



SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ATAXIL 300 mg/50 ml Concentrate for Solution for IV Infusion
Sterile, cytotoxic

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL solution contains:

Active substance:

Paclitaxel _____ 6 mg

Excipient(s) with known effect:

Ethanol anhydrous _____ 394.7 mg

Macroglycerol ricinoleate _____ 527.3 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colorless to pale yellow, slightly viscous, concentrate injectable solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ovarian cancer:

ATAXIL is indicated for:

- The first-line treatment of advanced or metastatic ovarian cancer in combination with a platinum-containing medicine,
- The second-line treatment of advanced or metastatic ovarian cancer.

Breast cancer:

Adjuvant treatment of early stage:

- ATAXIL is indicated for adjuvant treatment of node-positive breast cancer following anthracycline and cyclophosphamide therapy.

First-line treatment:

- ATAXIL is indicated for the first-line treatment of advanced or metastatic breast cancer:
 - In combination with an anthracycline in patients for whom anthracycline therapy is suitable, or
 - As a single agent in patients for whom anthracycline therapy is not suitable, or
 - In combination with trastuzumab, in patients whose HER-2 is strong positive (3 positive or positive by FISH technique) as determined by immunohistochemistry method.

Second-line treatment:

- ATAXIL is indicated for the second-line treatment of metastatic breast cancer after failure of combination chemotherapy. Prior first-line treatment should have included an anthracycline unless it is not clinically contraindicated.

Non-small cell lung cancer (NSCLC):

ATAXIL is indicated for the first-line treatment of non-small cell lung cancer, in combination with a platinum compound, in patients who are not candidates for curative surgical intervention and/or radiation therapy.

Kaposi's sarcoma:

ATAXIL is indicated for the second-line treatment of AIDS-related Kaposi's sarcoma.



4.2 Posology and method of administration

Posology/frequency and duration of administration

All patients must be premedicated prior to ATAXIL administration to reduce the risks for severe hypersensitivity reaction. Such premedication may include 20 mg dexamethasone (or its equivalent) orally around 6 and 12 hours or IV 30 to 60 minutes before ATAXIL administration, 50 mg IV diphenhydramine (or its equivalent) 30 to 60 minutes before ATAXIL administration, and 300 mg cimetidine or 50 mg IV ranitidine 30 to 60 minutes before ATAXIL administration.

In patients with solid tumors, doses of ATAXIL should not be repeated until the neutrophil count is >1500 cells/mm³ and the platelet count is $>100,000$ cells/mm³ (neutrophil count is <1000 cells/mm³ in patients with Kaposi's sarcoma). Patients who experience severe neutropenia (<500 cells/mm³) or severe peripheral neuropathy should have dosage reduced by 20% for subsequent courses of drug. The incidence of neurotoxicity and the severity of neutropenia increase with dose.

Advanced or metastatic ovarian cancer

Combination treatment:

The dose of 175 mg/m² is administered by a 3-hour IV infusion every 3 weeks in untreated patients. Alternatively, more myelosuppressive dose of 135 mg/m² can be administered by a 24-hour IV infusion every 3 weeks. ATAXIL should be given before a platinum compound when it is given in combination with a platinum compound.

Single agent treatment:

In patients previously treated with chemotherapy, the recommended schedule is 175 mg/m² administered intravenously over 3 hours every 3 weeks.

Breast cancer

Adjuvant treatment:

ATAXIL is administered at a dose of 175 mg/m² intravenously over 3 hours every 3 weeks for 4 courses following anthracycline and cyclophosphamide (AC) therapy.

First-line combination treatment of advanced or metastatic breast cancer:

When used in combination with doxorubicin (50 mg/m²), ATAXIL should be administered 24 hours after doxorubicin. The recommended dose of ATAXIL is 220 mg/m² administered intravenously over 3 hours every 3 weeks.

When used in combination with trastuzumab, the recommended dose of ATAXIL is 175 mg/m² administered intravenously over 3 hours, with a 3-week interval between courses. ATAXIL infusion may be started the day following the first dose of trastuzumab or immediately after the subsequent doses of trastuzumab if the preceding dose of trastuzumab was well tolerated.

Single agent treatment of metastatic breast cancer:

The dose of 175 mg/m² is administered intravenously over 3 hours every 3 weeks.

Weekly dosage: Medicines containing paclitaxel can be given at a dose of 80-100 mg/m² weekly.

Premedicate with IV dexamethasone sodium phosphate injection (8 mg dexamethasone) and ranitidine hydrochloride injection (50 mg ranitidine) or famotidine injection (20 mg famotidine), and diphenhydramine hydrochloride tablet (50 mg diphenhydramine hydrochloride) 30 minutes before ATAXIL administration.

Initial dose of dexamethasone is 8 mg. If no clinically significant hypersensitivity reaction has been reported until the subsequent administration, the dose of dexamethasone is reduced by half of the previous dose (4 mg) in the following week. If no clinically significant hypersensitivity reaction has been reported in the following weeks, the dose is reduced by half of the previous dose until the minimum dose of 1 mg is reached.



Non-small cell lung cancer

Combination treatment:

The dose of 175 mg/m² is administered by a 3-hour IV infusion every 3 weeks in untreated patients. Alternatively, more myelosuppressive dose of 135 mg/m² can be administered by a 24-hour IV infusion every 3 weeks. ATAXIL should be given before a platinum compound when it is given in combination with a platinum compound.

Single agent therapy:

ATAXIL is administered at a dose of 175-225 mg/m² by a 3-hour IV infusion every 3 weeks.

AIDS-related Kaposi's sarcoma

Second-line treatment:

ATAXIL 135 mg/m² is administered intravenously over 3 hours with a 3-week interval between courses or ATAXIL 100 mg/m² is administered intravenously over 3 hours with a 2-week interval between courses (dose intensity is 45-50 mg/m²/week).

Based upon the immunosuppression observed in patients with advanced HIV disease, the following modifications are recommended in these patients:

1. The dose of dexamethasone as one of the three premedication drugs should be reduced to 10 mg orally.
2. Treatment with ATAXIL should be initiated or repeated only if the neutrophil count is at least 1000 cells/mm³.
3. The dose of subsequent courses of ATAXIL should be reduced by 20% for those patients who experience severe neutropenia (<500 cell/mm³ for a week or longer).
4. Concomitant hematopoietic growth factor (G-CSF) should be initiated as clinically indicated.

Method of administration

ATAXIL is administered as IV infusion.

ATAXIL should be administered through an in-line filter with a microporous membrane ≤0.22 µm.

Additional information on special populations

Renal/Hepatic impairment

Patients with hepatic impairment may be at increased risk of toxicity (particularly grade III-IV myelosuppression). Recommendations for dosage adjustment are given in the below table for both 3- and 24-hour infusions.

Patients should be monitored closely for the development of profound myelosuppression.

Dosage Recommendations in Patients with Hepatic Impairment

Degree of Hepatic Impairment			
Transaminase Levels		Bilirubin Levels ^a	Recommended ATAXIL Dose ^b
24-hour infusion			
<2×ULN	and	≤1.5 mg/dl	135 mg/m ²
2 to <10×ULN	and	≤1.5 mg/dl	100 mg/m ²
<10×ULN	and	1.6 – 7.5 mg/dl	50 mg/m ²
≥10×ULN	or	>7.5 mg/dl	Not recommended



3-hour infusion			
<10×ULN	and	≤1.25×ULN	175 mg/m ²
<10×ULN	and	1.26 – 2×ULN	135 mg/m ²
<10×ULN	and	2.01 – 5×ULN	90 mg/m ²
≥10×ULN	or	>5×ULN	Not recommended

a Differences in criteria for bilirubin levels between the 3- and 24-hour infusion are due to differences in clinical trial design.

b Dosage recommendations are for the first course of therapy; further dose reduction in subsequent courses should be based on individual tolerance.

ULN= Upper Limit of Normal

Pediatric population

The safety and efficacy of ATAXIL in children and adolescents below 18 years of age have not been established.

Geriatric population

There is limited data on the use of ATAXIL in the elderly (*see section 4.4 Special warnings and precautions for use, Geriatric Use*)

4.3 Contraindications

ATAXIL is contraindicated:

- In patients with hypersensitivity to paclitaxel or to any of the excipients, especially macroglycerol ricinoleate.
- During pregnancy and lactation (*see section 4.6*).
- In patients with solid tumors with baseline neutrophil counts of less than 1500 cells/mm³ and in patients with AIDS-related Kaposi's sarcoma with baseline or subsequent neutrophil counts of less than 1000 cells/mm³.
- In patients with concurrent, serious and uncontrolled infections in Kaposi's sarcoma.

4.4 Special warnings and precautions for use

ATAXIL should be administered under supervision of physician experienced in the use of cancer chemotherapy agents. Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available.

ATAXIL should be administered as a diluted infusion.

Patients must be pre-treated with corticosteroids, antihistamines and H₂ antagonists before treatment with ATAXIL (*see section 4.2 Posology and method of administration*).

ATAXIL should be administered before cisplatin if used in combination with cisplatin.

Anaphylaxis and Hypersensitivity Reactions

Anaphylaxis and severe hypersensitivity reactions have been commonly observed in patients given paclitaxel. These reactions possibly associate with histamine. Fatal reactions have rarely occurred in patients despite pre-medication. All patients should be pre-treated with corticosteroids, antihistamines, H₂ antagonists.

In the case of severe hypersensitivity reactions, ATAXIL infusion should be discontinued immediately and patients should not be rechallenged with ATAXIL. Hypersensitivity reactions such as flushing, skin reactions, tachycardia, dyspnea and hypotension may not require interruption of treatment with ATAXIL; however, caution should be exercised.

Hematologic Toxicity



Bone marrow suppression (primarily neutropenia) is dose- and administration schedule-dependent and a dose-limiting toxicity. Frequent monitoring of blood cell counts should be performed during ATAXIL treatment. ATAXIL should not be administered in patients who have baseline neutrophil count is less than 1500 cells/mm³ (less than 1000 cells/mm³ in patients with Kaposi's sarcoma).

If there is severe neutropenia during a course of treatment with ATAXIL (less than 500 cells/mm³), the dose in subsequent cycles should be reduced by 20%.

Severe cardiac conduction abnormalities

Severe cardiac conduction abnormalities have been reported rarely during treatment. If patients develop significant conduction abnormalities during ATAXIL administration, appropriate therapy should be administered and continuous electrocardiographic monitoring should be performed during subsequent therapy with ATAXIL.

Cardiovascular toxicity

Hypotension, hypertension, and bradycardia have been observed during ATAXIL administration; patients are usually asymptomatic and generally do not require treatment. In severe cases, ATAXIL infusion may need to be interrupted or discontinued at the discretion of the physician. Frequent monitoring of vital signs, particularly during the first hour of ATAXIL infusion is recommended. Continuous electrocardiographic monitoring is not required except for patients with serious conduction abnormalities.

When ATAXIL is used in combination with doxorubicin or trastuzumab for initial treatment of metastatic breast cancer, monitoring of cardiac functions is recommended (see section 4.8).

When patients are candidates for treatment with ATAXIL in these combinations, they should undergo baseline cardiac assessment including history, physical examination, ECG, echocardiogram, and/or MUGA scan. Cardiac function should be monitored during treatment every three months. Monitoring may help to identify patients who develop cardiac dysfunction. Treating physicians should carefully assess the cumulative dose (mg/m²) of anthracycline administered when making decisions regarding frequency of ventricular function assessment. When testing indicates deterioration in cardiac function, even asymptomatic, treating physicians should carefully assess the clinical benefits of further therapy against the potential for producing cardiac damage, including potentially irreversible damage. If further treatment is decided to be continued, cardiac function should be more frequently monitored (e.g. every 1-2 cycles).

Nervous System

Although the incidence of peripheral neuropathy is frequent, the development of severe symptoms is rare. In severe cases, a dose reduction of 20% for all subsequent courses of ATAXIL is recommended.

ATAXIL contains anhydrous ethanol, and consideration should be given to possible central nervous system (CNS) and other effects of ethanol in all patients. For instance, children may be more sensitive than adults to the effects of ethanol (see *Pediatric Use* in *Special warnings and precautions for use*).

Injection Site Reactions

Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently with the 24-hour infusion than with the 3-hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of ATAXIL at a different site, i.e. "recall", has been reported rarely. Rare reports of more severe



events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis and fibrosis have been reported in study of ATAXIL safety. In some cases, the onset of the injection site reaction either occurred during a prolonged infusion or it was delayed by a week to ten days.

A specific treatment for extravasation reactions is not known at this time. Given the possibility of extravasation, close monitoring of the infusion site for possible infiltration during administration of the medicine is recommended.

Hepatic Impairment

Patients with hepatic impairment may be at increased risk of toxicity (particularly Grade 3-4 myelosuppression). Recommended dose adjustment for 3- and -24-hour infusions is given in table in section 4.2.

Patients should be monitored closely for the development of profound myelosuppression.

ATAXIL may cause interstitial pneumonia in combination with radiotherapy to the lungs, regardless of chronological order.

Severe mucositis is rare in patients with Kaposi's sarcoma. If severe reactions occur, the dose of paclitaxel should be reduced by 25%.

Pseudomembranous colitis has been reported rarely, including in patients without concurrent antibiotic therapy. This reaction should be taken into account in the differential diagnosis of severe or persistent diarrhea occurring during or shortly after paclitaxel treatment.

Pediatric Use

The safety and efficacy of ATAXIL in pediatric patients has not been established. There have been reports of CNS toxicity (rarely associated with death) in a clinical trial that ATAXIL was infused intravenously over 3 hours at doses ranging from 350 mg/m² to 420 mg/m². The toxicity is most likely attributable to the high dose of the ethanol component of the paclitaxel vehicle given over a short infusion time. The use of concomitant antihistamines may intensify this effect. Although a direct effect of the paclitaxel itself cannot be discounted, the high doses used in this study (over twice the recommended adult dosage) must be considered in assessing the safety of paclitaxel for use in this population.

Geriatric Use

Of 2228 patients who received paclitaxel in eight clinical studies evaluating its safety and efficacy in the treatment of advanced ovarian cancer, breast carcinoma, or NSCLC, and 1570 patients who were randomized to receive paclitaxel in the adjuvant breast cancer study, 649 patients (17%) were 65 years or older and 49 patients (1%) were 75 years or older. In most studies, severe myelosuppression was more frequent in elderly patients; in some studies, severe neuropathy was more common in elderly patients. In two clinical studies in NSCLC, the elderly patients treated with paclitaxel had a higher incidence of cardiovascular events. Estimates of efficacy appeared similar in elderly patients and in younger patients; however, comparative efficacy cannot be determined with confidence due to the small number of elderly patients studied. In a study of treatment of ovarian cancer, elderly patients had a lower median survival than younger patients did, but no other efficacy parameters favored the younger group.

ATAXIL contains 50% vol ethanol (alcohol), i.e. up to 20 g per average dose, equivalent to 200 ml of a beer and a glass (210 mL) of wine per dose. This may be harmful to patients suffering from alcoholism. It should also be taken into account when considering using this medicine in children and high-risk groups such as those with liver disease or epilepsy.



ATAXIL contains 527.3 mg macrogolglycerol ricinoleate (polyoxyl castor oil) which may cause severe allergic reactions.

It can be harmful for those with alcohol addiction.

It should be taken into consideration in pregnant or breastfeeding women, in children, and in patients in high-risk groups such as those with liver disease or epilepsy.

The amount of alcohol in this medicinal product may alter the effects of other medicines. The amount of alcohol in this medicinal product may affect your ability to drive and operate machines.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicines on ATAXIL:

Cisplatin

When compared to administration of paclitaxel BEFORE cisplatin in clinical combination studies; when paclitaxel was given AFTER cisplatin, a more profound myelosuppression and an approximately 33% decrease in paclitaxel clearance was demonstrated.

Cytochrome P450 2C8 and 3A4 Substrates, Inducers and Inhibitors

The metabolism of ATAXIL is catalyzed by cytochrome P450 isoenzymes, CYP2C8 or CYP3A4. Caution should be exercised when administering ATAXIL concomitantly with known substrates, inhibitors (e.g. erythromycin, fluoxetine, gemfibrozil) or inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. *In vitro*, the metabolism of paclitaxel to 6 α -hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17 α -ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6 α -hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4.

Cimetidine

The clearance of paclitaxel was not affected by cimetidine pre-treatment.

Effects of ATAXIL on other medicines:

Doxorubicin

Sequence effects characterized by more profound neutropenic and stomatitis episodes, have been observed with combination use of paclitaxel and doxorubicin when paclitaxel was administered BEFORE doxorubicin and using longer than recommended infusion times (paclitaxel administered over 24 hours; doxorubicin administered over 48 hours). Plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination. However, data from a trial using bolus doxorubicin and 3-hour paclitaxel infusion found no sequence effects on the pattern of toxicity.

Since the elimination of doxorubicin and its active metabolites can be reduced when paclitaxel and doxorubicin are given closer in time, ATAXIL for initial treatment of metastatic breast cancer should be administered 24 hours after doxorubicin.

Epirubicin

Reports in literature suggest that plasma levels of epirubicinol, metabolites of epirubicin, may be increased when paclitaxel and epirubicin are used in combination. The clinical significance of increased epirubicinol plasma levels is unknown.



Additional information on special populations

No data are available from interaction studies in special populations.

Pediatric population

No data are available from interaction studies in the pediatric population.

4.6 Fertility, pregnancy and lactation

General principles

Pregnancy category “D”.

Women of childbearing potential/Contraception

Women of childbearing potential should be warned to avoid becoming pregnant during treatment with ATAXIL.

Female and male patients of reproductive age and/or their partners should use contraceptive for at least 6 months after paclitaxel treatment. Male patients should seek advice on sperm storage before paclitaxel treatment due to the possibility of infertility.

Pregnancy

ATAXIL may harm the fetus when administered to a pregnant woman. Paclitaxel has been shown to be toxic to the embryo and fetus in rabbits and to reduce fertility in rats.

There are no studies conducted in pregnant women.

Paclitaxel has harmful pharmacological effects on pregnancy and/or fetus/newborn.

ATAXIL should not be used during pregnancy unless necessary.

If ATAXIL is used during pregnancy or if the patient becomes pregnant while taking this medicine, the patient should be informed of the possible danger.

Breast-feeding

It is not known whether paclitaxel is excreted in human milk. Breast-feeding should be discontinued for the duration of therapy with ATAXIL.

Fertility

Paclitaxel has been shown to reduce fertility in rats.

4.7 Effects on ability to drive and use machines

Possible effects and other effects of ATAXIL on CNS should be taken into consideration as it contains ethanol. Possible effects of pre-medications on CNS used to reduce risk of severe hypersensitivity reactions should be taken into consideration.

Patients should be advised to be careful about these matters while driving or using machines.

4.8 Undesirable effects

The frequency and severity of undesirable effects are generally similar between patients receiving paclitaxel for the treatment of ovarian, breast, or non-small cell lung cancer or Kaposi's sarcoma. However, patients with AIDS-related Kaposi's sarcoma may have more frequent and severe hematologic toxicity, infections (including opportunistic infections*), and febrile neutropenia. These patients require a lower dose intensity and supportive care.

Patients with Kaposi's sarcoma have a higher incidence of elevations in liver function tests or renal toxicity than in patients with solid tumors.

*Cytomegalo virus, Herpes simplex, *Pneumocystis carinii*, *M. avium intracellulare*, esophageal candidiasis, cryptosporidiosis, cryptococcal meningitis and leukoencephalopathy



Undesired Side effects reported in Clinical Trials and Post-marketing Experiences

The following classification of frequency is used: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (frequency cannot be estimated from the available data).

Infections and infestations

Very common : Infection (mainly urinary tract and upper respiratory tract infections)

Uncommon : Septic shock

Not known : Cryptococcal meningitis, sepsis, leukoencephalopathy, opportunistic infection, cytomegalovirus infection, *Pneumocystis carinii* infection, *Mycobacterium avium* complex infection, esophageal candidiasis, cryptosporidial gastroenteritis, pneumonia, *Herpes simplex*, urinary tract infection, upper respiratory tract infection, sinusitis, rhinitis

Blood and the lymphatic system disorders

Very common : Bone marrow failure, bleeding, neutropenia, thrombocytopenia, leucopenia

Rare : Febrile neutropenia

Very rare : Acute myeloid leukemia, myelodysplastic syndrome, hematotoxicity, decreased platelet count

Immune system disorders

Very common : Hypersensitivity reactions, flushing

Uncommon : Respiratory distress, angioedema, generalized urticaria

Not known : Anaphylactic shock, anaphylactic reaction (may be fatal)

Metabolism and nutrition disorders

Not known : Anorexia

Psychiatric disorders

Very rare : Confusional state

Nervous system disorders

Very common : Neurotoxicity (peripheral neuropathy), abnormal visual evoked potentials

Not known : Motor neuropathy (resulting in minor distal weakness), Grand mal seizures, autonomic neuropathy, encephalopathy, convulsions, peripheral motor neuropathy, dizziness, coordination abnormality, hypertonia, paresthesia, headache, insomnia

Eye disorders

Not known : Optic nerve disorder, flashing eyes, photopsia, visual floaters.

Ear and labyrinth disorders

Not known : Loss of hearing, ototoxicity, vertigo, tinnitus

Cardiac disorders

Very common : Abnormal electrocardiogram

Common : Bradycardia

Uncommon : Myocardial infarction, cardiomyopathy, ventricular tachycardia, atrioventricular block and tachycardia

Not known : Ventricular failure, cardiac failure, congestive heart failure, atrial fibrillation,



decreased ejection fraction, supraventricular tachycardia, conduction disturbance, extrasystoles, sinus bradycardia, electrocardiogram repolarization abnormality

Vascular disorders

Very common : Hypotension

Uncommon : Thrombosis, hypertension, thrombophlebitis

Not known : Shock, phlebitis

Respiratory, thoracic and mediastinal disorders

Not known : Respiratory failure, pulmonary embolism, pulmonary fibrosis, interstitial pneumonia, dyspnea, pleural effusion, epistaxis, cough

Gastrointestinal disorders

Very common : Abdominal pain, diarrhea, nausea, vomiting

Not known : Bowel obstruction, bowel perforation, mesenteric thrombosis, ischemic colitis, pancreatitis, pseudo-membranous colitis, neutropenic enterocolitis, ascites, esophagitis, mucosal inflammation, constipation

Hepatobiliary disorders

Common : Increase in aspartate aminotransferase, increase in blood alkaline phosphatase, liver function test abnormality

Uncommon : Increase in blood bilirubin

Not known : Hepatic necrosis (may be fatal), hepatic encephalopathy (may be fatal)

Skin and subcutaneous tissue disorders

Very common : Alopecia

Common : Skin and nail changes

Not known : Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, recall phenomenon, flaky skin, skin fibrosis, cellulite, pruritus, rash, erythema, onycholysis, acne

Musculoskeletal and connective tissue and bone disorders

Very common : Arthralgia, myalgia

Uncommon : Lower back pain

Not known : Pain in extremities

Kidney and urinary tract disorders

Not known: Renal failure, renal toxicity

General disorders and administration site conditions

Common : Extravasation injection site reaction, localized edema, pain, tissue hardening, softness, skin discoloration, shivering, bruising

Not known : Dehydration, pyrexia, edema, chest pain, hyperhidrosis, asthenia, malaise

Investigations

Not known : Increase in blood creatinine

Collaborative Analysis of Adverse Event Experiences in Single-agent Studies



Unless otherwise noted, the following discussion refers to the overall safety database of 812 patients with solid tumors treated with single-agent paclitaxel (with 135 or 175 mg/m² dose, and in 3 or 24-hour administration) in clinical studies.

Hematologic toxicity

Bone marrow suppression was the major dose-limiting toxicity of paclitaxel. Neutropenia, the most important hematologic toxicity, was dose and schedule dependent and was generally rapidly reversible. Severe neutropenia (<500 cells/mm³) was more frequent with the 24-hour than with the 3-hour infusion; infusion duration had a greater impact on myelosuppression than dose. Neutropenia did not appear to increase with cumulative exposure and did appear to be neither more frequent nor more severe for patients previously treated with radiation therapy.

Infectious episodes were observed very commonly; and were fatal in 1% of all patients, and included sepsis, pneumonia and peritonitis. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications. In the immunosuppressed patient population with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma, 61% of the patients reported at least one opportunistic infection. The use of supportive therapy, including G-CSF, is recommended for patients who have experienced severe neutropenia.

20% of the patients experienced a drop in their platelet count below 100,000 cells/mm³ at least once while on treatment; 7% had a platelet count <50,000 cells/mm³ at the time of their worst nadir. Bleeding episodes were reported in 4% of all courses and by 14% of all patients, but most of the hemorrhagic episodes were localized and the frequency of these events was unrelated to the paclitaxel dose and schedule.

Neurologic

In general, the frequency and severity of neurologic manifestations were dose-dependent in patients receiving single-agent paclitaxel. The frequency of peripheral neuropathy increased with cumulative dose. In general, paresthesia occurs as hyperesthesia. Peripheral neuropathy was the cause of paclitaxel discontinuation in 1% of all patients. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paclitaxel therapy.

Reports in the literature of abnormal visual evoked potentials in patients have suggested persistent optic nerve damage.

Hypersensitivity Reactions (HSRs)

All patients received premedication prior to paclitaxel. The frequency and severity of HSRs were not affected by the dose or schedule of paclitaxel. The most frequent symptoms observed during these severe reactions were dyspnea, flushing, chest pain, and tachycardia. In addition, abdominal pain, pain in the extremities, diaphoresis, and hypertension were also noted. The minor hypersensitivity reactions particularly flushing and rash did not require therapeutic intervention or discontinuation of paclitaxel treatment.

Injection Site Reactions

Injection site reactions were usually mild and revealed as localized edema, pain, erythema, tenderness and induration. Sometimes extravasation may result in cellulites. Sometimes skin exfoliation and peeling depending on extravasation has been reported. Additionally, skin discoloration can be observed. These reactions have been seen in 24-hour infusion more frequent



than 3-hour infusion. In some cases, the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to 10 days.

Cardiovascular

Hypotension, during the first 3 hours of infusion, occurred in 12% of all patients and 3% of all courses administered. Bradycardia, during the first 3 hours of infusion, occurred in 3% of all patients and 1% of all courses. The reported ECG modifications were repolarization abnormalities, sinus bradycardia, sinus tachycardia, and premature beats in clinical trials. Severe cardiac conduction abnormalities have been reported in <1% of patients during paclitaxel treatment. If patients develop significant conduction abnormalities, appropriate medication should be applied and continuous electro cardiogram monitoring should be performed during paclitaxel treatment.

Gastrointestinal (GI) Toxicity

Nausea/vomiting, diarrhea, and mucositis were reported very commonly by all patients. Mucositis was schedule dependent and occurred more frequently with the 24-hour than with the 3-hour infusion.

Neutropenic enterocolitis (typhlitis), despite the co-administration of G-CSF, was observed in patients treated with paclitaxel alone and in combination with other chemotherapeutic agents.

The adverse effects reported in administration of single-agent paclitaxel (clinically treated 812 patients in trials) or post-marketing experiences with paclitaxel are given below.

The following classification of frequency is used: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Infections and infestations

Very common : Infections

Uncommon : Septic shock

Not known : Pneumonia, sepsis

Blood and the lymphatic system disorders

Very common : Myelosuppression, neutropenia, anemia, thrombocytopenia, leucopenia, fever, bleeding

Rare : Febrile neutropenia

Very rare : Acute myeloid leukemia, myelodysplastic syndrome

Immune system disorders

Very common : Minor hypersensitivity reactions (mostly flushing and rash)

Uncommon : Hypersensitivity reaction states requiring treatment (e.g. hypotension, angioneurotic edema, difficult breathing, general urticaria, edema, low back pain, tremors)

Rare : Anaphylactic reaction (fatal outcomes)

Very rare : Anaphylactic shock

Metabolism and nutrition disorders

Very rare : Anorexia

Psychiatric disorders



Very rare : Confusional state

Nervous system disorders

Very common : Neurotoxicity (generally peripheral neuropathy)

Rare : Motor neuropathy (resulting in minor distal weakness)

Very rare : Autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension),
Grand mal attacks, convulsions, encephalopathy, dizziness, headache, ataxia

Eye disorders

Very rare : Reversible optic nervous and/or visual disturbances (scintillating scotoma),
photopsy and visual floaters especially at higher doses than recommended

Ear and labyrinth disorders

Very rare : Loss of hearing, vertigo, tinnitus, ototoxicity

Cardiac disorders

Very common : Abnormal ECG

Common : Bradycardia

Uncommon : Cardiomyopathy, asymptomatic ventricular tachycardia, bigeminal tachycardia, AV
block and syncope, myocardial infarcts

Very rare : Atrial fibrillation, supra-ventricular tachycardia

Vascular disorders

Very common : Hypotension

Uncommon : Hypertension, thrombosis, thrombophlebitis

Not known : Shock

Respiratory, thoracic and mediastinal disorders

Rare : Dyspnea, pleural effusion, respiratory failure, intestinal pneumonia, lung fibrosis,
pulmonary embolism

Very rare : Cough

Gastrointestinal disorders

Very common : Nausea, vomiting, diarrhea, mucosal inflammation

Rare : Bowel obstruction, intestinal perforation, ischemic colitis, pancreatitis

Very rare : Mesenteric thrombosis, pseudo-membranous colitis, esophagitis, constipation,
ascites

Hepatobiliary disorders

Very rare : Hepatitis necrosis (can be fatal), hepatic encephalopathy (can be fatal)

Skin and subcutaneous tissue disorders

Very common : Alopecia

Common : Temporal slight skin and nail changes

Rare : Pruritus, skin rash, erythema, phlebitis, cellulites, skin eruption, necrosis and
fibrosis, radiation recall

Very rare : Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative
dermatitis, urticaria, onycholysis (patients receiving treatment should use suntan
lotion on hand and foot)



Not known : Scleroderma

Musculoskeletal and connective tissue disorders

Very common : Arthralgia, myalgia

General disorders and administration site conditions

Common : Injection site reactions (localized edema, pain, erythema, induration of tissues may rarely result in extravasation cellulites)

Rare : Asthenia, malaise, pyrexia, dehydration, edema

Laboratory findings

Common : Severe elevation in AST (SGOT), severe elevation in alkaline phosphatase

Uncommon : Severe elevation in bilirubin

Rare : Increase in blood creatinine

Side Effect Experiences of Combination Treatment Studies

The following discussion refers to untreated patients with ovarian carcinoma or NSCLS who receives paclitaxel in combination with cisplatin, patients with NSCLC receiving single-agent paclitaxel with the Best Supportive Care with whom operation cannot be performed, or patients with breast cancer who received paclitaxel after doxorubicin/cyclophosphamide in the adjuvant setting, or patients with metastatic breast cancer and AIDS-associated Kaposi's sarcoma that receive trastuzumab with paclitaxel as first-line treatment. In addition, rare events reported from post-marketing experiences or in other clinical studies.

Paclitaxel with cisplatin

When administered as a three hour infusion for the first-line chemotherapy of ovarian cancer, neurotoxicity, arthralgia/myalgia, and hypersensitivity were reported as more frequent and severe by patients treated with paclitaxel followed by cisplatin than patients treated with cyclophosphamide followed by cisplatin. Myelosuppression appeared to be less frequent and severe with paclitaxel as a three hour infusion followed by cisplatin compared with cyclophosphamide followed by cisplatin.

Cross-study comparison of neurotoxicity in CA139-209 and CA139-022 trials suggests that when paclitaxel is given in combinations with cisplatin 75 mg/m², the incidence of severe neurotoxicity is more common at a paclitaxel dose of 175 mg/m² given by 3-hour infusion (21%) than at a dose of 135 mg/m² given by 24-hour infusion (3%).

Patients treated with paclitaxel and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynecological cancers.

Paclitaxel with trastuzumab:

When paclitaxel was administered as a 3-hour infusion in combination with trastuzumab for the first-line treatment of metastatic breast cancer, the following events (regardless of relationship to paclitaxel or trastuzumab) were reported more frequently than with single-agent paclitaxel: heart failure, infection, chills, fever, cough, rash, arthralgia, tachycardia, diarrhea, hypertonia, epistaxis, acne, herpes simplex, accidental injury, insomnia, rhinitis, sinusitis, and injection site reaction. Some of these frequency differences may be due to the increased number and duration of treatments with paclitaxel/trastuzumab combination vs. single-agent paclitaxel. Severe events were reported at similar rates for paclitaxel/trastuzumab and single-agent paclitaxel.



In patients previously treated with anthracyclines, paclitaxel/trastuzumab combination therapy has resulted in an increased incidence and severity of cardiac dysfunction compared with single-agent paclitaxel therapy and, in rare cases, has been associated with death. Except for these rare cases, patients responded favorably to all treatments.

Paclitaxel with doxorubicin:

Congestive heart failure has been reported in combination treatment with paclitaxel and doxorubicin in patients who were not previously treated and received chemotherapy in metastatic breast carcinoma.

Cases of myocardial infarction have been reported rarely. Cardiac dysfunction and reduction of left ventricular ejection fraction or ventricular failure have been reported typically in patients receiving paclitaxel treatment and have received chemotherapy, notably anthracyclines.

Paclitaxel with radiotherapy:

Radiation pneumonia has been reported in patients receiving concurrent radiotherapy.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

There is no known antidote of ATAXIL overdose. The main complications are bone marrow suppression, peripheral neurotoxicity and mucositis. The treatment is symptomatic. Overdose in pediatric patients can be associated with acute ethanol toxicity (see section 4.4 *Special warning and precautions for use*).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : Antineoplastic agents
ATC code : L01CD01

Mechanism of action

Paclitaxel, the active substance of ATAXIL, is an agent with anti-tumor activity. Paclitaxel is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

5.2 Pharmacokinetic properties

General properties

The pharmacokinetics of paclitaxel have been evaluated over a wide range doses, up to 300 mg/m², and infusion schedules, ranging from 3 to 24 hours. The pharmacokinetics of paclitaxel have been shown to be non-linear and saturable. There is a disproportionately increase in C_{max} and AUC with increasing dose. Total body clearance appeared to decrease with higher plasma concentration of paclitaxel.



The initial rapid decline represents distribution to the peripheral compartment and elimination of the drug. The later phase is due, in part, to a relatively slow efflux of paclitaxel from the peripheral compartment.

Variability in systemic paclitaxel exposure, as measured by $AUC_{(0-4)}$, for successive treatment courses was minimal; there was no evidence of accumulation of paclitaxel with multiple treatment courses.

Absorption

Administered intravenously. Following intravenous administration, paclitaxel plasma concentrations declined in a biphasic manner. The pharmacokinetics of paclitaxel was determined following 3 and 24-hour infusions at doses of 135 and 175 mg/m². Mean terminal half-life estimates ranged from 13.1 to 52.7 hours, and mean, non-compartmentally derived, values for total body clearance ranged from 12.2 to 23.8 l/hr/m²; total body clearance appeared to decrease with higher plasma concentrations of paclitaxel.

Distribution

On average, 89% of drug is bound to serum proteins; the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine does not affect protein binding of paclitaxel. Mean steady-state volume of distribution ranged from 198 to 688 l/m², indicating extensive extravascular distribution and/or tissue binding.

Biotransformation

In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6 α -hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to 2 minor metabolites, 3'-p-hydroxypaclitaxel and 6 α , 3'-p-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6 α -hydroxypaclitaxel was inhibited by a number of agents (see section 4.5 *Interaction with other medicinal products and other forms of interaction*).

Elimination

Paclitaxel may be eliminated primarily by hepatic metabolism and biliary clearance. Paclitaxel is thought to be metabolized mainly by cytochrome P450 enzymes. After intravenous administration of 15 to 275 mg/m² doses of paclitaxel as 1-, 6-, or 24-hour infusions, mean values for cumulative urinary recovery of unchanged drug ranged from 1.3% to 12.6% of the dose, indicating extensive non-renal clearance. In 5 patients administered a 225 or 250 mg/m² dose of radiolabeled paclitaxel as a 3-hour infusion, a mean of 71% of the radioactivity was excreted in the feces in 120 hours, and 14% was recovered in the urine. Total recovery of radioactivity ranged from 56% to 101% of the dose. Paclitaxel represented a mean of 5% of the administered radioactivity recovered in the feces, while metabolites, primarily 6 α -hydroxypaclitaxel, accounted for the balance.

Linearity/Non-linearity

Dose increases associated with the 3-hour infusion resulted in non-linear pharmacokinetics. When the dose increased by 30% from 135 mg/m² to 175 mg/m², the maximum plasma concentration (C_{max}) increased by 75% and the area under the plasma concentration time curve ($AUC_{0-\infty}$) by 81%. There has been no significant differences in responses given by treated patients to systemic paclitaxel, there is no proof regarding accumulation of paclitaxel in multi treatment courses.

Characteristics in patients



Renal impairment

The effect of renal dysfunction on the disposition of paclitaxel has not been investigated.

Hepatic impairment

The disposition and toxicity of paclitaxel 3-hour infusion were evaluated in 35 patients with varying degrees of hepatic function. Relative to patients with normal bilirubin, plasma paclitaxel exposure in patients with abnormal serum bilirubin ≤ 2 times upper limit of normal (ULN) administered 175 mg/m² was increased, but with no apparent significant increase in the frequency or severity of toxicity. In 5 patients with serum total bilirubin >2 times ULN, there was a statistically non-significant higher incidence of severe myelosuppression, even at a reduced dose (110 mg/m²), but no observed increase in plasma exposure (see sections 4.2 *Posology and method of administration-Hepatic impairment* and 4.4 *Special warnings and precautions for use-Hepatic impairment*).

5.3 Preclinical safety data

The carcinogenic potential of paclitaxel has not been studied. Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay. Decreased fertility and decreased numbers of implantations and live fetuses occurred in rats receiving paclitaxel. Paclitaxel has also been shown to be embryotoxic and fetotoxic in rabbits receiving the drug during organogenesis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Ethanol anhydrous
Macrogolglycerol ricinoleate
Citric acid anhydrous

6.2 Incompatibilities

Macrogolglycerol ricinoleate may cause the release of DEHP (di-(2-ethylhexyl)phthalate) from polyvinyl chloride (PVC) containers containing increased levels of plasticizers with time and concentration. Consequently, PVC-free equipment should be used for the preparation, storage and dilution of paclitaxel.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store unopened vials at room temperature at 25°C in their original packaging.
Diluted solutions should not be stored in the refrigerator, but should be used within 27 hours at room temperature at 25°C and any unused product should be discarded within this period.

6.5 Nature and contents of container

ATAXIL 300 mg/50 ml Concentrate for Solution for IV Infusion: in a package of 1 multi-dose vial.

6.6 Special precautions for disposal and other handling

ATAXIL is a cytotoxic anticancer drug and caution should be exercised in handling. Protective gloves should always be worn when handling vials containing paclitaxel. Dilution should be performed under aseptic conditions by responsible person in a designated area. Measures should be taken to avoid contact with skin and mucosa membranes. In the event of contact of ATAXIL with



the skin, wash your skin with soap and water. In the event of contact with the mucous membranes, flush thoroughly with water. Following topical exposure, tingling, burning and redness have been observed. Upon inhalation, dyspnea, chest pain, burning eyes, burning throat and nausea have been reported. Given the possibility of extravasation, it is advisable to monitor the infusion site closely for possible infiltration during administration of the product.

ATAXIL should be administered through an in-line filter with microporous membrane $\leq 0.22 \mu\text{m}$. Use of filter devices that incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

Prior to infusion, ATAXIL should be diluted using aseptic techniques in 0.9% sodium chloride injection, 5% dextrose injection, 5% dextrose and 0.9% sodium chloride injection, or 5% dextrose in Ringer's solution, to a final concentration of 0.3 to 1.2 mg/ml.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. It should be administered through an in-line filter with a microporous membrane $\leq 0.22 \mu\text{m}$. No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in-line filter.

ATAXIL solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-PVC containing administration sets, such as those that are polyethylene-lined, should be used.

The diluted solution remains chemically and physically stable for 27 hours at room temperature (about 25°C) and in room light; infusions must be completed within this time. Precipitation has rarely been reported when the recommended 3-hour infusion schedule is extended. Excessive shaking, agitation, or vibration may induce precipitation and should be avoided. Before use, infusion sets should be shaken with a compatible diluent.

The Chemo-Dispensing Pin device or similar devices with spikes should not be used since they can cause the vial stopper to collapse, resulting in loss of sterile integrity.

Procedures for proper handling and disposal of anticancer drugs should be considered.

To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing ATAXIL injection. This includes all handling activities in clinical settings, pharmacies, storerooms, and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration.

Any unused material should be disposed according to local disposal regulations.

Both the remaining medicinal product and the entire solution prepared for dilution or infusion must be disposed of in accordance with the hospital's standard procedures for cytotoxic substances and in accordance with applicable legal requirements for the disposal of hazardous waste.

The waste of the inner packaging of cytotoxic and cytostatic medicinal products for human use is considered **HAZARDOUS WASTE** and the management of this waste is carried out in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.

Halkalı Merkez Mah. Basın Ekspres Cad. No: 1

34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER(S)

234/23



9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

Date of first authorization : 08.08.2011

Date of last renewal :

10. DATE OF REVISION OF THE TEXT