methotrexate may cause pain in the upper left quadrant (perisplenitis due to the destruction of the leukaemia cells).

Hepatic function
Due to its potentially **hepatotoxic effects** it is recommended that no additional hepatotoxic or potentially hepatotoxic medicinal products are used during methotrexate therapy. Furthermore, alcohol should be avoided, or alcohol consumption decreased significantly.

Methotrexate can cause acute **hepatitis** and chronic, possibly fatal, **hepatotoxicity** (fibrosis, cirrhosis), but generally only after extended use. Acute increases of liver enzymes are observed frequently. These are usually temporary and asymptomatic and not preliminary signs of subsequent hepatic disease.

Methotrexate caused a **reactivation of hepatitis B or an exacerbation of hepatitis C infections,** which were fatal in some cases. Some cases of hepatitis B reactivation appeared after discontinuation of methotrexate. Clinical and laboratory investigations should be performed to be able to evaluate an existing liver disease in patients who have a history of hepatitis B or C infection. This may result in methotrexate treatment being incompatible with some patients.

If other **inactive, chronic infections** are present, such as herpes zoster, or tuberculosis, special caution is advised due to a possible activation.

Increased caution is generally required in patients with **insulin-dependent diabetes mellitus** as liver cirrhosis without an intermittent increase in transaminases may develop in individual cases during methotrexate therapy.

Renal function
Because of the delayed methotrexate elimination, the methotrexate therapy should be performed with increased caution and at a low dosage in patients with **impaired renal function**.
During methotrexate therapy, renal function may deteriorate, with an increase in certain lab values (creatinine, urea, and uric acid in serum), which may lead to **acute kidney failure** with oliguria/anuria. This is likely to be caused by precipitation of methotrexate and its metabolites in the renal tubules.
Conditions leading to **dehydration**, such as vomiting, diarrhoea, stomatitis, may increase the toxicity of methotrexate due to increased levels of the active substance. In these cases, supportive treatment should be introduced, and the suspension of methotrexate should be considered until the symptoms have disappeared.

Gastrointestinal disorders
If **ulcerative stomatitis** or **diarrhoea, haematemesis, black stool** or **blood in the stool** (melaena) occur, the therapy must be suspended as haemorrhagic enteritis and fatalities due to perforation of the intestine may occur otherwise.

Nervous system
In case of **patients with previous cranial radiotherapy**, there have been reports of **leukoencephalopathy** after intravenous administration of methotrexate.
Chronic leukoencephalopathy was also observed in patients who had received a repeated high-dose methotrexate therapy with calcium folinate rescue without previous cranial radiotherapy.
There is evidence that the combined use of cranial irradiation together with intrathecal administration of methotrexate increases the incidence of leukoencephalopathy (see also section 4.8).

There are reports of leukoencephalopathy in patients who received oral methotrexate.

Progressive multifocal leukoencephalopathy (PML)
Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients receiving methotrexate, usually in combination with other immunosuppressants. PML can be fatal and should be considered in the differential diagnosis in immunosuppressed patients with newly occurring or worsening neurological symptoms.

After **intrathecal administration** of methotrexate, patients should be monitored for signs of neurotoxicity (damage to the nervous system, such as meningitis, transient or permanent paralysis, or encephalopathy).

Cases of severe neurological undesirable effects, ranging from headache to paralysis, coma and stroke-like episodes, have been reported predominantly in children and adolescents who received intrathecal methotrexate in **combination with IV cytarabine**.

A temporary **acute neurological syndrome** was also observed during high dose methotrexate therapy, which can manifest e.g. through behavioural anomalies, focal sensory motor symptoms (including temporary blindness) and abnormal reflexes. The exact cause is unknown.

Lung function
Particular caution is required in case of patients with **impaired pulmonary function.**

Pulmonary complications, pleural effusion, alveolitis or pneumonitis, with symptoms such as dry tickly cough, fever, general malaise, cough, thoracic pain, dyspnoea, hypoxaemia and infiltrates in the chest X-rays or a non-specific pneumonia occurring during the methotrexate therapy, may indicate potentially dangerous and possibly fatal injury. Lung biopsies revealed different findings (e.g. interstitial oedema, mononuclear infiltrates or non-necrotising granuloma). If these complications are suspected, treatment with methotrexate must be suspended at once and a careful examination to rule out infections, tumours etc. is required. Methotrexate-induced lung diseases may occur acutely at any time during the therapy; they were not always fully reversible and have been reported with doses as low as 7.5 mg/week.

Pulmonary alveolar bleeding may also be linked to vasculitis and other comorbidities. An immediate examination should be considered to confirm the diagnosis if pulmonary alveolar bleeding is suspected.

Skin and subcutaneous tissue disorders
There are reports about the onset of severe, sometimes fatal, **skin reactions**, such as the Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell syndrome) after single or continuous administration of methotrexate.

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 UV rays should be avoided unless medically indicated. Patients should use adequate sun-protection to protect themselves from intense sunlight.

Psoriatic lesions may deteriorate through **ultraviolet irradiation** during concomitant methotrexate therapy. Radiation-induced dermatitis and sunburns can re-appear during methotrexate administration (recall reactions).

Immune system
Opportunistic infections, including pneumocystis jirovecii pneumonia, may occur during methotrexate therapy and may be fatal. If a patient should present with pulmonary symptoms, the possibility of pneumocystis jirovecii pneumonia should be considered.

Because of its potential effects on the immune system, methotrexate may distort **vaccination and test results** (immunological test methods used to collect data on immune reaction). Vaccinations carried out during methotrexate therapy may be ineffective. Due to the higher risk of infection no **vaccinations with live vaccines** must be performed during methotrexate treatment.

Methotrexate should be used with particular caution in patients with florid infections. Methotrexate is contraindicated for patients with immunodeficiency syndromes that are obvious or confirmed by laboratory tests. Furthermore, care should be taken when administering methotrexate if the patients are exposed to the viruses that cause chickenpox and herpes zoster.

Neoplasms
In patients with fast-growing tumours, methotrexate may, like other cytostatic medicinal products, induce **tumour lysis syndrome**. Suitable supportive and pharmacological measures may prevent or mitigate this complication.

There are occasional reports of the **occurrence of malignant lymphoma** during the administration of low doses of methotrexate, which regressed in some cases after discontinuation of methotrexate therapy. In the event of lymphoma, the first step should therefore be to suspend the methotrexate therapy and to only initiate a suitable therapy if the lymphoma does not regress. In a more recent study, no increased incidence of the occurrence of lymphoma during methotrexate treatment could be determined.

The use of high-dose regimens in the therapy of neoplastic diseases outside of the approved indications is investigative; a therapeutic benefit has not been proven for this.

Musculoskeletal and connective tissue disorders
In **radiotherapy** during the administration of methotrexate, the risk of soft tissue or bone necrosis may be increased.

Folic acid supplementation
Folate deficiency conditions may increase methotrexate toxicity (see section 4.5).
The administration of folic or folinic acid may reduce the toxicity of methotrexate (gastrointestinal symptoms, stomatitis, alopecia, and increase in liver enzymes).
Before taking folic acid preparations, vitamin B12 levels should be checked, as folate administration may mask vitamin B12 deficiency, especially in adults over 50 years of age.

Recommended medical check-ups and safety measures

Patients receiving methotrexate treatment must be closely monitored in order to immediately determine the toxic effects.

The following tests should be carried out prior to initiating therapy:
- complete blood count with differential blood count,
- liver enzymes (ALAT [GPT], ASAT [GOT], AP), bilirubin,
- serum albumin,
- kidney retention parameters (if necessary with creatinine clearance)
- hepatitis serology (A, B, C)
- rule out the possibility of tuberculosis, if required
- chest X-ray, if required.

Pulmonary function tests may be beneficial if lung disease (e.g. interstitial pneumonia) is suspected, especially if corresponding reference values from the initial examination are available.

Depending on the dosage or the applied therapy protocol, frequent **checks of methotrexate serum levels** are necessary, in particular during and after high-dose therapy with methotrexate

(see also section 4.9). The adjustment of methotrexate dose and implementing suitable rescue measures can significantly reduce the toxicity and potential mortality of methotrexate treatment.
Patients suffering from pleural effusions, ascites, obstruction in the gastrointestinal tract, previous cisplatin therapy, dehydration, decreased urine pH or impaired renal function, are particularly at risk of developing increased or only slowly decreasing methotrexate levels and must be monitored particularly closely.
Some patients may also have delayed methotrexate elimination without the recognisable causes listed above. It is important to identify these patients within 48 hours of therapy as the methotrexate toxicity may be irreversible otherwise.

After methotrexate therapy with a dose of 100 mg/m^2 BSA or more, **calcium folinate rescue therapy** must be carried out. Depending on the methotrexate dose and the infusion duration, different calcium folinate doses are required to protect the normal tissue from serious toxic undesirable effects.
Adequate calcium folinate rescue therapy must be initiated within 42 to 48 hours of methotrexate therapy. Monitoring of methotrexate levels should therefore take place at least after 24, 48 and 72 hours and should, if necessary, be continued in order to determine how long the calcium folinate rescue therapy must be continued.

During the therapy with methotrexate, **complete blood count monitoring** with differential blood count, including platelet and leukocyte counts, must take place (daily to weekly).
Prior to initiating combination therapy including high-dose methotrexate, the leukocyte and platelet counts should be above the minimum values stated in the respective protocol (leukocytes 1,000 to 1,500/µl, platelets 50,000 to 100,000/µl).

The nadir for circulating leukocytes, neutrophil granulocytes, and platelets usually appears 5–13 days after intravenous application of methotrexate (with a rebound after 14–28 days). Leukocytes and neutrophil granulocytes sometimes show two nadirs, with the first at 4–7 days, and the second after 12–21 days, followed by a rebound.

Hepatic and renal function tests as well as **urine tests** should be carried out in regular intervals.

In 13–20% of patients undergoing methotrexate therapy, a temporary 2 to 3 fold **increase in transaminases** can be observed. This is usually no reason to change the dose regimen. Prolonged anomalies in liver enzymes and/or decreased serum albumin levels may, however, be signs of severe hepatotoxicity. In the event of a **prolonged increase** in liver enzymes, a dose reduction or suspension of the therapy must be considered. In patients with **prolonged hepatic impairment**, methotrexate must be discontinued in any case.
Enzyme determination does not allow for a reliable prognosis of the development of liver injury that would be identifiable by morphological means, i.e. even with normal transaminase levels, hepatic fibrosis and less frequently hepatic cirrhosis, that can only be identified by histological examination.

Renal function may deteriorate due to use of methotrexate.
Creatinine, urea and electrolyte monitoring, especially in high-dose therapy with methotrexate, are recommended on Days 2 and 3 to detect any impending methotrexate elimination disorder at an early stage.
Therapy with methotrexate may lead to acute renal failure with oliguria/anuria and an increase in creatinine levels. This is likely to be caused by precipitation of methotrexate and its metabolites in the renal tubules. It is recommended that renal function is monitored, including adequate hydration and alkalisation of the urine, as well as measuring the methotrexate levels in serum and monitoring urine elimination.

If there are signs of **renal impairment** (e.g. pronounced undesirable effects of previous methotrexate therapy or urinary obstruction), the creatinine clearance must be determined.

High-dose methotrexate therapy (methotrexate doses > 100 mg/m^2) should only be administered if creatinine values are within the normal range (creatinine clearance > 80 ml/min) (see section 4.3). As methotrexate is predominantly eliminated through the kidneys, increased concentrations are expected in impaired renal function, which may lead to severe undesirable effects.The dose should be reduced in case of a serum creatinine increase.During the conventional dose of methotrexate a dose reduction of 50% is recommended if the serum creatinine values are 1.2-2 mg/dl.If creatinine clearance is below 30 ml/min, methotrexate must not be administered. If serum creatinine values are over 2 mg/dl and the creatinine clearance is below 60 ml/min, the therapy is contraindicated for methotrexate doses of over 100 mg/m^2 (see section 4.3). A treatment with methotrexate exceeding 100 mg/m^2 should not be introduced if the urine pH value is below 7.0. Alkalisation of urine must be tested at least 24 hours before the start of methotrexate use by repeated pH monitoring (values of 6.8 or more). Within the scope of a high dose methotrexate treatment, sufficient intravenous fluid supply is absolutely required.
If renal dysfunction is possible, or in borderline renal function (e.g. old age), monitoring should be performed in short intervals. This applies particularly, if additional medicinal products are administered, which adversely affect the elimination of methotrexate, cause renal damage (for example non-steroidal anti-inflammatory drugs), or may lead to dyshaematopoiesis. If risk factors, such as renal impairment including mild renal impairment, are present, concomitant administration with NSAIDs is not recommended. Concomitant administration of proton pump inhibitors and high-dose methotrexate should therefore be avoided, particularly in patients with impaired renal function.

Conditions leading to **dehydration**, such as vomiting, diarrhoea, stomatitis, may increase the toxicity of methotrexate due to increased levels of the active substance. In these cases, administration of methotrexate should be suspended until the symptoms have stopped.

An **examination of the oral cavity and the throat** for mucosal alterations must be performed daily.

Particularly close monitoring of the patient is mandatory in cases of previous intensive radiotherapy, reduced general condition, juvenile or elderly patients.

More frequent monitoring may be necessary at the beginning of treatment, at dose adjustment or during a period of higher risk of increased methotrexate levels (e.g. dehydration, impaired renal function, additional or increased administration of concomitant medicinal products such as non-steroidal anti-inflammatory drugs).

<u>Use in paediatric patients</u>
Particular caution is required if methotrexate is used in the treatment of children and adolescents. Treatment should comply with the therapy protocols that were specifically developed for children. In **paediatric patients with acute lymphoblastic leukaemia (ALL)**, severe **neurotoxicity** can occur after treatment with moderately high doses (1 g/m^2 BSA) of methotrexate. This is often seen as a generalised or focal epileptic seizure. In symptomatic patients, diagnostic imaging usually shows leukoencephalopathy and/or microangiopathic calcification.

<u>Use in elderly patients</u>
Particular caution is also required in elderly patients. The patients should be examined in short intervals for early signs of toxicity. The clinical pharmacology of methotrexate in the elderly has not yet been fully researched. The methotrexate dose should be adjusted to the hepatic and renal performance, which is reduced due to old age. Partially modified therapy protocols, for example for the treatment of ALL, have been developed for elderly patients (aged 55 and over).

<u>Fertility</u>
Methotrexate has been reported to cause oligospermia, dysmenorrhoea, fertility issues, and amenorrhoea in humans, during and for a short period after cessation of therapy, and to cause impaired fertility, 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 foetal defects in humans. Therefore, the possible effects on reproduction, miscarriages and congenital malformations should be discussed with female patients of child-bearing age (see section 4.6). If women of child-bearing age are treated, effective contraception must be used during treatment and for at least six months after discontinuing treatment.

Use in men
Methotrexate may have **genotoxic** effects. It is therefore recommended that men treated with methotrexate do not father a child during and up to 6 months after treatment. Since treatment with methotrexate can lead to serious and possibly irreversible spermatogenesis disorders, men should seek advice about the possibility of **sperm preservation** before starting therapy (see section 4.6 for advice on birth control in men).

This medicinal product contains 10.13 mg sodium per ml.

4.5 Interaction with other medicinal products and other forms of interaction

The use of **nitrous oxide ("laughing gas")** potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe, unpredictable myelosuppression, stomatitis and increased severe unpredictable neurotoxicity with **intrathecal administration.** Whilst this effect can be alleviated by administering calcium folinate, the concomitant use of methotrexate and nitrous oxide should be avoided.

Concomitant administration of **L-asparaginase** has an antagonistic effect on methotrexate.**Disease-modifying antirheumatic drugs (DMARD) and non-steroidal anti-inflammatory drugs (NSAIDs)** should not be administered before or during high-dose methotrexate therapy. Concomitant use of certain NSAIDs and high-dose methotrexate therapy led to increased and persistent methotrexate serum levels, with some fatal outcomes due to severe haematological (bone marrow suppression and aplastic anaemia) and gastrointestinal toxicity.
In animal studies, NSAIDs including salicylic acid have been found to decrease the tubular secretion of methotrexate and thus to an increase of its toxicity due to increased methotrexate levels. Therefore, NSAIDs and low-dose methotrexate should only be used concomitantly with caution. In the presence of risk factors, such as an impaired renal function (even in cases of threshold values), the concomitant administration of non-steroidal anti-inflammatory drugs is not advised.

Increased methotrexate toxicity has not been investigated when methotrexate is used concomitantly with other **basic therapeutic drugs** (e.g. gold compounds, penicillamine, hydroxychloroquine, sulphasalazine, azathioprine, cyclosporine), and a potentiation of the toxic effects of methotrexate cannot be ruled out.

The concomitant use of **proton pump inhibitors** (omeprazole, pantoprazole, or lansoprazole) may lead to a delay in or inhibition of the renal elimination of methotrexate and thus to increased methotrexate plasma levels, with clinical signs and symptoms of methotrexate toxicity.
Concomitant administration of proton pump inhibitors with high-dose methotrexate should therefore be avoided, and especially in patients with impaired renal function.

Hepatotoxicity may be increased with regular consumption of alcohol or if hepatotoxic medicinal products are administered, e.g. **azathioprine, leflunomide, retinoids and sulphasalazine.**

Patients who take additional hepatotoxic medicinal products should be closely monitored. Alcohol consumption should be avoided during treatment with methotrexate.

Due to the **displacement of methotrexate from plasma protein binding**, the following medicinal products may increase the bioavailability of methotrexate (indirect dose increase), causing an increased toxicity of methotrexate: amidopyrine derivatives, para-aminobenzoic acid, barbiturates, doxorubicin, oral contraceptives, phenylbutazone, phenytoin, probenecid, salicylates, sulphonamides, tetracyclines, tranquillisers, sulfonylurea, penicillins, pristinamycin, and chloramphenicol. Concomitant use of methotrexate should therefore be closely monitored.

A **decrease in tubular secretion** with a consequent increase of methotrexate toxicity, especially at low doses, can be caused by the following medicinal products: para-aminohippuric acid, NSAIDs, probenecid, salicylate, sulphonamides and other weak organic acids. Concomitant use of methotrexate should therefore be closely monitored.

Penicillins and **sulphonamides** can reduce the renal clearance of methotrexate in individual cases, which may result in increased serum concentrations of methotrexate with simultaneous haematological and gastrointestinal toxicity.

Tubular renal secretion is reduced by **ciprofloxacin**. Concomitant use of methotrexate with this medicinal product should be monitored carefully.

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

In cases of **(pre-)treatment with medicinal products which may have adverse effects on the bone marrow** (e.g. aminopyridine derivatives, chloramphenicol, phenytoin, pyrimethamine, sulphonamides, trimethoprim/sulfamethoxazole, cytostatics), the possibility of severe impairment of haematopoiesis should be taken into account during methotrexate therapy.

Concomitant use of **medicinal products that cause a folate deficiency** (e.g. sulphonamides, trimethoprim/sulfamethoxazole) may increase methotrexate toxicity. Particular caution should therefore also be exercised in the presence of existing folic acid deficiency. On the other hand, concomitant use of **folinic acid-based medicinal products** as well as **vitamin supplements which contain folic acid or its derivatives**, may impair methotrexate efficacy.

Although the combination of methotrexate and **sulphasalazine** may potentiate the methotrexate effect because of the inhibition of the folic acid synthesis by sulphasalazine — and therefore increased side effects — these were observed in the course of several patient trials only in rare isolated cases.

Methotrexate can reduce clearance of **theophylline**. Theophylline levels must therefore be monitored during concomitant treatment with methotrexate.

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 the adenosine receptors.

The combined administration of methotrexate and **leflunomide** may increase the risk of pancytopenia.

Concomitant use of methotrexate and **mercaptopurine** may lead to increased plasma levels of mercaptopurine. Therefore, concomitant use may require dose adjustment.

In the context of concomitant administration of **triamterene** and methotrexate, cases of bone marrow suppression and decreased folate levels have been described.

Radiotherapy during the administration of methotrexate may increase the risk of soft tissue or bone necrosis.

Cholestyramine may increase the non-renal elimination of methotrexate by interrupting the enterohepatic circulation.

In concomitant use of **erythrocyte concentrates** and methotrexate special monitoring of the patient is required. Increased toxicity due to prolonged high serum concentrations of methotrexate may occur in patients who receive blood transfusions for 24 hours after methotrexate infusions.

In isolated cases, **corticosteroids** caused disseminated herpes zoster in patients with herpes zoster or post-herpetic neuralgia when methotrexate was administered concomitantly.

High doses of calcium folinate may reduce the efficacy of intrathecally administered methotrexate.

Anaesthetics based on nitric oxide potentiate the effect of methotrexate on folic acid metabolism and cause increased toxicity, such as severe, unpredictable myelosuppression, stomatitis, and neurotoxicity in intrathecal use. This can be reduced by the administration of calcium folinate.

Pyrimethamine or **co-trimoxazole** used in combination with methotrexate may cause pancytopenia, probably due to the additive inhibition of dihydrofolate reductase by these substances and methotrexate. See above for interactions between sulphonamides and methotrexate.

Regular **alcohol consumption** and administration of additional hepatotoxic medicinal products increase the probability of hepatotoxic adverse 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.

The pharmacokinetic interactions between methotrexate, anticonvulsants (reduced methotrexate blood levels), and 5-fluorouracil (increased half-life of 5-fluorouracil) must be taken into consideration.

Particularly in the event of orthopaedic surgery, where the risk of infection is very high, a combination of methotrexate with immunomodulatory agents must be used with caution.

Delayed methotrexate clearance should be taken into account in combination with other cytostatic agents.

A decrease in **phenytoin** plasma levels has been observed in patients with acute lymphoblastic leukaemia during induction therapy that included high-dose methotrexate with calcium folinate rescue in addition to prednisone, vincristine and 6-mercaptopurine.

The administration of **procarbazine** during high-dose methotrexate therapy increases the risk of renal impairment.

Concomitant therapy with **intravenous cytarabine** and intrathecal methotrexate can increase the risk of severe neurological undesirable effects ranging from headache to paralysis, coma and stroke-like episodes.

An **increase in nephrotoxicity** may occur in the combination of high-dose methotrexate with a potentially nephrotoxic chemotherapeutic agent, e.g. cisplatin.

On account of its possible effect on the immune system, methotrexate can lead to false vaccine and test results (immunological procedures to evaluate the immune reaction).

During methotrexate therapy concomitant **vaccination with live vaccines** must not be carried out (see sections 4.3 and 4.4).

Methotrexate may increase the effects of coumarin-like oral anticoagulants (acenocoumarol, phenprocoumon), resulting in increased prothrombin time due to the decreased breakdown of coumarin derivatives.

Concomitant administration of levetiracetam and methotrexate has been reported to decrease methotrexate clearance, resulting in increased/prolonged blood methotrexate concentration to potentially toxic levels. Blood methotrexate and levetiracetam levels should be carefully monitored in patients treated concomitantly with the two medicinal products.

4.6 Fertility, pregnancy and lactation

Women of child-bearing age/contraception in women
Women must not get pregnant during methotrexate therapy. Effective contraception must be used during treatment with methotrexate and at least 6 months after discontinuation (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 ruled out 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 child-bearing age must be counselled regarding pregnancy prevention and planning. Couples should be given extensive counselling on the severe risks to the foetus if a pregnancy occurs during the treatment.

Contraception in men
It is not known if methotrexate is accumulated in semen. Methotrexate has been shown to be genotoxic in animal studies, such that the risk of genotoxic effects on sperm cells cannot be completely ruled out. 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 discontinuation of methotrexate. Men should not donate semen during therapy or for 6 months following discontinuation of methotrexate.

Pregnancy:
Methotrexate is contraindicated during pregnancy for 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 ultrasound 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). This compares to a reported rate of abortions of 22.5% in disease-matched patients treated with medicinal products other than methotrexate.
- Serious birth defects occurred in 6.6% of live births in women exposed to low-dose methotrexate treatment (less than 30 mg/week) during pregnancy. This compared to approximately 4% of live births in disease-matched patients treated with medicinal products other than methotrexate.

Insufficient data is available for methotrexate doses during pregnancy higher than 30 mg/week, but higher rates of spontaneous abortions and congenital malformations are expected.
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 potential risk to the foetus. If the medicinal product 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
As methotrexate passes into breast milk and may cause toxicity in nursing infants, therapy is contraindicated during the breast-feeding period (see section 4.3). If therapy during the breast-feeding period should become necessary, breast-feeding must be stopped before starting treatment.

Fertility
Methotrexate affects spermatogenesis and oogenesis and may decrease fertility. In humans, methotrexate has been reported to cause oligospermia, dysmenorrhoea 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 centre, 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 section 4.4).

4.7 Effects on ability to drive and use machines

Methotrexate has minor or moderate influence on the ability to drive and use machines. Since central nervous system effects, such as fatigue and vertigo may occur during treatment, the ability to drive and use machines may be impaired in individual cases. This is especially true in combination with alcohol.

4.8 Undesirable effects

In general, the incidence and severity of undesirable effects are dependent on the dose and duration of methotrexate treatment. Since serious adverse reactions can, however, occur even at a low dose and at any time during therapy, patients should be closely and frequently monitored by the doctor. Most undesirable effects are reversible if recognised soon enough. However, some of the serious adverse reactions listed below, can in very rare cases lead to sudden death.

If undesirable effects appear, the dosage should be reduced as necessary according to their severity and intensity, or the therapy should be discontinued and appropriate countermeasures

taken (see section 4.9). If methotrexate therapy is continued, this should be done with caution and after carefully evaluating the need for the therapy. The patients must be closely monitored for the possible recurrence of toxicity.

Myelosuppression and mucositis are generally the dose-limiting toxic effects. Their severity depends on the dosage, method and duration of methotrexate administration. Mucositis appears approximately 3–7 days after methotrexate administration, while leukopenia and thrombocytopenia appear 5–13 days after methotrexate administration. Myelosuppression and mucositis are generally reversible within 14 days in patients with no impairment to the elimination mechanisms.

The most commonly reported undesirable effects include thrombocytopenia, leukopenia, headache, vertigo, coughing, anorexia, diarrhoea, abdominal pain, nausea, vomiting, inflammation, and ulcerations of the mucosa in the mouth and the throat (especially in the first 24–48 hours after administering methotrexate), increased liver enzymes and bilirubin, alopecia, reduced creatinine clearance, fatigue and malaise.

Ulcerations of the oral mucosa are usually the first clinical signs of toxicity.

The following frequencies are used for classifying undesirable effects:

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)

Infections and infestations

Common:	herpes zoster
Uncommon:	opportunistic infections that may have a fatal outcome
Rare:	sepsis (including a fatal outcome)
Very rare:	herpes simplex, hepatitis, cryptococcosis, histoplasmosis, cytomegalovirus infections (including pneumonia), disseminated herpes simplex, nocardiosis, pneumocystis jirovecii pneumonia*
Not known:	pneumonia, reactivation of hepatitis B infection, exacerbation of hepatitis C infection

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

Uncommon:	malignant lymphoma*
Very rare:	tumour lysis syndrome*

Blood and lymphatic system disorders*

Very common:	leukopenia, thrombocytopenia
Common:	anaemia, pancytopenia, bone marrow suppression, agranulocytosis
Rare:	megaloblastic anaemia
Very rare:	aplastic anaemia, eosinophilia, neutropenia, lymphadenopathy (partially reversible), and lymphoproliferative disorders (partially reversible)

Immune system disorders

Uncommon:	allergic reactions up to and including anaphylactic shock, immunosuppression
Very rare:	hypogammaglobulinaemia

Metabolism and nutrition disorders

Uncommon:	diabetes mellitus

Psychiatric disorders

Uncommon:	depression

Rare: mood swings, transient perception disorders

Nervous system disorders
Very common: headaches, vertigo
Common: drowsiness, paraesthesia
Uncommon: hemiparesis, confusion, seizures (in parenteral administration), leukoencephalopathy/encephalopathy* (in parenteral administration)
Rare: paresis, speech disorders including dysarthria and aphasia, myelopathy (after lumbar application)
Very rare: muscle weakness and pain in the extremities, dysgeusia (metallic taste), acute aseptic meningitis (paralysis, vomiting), cranial nerve syndrome, hypoaesthesia
Not known: neurotoxicity, arachnoiditis, paraplegia, stupor, ataxia, dementia, increase in cerebrospinal fluid pressure
The intravenous use of methotrexate may lead to acute encephalitis and acute encephalopathy with fatal outcome.

Eye disorders
Common: conjunctivitis
Rare: visual disturbances (partially serious), severe retinal vein thrombosis
Very rare: periorbital oedema, blepharitis, epiphora, photophobia, temporary blindness, loss of vision.

Cardiac disorders
Very rare: pericarditis, pericardial effusion, pericardial tamponade

Vascular disorders
Uncommon: vasculitis, allergic vasculitis
Rare: hypotension, thromboembolic events (including arterial and cerebral thrombosis, thrombophlebitis, deep vein thrombosis)

Respiratory, thoracic and mediastinal disorders*
Very common: cough
Common: pulmonary complications due to interstitial alveolitis/pneumonia and the fatalities caused by them (regardless of the dose or duration of treatment with methotrexate)
Uncommon: pulmonary fibrosis, pleural effusion
Rare: pharyngitis, respiratory arrest, pulmonary embolism
Very rare: chronic interstitial pulmonary disease, asthma-like reactions such as coughing, dyspnoea and pathological changes in lung function tests
Not known: chest pain, hypoxia, pulmonary alveolar bleeding (reported in use of methotrexate in rheumatic and related indications)

Gastrointestinal disorders*
Very common: loss of appetite, diarrhoea (especially in the first 24–48 hours after using methotrexate), abdominal pain, nausea, vomiting, inflammation and ulceration of the mucosa in the mouth and the throat (especially in the first 24–48 hours after using methotrexate)
Uncommon: gastrointestinal ulcerations and bleeding, pancreatitis
Rare: enteritis, gingivitis, melaena
Very rare: haematemesis
Not known: non-infectious peritonitis, toxic megacolon, colon perforation, glossitis

Hepatobiliary disorders*
Very common: increase in liver enzymes (ALAT [GPT], ASAT [GOT]), alkaline phosphatase and bilirubin
Uncommon: hepatotoxicity, hepatic steatosis, chronic liver fibrosis and liver cirrhosis, serum albumin decrease
Rare: acute hepatitis

Very rare: acute hepatic necrosis, acute hepatolysis, hepatic failure

Skin and subcutaneous tissue disorders*

Very common: alopecia
Common: exanthema, erythema, pruritus, skin ulcerations
Uncommon: severe toxic manifestations: herpetiform skin eruptions, Stevens-Johnson syndrome*, toxic epidermal necrolysis (Lyell's syndrome)*, urticaria, increased skin pigmentation, nodulosis, painful erosions of psoriatic plaques, impaired wound healing, photosensitivity reactions
Rare: acne, petechiae, ecchymosis, erythema multiforme, erythematous skin rashes, increased pigment changes of the nails, onycholysis
Very rare: furunculosis, telangiectasia, acute paronychia
Not known: Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), exfoliative dermatitis

Musculoskeletal and connective tissue disorders

Uncommon: arthralgia, myalgia and osteoporosis
Rare: stress fracture
Not known: Osteonecrosis of the jaw (secondary to lymphoproliferative diseases)

Renal and urinary disorders*

Very common: decreased creatinine clearance
Uncommon: nephropathy, kidney failure, cystitis with ulcerations (eventually with haematuria), bladder voiding disorders, dysuria, oliguria, anuria
Rare: hyperuricemia, increased serum urea and creatinine concentrations, azotaemia
Very rare: haematuria, proteinuria

Pregnancy, puerperium and perinatal conditions

Uncommon: Foetal birth deformities
Rare: abortion
Very rare: foetal death

Reproductive system and breast disorders

Uncommon: vaginal ulcerations and inflammations
Rare: transient oligospermia, transient irregular menstrual cycles
Very rare: impaired oogenesis/spermatogenesis*, infertility*, menstrual disorders, loss of libido, impotence, vaginal discharge, gynecomastia
Not known: urogenital dysfunction

General disorders and administration site reactions

Very common: fatigue, malaise
Uncommon: pyrexia,
Not known: chills

* For information on severe undesirable effects see section 4.4.

Adverse reactions to intrathecal administration of methotrexate

CNS toxicity may occur after intrathecal administration of methotrexate and may manifest in different forms:

- acute chemical arachnoiditis (inflammation of the arachnoid membrane), which can manifest as headache, dorsalgia , neck stiffness and fever;
- subacute myelopathy, characterised by e.g. paraparesis/paraplegia (with the involvement of one or more spinal nerve);
- chronic leukoencephalopathy, which can manifest as confusion, irritability, sleepiness, ataxia, dementia, convulsions and coma, for example. This CNS toxicity may advance up to and including death.

There are indications that the combined use of cranial irradiation and intrathecal methotrexate increases the incidence of leukoencephalopathy. Intrathecal administration of methotrexate should be followed by close monitoring for signs of neurotoxicity (meningitis, transient or persistent paralysis, encephalopathy).

The intrathecal and intravenous use of methotrexate may lead to acute encephalitis and acute encephalopathy with fatal outcome.

There have been reports of patients with periventricular CNS lymphoma who developed cerebral herniation after intrathecal application of methotrexate.

Adverse reactions to intramuscular administration of methotrexate
After intramuscular use of methotrexate, local adverse reactions (such as a burning sensation) or tissue damage (such as sterile abscess formation, adipose tissue necrosis) can appear.

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

Symptoms of an overdose
Post-marketing experience of methotrexate has shown that methotrexate overdose generally occurred after oral administration but also after intravenous, intramuscular or intrathecal administration.

The symptoms following an oral or intravenous overdose principally affect the haematopoietic and gastrointestinal system. Events included leukopenia, thrombocytopenia, anaemia, pancytopenia, neutropenia, bone marrow depression, inflammation of the mucosa (mucositis), stomatitis, mouth ulcers, nausea, vomiting as well as gastrointestinal ulcerations and bleeding. In some cases, there were no signs of intoxication. There are reports of fatalities following an overdose. In these cases, there were also reports of sepsis, septic shock, renal failure and aplastic anaemia.

After an intrathecal overdose, CNS symptoms usually appear, associated with headache, nausea and vomiting, seizures or convulsions and acute toxic encephalopathy. In some cases, no symptoms were observed. In other cases, an intrathecal overdose had a fatal outcome; a cerebral herniation with increased intracranial pressure was reported in this context, as was acute toxic encephalopathy.

Therapeutic measures in the event of an overdose
For the prevention and therapy of toxic side effects, calcium folinate is available as the specific antidote.
a) Prevention:
At a methotrexate dose of 100 mg/m^2 BSA or more, this treatment must be followed by the administration of calcium folinate. Please refer to the specialist literature for information on the dosing and duration of use of calcium folinate as an antidote.
b) Treatment:
Treatment of intoxication symptoms of a low-dose methotrexate therapy (individual dosage < 100 mg/m^2 body surface area methotrexate) that can be attributed to a tetrahydrofolic acid deficiency:
Immediately administer 6–12 mg of calcium folinate intravenously or intramuscularly, followed by the same amount of calcium folinate several times (at least 4 times) at 3–6 hour intervals.

For more intensive calcium folinate rescue in the event of delayed methotrexate elimination during methotrexate therapy in medium-high and high doses, refer to the specialist literature.

The longer the time interval between methotrexate administration and calcium folinate administration, the lower the efficacy of calcium folinate. In order to determine the optimum dose and duration of calcium folinate administration, methotrexate serum levels must be monitored.

In the event of a massive overdose, hydration and urinary alkalisation may be required to prevent precipitation of methotrexate and/or its metabolites within the renal tubules. If the intoxication is caused by substantially delayed elimination (methotrexate serum levels), e.g. due to acute kidney failure, haemodialysis and/or haemoperfusion can be considered. Effective methotrexate clearance was achieved through haemodialysis with a high-flux-dialyser. Neither standard haemodialysis nor peritoneal dialysis led to an improved methotrexate elimination.

An accidental intrathecal overdose may require intensive systemic countermeasures:
A high-dose, **systemic, non-intrathecal** administration of calcium folinate, alkaline diuresis and quick draining of cerebrospinal fluid and ventriculolumbar perfusion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
As a folic acid analogue, methotrexate is classified as an antimetabolite. It competitively inhibits the enzyme dihydrofolate reductase. This enzyme has to reduce dihydrofolic acid to tetrahydrofolic acid, before it can be used for the transport of a carbon group in the synthesis of purine nucleotides and thymidylates. Thus, methotrexate actively interferes with DNA synthesis and repair and cell replication.

Clinical efficacy and safety
Highly proliferating tissues such as malignant cells, bone marrow, foetal cells, skin epithelium and mucosa are generally more susceptible to this effect of methotrexate. Since cell proliferation is usually higher in malignant growths than in normal tissue, methotrexate may have a lasting effect on malignant growth without causing irreversible damage to normal tissue.

5.2 Pharmacokinetic properties

Absorption
100% in intravenous and intramuscular administration.

After oral administration, methotrexate is absorbed from the gastrointestinal tract. When administered in low doses (7.5 mg/m^2 to 80 mg/m^2 body surface area), methotrexate has a mean bioavailability of approximately 70%, although considerable inter- and intra-individual variations are possible (25–100%). Peak serum concentration is achieved within 1–2 hours.

Subcutaneous, intravenous and intramuscular administration demonstrated similar bioavailability.
Approximately 50% of methotrexate is bound to serum proteins. After distribution, high concentrations can be found in the form of polyglutamates, particularly in the liver, kidneys and spleen, which can be retained for weeks or months.
After intrathecal administration of methotrexate, absorption into the plasma component is slow and results in a possibly toxic plasma concentration being maintained over a longer period.

Distribution

After intravenous application the initial volume of distribution is approximately 0.18 l/kg (18% of the body weight), and 0.4 to 0.8 l/kg (40% to 80% of the body weight) under steady state conditions. Methotrexate competes with reduced folates for the active carrier-mediated cell membrane transport. In serum concentrations of more than 100 µmol/l the intracellular concentration is predominantly achieved by passive diffusion.
The plasma protein binding of methotrexate is approx. 50%.
The highest concentrations of methotrexate are found in the kidneys, the gallbladder, the spleen, the liver, the skin and in the small and large intestine. Methotrexate slowly enters into the 'third space' (pleural effusions and ascites) and is only released slowly, which may cause an increase in toxicity. In oral or parenteral administration in therapeutic doses methotrexate does not pass the blood–cerebrospinal fluid barrier. Only after intrathecal administration or high-dose therapy were therapeutically effective doses found in the cerebrospinal fluid.

When administered in small doses, methotrexate passes into the cerebrospinal fluid in minimal amounts only; at high doses (300 mg/kg body weight), concentrations of between 4 and 7 µg/ml have been measured in the cerebrospinal fluid. The mean terminal half-life is 6–7 hours, with considerable variation (3–17 hours). In patients with a third space (pleural effusion, ascites), the half-life can be increased by up to four-fold.

Biotransformation
After absorption, methotrexate undergoes hepatic and intracellular biotransformation to polyglutamates, which can be transformed back into methotrexate with hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamate may remain in the tissues for a longer period. The retention and the prolonged duration of effect of these active metabolites varies by cell, tissue and tumour type. In usual dosages, a small amount is metabolised to 7-hydroxymethotrexate, while in higher doses, the accumulation of this metabolite may be significant. Water solubility of 7-hydroxymethotrexate is three to five times lower than of the original compound.
The terminal half-life is approx. 3–10 hours in the administration of low methotrexate doses (30 mg/m^2 BSA). The terminal half-life in high-dose therapy is 8–15 hours.

Elimination
Methotrexate elimination is predominantly renal, by glomerular filtration, and active secretion in proximal tubules. It depends on the dose and the administration form. After intravenous administration, 80–90% of the administered dose is eliminated unchanged via the urine within 24–30 hours. Biliary elimination is limited, reaching a maximum of 10% of the administered dose. Methotrexate undergoes pronounced enterohepatic circulation, so that a maximum of 10% of the administered dose is eliminated through faeces. After intravenous injection, methotrexate undergoes a distribution phase lasting a few minutes. Methotrexate is eliminated during the second, 12- to 24-hour phase with a plasma half-life of 2 to 3 hours, and during the third phase with a plasma half-life of 12 to 24 hours. In impaired renal function, delayed elimination must be expected, which may lead to severe undesirable effects. The correlation between methotrexate clearance and endogenous creatinine clearance was found to be good. Elimination restrictions in hepatic impairment are currently not known.
Methotrexate passes the placental barrier in rats and monkeys.

5.3 Preclinical safety data

Chronic toxicity
Toxic effects in the form of gastrointestinal lesions, myelosuppression and hepatotoxicity were found during studies into chronic toxicity in mice, rats and dogs.

Mutagenic and carcinogenic potential
There were no indications of a carcinogenic potential of methotrexate in long-term trials with rats, mice and hamsters. Methotrexate induces *in vitro* and *in vivo* gene and chromosome mutations. It is suspected that it has a mutagenic effect in humans.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide, water for injections

6.2 Incompatibilities

Known incompatibilities:
Strong oxidants and strong acids
Chlorpromazine HCl (turbidity, yellow precipitate)
Droperidol
Idarubicin
Metoclopramide HCl
Prednisolone sodium phosphate
Promethazine HCl

Incompatibilities of methotrexate with cytarabine and fluorouracil have been reported; however, the incompatibility with fluorouracil is in doubt.

As a rule, the prepared solution for infusion should be used within 24 hours of preparation. Furthermore, incompatibilities with other substances may occur (e.g. bleomycin) during longer storage.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials
The medicinal product must be used immediately after opening.
For single use only. Discard any remaining product.

Infusion solution after dilution

Methotrexat “Ebewe” diluted in 5% glucose solution and 0.9% sodium chloride solution is stable at 25ºC (exposed to light) for 24 hours.
Chemical and physical stability of the ready-to-use preparation were demonstrated after first opening over 28 days at 2–8°C and under 25ºC with light protection.

From a microbiological point of view, the ready-for-use preparation should be used immediately. If not used immediately, the user is responsible for the duration and conditions of storage. If the ready-for-use preparation is not prepared under controlled and validated aseptic conditions, it must not be stored longer than 24 hours at 2 to 8°C.

6.4 Special precautions for storage

Do not store above 25°C.
Keep container in the outer carton, in order to protect from light.
For storage conditions after dilution, see section 6.3.

6.5 Nature and contents of container

Vials.
Vials with or without a transparent plastic container (Onco-Safe).

Pack sizes:
Vial: 1 x 5 ml, 1 x 10 ml, 1 x 50 ml
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution must be visually inspected prior to use.
Only clear solutions practically free from particles should be used.

All contact of methotrexate with skin and mucosa is to be avoided.
In the event of contamination, the affected areas must be rinsed immediately with plenty of water.

Instructions for healthcare professionals:
As is usual when dealing with cytostatics, handling methotrexate requires extreme care: gloves, masks, protective clothes and if possible ventilation should be used. Skin and mucous membrane contact must be prevented. Pregnant women should not come into contact with methotrexate.

Observe the disposal and handling regulations for cytostatic agents.

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

7. LICENSE HOLDER AND IMPORTER'S NAME AND ADDRESS

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

8. MARKETING AUTHORISATION NUMBER

129-09-30803-00

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