# Part II

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Methotrexate-Teva 25 mg/ml Solution for Injection or Infusion.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of solution contains 25mg of Methotrexate (present in solution as methotrexate sodium).

Each 40ml flask contains 1000mg of Methotrexate
Each 200ml flask contains 5000mg of Methotrexate

For excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for Injection or Infusion.
A clear, yellow-brown solution.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Methotrexate is an antimetabolite used in the treatment of certain neoplastic diseases and severe psoriasis.

*Neoplastic Diseases:* Methotrexate is indicated in the treatment of gestational choriocarcinoma, chorioadenoma destruens, and hydatidiform mole. In acute lymphocytic leukaemia, methotrexate is indicated in the prophylaxis of meningeal leukaemia and is used in maintenance therapy in combination with other chemotherapeutic agents. Methotrexate is also indicated in the treatment of meningeal leukaemia. The greatest effect has been observed in the palliation of acute lymphoblastic (stemcell) leukaemia's. Methotrexate is also 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. Methotrexate is used alone or in combination with other anticancer agents in the treatment of breast cancer, epidermoid cancers of the head and neck, lung cancer, particularly squamous cell and small cell types, bladder and osteogenic cancer. Methotrexate is also used in combination with other chemotherapeutic agents in the treatment of advanced stage non-Hodgkin's lymphomas.

*Psoriasis:* Methotrexate is indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultation. It is important to ensure that a psoriasis "flare" is not due to an undiagnosed concomitant disease affecting immune responses.

*Rheumatoid arthritis:* 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

Parenteral drug products should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution and container permit. Methotrexate-Teva may be given by intramuscular, intravenous (bolus injection or infusion), intrathecal and intra-arterial routes of administration. Dosage should be reduced in cases of haematological deficiency and hepatic or renal impairment. Larger doses (greater than 100 mg) are usually given by intravenous infusion over periods not exceeding 24hours. Part of the dose may be given as an initial rapid intravenous injection.

Methotrexate-Teva may be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection. Methotrexate-Teva is chemically and physically stable for 24 hours when diluted in 0.9% Sodium Chloride Injection or 5% Dextrose Injection, when protected from light. From a microbial point of view, when aseptically diluted, the solution should be used within 24 hours of preparation, when stored in the refrigerator (2-8°C), or within 8 hours, when stored at room temperature (below 25°C).

Any unused solution should be discarded. Other drugs should not be mixed with methotrexate in the same infusion container.

This drug does not contain any antimicrobial preservatives, and is intended for single dose administration only.

***Neoplastic Diseases:***
*Choriocarcinoma and Similar Trophoblastic Diseases*: A daily dose of 15-30 mg administered intramuscularly for a 5-day treatment course is recommended. Such a course is usually repeated 3-5 times as required, with rest periods of one or more weeks between courses until any toxic symptoms subside.

The effectiveness of therapy is ordinarily evaluated by 24-hour quantitative analysis of urinary chorionic gonadotrophin (HCG), which should return to normal, or less than 50 IU/24 hours, usually after the 3rd or 4th course of treatment, and is usually followed by a complete resolution of measurable lesions in 4-6 weeks.

One or two courses of methotrexate after the normalisation of HCG is usually recommended. Before each course of the drug, careful clinical assessment is essential.

Higher doses of up to 60 mg intramuscularly every 48 hours may be given, for 4 doses, followed by leucovorin rescue (see Guidelines for Methotrexate Therapy with Leucovorin Rescue). This course is to be repeated at seven-day intervals until levels of urinary HCG return to normal. At least four courses of treatment are usually necessary. Patients with complications, such as extensive metastases, may be treated with methotrexate in cyclic combination with other cytotoxic drugs.

*Chorioadenoma Destruens and Hydatidiform Mole:* Since hydatidiform mole may be followed by choriocarcinoma, prophylactic chemotherapy with methotrexate has been recommended.

Chorioadenoma destruens is considered to be an invasive form of hydatidiform mole. Methotrexate is administered in these disease states in doses similar to those recommended for choriocarcinoma.

*Leukaemia:* Acute lymphoblastic leukaemia in children and young adolescents is the most responsive type to present day chemotherapy. In young adults and older patients, clinical remission is more difficult to obtain and early relapse is more common. Methotrexate alone or in combination with steroids was used initially for induction of remission in acute lymphoblastic leukaemia's.

More recently corticosteroid therapy, in combination with other antileukaemic drugs or in cyclic combinations including methotrexate, has appeared to produce rapid and effective remissions. When used for induction, methotrexate in doses of 3.3 mg/$m^2$ in combination with 60 mg/$m^2$ of prednisone, administered daily, produced remissions in 50% of patients treated, usually within a period of 4-6 weeks.

Methotrexate in combination with other agents appears to be the drug of choice for securing maintenance of drug-induced remissions. When remission is achieved and supportive care has produced general clinical improvement, maintenance therapy is initiated as follows:

Methotrexate administered intramuscularly twice weekly in total weekly doses of 30 mg/$m^2$. It has also been given in doses of 2.5 mg/kg intravenously every 14 days. If and when relapse does occur, reinduction of remission can usually be obtained again by repeating the initial induction regimen.

*Meningeal Leukaemia:* In the treatment or prophylaxis of meningeal leukaemia, methotrexate must be administered intrathecally. Preservative-free methotrexate is diluted to a concentration of 1 mg/ml in an appropriate sterile, preservative-free medium such as 0.9% Sodium Chloride Injection. The cerebrospinal fluid (CSF) volume is dependent on age and not on body surface area. The CSF is at 40% of the adult volume at birth and reaches the adult volume in several years. Therefore the following dosage regimen, is based on age instead of body surface area is recommended:

| | |
|---|---|
| Less than 1 year of age | 6 mg |
| 1 year of age | 8 mg |
| 2 years of age | 10 mg |
| Over 3 years of age (including adults) | 12 mg |

Because the CSF volume and turnover may decrease with age, a dose reduction may be indicated in elderly patients.

For the treatment of meningeal leukaemia, intrathecal methotrexate may be given at intervals of 2-5 days. However, administration at intervals of less than 1 week may result in increased subacute toxicity. Methotrexate is administered until the cell count of the CSF returns to normal. At this point one additional dose is advisable. For prophylaxis against meningeal leukaemia, the dosage is the same as for treatment except for the intervals of administration. Untoward side effects may occur with any given intrathecal injection and are commonly neurological in character. Large doses may cause convulsions.

Methotrexate given by the intrathecal route appears significantly in the systemic circulation and may cause systemic methotrexate toxicity. Therefore, systemic therapy with the drug should be appropriately adjusted, reduced, or discontinued. Focal leukaemic involvement of the central nervous system may not respond to intrathecal chemotherapy and is best treated with radiotherapy.

*Lymphomas:* In Burkitt's Tumour, Stages I to II, methotrexate has produced prolonged remissions in some cases. Treatment is effected by oral methotrexate. In Stage III, methotrexate is commonly given concomitantly with other antitumour agents. Treatment in all stages usually consists of several courses of the drug interposed with 7-10 day rest periods. Lymphosarcomas in Stage III may respond to combined drug therapy with methotrexate given in doses of 0.625-2.5 mg/kg daily.

*Mycosis Fungoides:* The usual treatment is by orally-administered methotrexate. However, methotrexate has also been given intramuscularly in doses of 50 mg once weekly or 25 mg two times weekly.

*Breast Cancer:* Methotrexate, in intravenous doses of 10-60 mg/$m^2$, is commonly included in cyclical combination regimens with other cytotoxic drugs in the treatment of advanced breast cancer. Similar regimens have also been used as adjuvant therapy in early cases following mastectomy and/or radiotherapy.

*Head and Neck Cancer:* Intravenous infusion of 240-1080 mg/$m^2$ of methotrexate with leucovorin rescue may be used both as preoperative adjuvant therapy and in the treatment of advanced tumours. Intra-arterial infusions of methotrexate are indicated for certain head and neck cancers, although this route of administration is not now used extensively.

*Bronchogenic Carcinoma:* Intravenous infusions of 20-100 mg/$m^2$ of methotrexate have been included in cyclical combination regimens for treatment of advanced tumours. Higher doses of methotrexate with calcium leucovorin rescue may also be employed as sole treatment.

*Bladder Carcinoma:* Intravenous injections or infusions of methotrexate in doses up to 100mg every 1-2 weeks may be used in the treatment of bladder carcinoma. Diuretics and hydration are employed in an attempt to reduce excessive drug toxicity that may occur in patients with renal impairment.

*Osteosarcoma:* Effective therapy requires several cytotoxic chemotherapeutic agents. In addition to high-dose methotrexate with leucovorin rescue, these agents may include doxorubicin, cisplatin and the combination of bleomycin, cyclophosphamide and dactinomycin (BCD) in the doses and schedule shown in the following table. The starting dose for high dose methotrexate treatment is 12 $g/m^2$. If this dose is not sufficient to produce a peak serum concentration of 1000 micromolar ($10^{-3}$ mol/l) at the end of the methotrexate infusion, the dose may be increased to 15 $g/m^2$ in subsequent treatments. If the patient is vomiting or is unable to tolerate oral medication, give leucovorin IV or IM at the same dose and schedule.

***Chemotherapy Regimens for Osteosarcoma***

| *Drug* | *Dose* | *Treatment week after surgery* |
|---|---|---|
| Methotrexate | 12$g/m^2$ IV as 4-hour infusion (starting dose) | 4, 5, 6, 7, 11, 12, 15, 16, 29, 30, 44, 45. |
| Leucovorin | 15mg orally every 6 hours, for 10 doses starting at 24 hours after start of methotrexate infusion | same as above |
| Doxorubicin * as a single drug | 30 $mg/m^2$/day IV x 3 days | 8, 17 |
| Doxorubicin * | 50 $mg/m^2$ IV | 20, 23, 33, 36 |
| Cisplatin * | 100 $mg/m^2$ IV | 20, 23, 33, 36 |
| Bleomycin * | 15 units/$m^2$ IV x 2 days | 2,13,26,39,42 |
| Cyclophosphamide * | 600 $mg/m^2$ IV x 2 days | 2,13,26,39,42 |
| Dactinomycin * | 0.6 $mg/m^2$ IV x 2 days | 2,13,26,39,42 |

* See respective monographs for more complete information.
Dose modifications may be necessary because of drug-induced toxicity.

***Psoriasis:***
The patient should be fully informed of potential risks involved and should be under the constant supervision of the physician. Assessment of haematologic, hepatic, renal, and pulmonary function should be made by medical history, physical examination, and laboratory tests before beginning, periodically during, and before reinstituting methotrexate therapy (*see section 4.4, Special warnings and precautions for use*).
Appropriate steps should be taken to avoid conception during methotrexate therapy (*see sections 4.4, Special warnings and Precautions for use* and *4.8, Contraindications*).

The recommended starting dose schedule is a weekly single IM or IV dose of 10-25 mg per week until adequate response is achieved. This is then followed by oral methotrexate therapy. Particular attention should be given to the appearance of liver toxicity by performing liver function tests before starting methotrexate treatment and repeating them at 2 to 4 month intervals during therapy.

Therapy should not be instituted, or should be discontinued, if any abnormality of liver function tests or of a liver biopsy is present or develops during therapy. Such abnormalities should return to normal within 2 weeks, after which treatment may be recommended at the discretion of the physician. The use of methotrexate may permit the return to conventional topical therapy, which should be encouraged.

***Rheumatoid arthritis:***
Initially, 10 mg/week may be administered either intramuscularly or intravenously. The dosage may be increased to 25 mg/week.

Duration of treatment varied in clinical studies from 6 weeks to 13 weeks. An intramuscular dosage of 15 mg/week has been administered over a period of 6 months. An initial dosage of 10 mg/week IV, increased to a maximum of 50 mg/week IV has been administered over a period of 2 months.

Particular attention should be given to the appearance of liver toxicity by performing liver function tests before and after methotrexate treatment, and repeating the tests at 2 - 4 month intervals during therapy.

Therapy should not be instituted, or should be discontinued, if any abnormality of liver function tests or of a liver biopsy is present or develops during therapy. Such abnormalities should return within 2 weeks, after which, treatment may be recommended at the discretion of the physician. The use of methotrexate may permit the return to conventional topical therapy which should be encouraged.

When high doses of methotrexate are to be administered, the following safety guidelines should be closely observed.

*Guidelines for Methotrexate Therapy with Leucovorin Rescue:*

1. Administration of methotrexate should be delayed until recovery if:
   the WBC count is less than $1500/mm^3$.
   the neutrophil count is less than $200/mm^3$.
   the platelet count is less than $75,000/mm^3$.
   the serum bilirubin level is greater than 1.2 mg/dl.
   the SGPT level is greater than 450 U.
   mucositis is present, until there is evidence of healing.
   persistent pleural effusion is present; drain dry prior to infusion.

2. Adequate renal function must be documented.
   Serum creatinine must be normal and creatinine clearance must be greater than 60ml/min. before initiation of therapy.
   Serum creatinine must be measured prior to each subsequent course of therapy. If serum creatinine has increased by 50% or more compared to a prior value, the creatinine clearance must be measured and documented to be greater than 60 ml/min.(even if the serum creatinine is still within the normal range).

3. Patients must be well hydrated and must be treated with sodium bicarbonate for urinary alkalinisation.
   Administer 1000 $ml/m^2$ of intravenous fluid over 6 hours prior to initiation of the methotrexate infusion.
   Continue hydration at 125 $ml/m^2$/hr (3 $litres/m^2$/day) during methotrexate infusion, and for 2 days after the infusion has been completed. Alkalinise urine to maintain pH above 7.0 during methotrexate infusion and leucovorin calcium therapy by administering sodium bicarbonate orally or by incorporating into a separate IV solution.

4. Repeat serum creatinine and serum methotrexate determinations 24 hours after starting methotrexate and at least once daily until the methotrexate level is below $5 \times 10^{-8}$mol/l (0.05micromolar).

5. The following table provides guidelines for leucovorin calcium dosage based upon serum methotrexate levels.

**Leucovorin Rescue Schedules Following Treatment with Higher Doses of Methotrexate**

| *Clinical Situation* | *Laboratory Findings* | *Leucovorin Calcium Dosage & Duration* |
|---|---|---|
| Normal Methotrexate Elimination | Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0.2 micromolar at 72 hours. | 15 mg PO, IM or IV every 6 hours for 60 hours (10 doses starting 24 hrs after start of methotrexate infusion). |
| Delayed Late every Methotrexate Elimination | Serum methotrexate level remaining above 0.2 micromolar at 72 hours and more than 0.05 micromolar at at 96 hours after administration. | Continue 15 mg PO, IM or IV 6 hours until methotrexate level is less than 0.05 micromolar. |
| Delayed Early Methrotrexate Elimination and/or Evidence of Acute Renal Injury | Serum methotrexate level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR: a 100 % or greater increase in serum creatinine level at 24 hours after methotrexate administration (e.g. an increase from 0.5 mg/dl to a level of 1 mg/dl or more). | 150 mg IV every 3 hours until methotrexate level is less than 1 micromolar, then 15 mg IV every 3 hours until methotrexate level is less than 0.05 micromolar. |

Patients who experience delayed early methotrexate elimination are likely to develop irreversible oliguric renal failure.

In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinisation, and close monitoring of fluid and electrolyte status until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved.

Some patients will have abnormalities in methotrexate elimination, or abnormalities in renal function following methotrexate administration, which are significant but less severe than those described in the table. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, leucovorin rescue should be extended for an additional 24 hours (total 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (e.g. medications which may interfere with methotrexate binding to serum albumin, or methotrexate elimination) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

*Hepatic function impairment:* If the bilirubin is between 3 and 5, or aspartate aminotransferase (AST) is more than 180, the methotrexate dose should be reduced by 25%. If bilirubin is more than 5, the dose should be omitted.

*Use in Paediatrics:* Caution should be used in neonates and infants because of reduced renal and hepatic function.

*Use in the Elderly:* Due to diminished hepatic and renal function and increased folate stores in the elderly, relatively low doses should be considered. Patients should be monitored closely for early signs of toxicity.

## 4.3 Contraindications

Methotrexate is contraindicated in:

- Patients with a known hypersensitivity to the preparation.
- Patients with psoriasis with alcoholism, alcoholic liver disease, or other chronic liver disease.
- Patients with psoriasis who have overt or laboratory evidence of immunodeficiency syndromes.
- Patients with psoriasis who have pre-existing blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anaemia.

## 4.4 Special warnings and precautions for use

*Warnings* - Methotrexate should be only administered by, or under the supervision of physicians whose knowledge and experience includes the use of antimetabolite therapy. The use of methotrexate high-dose regimens recommended for osteosarcoma requires meticulous care (*see section 4.2, Posology and Method of Administration*). High-dosage regimens for other neoplastic diseases are investigational and a therapeutic advantage has not been established. Because of the possibility of serious toxic reactions, the patient should be informed by the physician of the risks involved and should be under a physician's constant supervision.

Deaths have been reported with the use of methotrexate in the treatment of malignancy, psoriasis and rheumatoid arthritis. In the treatment of psoriasis, methotrexate use should be restricted to patients with severe, recalcitrant, disabling disease, which is not adequately responsive to other forms of therapy, and only when the diagnosis has been established and after appropriate consultation.

Periodic monitoring for toxicity, including CBC with differential and platelet counts, and liver and renal function tests, is a mandatory part of methotrexate therapy.
Periodic liver biopsies may be indicated in some situations. Patients at increased risk for impaired methotrexate elimination (e.g. patients with renal dysfunction, pleural effusions, or ascites) should be monitored more frequently (*see section 4.4, Special warnings and Precautions for use*).

Methotrexate causes hepatoxicity, fibrosis, and cirrhosis, but generally only after prolonged use. Acutely, liver enzyme elevations are frequently seen; these are usually transient and asymptomatic, and also do not appear to be predictive of subsequent hepatic disease. Liver biopsy, performed after sustained use of methotrexate, often shows histologic changes, and as previously mentioned, fibrosis and cirrhosis have been reported. These latter lesions often are not preceded by symptoms of abnormal liver function tests (*see section 4.4, Special warnings and Precautions for use*).

Methotrexate-induced lung disease is a potentially dangerous lesion, which may occur acutely at any time during therapy and which has been reported at doses as low as 7.5 mg/week. It is not always fully reversible.

Pulmonary symptoms (especially a dry, non-productive cough) or a nonspecific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Methotrexate may produce marked bone marrow depression, resulting in anaemia, leukopenia, and/or thrombocytopenia.

Diarrhoea and ulcerative stomatitis require interruption of therapy; otherwise haemorrhagic enteritis and death from intestinal perforation may occur. Methotrexate therapy in patients with impaired renal function should be undertaken with extreme caution, and at reduced dosages, because renal dysfunction will prolong methotrexate elimination.

Unexpected severe (sometimes fatal) bone marrow suppression and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high dosage) and some non-steroidal anti-inflammatory agents (NSAIA's) (*see sections 4.4, Special warnings and precautions for use* and *4.5, Interaction with other medicinal products and other forms of interaction*).

When concurrent administration of methotrexate and radiotherapy takes place there can be an increased risk of necrosis of soft tissue (*see section 4.8, Undesirable effects*).

*Precautions* - Methotrexate has the potential for serious toxicity. Toxic effects may be related in frequency and severity to dose or frequency of administration but have been seen at all doses. Because they can occur at any time during therapy, it is necessary to follow patients receiving methotrexate closely. Patients undergoing therapy should be supervised, to ensure that signs or symptoms of possible toxic effects or adverse reactions are detected and evaluated with minimal delay. Most adverse reactions are reversible if detected early. When such reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken, including the use of leucovorin calcium if necessary (*see section 4.9, Overdosage*).

If methotrexate therapy is reinstituted, it should be carried out with caution, with adequate consideration of further need for the drug, and with increased alertness as to possible recurrence of toxicity. Pretreatment and periodic haematologic studies are essential to the use of methotrexate in chemotherapy because of its toxic effect of hematopoietic suppression. Any unexpected profound drop in the white blood cell count indicates immediate cessation of the drug and initiation of appropriate therapy.
If profound leukopenia occurs during therapy, bacterial infection may occur or become a threat. Cessation of the drug and appropriate antibiotic therapy is usually indicated. In severe bone marrow depression, blood or platelet transfusions may be necessary.

In patients with malignant disease who have pre-existing bone marrow aplasia, leukopenia, thrombocytopenia or anaemia, the drug should be used with caution, if at all. Methotrexate should be used with extreme caution in the presence of infection, peptic ulcer, ulcerative colitis, debility, in young children or in the elderly.
Since methotrexate may have an immunosuppressive action, this factor must be taken into consideration in evaluating the use of the drug where immune responses in a patient may be important or essential.

*Gastrointestinal:* If vomiting, diarrhoea, or stomatitis occur, which may result in dehydration, methotrexate should be discontinued until recovery occurs. Methotrexate should be used with extreme caution in the presence of peptic ulcer disease or ulcerative colitis.

*Haematopoietic:* Methotrexate can suppress haematopoiesis and cause anaemia, leukopenia, and/or thrombocytopenia. In patients with malignancy and preexisting haematopoietic impairment, the drug should be used with caution, if at all.

In psoriasis, methotrexate should not be stopped immediately if there is a significant drop in blood counts. In the treatment of neoplastic diseases, methotrexate should be continued only if the potential benefit warrants the risk of severe myelosuppression. Patients with profound granulocytopenia and fever should be evaluated immediately and usually require parental broad-spectrum antibiotic therapy.

*Hepatic:* Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity.

Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally 2 years or more) and after a total dose of at least 1.5 grams. In studies in psoriastic patients hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes, and advanced age.

An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known. Special caution is indicated in the presence of preexisting liver damage or impaired hepatic function. Liver function tests, including serum albumin, should be performed periodically prior to dosing but are often normal in the face of developing fibrosis or cirrhosis.

These lesions may be detectable only by biopsy. In psoriasis, the usual recommendation is to obtain a liver biopsy at a total cumulative dose of 1.5 grams. Moderate fibrosis or any cirrhosis normally leads to discontinuation of the drug; mild fibrosis normally suggests a repeat biopsy in 6 months.

Milder histologic findings, such as fatty change and low grade portal inflammation, are relatively common pre-therapy. Although these mild changes are usually not a reason to avoid or discontinue methotrexate therapy, the drug should be used with caution.

*Infection or Immunologic States:* Methotrexate should be used with extreme caution in the presence of active infection, and is usually contraindicated in patients with overt or laboratory evidence of immunodeficiency syndromes. Immunization may be ineffective when given during methotrexate therapy. Immunization with live virus vaccines is generally not recommended. There have been reports of disseminated vaccinia infections after smallpox immunization in patients receiving methotrexate therapy. Hypogammaglobulinemia has been reported rarely.

*Neurologic:* There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who have had craniospinal irradiation. Chronic leukoencephalopathy has also been reported in patients with osteosarcoma who received repeated doses of high-dose methotrexate with leucovorin rescue even without cranial irradiation.
Discontinuation of methotrexate does not always result in complete recovery.

A transient acute neurologic syndrome has been observed in patients treated with high-dose regimens. Manifestations of this neurological disorder may include behavioural abnormalities, focal sensorimotor signs and abnormal reflexes.

The exact cause is unknown. After intrathecal use of methotrexate, the central nervous system toxicity which may occur can be classified as follows: chemical arachnoiditis manifested by such symptoms as headache, back pain, nuchal rigidity, and fever; paresis, usually transient, manifested by paraplegia associated with involvement with one or more spinal nerve roots; leukoencephalopathy, manifested by confusion, irritability, somnolence, ataxia, dementia and occasionally major convulsions.

*Pulmonary:* Pulmonary symptoms (especially a dry, non-productive cough) or a non-specific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation.

Although clinically variable, the typical patient with methotrexate-induce lung disease presents with fever, cough, dyspnoea, hypoxemia, and an infiltrate on chest X-ray, infection needs to be excluded. This lesion can occur at all dosages.

*Renal:* Methotrexate is excreted primarily by the kidney. High doses of methotrexate used in the treatment of osteosarcoma may cause renal damage leading to acute renal failure.

Nephrotoxicity is due primarily to precipitation of methotrexate and 7-hydroxymethotrexate in the renal tubules. Close attention to renal function including adequate hydration, urine alkalinization and measurement of serum methotrexate and creatinine levels, are essential for safe administration.

*Use in Patients with Impaired Renal Function:* Methotrexate use in the presence of impaired renal function may result in accumulation of toxic amounts of methotrexate or even additional renal damage. For this reason, pre-existing kidney disease may be considered as a contraindication to methotrexate therapy. The patient's renal status should be determined during therapy, and proper caution exercised should significant renal impairment be disclosed. Drug dosage should be reduced or discontinued until renal function is improved or restored.

*Laboratory Tests Recommended*: Patient monitoring should include complete haemogram, haemocrit, urinalysis, renal function and liver tests, and chest x-ray. Perform tests prior to therapy, at appropriate periods during therapy and after termination of therapy. Perform liver biopsy or bone marrow aspiration studies when high dose or long term therapy is being followed.

During therapy of psoriasis, monitoring of the following parameters is recommended: haemotology, at least monthly, and liver and renal function every 1 - 3 months. More frequent monitoring is usually indicated during antineoplastic therapy. During initial changing doses, or during periods of increased risk of elevated methotrexate blood levels (i.e. dehydration), more frequent monitoring may also be indicated. Pulmonary function tests may also be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.

*Intrathecal Therapy:* Large doses may cause convulsions. Untoward effects may occur with any intrathecal injection and are commonly neurological. Intrathecal methotrexate appears significantly in systemic circulation and may cause systemic toxicity; therefore systemic therapy should be adjusted appropriately.

Focal leukaemic involvement of the central nervous system may not respond to intrathecal chemotherapy and is best treated with radiotherapy.
Physicians are advised to use smaller volumes of methotrexate for preparation and use in children where intrathecal use is intended as small quantities of methotrexate are required.

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

In the treatment of patients with osteosarcoma, caution must be exercised if high dose methotrexate is administered in combination with a potentially nephrotoxic chemotherapeutic agent (e.g. cisplatin).

*Methotrexate/ Antigout Medications:* Methotrexate may raise the level of blood uric acid. Dosage adjustment of antigout medications may be necessary to control hyperuricaemia and gout.

*Methotrexate/Asparaginase:* Concurrent use may block the effects of methotrexate by inhibiting cell replication. This inhibition of methotrexate's action appears to correlate with suppression of asparaginase levels.

*Methotrexate/Non-Steroidal Anti-Inflammatory Agents (NSAIA's)/Salicylates:* Nonsteroidal anti-inflammatory agents should not be administered prior to, or concomitantly with, the high doses of methotrexate used in the treatment of osteosarcoma. Concomitant administration of some NSAIAs with high-dose methotrexate has been reported to elevate and prolong serum methotrexate levels resulting in deaths from haematologic and gastrointestinal toxicity. Caution should be used when NSAIAs 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 may enhance its toxicity.

*Methotrexate/Phenytoin/Sulphonamides:* The therapeutic as well as toxic effects of methotrexate may be increased by these agents. Inhibition of renal tubular secretion, competition for a common elimination pathway or protein displacement may be the mechanisms involved. Phenytoin serum concentrations may be decreased by a combination chemotherapy regimen including methotrexate.

*Methotrexate/Oral Antibiotics:* Oral antibiotics such as tetracycline, chloramphenicol and non-absorbable antibiotics may decrease intestinal absorption of methotrexate or interfere with the enterohepatic circulation by inhibiting bowel flora and suppressing metabolism of the drug by bacteria. Caution should therefore be exercised upon the concomitant administration of these agents with methotrexate.

*Methotrexate/Other Myelosuppressive Medications/Radiation Therapy:* Concurrent use may increase the total myelosuppressive effects. Dosage adjustments may be required.

*Methotrexate/Folic acid or its derivatives:* Vitamin preparations containing folic acid or its derivatives may decrease responses to systemically administered methotrexate. Folate deficiency states may increase methotrexate toxicity.

*Methotrexate/Trimethoprim and Sulfamethoxazole:* Trimethoprim/sulfamethoxazole has been reported rarely to increase bone marrow suppression in patients receiving methotrexate, probably by an additive antifolate effect.

*Methotrexate/Alcohol/Other Hepatotoxic Medications:* Concurrent use may increase the risk of hepatotoxicity.

*Methotrexate/Procarbazine:* Procarbazine may increase the nephrotoxicity of methotrexate.

*Methotrexate/Thiopurines:* Methotrexate co-administration may increase the AUC and plasma levels of thiopurines.

*Methotrexate/Charcoal:* Charcoal lowers the plasma levels of both oral and IV methotrexate and may be particularly significant with high dose therapies. Depending on the clinical situation, this will reduce the effectiveness or toxicity of methotrexate.

*Methotrexate/Etretinate:* Hepatotoxicity occurred in two patients receiving etretinate and methotrexate for psoriasis, and methotrexate plasma levels increased in another patient.

*Methotrexate/Vaccines, killed virus:* Because normal defence mechanisms may be suppressed by methotrexatae therapy, the patient's antibody response to the vaccine may be decreased. The interval the patient's between discontinuation of medications that cause immunosuppression and restoration of the patient's ability to respond to the vaccine depends on the intensity and type of immuno-suppressive-causing medication used, the underlying disease, and other factors; estimates vary from 3 months to 1 year.

*Methotrexate/Vaccines, live virus:* Because normal defence mechanisms may be suppressed by methotrexate therapy, concurrent use with alive virus vaccine may potentiate the replication of the vaccine virus, may increase the adverse effects of the vaccine virus, and/or may decrease the patient's antibody response to the vaccine; immunization of these patients should be undertaken only with extreme caution after review of the patient's haematological status and only with the knowledge and consent of the physician managing the methotrexate therapy. The interval between discontinuation of medications that cause immunosuppression and restoration of the patient's ability to respond to the vaccine depends on the intensity and type of immunosuppression-causing medication used, the underlying disease, and other factors; estimates vary from 3 months to 1 year.

Patients with leukaemia in remission should not receive live virus until at least 3 months after their last chemotherapy. In addition, immunization with oral polio-virus vaccine should be postponed in persons in close contact with the patient, especially family members.

## 4.6 Pregnancy and lactation

Methotrexate has caused foetal deaths and congenital abnormalities. Methotrexate is contraindicated in pregnant patients with psoriasis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the foetus.

Women of childbearing potential should not be started on methotrexate until pregnancy has been ruled out and should be fully counselled on the serious risk to the foetus should they become pregnant while undergoing treatment. Pregnancy should be avoided if either partner is receiving methotrexate; during and for a minimum of 3 months after therapy for male patients, and during and for at least one ovulatory cycle after therapy for female patients.

It has been reported that methotrexate causes impairment of fertility, oligospermia, and menstrual dysfunction in humans during and for a short period after cessation of therapy. There is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, though the clinical significance remains uncertain. Benefit should be weighed against the potential risk before using methotrexate in combination with other drugs, especially in children or young adults. Methotrexate causes embryotoxicity, abortion and foetal defects in humans. Because of the potential for serious adverse reactions from methotrexate in nursing infants, breastfeeding should be avoided.

*Carcinogenicity:* Antimetabolites have been shown to be carcinogenic in animals and may be associated with an increased risk of development of secondary carcinomas in humans.
Carcinogenicity studies with methotrexate in animals have been inconclusive.

## 4.7 Effects on ability to drive and use machines

This medicine may cause blurred vision, drowsiness and paralysis of part of the body. During treatment patients are advised against performing activities which require concentration, such as participating in traffic, handling machines and working at heights.

## 4.8 Undesirable effects

In general, the incidence and severity of acute side-effects are related to dose and frequency of administration. The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness, and decreased resistance to infection.

Other adverse reactions that have been reported with methotrexate are listed below by organ system. In the oncology setting, concomitant treatment and the underlying disease make specific attribution of a reaction to methotrexate difficult.

*Gastrointestinal System:* Gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhoea, haematemesis, melena, gastrointestinal ulceration and bleeding, enteritis.

*Hepato-biliary disorders*: Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally 2 years or more) and after a total dose of at least 1.5 grams. Also see section 4.4, Special Warnings and Precautions for use'.

*Central Nervous System:* Headaches, drowsiness, blurred vision. Aphasia, hemiparesis, paresis and convulsions have occurred following administration of methotrexate. Following low doses, some patients have reported transient subtle cognitive dysfunction, mood alteration, or unusual cranial sensations. Leukoencephalopathy following IV use in patients who have had craniospinal irradiation has been reported. After intrathecal use, the CNS toxicity that may occur can be classified as follows:

1. Chemical arachnoiditis (headache, back pain, nuchal rigidity, fever)
2. Transient paresis (paraplegia with involvement of spinal nerve roots)
3. Leukoencephalopathy (confusion, irritability, somnolence, ataxia, dementia, occasionally major convulsions).

*Respiratory System:* Interstitial pneumonitis deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred. Deaths due to interstitial pneumonitis have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred.

*Skin:* Erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis. Lesions of psoriasis may be aggravated by concomitant exposure to ultraviolet radiation.

Musculoskeletal, connective tissue and bone disorders. In combination with radiotherapy there is an increased risk of soft tissue necrosis.

*Urogenital System:* Severe nephropathy or renal failure, azotemia, cystitis, hematuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction and vaginal discharge, infertility, abortion, foetal defects.

*Dermatological:* Radiation dermatitis and sunburn may be "recalled" by the use of methotrexate.

*Haematopoietic System:* The occurrence of acute leukaemia, which can occur with or without a preleukeamic phase, has been reported rarely in patients treated with etoposide in association with methotrexate.

*Others:* Metabolic changes precipitating diabetes, osteoporosis, conjunctivitis, abnormal tissue cell changes, arthralgia, myalgia increased homocysteine level, anaphylaxis and sudden death. Acute leukaemia, which can occur with or without a pre-leukaemic phase, has been reported rarely in patients treated with etoposide in association with other antineoplastic drugs, including methotrexate.

A few cases of toxic epidermal necrolysis and Steven-Johnson syndrome were reported.

## 4.9 Overdose

Overdosage may lead to severe toxicity, especially of the heamopoietic and gastrointestinal systems; death may result.

*Treatment:* Leucovorin (citrovorum factor) is used to neutralise toxic effects. Administer leucovorin as promptly as possible. As the time interval between methotrexate administration and leucovorin rescue increases, leucovorin's effectiveness in counteracting haematologic toxicity diminishes.

Leucovorin may be administered as follows: 10 mg/$m^2$ orally or parenterally initially, followed by 10 mg/$m^2$ orally every 6 hours for 72 hours. Leucovorin rescue is usually initiated within 24 hours of antifolate administration. If, after 24 hours following methotrexate administration, the serum creatinine is 50% or greater than the pre-methotrexate serum creatinine, immediately increase the leucovorin dose to 100 mg/$m^2$ every 3 hours until the serum methotrexate level is below 5 x $10^{-8}$ mol/l.

Charcoal haemoperfusion can lower serum methotrexate levels, and ventriculolumbar perfusion was used in one patient who received an overdose of intrathecal methotrexate. In cases of massive overdosage, hydration and urinary alkalinisation may be necessary to prevent the precipitation of methotrexate and its metabolites in the renal tubules. Neither haemodialysis nor peritoneal dialysis improves methotrexate elimination.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Actively proliferating tissues such as malignant cells, bone marrow, foetal cells, buccal and intestinal mucosa, and cells of the urinary bladder are in general more sensitive to 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.

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

High-dose methotrexate, followed by rescue therapy with leucovorin, is used in combination chemotherapy regimens as an adjunct to surgical resection or amputation of the primary tumour in patients with non-metastatic osteosarcoma.

The original rationale for high-dose methotrexate therapy was based on the concept of selective rescue of normal tissues by leucovorin (which is a derivative of tetrahydrofolic acid that blocks the effects of methotrexate if given shortly after the antineoplastic agent). Resistance to methotrexate may develop and has been associated with decreased cellular uptake of the drug; however, the precise mechanism of the development of this resistance has not been established.

More recent evidence suggests that high-dose methotrexate may also overcome methotrexate resistance caused by impaired active transport, decreased affinity of dihydrofolic acid reductase for methotrexate, increased levels of dihydrofolic acid reductase resulting from gene amplification, or decreased polyglutamation of methotrexate. The actual mechanism of action is unknown. Methotrexate also has immunosuppressive activity, in part possibly as a result of inhibition of lymphocyte multiplication.

## 5.2 Pharmacokinetic properties

*Absorption and Distribution:* Methotrexate is generally completely absorbed from parenteral routes of injection. Methotrexate is actively transported across cell membranes. The drug is widely distributed into body tissues, with highest concentrations in the kidneys, gallbladder, spleen, liver, and skin. Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved.

Approximately 50% of the drug in the blood is bound to serum proteins. Methotrexate is retained for several weeks in the kidneys and for months in the liver. Sustained serum concentrations and tissue accumulation of methotrexate may result from repeated daily doses. The drug does not reach therapeutic concentrations in the cerebrospinal fluid (CSF) when given orally or parenterally. High CSF concentrations of the drug may be attained by intrathecal administration. Following intrathecal administration, however, methotrexate passes into the systemic circulation. Peak serum concentrations are achieved within 2 hours following intrathecal injection. Methotrexate crosses the placental barrier, and is distributed into breast milk. The highest breast milk to plasma concentration ratio reached was 0.08:1.

*Metabolism:* After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamate forms which may be converted back to methotrexate by hydrolase enzymes.

These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods.

The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumours.

A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed. Accumulation of this metabolite may become significant at the high doses used in osteogenic sarcoma. The aqueous solubility of 7-hydroxymethotrexate is three- to five fold lower than the parent compound. Methotrexate is partially metabolised by the intestinal flora after oral administration.

*Half-Life:* The terminal half-life for methotrexate is approximately 3-10 hours for patients receiving treatment for psoriasis or low-dose antineoplastic therapy (less than 30 mg/$m^2$). For patients receiving high doses of methotrexate, the terminal half-life is 8-15 hours.

*Excretion:* 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.

Up to 92% of a single dose is excreted within 24 hours following IV administration, followed by excretion of 1-2% of the retained dose daily. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids, that also undergo tubular secretion, can markedly increase methotrexate serum levels.

Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance. Clearance rates vary widely and are generally decreased at higher doses.

Delayed drug clearance is one of the major factors responsible for toxicity, because the toxicity for normal tissues appears to be more dependent on the duration of exposure to the drug than on the peak level achieved. When a patient has delayed drug elimination due to compromised renal function or other causes, methotrexate serum concentrations may remain elevated for prolonged periods. The potential for toxicity from high-dose regimens or delayed excretion is reduced by leucovorin calcium during the final phase of methotrexate plasma elimination. Guidelines for monitoring serum methotrexate levels and for adjustment of leucovorin dosing to reduce the risk of toxicity are detailed in the *section 4.2. Posology and method of Administration*.

## 5.3 Preclinical safety data

No additional information available.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sodium chloride
Sodium hydroxide
Hydrochloric acid, dilute
Water for injection

## 6.2 Incompatibilities

Methotrexate-Teva 25mg/ml may be diluted with 5% dextrose and 0.9% sodium chloride infusion solutions. Such solutions will remain stable for 24 hours. Other drugs should not be mixed with Methotrexate-Teva in the same infusion container.

## 6.3 Shelf Life

Unopened: 3 years
After first opening: Use immediately after opening. Discard any unused contents.
After dilution: Methotrexate-Teva is chemically and physically stable for 24 hours when diluted in 0.9% Sodium Chloride Injection or 5% Dextrose Injection, when protected from light.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. When dilution has taken place under controlled and validated aseptic conditions, the solution should be used within 24 hours of preparation when stored in a refrigerator (2-8ºC), or within 8 hours when stored at room temperature (below 25 ºC). Any unused solution should be discarded.
Other drugs should not be mixed with methotrexate in the same infusion container.

## 6.4 Special precautions for storage

Unopened: Do not store above 25 ºC. Keep the container in the outer carton.
After dilution: *see Section 6.3, Shelf life*.

## 6.5 Nature and contents of container

Methotrexate-Teva 25mg/ml Solution for Injection is available in -
Colourless glass infusion flasks, Ph. Eur. type I of 40ml, 200ml capacity.
Rubber closures: 32mm.
Nature of Elastomer: chlorobutyl, siliconised, grey.

Not all flask sizes may be marketed.

## 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only. Discard any unused contents.
See *section 4.2, Posology and method of administration* for detailed instructions on administration.

As with all cytotoxic preparations, special precautions should be taken for safe handling and disposal. Local cytotoxic guidelines on safe handling of antineoplastic drugs should be consulted and followed.

1. Only trained personnel should handle the drug. Pregnant women should not be involved in the handling process.

2. Handling should be performed in a designated area, ideally in a vertical laminar flow hood (Biological Safety Cabinet - Class II). The work surface should be covered with disposable plastic-backed absorbent paper.

3. Adequate protective clothing should be worn, i.e. PVC gloves, safety glasses, disposable gowns and masks. In the event of contact with the eyes, wash with copious amount of water or saline.

4. Luer-Lock fittings on all syringes and sets should be used. The possible formation of aerosols may be reduced by using large bore needles and venting needles.

5. All unused material, needles, syringes, vials and other items which have come into contact with cytotoxic drugs should be incinerated at 1000°C or more. Excreta should be similarly treated. Liquid waste may be flushed away with copious amounts of water.

6. In the event of a spillage operators should put on gloves and mop up the spilled material with a sponge kept for that purpose. In the event of a powder spillage, cover with a cloth and moisten with water before mopping up. Rinse the area twice with water. Put all solutions and sponges in a plastic bag, seal and label with the words ‘CYTOTOXIC WASTE’ and incinerate.

## 7 MARKETING AUTHORISATION HOLDER

TEVA PHARMA
Industrieweg 23
P.O. Box 217
3640 AE Mijdrecht
Holland

## 8 MARKETING AUTHORISATION NUMBER

PA0749/003/003

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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