Summary of product characteristics

Abitrexate Teva
Solution for Injection
For I.V., Intrathecal, I.M, Intra-Arterial, Intra Ventricular Use

1. NAME OF THE MEDICINAL PRODUCT

Abitrexate Teva

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 25 mg Methotrexate.

Each vial of 2 ml of solution contains 50 mg methotrexate.
Each vial of 4 ml of solution contains 100 mg methotrexate.
Each vial of 8 ml of solution contains 200 mg methotrexate.
Each vial of 20 ml of solution contains 500 mg methotrexate.
Each vial of 40 ml of solution contains 1000 mg methotrexate.

Excipients with known effect
Each ml contains approximately 1.93 mg sodium
Abitrexate Teva 2 ml, 4 ml and 8 ml vials contain less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium free'.
Abitrexate Teva 20 ml contains approximately 38.6 mg sodium per vial, equivalent to 1.93% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
Abitrexate Teva 40 ml contains approximately 77.2 mg sodium per vial, equivalent to 3.86% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for I.V., intrathecal, I.M., intra-arterial and intra-ventricular injection.
Clear yellow-brown solution.
The solution is preservative-free.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Antineoplastic chemotherapy:

Treatment of gestational choriocarcinoma, chorioadenoma destruens and hydatidiform mole.

Palliation of acute lymphocytic leukemia. Abitrexate Teva is also indicated 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, Abitrexate Teva may be used for the induction of remission, but is most commonly used in the maintenance of induced remissions.

Abitrexate Teva may be used alone, or in combination with other antineoplastic drugs, 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. Abitrexate Teva is effective in the treatment of the advanced stages (III and IV, Peter's Staging system) of lymphosarcoma, particularly in children, and in advanced cases of mycosis fungoides.

Psoriasis:

Because of the high risk attending its use, Abitrexate Teva is indicated only in the symptomatic control of severe recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, and only when the diagnosis has been established, as by biopsy and/or after dermatological consultation.

Rheumatoid Arthritis:

Abitrexate can be used in the treatment of selected adults with severe rheumatoid arthritis, only when the diagnosis has been well established according to rheumatological standards, with inadequate response to other forms of antirheumatic therapy, including full dose NSAIDs and usually a trial of at least one or more disease-modifying antirheumatic drugs.

4.2 Posology and method of administration

WARNINGS
The dose must be adjusted carefully depending on the body surface area if methotrexate is used for the treatment of tumour diseases.
Fatal cases of intoxication have been reported after administration of incorrect calculated doses. Health care professionals and patients should be fully informed about toxic effects.

Treatment should be initiated by or occur in consultation with a doctor with significant experience in cytostatic treatment.

Abitrexate Teva may be administered by intramuscular, intravenous (bolus injection or infusion), intrathecal, intra-ventricular or intra-arterial route.

For intrathecal administration, Abitrexate Teva is administered as a 1 mg/ml solution, using an appropriate sterile preservative-free medium such as Sodium Chloride Injection.

Dosages are based on the patient's bodyweight or surface area, except in the case of intrathecal or intra-ventricular administration, when a maximum dose of 15 mg is recommended.

Dosage should be reduced in cases of hematological deficiency and hepatic or renal impairment. When administered by infusion, Abitrexate Teva should only be diluted with normal saline. Larger

doses (more than 100 mg) are usually administered by intravenous infusion over periods not exceeding 24 hours. Part of the dose may be administered as an initial rapid intravenous injection.

Abitrexate Teva has been used with beneficial effects in a wide variety of neoplastic diseases, alone and in combination with other cytotoxic agents, hormones, immunotherapy, radiotherapy or surgery. Therefore, dosage schedules vary considerably depending on the clinical use, particularly when intermittent high-dose regimens are followed by the administration of calcium leucovorin in order to rescue normal cells from toxic effects. Dosage regimens for calcium leucovorin rescue are discussed at the end of this section.

The following are some examples of the dosages of Abitrexate Teva that have been used for particular indications:

Choriocarcinoma and Other Trophoblastic Tumors

By the intramuscular route, in doses of 15-30 mg daily for a 5-day course. Such courses are usually repeated 3-5 times as required, with rest periods of 1 or more weeks between courses, until any toxic symptoms subside.

The effectiveness of therapy is ordinarily evaluated by 24-hour quantitative analysis of urinary human 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 also usually followed by a complete resolution of measurable lesions in 4-6 weeks. After the normalization of HCG, 1 or 2 courses of Abitrexate Teva are usually recommended. Before each course of the drug, careful clinical assessment is essential.

Higher doses of up to 60 mg I.M. every 48 hours may be administered for 4 doses, followed by calcium leucovorin rescue. This course is repeated at 7-day intervals until levels of urinary HCG return to normal. Not less than 4 courses of treatment are usually necessary. Patients with complications, such as extensive metastases, may be treated with Abitrexate Teva in cyclic combination with other cytotoxic drugs.

Chorioadenoma Destruens and Hydatidiform Mole

Since hydatidiform mole may be followed by choriocarcinoma, prophylactic chemotherapy with Abitrexate Teva has been recommended.

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

Lymphoblastic Leukemia

Daily administration of Abitrexate Teva 3.3 mg/m^2, in combination with prednisone 60 mg/m^2, is used as induction therapy in acute lymphatic (lymphoblastic) leukemia in children and young adolescents.

Abitrexate Teva alone, or in combination with other agents, appears to be a 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 with intramuscular methotrexate 30 mg/m^2, twice weekly. It has also been administered intravenously in doses of 2.5 mg/kg body weight, every 14 days. If relapse does occur, reinduction of remission can again usually be obtained by repeating the initial induction regimen.

Meningeal Leukemia

Administer 12 mg/m^2 intrathecally, or an empirical dose of 15 mg. Dilute methotrexate to a concentration of 1 mg/ml using a sterile, preservative-free medium such as 0.9% Sodium Chloride Injection. Administer at intervals of 2-5 days, and repeat until the CSF cell count returns to normal. Then administer one additional dose.

Administration at intervals of less than 1 week may result in increased subacute toxicity. For prophylaxis against meningeal leukemia, the dosage is the same as for treatment, except for the intervals of administration.

The CSF volume is dependent on age, and not on body surface area (BSA). The CSF is at 40% of the adult volume at birth and reaches the adult volume in several years.

Intrathecal methotrexate 12 mg/m^2 (maximum 15 mg) has resulted in low CSF methotrexate concentrations and reduced efficacy in children, and high concentrations and neurotoxicity in adults. The following dosage regimen is based on age instead of BSA, and appears to result in more consistent CSF methotrexate concentrations and less neurotoxicity.

Intrathecal Methotrexate Dosage According to Age.

Age (years)	Dose (mg)
Under 1	6
1	8
2	10
Over 3*	12

*equal or higher than 3 years of age.

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

Lymphomas

In stage III, give methotrexate concomitantly with other antitumor agents.
Treatment in all stages generally consists of several courses with 7-10 day rest periods between each course. Lymphosarcomas in stage III may respond to combined drug therapy with methotrexate 0.625-2.5 mg/kg body weight/day.

Mycosis Fungoides

Although the usual treatment is by orally-administered methotrexate, methotrexate has also been given intramuscularly in doses of 50 mg once a week, or 25 mg twice weekly.

Breast Cancer

Abitrexate Teva 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.

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 Table below.

The starting dose for high-dose methotrexate treatment is 12 g/m^2. If this is insufficient to produce a peak serum concentration of 1,000 micromole per L (0.001 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 unable to tolerate leucovorin orally, administer leucovorin I.V. or I.M. at the same dose and schedule.

Chemotherapy Regimens for Osteosarcoma

DRUG*	DOSE*	TREATMENT WEEK AFTER SURGERY
Methotrexate Leucovorin	12 g/m^2 I.V. as 4-hour infusion (starting dose) 15 mg orally every 6 hours for 10 doses, starting 24 hours after start of methotrexate infusion	4,5,6,7,11,12,15, 16,29,30,44,45
Doxorubicin as a single drug**	30 mg/m^2/day I.V. x 3 days	8,17
Doxorubicin**	50 mg/m^2 I.V.	20,23,33,36
Cisplatin**	100 mg/m^2 I.V.	20,23,33,36

Bleomycin**	15 units/m^2 I.V. x 2 days	2,13,26,39,42
Cyclophosphamide**	600 mg/m^2 I.V. x 2 days	2,13,26,39,42
Dactinomycin**	0.6 mg/m^2 I.V. x 2 days	2,13,26,39,42

* Link MP, Goorin AM, Miseer AW et al. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity, N. Engl. J. Med. 1986;3 14(25):1600-6.

** See each respective monograph for more complete information.
Dosage modifications may be necessary because of drug-induced toxicity.

Bronchogenic Carcinoma

Intravenous infusions of 20-100 mg/m^2 of Abitrexate Teva have been included in cyclical combination regimens for the treatment of advanced tumors. Higher doses of Abitrexate Teva with calcium leucovorin rescue may also be employed as sole treatment.

Head and Neck Cancer

Intravenous infusions of 240-1,080 mg/m^2 of Abitrexate Teva with calcium leucovorin rescue may be used both as preoperative adjuvant therapy and in the treatment of advanced tumors.

Intra-arterial infusions of Abitrexate Teva are indicated for certain head and neck cancers, although this route of administration is not used extensively.

Bladder Carcinoma

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

Psoriasis

Patients should be fully informed of the potential risks involved, and should be under the constant supervision of the treating physician.

The usual dose in cases of severe, uncontrolled psoriasis unresponsive to conventional therapy is 10-25 mg, administered intramuscularly or intravenously once a week and adjusted according to the patient's response.

Rheumatoid Arthritis

Note: The following recommendation is based on clinical studies whose tabulated dosages, as well as the references appear at the end of the paragraph.

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 I.V., increased to a maximum of 50 mg/week I.V. has been administered over a period of 2 months.

Tabulated Summary of Dosages for the Use of Methotrexate (Parenteral) in Rheumatoid Arthritis

STUDY	**DOSE**
Herman (1)	10 mg/m^2, I.V.
Ahern (2)	15 mg , oral 15 mg, I.V.
Campbell (3)	30 mg/m^2, oral 30 mg/m^2, I.V. 30 mg/m^2, I.M.
Steinson (4)	7.5 mg-25 mg per week; I.M./oral
Michaels (5)	10 mg-50 mg per week, I.V.
Andersen (6)	10 mg per week, I.M., increased up to 25 mg if required.
Thompson (7)	10 mg or 25 mg per week, I.M.
Hoffmeister (8)	10 mg-15 mg per week, oral and I.M.
Weinstein (9)	7.5 mg-25 mg per week, oral and I.M.
Szanto (10)	5 mg-15 mg per week oral/I.M.
Tishler (11)	12.5 mg (7.5 mg-15 mg) per week, oral/I.M.
Suarez-Almazor (12)	10 mg per week I.M.
Rau (13)	15 mg per week I.M.

References

1. Herman, R.A., Veng-Pedersen, P., Hoffman, J., Koehnke, R., and Furst, D.E.: Pharmacokinetics of Low-Dose Methotrexate in Rheumatoid Arthritis Patients. *J. Pharm. Sci.* 78: 165-171, 1989. **2.** Ahern, M., Booth, J., Loxton, A., McCarthy, P.M., Meffin, P., Kevant, S.: Methotrexate Kinetics in Rheumatoid Arthritis: Is there an Interaction with Nonsteroidal Anti-Inflammatory Drugs. *J. Rheumatol.* 15: 1356-

1360, 1988. **3.** Campbell, M.A., Perrier, D.G., Dorr, R. T., et. al.: Methotrexate Bioavailability .*Cancer Treat. Rev.* 69: 833-838, 1985. **4.** Steinson, K., Weinstein, A., Korn, J., Abeles, M.: Low-Dose Methotrexate in Rheumatoid Arthritis. *J. Rheumatol.* 9: 860-866, 1982. **5.** Michaels, R. M., Nashel, D.J., Leonard, A., Sliwinski, A.J., Derbes, A. J.: Weekly Intravenous Methotrexate in the Treatment of Rheumatoid Arthritis. *Arthritis Rheum.* 25: 339-341, 1982. **6.** Andersen, P.A., West S.G., O'Dell, J. R., Via C.S.,Claypool, R. G., Kotzin B. L. Weekly Pulse Methotrexate in Rheumatoid Arthritis. Clinical and Immunologic Effects in a Randomized, Double-Blind Study. *Ann. Intern. Med.,* 103: 489-496, 1985. **7.** Thompson, R. N., Watts, C., Edelman, J., Russell, A. S.,: A Controlled Two-Center Trial of Parenteral Methotrexate Therapy for Refractory Rheumatoid Arthritis. *J. Rheumatol.* 11: 760-763, 1984. **8.** Hoffmeister, R. T., :Methotrexate in Rheumatoid Arthritis: 15 Years Experience. *Am. J. Med.* 75: 69-73, 1983. **9.** Weinstein, A., Marlowe, S., Korn, J., Farouhan, F. Low-Dose Methotrexate Treatment of Rheumatoid Arthritis. Long-Term Observations. *Am. J. Med.* 79: 331-337, 1985. **10.** Szanto, E., Low-Dose Methotrexate in Rheumatoid Arthritis: Effect and Tolerance. An Open Trial and a Double- Blind Randomized Study. *Scand. J. Rheumatol.* 15: 97-102, 1986. **11.** Tishler, M., Caspi, D., Rosenbach, T. O., Fishel, B., Wigler, I., Segal, R., Gazit, E., Yaron, M.: Methotrexate in Rheumatoid Arthritis; A Prospective Study in Israeli Patients with immunogenetic Correlations. *Ann. Rheum. Dis.* 47: 654-659, 1988. **12.** Suarz-Almazor M. E., Fitzgerald, A., Grace, M., Russell, A. S.: a Randomized Controlled Trial of Parenteral Methotrexate Compared with Sodium Aurothiomalate (Myochrysine) in the Treatment of Rheumatoid Arthritis. *J. Rheumatol.* 15: 753-756, 1988. **13.** Rau, R., Herborn, G., Kargen, T., Menninger, H., Elhardt, D.A Blinded Randomized Trial of Methotrexate and Gold Sodium Aurothiomalate in Early Erosive Rheumatoid Arthritis. *Arthritis Rheum.* 32: S43, 1981 (Abstract).

Particular attention should be given to the appearance of liver toxicity by performing liver function tests before initiating Abitrexate Teva 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 to normal within 2 weeks, after which, treatment may be recommended at the discretion of the physician.

The use of Abitrexate Teva may permit the return to conventional topical therapy which should be encouraged.

Calcium Leucovorin Rescue

When administering high doses of methotrexate, the following guidelines for methotrexate therapy with leucovorin rescue should be closely observed:

- Methotrexate administration should be delayed until recovery if:
  - the WBC count is less than $1500mm^3$
  - the neutrophil count is less than $500mm^3$
  - the platelet count is less than $75,000mm^3$
  - the serum bilirubin level is more than 1.2 mg/dl
  - the ALT level is more than 450 U
  - mucositis is present, until there is evidence of healing
  - persistent pleural effusion and ascite are present; drain dry prior to infusion
- Adequate renal function must be documented.
- Serum creatinine must be normal and creatinine clearance must be more than 60 ml/min. before the initiating of therapy.

- Serum creatinine must be measured prior to each subsequent course of therapy. If serum creatinine has increased by 50% or more in comparison to a prior value, the creatinine clearance must be measured and documented to be more than 60 ml/min. (even if the serum creatinine is still within the normal range).
- Patients must be well hydrated, and must be treated with sodium bicarbonate for urinary alkalinization. Administer 1,000 ml/m^2 of intravenous fluid over 6 hours prior to initiating of the methotrexate infusion. Continue hydration at 125 ml/m^2/hour (3L/m^2/day) during methotrexate infusion, and for 2 days after the infusion has been completed.
- Alkalinize urine to maintain a pH above 7.0 during methotrexate infusion and leucovorin calcium therapy by giving sodium bicarbonate orally or by incorporation into a separate I.V. solution.
- Repeat serum creatinine and serum methotrexate 24 hours after starting methotrexate, and at least once daily until the methotrexate level is below $5x10^{-8}$ mol/l (0.05 micromolar).

Leucovorin Rescue Schedules Following Treatment

with Higher Doses of Methotrexate

CLINICAL SITUATION	LABORATORY FINDINGS	LEUCOVORIN CALCIUM DOSAGE AND 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 or I.V. every 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).
Delayed Late Methotrexate Elimination	Serum methotrexate level remaining above 0.2 micromolar at 72 hours and more than 0.05 micromolar at 96 hours after administration.	Continue 15 mg PO or I.V. every 6 hours until methotrexate level is less than 0.05 micromolar.
Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury.	Serum methotrexate level of equal or higher than 50 micromolar at 24 hours or equal or higher than 5 micromolar 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 equal or higher than 1.0 mg/dl or more)	150 mg I.V. every 3 hours, until methotrexate level is less than 1 micromolar; then 15 mg I.V. 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 alkalinization and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to less than 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 of 14 doses over 84 hours) in subsequent courses of therapy.

When laboratory abnormalities or clinical toxicities are observed, the possibility that the patient is taking other medications which interact with methotrexate should be considered.

Older People

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

Hepatic Function Impairment

If the bilirubin is between 3-5, or AST more than 180, dosage should be reduced by 25%. If bilirubin is more than 5, omit the dose.

Methotrexate should be administered with great caution, if at all, to patients with significant current or previous liver disease, especially when caused by alcohol. Methotrexate is contraindicated if bilirubin values are >5 mg/dl (85.5 µmol/L).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Methotrexate must not be administered during pregnancy (see section 4.6) or to patients with general poor nutritional status. Furthermore, methotrexate is contraindicated in patients with severe renal or hepatic impairment, bone marrow hypoplasia, leukopenia, thrombocytopenia, anemia, alcohol abuse, hypersensitivity to methotrexate and lung toxicity due to methotrexate. Breast-feeding must not be performed while taking methotrexate (see section 4.6).

4.4 Special warnings and precautions for use

The cytostatic drug methotrexate should be used only under the strict supervision of a specialist with experience in oncology. Treatment should be carried out in a hospital experienced in cancer chemotherapy.
Similarly, the administration of methotrexate in the treatment of psoriasis and rheumatoid arthritis should only take place once a week and under the strict control of a specialist with experience in dermatology and rheumatology.
Patients should be made aware of the importance of strictly following the intake schedule of once a week in the treatment of psoriasis and rheumatoid arthritis.

In general, the following laboratory tests are advised during methotrexate use: CBC (including platelet count and hematocrit); renal function tests and urinalysis; liver enzyme determination. Subsequently, thoracic X-rays are recommended. During the treatment of psoriasis, regular monitoring of these parameters is recommended: monthly for hematology, every 1-3 months for liver and kidney function. More frequent monitoring is usually applied during antineoplastic treatment. More frequent monitoring is also indicated at the beginning of or during changes in dose or during periods of greater risk of elevated methotrexate blood levels (e.g., dehydration).

Transient abnormalities in liver function tests were often observed after methotrexate administration and usually did not lead to a change in therapy. Persistent abnormalities in liver function tests just prior to administration and/or a decrease in serum albumin may indicate severe liver toxicity and require investigation.
Pulmonary function tests may be useful if methotrexate-induced lung disease is suspected, especially if baseline measurements are available.
Methotrexate should be used with extreme care in infections, peptic ulcer disease, ulcerative colitis, physical weakness and in very young or very old persons. If severe leukopenia occurs during therapy, there is a risk of bacterial infection. If infection occurs, discontinuation of treatment and adequate antibacterial therapy is indicated. If nephrotoxicity occurs, immediate discontinuation of treatment is also indicated. Severe bone marrow depression may require blood or platelet transfusion.

Methotrexate-induced lung disease is a potentially dangerous condition that can occur acutely at any time during therapy from doses of 7.5 mg/week. The disease is not always completely reversible. Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment as well as a thorough examination. In methotrexate-induced pneumonitis, therapy with corticosteroids is indicated after immediate discontinuation of therapy. If pulmonary toxicity occurs, re-administration of methotrexate is contraindicated.

In addition, diffuse alveolar hemorrhage has been reported with the use of methotrexate for rheumatologic and related indications. This event may also be associated with vasculitis and other comorbidities. When diffuse alveolar hemorrhage is suspected, immediate investigation should be considered to confirm the diagnosis.

Diarrhea and ulcerative stomatitis require discontinuation of treatment, otherwise there is a risk of hemorrhagic enteritis and death from intestinal perforation.

Treatment of patients with impaired renal function should be done with great caution, and with reduced dose, because in renal dysfunction, methotrexate elimination is prolonged.

Research on carcinogenicity risk when used by rheumatoid arthritis patients is limited.

Protective gloves, an oral mask and safety goggles should be worn when preparing methotrexate injections. Preparation of methotrexate, like that of any cytostatic, should preferably take place in a protective cabinet with vertical airflow. If methotrexate is spilled, rinse with plenty of water.

Although the dosage of methotrexate in psoriasis and rheumatoid arthritis is generally lower than in antineoplastic therapy, poisoning and death may occur with treatment. Patients should be fully informed of the risks and instructed to report any manifestation of toxic symptoms immediately.

Malignant lymphomas may occur in patients receiving low doses of methotrexate. These may diminish after discontinuation of methotrexate treatment; therefore, cytostatic treatment may not be necessary. If necessary, methotrexate treatment should be discontinued first. If the lymphoma does not decrease, adequate treatment should be started.

Methotrexate administration simultaneously with radiotherapy may increase the risk of soft tissue necrosis (see section 4.8).

In children, periodic specific cognitive testing is recommended to detect cognitive impairment at an early stage.

Liver function tests (in non-oncologic indications)
Treatment should not be initiated, or should be discontinued, if persistent or significant abnormalities are detected in liver function tests, in other non-invasive investigations for liver fibrosis, or in liver biopsies.

Temporary elevations in transaminases up to two or three times the normal upper limit have been reported in patients at a frequency of 13-20%. Persistent elevation in liver-related enzymes and/or a decrease in serum albumin may indicate severe hepatotoxicity. In case of persistent elevation in liver-related enzymes, dose reduction or treatment discontinuation should be considered.

Histologic changes, fibrosis, and in rarer cases, liver cirrhosis, are not necessarily preceded by abnormal liver function tests. There are cases of cirrhosis in which transaminases are normal. Therefore, noninvasive diagnostic methods for monitoring liver condition should be considered in addition to liver function tests. Liver biopsy should be considered on an individual basis taking into account the patient's comorbidities, medical history and risks associated with biopsy. Risk factors for hepatotoxicity include excessive prior alcohol consumption, persistent elevation of liver enzymes, history of liver disease, family history of hereditary liver disease, diabetes mellitus, obesity and previous contact with hepatotoxic agents or chemicals and long-term treatment with methotrexate.

Other hepatotoxic drugs should not be used during treatment with methotrexate unless strictly necessary. Consumption of alcohol should be avoided (see sections 4.3 and 4.5). In patients taking other hepatotoxic drugs concomitantly, liver enzymes should be monitored more closely.

Extra caution is required in patients with insulin-dependent diabetes mellitus, since in isolated cases during treatment with methotrexate, liver cirrhosis occurred without any increase in transaminases.

Fertility
Methotrexate has been reported to cause reduced fertility, oligospermia, menstrual dysfunction and amenorrhea in humans during and for a short time after discontinuation of treatment with influence on spermatogenesis and oogenesis during the period of administration - effects that appear to be reversible after discontinuation of treatment.

Teratogenicity - Risk to reproduction
Methotrexate causes embryotoxicity, spontaneous abortion and fetal defects in humans. For this reason, possible effects on reproduction, miscarriage and congenital defects should be discussed with female patients of childbearing age (see section 4.6). In non-oncologic indications, before using Abitrexate Teva, it should be confirmed that the patient is not pregnant. If women of childbearing age are being treated, they should use effective contraception during treatment and for at least six months afterwards.

For contraceptive advice for men, see section 4.6.

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

Photosensitivity
Photosensitivity in the form of extreme sunburn reactions has been observed in some individuals taking methotrexate (see section 4.8). Exposure to bright sunlight or UV radiation should be avoided unless medically indicated. Patients should take appropriate measures to protect themselves from bright sunlight.

Radiodermatitis and sunburn may recur during treatment with methotrexate (recall phenomenon). Psoriatic lesions may worsen with UV radiation and co-administration of methotrexate.

Excipients

Sodium
Abitrexate Teva 2 ml, 4 ml and 8 ml vials contain less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium free'.Abitrexate Teva 20 ml contains approximately 38.6 mg sodium per vial, equivalent to 1.93% of the WHO recommended maximum daily intake of 2 g sodium for an adult. Abitrexate Teva 40 ml contains approximately 77.2 mg sodium per vial, equivalent to 3.86% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interactions with other medicinal products and other forms of interaction

Glutamine may cause a reduction in the tubular secretion of methotrexate and therefore potentiate the toxic effects of methotrexate.
Non-steroidal anti-inflammatory drugs (NSAIDs) should not be administered before or simultaneously with high-dose methotrexate treatment (> 10 mg methotrexate per week). Increased serum levels of methotrexate have been reported with concomitant administration of some NSAIDs with high-dose methotrexate, resulting in death from severe hematologic and gastrointestinal toxicity.
NSAIDs, salicylates, other weak organic acids (such as probenecid) and penicillins (such as amoxicillin) may decrease the tubular secretion of methotrexate, which may increase toxicity. Use of methotrexate with these drugs should be done with caution and closely monitored. The potential toxicity of methotrexate is particularly increased with concomitant use of NSAIDs when diuretics are also used.
In rheumatology, combination therapy of low doses of methotrexate with an NSAID is common.
Plasma protein-bound methotrexate can be displaced by salicylates, NSAIDs, sulfonamides, phenytoin, tetracyclines, chloramphenicol, p-aminobenzoic acid, doxorubicin, bleomycin, cyclophosphamide, aminoglycosides, allopurinol, vincristine, hydrocortisone, prednisone, asparaginase, and cytosine arabinoside, resulting in increased plasma concentrations of unbound methotrexate.
Caution should be exercised when combining high-dose methotrexate with potentially nephrotoxic chemotherapy (e.g., with cisplatin).
The use of nitrous oxide potentiates the effect of methotrexate on folate metabolism and results in increased toxicity, such as severe unpredictable myelosuppression, stomatitis, and in the case of intrathecal administration, increased severe unpredictable neurotoxicity. Although this effect can be reduced by the administration of calcium folinate, the concomitant use of nitrous oxide and methotrexate should be avoided.
Oral antibiotics (including tetracyclines, chloramphenicol and non-absorbable broad-spectrum antibiotics) may affect intestinal flora and interfere with methotrexate absorption.
Administration of additional hematotoxic drugs increases the risk of serious hematotoxic side effects of methotrexate. Co-administration of metamizole and methotrexate may exacerbate the hematotoxic effects of methotrexate, especially in the elderly. Therefore, concomitant administration should be avoided.
Interaction with radiation in radiotherapy may occur (see sections 4.4 and 4.8). Pharmacodynamic interaction with other cytostatic agents may occur: therapeutic and toxic effects are enhanced.
Vaccination with live virus should not be used in patients treated with methotrexate. Partial or complete protection can be obtained using inactivated vaccine.
Vitamin preparations containing folic acid or folic acid derivatives may decrease the effect of systemically administered methotrexate. Preliminary studies in humans and animals have shown that after intravenous administration of calcium folinate, a small amount penetrates the cerebrospinal fluid, mainly as 5-methyltetrahydrofolate, and that this amount in humans is 1 to 3

orders of magnitude lower than the normal methotrexate concentration after intrathecal administration. However, high doses of calcium folinate may decrease the efficacy of intrathecal methotrexate administration.
Folate deficiencies may increase the toxicity of methotrexate. In rare cases, potentiation of bone marrow suppression in methotrexate-treated patients with trimethoprim/sulfamethoxazole has been reported, probably due to additional folate antagonism. The combined use of methotrexate and sulfonamides is therefore strongly discouraged.

4.6 Fertility, pregnancy and lactation

Observations in humans have shown that methotrexate is harmful to the fetus or embryo: miscarriage, fetal death and congenital anomalies have occurred when treating pregnant women, especially during the first trimester of pregnancy.
There should be no breastfeeding during methotrexate treatment.

Women of child-bearing age/ contraception for women
Women must not become pregnant during methotrexate treatment, and effective contraception must be used during methotrexate treatment and for at least 6 months afterwards (see section 4.4). Prior to the start of treatment, women of child-bearing age should be informed about the risk of malformations associated with methotrexate and an existing pregnancy should be excluded with certainty by taking appropriate measures, e.g., a pregnancy test. During treatment, pregnancy tests should be repeated if clinically necessary (e.g., after contraception has not been used). Women of child-bearing age should be advised on contraception and family planning.

Contraception in men
It is not known whether methotrexate is present in semen. Methotrexate has been found to be genotoxic in animal studies. Therefore, the risk of genotoxic effects on sperm cannot be completely ruled out. Limited clinical evidence does not suggest an increased risk of malformations or miscarriage after paternal exposure to low doses of methotrexate (less than 30 mg/week). For higher doses, there are insufficient data to estimate the risk of malformations or miscarriage after paternal exposure.

As a precaution, sexually active male patients or their female partners are recommended to use reliable contraception during the male patient's treatment and for at least 3 months after methotrexate discontinuation. Men should not donate sperm during treatment or for at least 3 months after methotrexate discontinuation.

Pregnancy
Methotrexate is contraindicated during pregnancy in non-oncologic indications (see section 4.3). If pregnancy occurs during methotrexate treatment or up to six months afterwards, medical advice should be given regarding the treatment-related risk of adverse effects to the child and ultrasound examinations should be performed to confirm normal fetal development. In animal studies, methotrexate has been shown to cause reproductive toxicity, especially during the first trimester (see section 5.3). Methotrexate has been shown to be teratogenic in humans; methotrexate has been reported to cause fetal death, miscarriages, and/or congenital anomalies (e.g., craniofacial, cardiovascular, of the central nervous system, and of limbs).

Methotrexate is a potent teratogen in humans, with an increased risk of spontaneous abortions, intrauterine growth retardation and congenital anomalies with exposure during pregnancy.

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

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

Insufficient data are available on exposure to methotrexate during pregnancy at doses higher than 30 mg/week, but higher rates of spontaneous abortions and congenital anomalies are expected, especially at doses commonly used in oncologic indications.

When methotrexate treatment was discontinued prior to conception, normal pregnancies were reported.

When used in oncologic indications, methotrexate should not be administered during pregnancy, especially during the first trimester of pregnancy. The benefit of treatment must be weighed against the potential risk to the fetus on a case-by-case basis. If the drug is used during pregnancy or if the patient becomes pregnant while taking methotrexate, the patient should be informed of the potential risk to the fetus.

Fertility

Methotrexate affects spermatogenesis and oogenesis and may reduce fertility. Methotrexate has been reported to cause oligospermia, menstrual dysfunction and amenorrhea in humans. These effects appear to be reversible in most cases after discontinuation of treatment. In oncologic indications, women who wish to become pregnant are advised to attend genetic consultation, if possible before starting treatment. Men should seek advice on the possibility of sperm storage before starting treatment. Methotrexate may in fact be genotoxic in higher doses (see section 4.4).

4.7 Effects on ability to drive and use machines

Because methotrexate can cause blurred vision, paresis and hemiparesis, the ability to drive and the ability to operate machinery may be adversely affected.

4.8 Undesirable effects

In general, the incidence and severity of acute side effects is proportional to the dose and frequency of administration.
The most frequently reported side effects are ulcerative stomatitis, leukopenia, nausea and abdominal issues. Other common side effects include discomfort, unexplained fatigue, chills and fever, dizziness and decreased resistance to disease.
Given the oncology background, the combination treatment and underlying disease, it is difficult to attribute any particular reaction to Abitrexate Teva.

The following side effects may occur during the use of Abitrexate Teva.

The side effects are listed below by system/organ class and frequency.
Within each frequency group, adverse reactions are ranked by decreasing severity.
Frequencies are defined as follows:
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 determined with available data).

Blood and lymphatic system disorders
Methotrexate may suppress hematopoiesis and cause anemia, leukopenia and/or thrombocytopenia. In patients with pre-existing hematopoietic insufficiency, this drug should be used with caution, or not used at all. In psoriasis, treatment with methotrexate should be discontinued immediately if a significant decrease in blood count occurs. In the treatment of neoplastic diseases, methotrexate can only be continued if the potential cure justifies the risk of severe myelosuppression. Myelosuppression may also occur after intrathecal administration of methotrexate. Patients with severe granulocytopenia and fever should be evaluated immediately and usually require parenteral broad-spectrum antibiotics.
Very rare: Lymphoproliferative disorders.

Immune system disorders
Methotrexate should be administered with extreme caution in case of active infection, and is usually contraindicated in patients with immunodeficiency syndromes.
During methotrexate treatment, immunization may be ineffective. Immunization with a live vaccine is usually not recommended.
Disseminated vaccinia infections were reported after chickenpox immunization in patients on methotrexate treatment.
Rare: Hypogammaglobulinemia.

Nervous system disorders
Headache, drowsiness, blurred vision, aphasia, hemiparesis, paresis and seizures occurred after methotrexate administration.
There have been reports of leukoencephalopathy following intravenous administration of methotrexate to patients who had undergone craniospinal irradiation. Chronic leukoencephalopathy was also reported in patients with osteosarcoma who had received several

high doses of methotrexate with calcium folinate rescue, even without craniospinal irradiation. Discontinuation of methotrexate treatment does not always lead to complete recovery.
A transient acute neurological syndrome was observed in patients treated with high doses of methotrexate. The manifestations of these neurological abnormalities may include abnormal behaviors, focal sensorimotor symptoms and abnormal reflexes. The exact cause of these is not known.
After intrathecal administration of methotrexate, the possible toxic side effects involving the central nervous system can be classified as follows:
- chemical arachnoiditis with symptoms such as headache, back pain, stiff neck and fever
- paresis, usually transient, with paraplegia involving one or more spinal nerve roots
- leukoencephalopathy with confusion, irritability, drowsiness, ataxia, dementia and sometimes severe seizures
- myelopathy.

Very rare: Paresthesia/hypesthesia.

Respiratory, thoracic and mediastinal disorders
Death from interstitial pneumonitis was reported and chronic interstitial obstructive pulmonary disease occasionally occurred.
Pulmonary symptoms (especially a dry, nonproductive cough) or nonspecific pneumonitis during methotrexate treatment may indicate a potentially dangerous injury and require discontinuation of treatment along with a thorough examination. Although symptoms may be variable, the typical patient with methotrexate-induced lung disease presents with fever, cough, dyspnea, hypoxemia and an infiltrate on pulmonary radiography. An infection should be ruled out. This lesion can occur at any dose.
Rare: Methotrexate-associated lung abnormalities after intrathecal administration of methotrexate. If methotrexate-induced lung abnormalities occur, re-administration of methotrexate is contraindicated.
Not known: Diffuse alveolar hemorrhage has been reported with use of methotrexate for rheumatologic and related indications.

Gastrointestinal disorders
Gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration, hemorrhage, abdominal pain and enteritis. If vomiting, diarrhea or stomatitis occur, with possible dehydration, methotrexate treatment should be stopped until recovery occurs.

Methotrexate should be used with extreme caution in cases of gastric ulcers or ulcerative colitis.

Hepatobiliary disorders
Methotrexate can cause acute (increased transaminases) or chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it usually occurs after long-term use.
Hepatotoxicity is exacerbated by alcoholism, obesity, diabetes and advanced age. A proper correlation coefficient was not determined.
Progression and reversibility of lesions are not known.
Caution is required in case of existing liver damage or impaired liver function.
Liver function tests, including serum albumin, should be performed regularly before administration.
Fibrosis, and in rarer cases, liver cirrhosis, are not necessarily preceded by abnormal liver function tests. Therefore, in psoriasis and rheumatoid arthritis, non-invasive diagnostic methods for monitoring liver condition should be considered in addition to liver function tests. Liver biopsy

should be considered on an individual basis taking into account the patient's comorbidities, medical history and risks associated with biopsy. Treatment should not be initiated, or should be discontinued, if persistent or significant abnormalities are detected in liver function tests, in other non-invasive liver fibrosis studies or in liver biopsies.

Skin and subcutaneous tissue disorders
Erythematous rashes, pruritus, urticaria, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis. Psoriatic lesions may be aggravated by exposure to ultraviolet radiation. Radiation dermatitis and sunburn may rebound with the administration of methotrexate.
Uncommon: Photosensitivity reactions.
Not known: Skin peeling/exfoliative dermatitis.

Musculoskeletal and connective tissue disorders
In combination with radiotherapy, there is an increased risk of soft tissue necrosis.
Not known: Osteonecrosis of the jaw (due to lymphoproliferative disorders).

Renal and urinary disorders
Severe nephropathy or kidney failure, azotemia, cystitis, hematuria.
High doses of methotrexate can cause renal damage resulting in acute kidney injury. Nephrotoxicity is usually caused by deposition of methotrexate and 7-hydroxymethotrexate in the renal tubules.

Reproductive system and breast disorders
Gynecomastia, defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction and vaginal discharge; infertility, abortion; fetal abnormalities. Suppression of spermatogenesis may occur, as well as loss of libido and impotence.

General disorders and administration site reactions
Rare: Other reactions associated with or attributed to the use of methotrexate include opportunistic infections and sudden death, lymphomas, arthralgia/myalgia, diabetes, osteoporosis, and vasculitis. A few cases of anaphylactic reactions were reported.
Pancytopenia and sudden increase in rheumatoid nodules have also been reported in patients with rheumatoid arthritis.
Not known: edema, opportunistic infections.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 overdose include one or more severe side effects. With prolonged treatment, toxic effects will become more prominent. In case of overdose, Leucovorin Calciumshould be given as soon as possible. (see also high-dose methotrexate). In case of intrathecal overdose, immediate lumbar puncture followed by ventriculolumbar perfusion and systemic Leucovorin Calciumtherapy

can take place. If necessary, general supportive measures should be taken and blood transfusion administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic category: antimetabolites, folic acid analogues, ATC code: L01B A01.
Other immunosuppressants, ATC code: L04A X03.

Methotrexate is an antimetabolite. It is a folate antagonist, binding to dihydrofolate reductase, the enzyme that converts dihydrofolic acid to tetrahydrofolic acid. This results in inhibition of thymine and purine biosynthesis. In high concentrations, methotrexate also prevents folate influx into the cell. Resistance can occur by reduced transport of methotrexate through cell membranes, and by changes in the affinity for methotrexate of dihydrofolate reductase, among other things. At very high concentrations (> 20 µmol/l), it is possible that methotrexate enters cells by diffusion in addition to active transport. This aspect is taken advantage of in high-dose therapy.

5.2 Pharmacokinetic properties

Absorption
Methotrexate is usually completely absorbed after parenteral administration. After intramuscular injection, the blood serum peak is reached after 30-60 minutes.

Distribution
After intravenous administration, the initial volume of distribution is about 0.18 l/kg (18% of body weight) and at steady state about 0.4-0.8 l/kg (40-80% of body weight).
Methotrexate slowly penetrates the third fluid compartments such as pleural effusions and ascites, where steady-state with plasma concentrations occurs after 6 hours. Methotrexate competes with reduced folates for the carrier of active transport through cell membranes.
At serum concentrations greater than 100 µM, passive diffusion becomes the main route by which effective intracellular concentrations are achieved. In serum, methotrexate is approximately 50% bound to proteins.
Methotrexate does not cross the blood-brain barrier in therapeutic amounts after parenteral administration. High concentrations can be achieved in the cerebrospinal fluid by intrathecal administration.

Biotransformation
After absorption, methotrexate is metabolized hepatically and intracellularly to polyglutamated forms that can be converted back into methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates can remain in the tissue for extended periods of time. The retention and prolonged activity of these active metabolites varies among different cells, tissues and tumors.
At normal doses, a small amount may be metabolized in the liver to 7-hydroxymethotrexate. Accumulation of this inactive metabolite may become important in high-dose treatment. The water solubility of 7-hydroxymethotrexate is 3 to 5 times lower than the original molecule. The half-life of methotrexate is approximately 3-10 hours in patients under treatment for psoriasis and in low-dose antineoplastic therapy (less than 30 mg/m^2). In patients receiving high-dose methotrexate, the half-life is 8-15 hours.

Elimination
Elimination occurs mainly by renal excretion and depends on the dose and route of administration. With intravenous administration, 44-100% of the administered dose is excreted unchanged in the urine within 24 hours.
Of the administered dose, 10% or less is excreted through the bile. Enterohepatic recirculation of methotrexate is thought to occur. Renal excretion is by glomerular filtration and active tubular excretion. Nonlinear elimination due to saturation of renal tubular reabsorption was observed in patients with psoriasis with doses of 7.5-30 mg. Impaired renal function, as well as concomitant intake of drugs that also undergo tubular secretion (such as weak organic acids), can significantly increase serum methotrexate concentration. There is a very good correlation between methotrexate clearance and endogenous creatinine clearance. Methotrexate clearance varies widely and is normally reduced at high doses. Delayed clearance was shown to be one of the main factors responsible for methotrexate toxicity. The toxicity of methotrexate in normal tissue depends on the duration of exposure rather than the peak concentration achieved. If the patient exhibits delayed elimination because of compromised renal function, third compartment effusion, or other cause, the serum methotrexate concentration may remain elevated for a longer period of time.
The risk of toxicity during high-dose administration or delayed elimination is reduced by the administration of calcium folinate during the final phase of elimination of methotrexate from the plasma. Regarding the solubility of methotrexate in the kidneys: in high-dose therapy, the risk of precipitation is higher at pH < 7. Therefore, when administering high-dose methotrexate, hyperhydration and alkalization of the urine is recommended to avoid renal toxicity.
Pharmacokinetic monitoring of serum methotrexate concentration may be useful to detect patients at increased risk of methotrexate toxicity and may help adjust calcium folinate dose.
Guidelines for monitoring serum methotrexate levels and adjusting the calcium folinate dose to reduce the risk of methotrexate toxicity are listed under “Posology and method of administration".

5.3 Preclinical safety study data

No particulars.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Composition:
Each milliliter contains 25 mg of methotrexate with the following non-medicinal ingredients: sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), water for Injections.

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6.2 Incompatibilities

This medicinal product must not be mixed with medicinal products other than those mentioned in section 6.6.

6.3 Shelf life

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

Do not use Abitrexate Teva solution for injection if the solution is not clear.

Abitrexate Teva diluted solution stored between 15-25^{0}C and protected from light has a chemical and physical in-use stability of 24 hours.
From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a dry place at 15°C -25°C in a well closed packaging.
Protect from light.

For storage conditions of the medicinal product after dilution, see section 6.3.

6.5 Nature and contents of container and other instructions

colorless type I glass vials
Abitrexate Teva is packaged in 2 ml, 4 ml, 8 ml, 20 ml and 40 ml vials of solution for injection.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other instructions

Solutions may be further diluted (in the range of 1 mg/ml to 10 mg/ml) with 0.9% sodium chloride solution or 5% Dextrose solution.

Any contact with liquid should be avoided. During preparation, a strictly aseptic working technique should be applied; in terms of protective measures, the use of gloves, mask, goggles and protective clothing are necessary. The use of an LAF cabinet with vertical flow direction is recommended. Gloves should be worn during administration.
The cytotoxic nature of this drug should be considered during waste disposal.

All unused drug or waste material should be disposed of in accordance with local regulations.

7. LICENCE HOLDER AND MANUFACTURER

Teva Israel Ltd.,
124 Dvora HaNevi'a St., Tel Aviv, Israel.

8. REGISTRATION NUMBER
040.04.22978
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