# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

ATAXIL 150 mg/25 ml Concentrate for Solution for IV Infusion
Sterile, cytotoxic

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL solution contains:
**Active substance:**
Paclitaxel_____6 mg/mL
**Excipient(s) with known effect:**
Ethanol_____q.s.
Macrogolglycerol ricinoleate (Cremophor EL)_____527.28 mg/mL
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, yellowish (< Reference Solution Y4), viscous 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/mm$^3$ and the platelet count is >100,000 cells/mm$^3$ (neutrophil count is <1000 cells/mm$^3$ in patients with Kaposi's sarcoma). Patients who experience severe neutropenia (<500 cells/mm$^3$) 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/mm$^3$.
3. The dose of subsequent courses of ATAXIL should be reduced by 20% for those patients who experience severe neutropenia (<500 cell/mm$^3$ 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.

ATAXIL can be administered as multi-dose. After dilution, the solution is for single use only.

**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 Paclitaxel Dose[b]** |
| **24-hour infusion** | | | |
| <2×ULN | and | ≤1.5 mg/dl | 135 mg/m² |
| 2 to <10×ULN | and | ≤1.5 mg/dl | 100 mg/m² |
| <10×ULN | and | 1.6 – 7.5 mg/dl | 50 mg/m² |
| ≥10×ULN | or | >7.5 mg/dl | Not recommended |

| 3-hour infusion | | | |
|---|---|---|---|
| <10×ULN | and | ≤1.25×ULN | 175 mg/m² |
| <10×ULN | and | 1.26 – 2×ULN | 135 mg/m² |
| <10×ULN | and | 2.01 – 5×ULN | 90 mg/m² |
| ≥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 polyoxyethylated castor oil.
- During pregnancy and lactation (see section 4.6).
- In patients with solid tumors with baseline neutrophil counts of less than 1500 cells/mm$^3$ and in patients with AIDS-related Kaposi's sarcoma with baseline or subsequent neutrophil counts of less than 1000 cells/mm$^3$.
- 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 $H_2$ 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, $H_2$ 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/$mm^3$ (less than 1000 cells/$mm^3$ in patients with Kaposi's sarcoma).

If there is severe neutropenia during a course of treatment with ATAXIL (less than 500 cells/$mm^3$), 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/$m^2$) 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 ATAXIL 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 527.28 mg macrogolglycerol ricinoleate (Cremophor EL) 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 6α-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, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥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, leucopoenia
*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 colitis, 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, hyperhidrosis, chest pain, 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/mm$^3$) 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/mm$^3$ at least once while on treatment; 7% had a platelet count <50,000 cells/mm$^3$ 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥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, leucopoenia, 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/m$^2$. 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 6α-hydroxypaclitaxel by the cytochrome P450 isozyme CYP2C8; and to 2 minor metabolites, 3'-p-hydroxypaclitaxel and 6α, 3'-p-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α- 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 6α-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
Macrogolglycerol ricinoleate (Cremophor EL)
Citric acid anhydrous
Ethanol anhydrous

### 6.2 Incompatibilities
Macrogolglycerol ricinoleate can result in DEHP (di-(2-ethylhexyl)phthalate) leaching from plasticized polyvinyl chloride (PVC) containers, at levels, which increase with time and concentration. Consequently, the preparation, storage and administration of diluted ATAXIL should be carried out using non-PVC-containing equipment.

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.

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

### 6.3 Shelf life
24 months.

### 6.4 Special precautions for storage
Store at room temperature below 25°C and protect from light and moisture.

### 6.5 Nature and contents of container
The primary packaging materials for ATAXIL 150 mg/25 ml Concentrate for Solution for IV Infusion are 30 mL colorless TYPE I glass vials and gray-colored bromobutyl rubber stoppers. Aluminum safety rings and green flip-off caps are used to seal the vials.

30 mL colorless TYPE I glass vials are packaged in cardboard boxes. Each cardboard box contains 1 glass vial and a package leaflet.

### 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 ≤0.22 µm. 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 ≤0.22 µm. 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 solutions diluted with 0.9% sodium chloride injection + 5% dextrose injection + 5% dextrose in Ringer’s solution + 5% dextrose + 0.9% sodium chloride are physically and chemically stable for up to 27 hours at room temperature (approximately 25°C).

There have been rare reports of precipitation during paclitaxel infusions, usually towards the end of a 24-hour infusion period. To reduce the precipitation risk, paclitaxel should be used as soon as possible after dilution, and excessive agitation, vibration or shaking should be avoided. The infusion sets should be flushed thoroughly before use. During infusion, the appearance of the solution should be regularly inspected and the infusion should be stopped if precipitation is present.

After dilution, the solution is for single use only.

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)

2017/411

## 9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

Date of first authorization : 14.06.2017
Date of last renewal :

## 10. DATE OF REVISION OF THE TEXT