SUMMARY OF PRODUCT CHARACTERISTICS

Paclitaxel Teva

1. NAME OF THE MEDICAL PRODUCT

Paclitaxel Teva

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

COMPOSITION

5 ml vial:	30 mg paclitaxel in a clear, colourless or slightly yellow viscous solution
16.7 ml vial:	100 mg paclitaxel in a clear, colourless or slightly yellow viscous solution
50 ml vial:	300 mg paclitaxel in a clear, colourless or slightly yellow viscous solution

Excipient with known effect:
Ethanol anhydrous: 396 mg/ml
Macrogolglycerol ricinoleate: 527 mg/ml

For full list of excipients, see section 6.1 "List of Excipients".

3. PHARMACEUTICAL FORM

Concentrate for solution for I.V. infusion

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications:

Paclitaxel Teva is indicated, alone or in combination, for the treatment of advanced carcinoma of the ovary.

For the treatment of metastatic breast cancer after failure of combination chemotherapy.
Prior therapy should have included an anthracycline unless clinically contraindicated.

Paclitaxel Teva is indicated for the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy.

Advanced non-small cell lung cancer: Paclitaxel Teva, in combination with cisplatin, is indicated for the treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.

Kaposi's sarcoma: Paclitaxel Teva is indicated in the second-line treatment of AIDS- related Kaposi's sarcoma.

For the treatment of advanced gastric carcinoma.

Pharmacotherapeutic Group

Taxanes: Paclitaxel-ATC Code: L01CD01

4.2 Posology and Method of Administration

Dosage and Method of Administration

First-line chemotherapy of ovarian cancer

Since other dosage regimens have not yet been evaluated, the recommended first- line treatment of ovarian cancer is 135 mg/m^2 of Paclitaxel Teva as an infusion over 24 hours, followed by 75 mg/m^2 of cisplatin and a therapy-free interval of three weeks (see *"Interactions with Other Medicinal Products").*

Second-line chemotherapy of ovarian and metastatic breast cancer

The recommended dosage is 175 mg/m^2 of Paclitaxel Teva, given as an intravenous infusion. Paclitaxel Teva should be administered as a three-hour infusion, with an interval of three weeks between therapy courses.

Adjuvant therapy of node-positive breast cancer

Paclitaxel Teva 175 mg/m^2 administered intravenously over 3 hours every 3 weeks for 4 courses sequentially to standard combination therapy containing doxorubicin.

Advanced non-small cell lung cancer

The recommended regimen, given every 3 weeks, is Paclitaxel Teva administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin 75 mg/m^2.

Kaposi's sarcoma

Paclitaxel Teva administered at a dose of 135 mg/m^2 given intravenously over 3 hours every 3 weeks or at a dose of 100 mg/m^2 given intravenously over 3 hours every 2 weeks is recommended (dose intensity 45-50 mg/m^2/week).

In two clinical trials evaluating these schedules, the former schedule (135 mg/m^2 every 3 weeks) was more toxic than the latter. In addition, all patients with low performance status were treated with the latter schedule (100 mg/m^2 every 2 weeks).

Advanced gastric carcinoma

Paclitaxel Teva administered at a dose of 210 mg/m^2 given intravenously over 3 hours every 3 weeks.

Dose adjustment during treatment

Treatment courses with paclitaxel may be repeated only if blood counts with at least 1,000/mm^3 of neutrophils and at least 75,000/mm^3 of platelets have been reached. In patients who exhibit severe neutropenia (neutrophils <500/mm^3 over a one-week period or longer) or severe peripheral neuropathies during paclitaxel therapy, subsequent dosing should be reduced by 25% to 75 mg/m^2.

Special therapeutic groups

- *Patients with hepatic insufficiency*
- Studies in patients with hepatic dysfunction have not been performed. The available data are insufficient to recommend a dose adjustment for these patients (see *"Pharmacokinetic Properties").* Paclitaxel should not be administered to patients with severe hepatic dysfunction.

- *Patients with renal insufficiency*
- Studies in patients with renal impairment have not been performed. There are no sufficient data for dosage recommendations (see *"Pharmacokinetic Properties").*

- *Paediatric use*
- Studies demonstrating the safety and efficacy of paclitaxel in children and adolescents (below 18 years of age) have not been performed. Paclitaxel is therefore not recommended for paediatric use.

- *Elderly patients*
- Studies demonstrating the safety and efficacy of paclitaxel in elderly patients (over 65 years of age) have not been performed. Paclitaxel is therefore not recommended for use in elderly patients.

Subsequent dosing of paclitaxel depends on individual patient tolerance levels. Treatment with paclitaxel should only be continued after blood counts with at least 1,500/mm^3 of neutrophils and at least 100,000/mm^3 of platelets have been achieved. If patients develop severe neutropenia (with neutrophils <500/mm^3 for 7 days or longer) or severe peripheral neuropathy, dosage should be reduced by 20% in subsequent courses (see *"Special Warnings and Precautions for Use").*

All patients must receive premedication treatment with corticosteroids, antihistaminic agents and H_2 antagonists prior to paclitaxel therapy:

Active ingredient	**Dosage**	**Interval prior to paclitaxel administration**
Dexamethasone	20 mg orally	approx. 12 and 6 hours
Diphenhydramine	50 mg IV	30-60 minutes
Cimetidine or Ranitidine	300 mg IV 50 mg IV	30-60 minutes

Paclitaxel Teva should be administered using a microporous filter with a pore size ≤0.22 μm (in-line filter) - see *"Instructions for Use and Handling'.*

4.3 Contraindications

- Paclitaxel is contraindicated in patients who have shown severe hypersensitivity to either paclitaxel or any of the excipients, or to macrogolglycerol ricinoleate, and in patients with an initial blood count of <1,500/mm^3 of neutrophils.

- Paclitaxel is also contraindicated in patients with concurrent, serious, uncontrolled infections.

- The use of paclitaxel in pregnant women is contraindicated.

- Paclitaxel is contraindicated during breast-feeding.
  Breast-feeding should be discontinued before treatment with paclitaxel.

4.4 Special Warnings and Precautions for Use

Paclitaxel should only be administered by specially trained physicians with experience in the use of (antineoplastic) chemotherapy. Therapy should be adjusted in the hospital.

Intra-arterial application must be strictly avoided.

Adequate emergency equipment must be kept ready as severe anaphylactic reactions may occur. Patients should be monitored carefully during paclitaxel infusion.

Regular respiratory and cardiac examinations are particularly important in the first hour of administration.

To avoid severe hypersensitivity reactions, all patients must undergo prior treatment with corticosteroids, antihistaminic agents and H_2 antagonists.

Severe anaphylactic reactions, characterised by dyspnoea, hypotension, angioedema and generalised urticaria may occur in less than 2% of the patients despite premedication treatment. In this case treatment with paclitaxel must be discontinued immediately and followed by a symptomatic therapy. Repeated treatment courses with paclitaxel are contraindicated in these patients.

Mild hypersensitivity reactions, such as skin reactions, flush, mild dyspnoea, hypotension or tachycardia, do not necessitate discontinuation of therapy.

If severe disorders of impulse conduction in the heart during paclitaxel therapy occur, adequate treatment should be initiated and careful regular monitoring of the cardiac function must be performed throughout subsequent paclitaxel therapy.

Myelosuppression (especially neutropenia) is a dose-limiting reaction. Frequent monitoring of haematological parameters is indicated. Treatment should only be continued after blood counts have adequately recovered and demonstrate neutrophils of at least 1,500/mm^3 and platelets of at least 100,000/mm^3.

Since with neutropenia and thrombocytopenia the risk of infection and bleeding is increased, dental treatment during paclitaxel therapy should only be carried out in exceptional cases. Patients must be advised of the importance of appropriate oral hygiene.

Peripheral neuropathy commonly occurs during treatment with paclitaxel, but severe symptoms rarely develop. In case of severe peripheral neuropathies a dose reduction by 20% in subsequent treatment courses is recommended. Prior treatment with other neurotoxic agents may result in a dose-limiting cumulative neurotoxicity.

In patients with non-small cell lung cancer receiving combination therapy with cisplatin and paclitaxel, neurological symptoms are more common than in patients who are treated with paclitaxel alone.

Increased bone marrow depression was observed in patients with moderate to severe hepatic dysfunction. Paclitaxel should not be administered to patients with severe hepatic dysfunction.

The use of paclitaxel is relatively contraindicated in patients with hepatic dysfunction, herpes zoster, varicella zoster, serious infections or bone marrow depression, in patients who have previously undergone chemotherapy or radiotherapy, and in patients who either suffer from cardiac dysfunction or have had a prior cardiac infarction.

Since Paclitaxel Teva contains ethanol (396 mg/ml), attention must be paid to a potential impact on the central nervous system or other effects. Special care should be taken in patients with alcohol abuse disorders, patients with hepatic impairment, epileptic patients, and patients with cerebral impairment. Diphenhydramine (premedication) may intensify the effect of alcohol.

Concomitant or preceding therapy with cytotoxic agents or radiotherapy may increase the myelotoxicity of paclitaxel.

In first-line therapy of ovarian cancer, the recommended treatment regimen is to give paclitaxel before cisplatin. If paclitaxel is administered prior to cisplatin, the safety profile is similar to the use of paclitaxel as a single agent. Administration of paclitaxel after cisplatin has led to an increase in myelotoxicity and a 20% increase in paclitaxel clearance.

Premedication with cimetidine has no influence on paclitaxel clearance, although a cimetidine-induced inhibition of cytochrome P450 in the liver has been observed; nor does it seem to have an impact on the efficiency of paclitaxel.
The metabolisation of paclitaxel is catalysed by the cytochrome P450 isoenzymes CYP2C8 and CYP3A4 (see *"Pharmacokinetic Properties").* CYP2C8-mediated metabolisation to 6a-hydroxypaclitaxel is the main step in human metabolism. According to current knowledge, no clinically relevant interactions between paclitaxel and other CYP2C8 substrates are expected. Concomitant use of ketoconazole, an inhibitor of CYP3A4, does not inhibit the elimination of paclitaxel in patients. Therefore no further dose adjustment is necessary in combination therapy of paclitaxel and ketoconazole. Since additional data on paclitaxel and other CYP3A4 substrates/inhibitors are limited, special care must be exercised when using paclitaxel in combination with known substrates or inhibitors of CYP3A4.

Since myelotoxicity may result in a changed immune reaction mechanism, immunisation with live virus vaccines should be avoided. Patients undergoing paclitaxel therapy should also avoid contact with persons who recently received oral polio vaccine.

When using paclitaxel in combination with cisplatin, paclitaxel should be applied first as in that case tolerability of paclitaxel corresponds to its use as a single agent. Prior application of cisplatin may result in greater myelosuppression as under these circumstances paclitaxel clearance has been shown to decrease by one fifth.

Patients undergoing treatment with paclitaxel are advised to use effective contraception. If women do get pregnant during treatment with paclitaxel, they must inform their treating physician immediately.

Paclitaxel, particularly in combination with radiation of the lung, irrespective of their chronological order, may contribute to development of interstitial pneumonitis.

Paclitaxel Teva contains macrogolglycerol ricinoleate which may cause severe allergic reactions.

4.5 Interactions with Other Medicinal Products

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4.6 Pregnancy and Lactation

Data on the use of paclitaxel in pregnant women are not available. As with other cytotoxic agents, the use of paclitaxel during pregnancy may result in a potential hazard to the foetus.

The use of paclitaxel in pregnant women is contraindicated.

Patients undergoing treatment with paclitaxel are advised to use effective contraception. If women do get pregnant during treatment with paclitaxel, they must inform their treating physician immediately.

It is not known whether paclitaxel is secreted into human milk.

Paclitaxel is contraindicated during breast-feeding. Breast-feeding should be discontinued before treatment with paclitaxel.

4.7 Effects on Ability to Drive and Use Machines

Paclitaxel may impair the ability to drive and use machines. Paclitaxel contains ethanol (see section 6.1 *"List of Excipients").*

4.8 Undesirable Effects

Results from clinical trials reveal that, when used at the recommended dosage and treatment regimen, paclitaxel is generally well tolerated.
Frequency and severity of adverse effects were shown to correlate with the administered dosage and depended on the patients' baseline condition, but were generally equal in patients with ovarian cancer, breast cancer or non-small cell lung cancer (NSCLC). No association has been established between the age of the patients and any occurring adverse effects.

The following safety data relate to patients with ovarian or breast cancer, who in phase III trials received 175 mg/m^2 of paclitaxel as a single dose over three hours.

Data on the paclitaxel-plus-platinum chemotherapy were generally derived from a large randomised study of ovarian cancer therapy (24-hour infusion, GOG-111) and phase III trials in non-small cell lung cancer (three-hour infusion). Neither the combination of paclitaxel and platinum components nor the infusion of paclitaxel over 24 hours showed a clinically relevant difference with respect to the safety profile of paclitaxel for single-agent use.

The following adverse effects were described:

Infections and infestations
Very common: One quarter of the patients presented symptoms of infection; two of these cases with recommended dosage and infusion regimen had a fatal outcome in the phase III trials.

The most common infections related to neutropenia are urinary tract infections, respiratory infections and sepsis.

Blood and lymphatic system disorders
Very common:

- *Haematopoietic system:* Myelosuppression is the most common serious adverse reaction of paclitaxel therapy. Neutropenia (values <2,000/mm^3) occurred in 28% of patients, but has not been associated with fever; severe neutropenia occurred in only 1% of the cases for seven days or longer. Neutropenia was in general rapidly reversible.

- *Thrombocytopenia* occurred in 11% of patients, 3% had a nadir of <50,000/mm^3 at least once during the trial.

- *Anaemia* was observed in 64%, severe anaemia (Hb<5 mmol/l) occurred in only 6% of patients. Frequency and severity depended on baseline haemoglobin status.

- *Myelosuppression* was less common and less severe if paclitaxel was administered as an infusion over three hours instead of 24 hours. In first-line chemotherapy of ovarian cancer the recommended paclitaxel/cisplatin regimen resulted in greater myelosuppression than the use of paclitaxel as a single agent (175 mg/m2/3h), but without causing an increase in clinical reactions.

Very rare: Acute myeloid leukaemia and myelodysplastic syndrome were very rarely reported.

Benign and malignant tumours (including cysts and polyps)
Very rare: One case of acute myeloid leukaemia and one case of myelodysplastic syndrome were reported.

Hypersensitivity reactions
Very common: One third of patients exhibited mild hypersensitivity reactions (especially flush and skin rash), which did not necessitate therapeutic treatment nor discontinuation of paclitaxel therapy.

Common: With adequate premedication, severe hypersensitivity reactions (hypotension requiring treatment, angioedema, severe dyspnoea, or generalised urticaria) are expected to occur in only 2% of the cases.

Nervous system disorders
Very common: Mild peripheral neuropathy (in particular paraesthesia) occurred in two thirds of patients.

Common: 5% of patients experienced severe peripheral neuropathy. This was slightly more common (6%) in patients with non-small cell lung cancer. More frequent use of paclitaxel may result in greater peripheral neuropathy, and in some cases a discontinuation of the therapy may be strongly recommended. Pre-existing neuropathy resulting from earlier treatment courses does not constitute a contraindication, yet existing symptoms may be intensified as a result of cumulative toxicity.

Neuropathic symptoms improved and/or disappeared only a few months after discontinuation of paclitaxel therapy.

Very rare: Grand mal attacks, encephalopathy, neuropathy (autonomous, resulting in paralytic ileus) and orthostatic hypotension were exhibited in the course of non- randomised clinical trials.

Optical nerve disorders and/or visual impairment (scintillating scotoma) were observed in patients receiving a higher than the recommended dosage. Such symptoms were generally reversible.

Ototoxicity (hearing loss, tinnitus) occurred very rarely and may have been associated with neuropathy, the underlying disease, or the patient's previous medical condition.

Cardiac disorders
Very common: Hypotension and bradycardia have been commonly observed (in 22% and 5% of patients, respectively). However, therapeutic treatment was not necessary.

Uncommon: ECG changes of no or minor clinical relevance were reported, but were not safely associated with paclitaxel.

Very rare: Hypertension, hypotension with aseptic shock and severe thrombotic events (thrombophlebitis and thrombosis of the upper extremities) were very rarely reported.

The following cardiovascular events may occur during paclitaxel therapy, especially in the case of prior anthracycline exposure or non-small cell lung cancer: junctional ventricular tachycardia with bigeminal beats, AV block, syncope, cardiomyopathy, cardiac insufficiency, myocardial infarction and hypotension.

Gastrointestinal disorders
Very common: Adverse gastrointestinal reactions (anorexia, nausea, vomiting, diarrhoea) were mild and occurred in approximately half of patients; nausea and vomiting in approx. 40%, diarrhoea in approx. 30% and mucositis in approx. 20%.

Rare: Intestinal obstruction (ileus), perforation and thrombosis of the mesentery including ischaemic colitis have been reported.

In case of concomitant radiotherapy: neutropenic enterocolitis and pneumonitis.

Hepato-biliary disorders
Common: Significant increase in AST (SGOT) levels (up to five times the normal values) in 5% of patients, and of alkaline phosphatase in 4%.

Uncommon: Increased bilirubin levels were observed in less than 1% of patients.

Very rare: Hepatic necrosis, hepatic encephalopathy and peripheral oedema were reported.

Skin and subcutaneous tissue disorders
Very common: Alopecia was observed in nearly all patients.

Very rare: Exfoliative dermatitis was reported. Stevens-Johnson syndrome, epidermal necrolysis and erythema multiforme were reported, but it is unknown whether these effects may have been the result of other concomitant circumstances.

Musculoskeletal, connective tissue and bone manifestations
Very common: Arthralgia and myalgia were very common (60%). Pain normally occurred 2-3 days following therapy and disappeared within five days.

General disorders and administration site conditions
Very common: Injection site reactions (oedema, pain, erythema, hardening) occurred in 13% of patients.

Rare: In rare cases a "recall" phenomenon was observed, i.e. a recurring local skin reaction at sites of previous extravasation following paclitaxel infusion at a different site. Extravasation may result in cellulitis or discoloration of the skin.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il.

4.9 Overdose

Initial symptoms of paclitaxel overdosage may be bone marrow depression, peripheral neuropathy and mucositis.
There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Paclitaxel promotes the formation of microtubules from tubulin dimers as well as microtubule assembly; it stabilises the microtubules and prevents their depolymerisation. The suppression of microtubule depolymerisation prevents their intracellular reorganisation and leads to aggregation of free tubulin units. The stabilised and dysfunctional microtubules inhibit the formation of a new spindle apparatus and prevent a new regular mitosis. Paclitaxel thus inhibits the cell cycle in the G_2 and M phases.

Tumour cells can also develop resistance to paclitaxel: In cell lines of ovarian cancer a secondary resistance to paclitaxel in cells with modified alpha- and beta-tubulin could be shown.

The second resistance mechanism is associated with the MDR gene. P- glycoprotein, a phosphorylated glycoprotein of the plasma membrane, acts as an efflux pump, thus keeping intracellular concentration of the drug below toxicity level.

In a large randomised controlled study, the safety and efficacy of paclitaxel (135 mg/m^2/24h) followed by cisplatin (75 mg/m^2) versus 750 mg/m^2 of cyclophosphamide and 75 mg/m^2 of cisplatin (GOG-111/B-MS CA 139-022) for first- line chemotherapy of ovarian cancer was evaluated. This study comprised more than 400 patients with untreated stage III/IV ovarian cancer, residual tumours >1 cm after laparotomy or metastatic ovarian cancer. The paclitaxel arm showed a significant increase in median progression-free survival (>3.5 months) and median overall survival (>11 months), while the (severe) toxicity potential was similar in both arms.

For the treatment of advanced non-small cell lung cancer, a therapy regimen consisting of 175 mg/m2 of paclitaxel, followed by 80 mg/m2 of cisplatin, was evaluated in two phase III trials (367 patients received paclitaxel). Both were randomised studies, one drawing a comparison to 100 mg/m2 of cisplatin, the other to 100 mg/m2 of teniposide, followed by 80 mg/m2 of cisplatin (367 patients in the control group). Both studies exhibited similar results. With regard to mortality as the primary end point, no significant difference between the paclitaxel arm and the control arm was detected (median survival was 8.1 and 9.5 months in the paclitaxel group and 8.6 and 9.9 months in the control group). Likewise, there was no significant difference in progression-free survival. A significant benefit in clinical response was observed. Data on paclitaxel therapy conclude that the quality of life as regards appetite is improved and show a clear disadvantage of paclitaxel with respect to the occurrence of peripheral neuropathy ($p>0.008$).

In a study of non-small cell lung cancer therapy in 599 patients with advanced and metastatic NSCLC publicised by the Eastern Cooperative Oncology Group (ECOG), two dosage regimens of paclitaxel (135 and 250 mg/m^2 as a 24-hour infusion) plus cisplatin (75 mg/m^2) were compared with etoposide (100 mg/m^2) plus cisplatin (75 mg/m^2). Responses were 27% and 32% in the paclitaxel combination groups compared to 12% in the etoposide-plus-cisplatin group. Superior overall survival was observed in the groups with combined paclitaxel regimens (9.9 months vs. 7.6 months). Granulocytopenia, myalgia, neurotoxicity and possibly also cardiotoxicity were more common in the paclitaxel-plus-cisplatin group than in the etoposide-plus- cisplatin group.

5.2 Pharmacokinetic Properties

Intravenous administration of paclitaxel demonstrates a biphasic plasma clearance.

Plasma binding is extensive and ranges from 89% to 98% *(in vitro* studies, at concentrations of 0.1-50 µg/l).

The steady-state volume of distribution of paclitaxel ranges from 198 to 688 l/h/m^2, indicating extensive extravascular and/or tissue binding. A half-life of 3-52 hours has been registered.
The pharmacokinetic data were derived after three-hour and 24-hour infusions of 135 mg/m^2 and 175 mg/m^2.

A mean terminal elimination half-life of 3-53 hours has been registered. The mean non-compartment-dependent values for overall body clearance range from 11.6 to 24 l/h/m^2. Overall clearance of the drug from the body seems to decrease with higher paclitaxel concentrations in the plasma.

Increasing dose levels in a three-hour infusion exhibit non-linear pharmacokinetics. Increasing dosage by 30% from 135 mg/m^2 to 175 mg/m^2 resulted in an increase in Cmax and AUC0 values by 75% and 81%, respectively. Intraindividual variability after systemic administration was minimal. No evidence of a cumulative effect of paclitaxel in several treatment courses has been found.

The elimination pathways of paclitaxel in humans are currently not fully known.

The mean values for cumulative urinary recovery of unchanged paclitaxel range from 1.3 to 13% of the administered dose, indicating pronounced non-renal clearance. Paclitaxel is assumed to be primarily eliminated through the hepatic metabolism (generally through cytochrome P450 enzymes). After administration of radioactively marked paclitaxel, mean recovery of the radioactive substance in the faeces is 26% as 6a-hydroxypaclitaxel, 2% as 3'-p-hydroxypaclitaxel and 6% as 6a, 3'-p-dihydroxypaclitaxel. The formation of these hydroxylated metabolites is catalysed by the isoenzymes CYP2C8 and CYP3A4. There are no current data on elimination after three-hour infusion of paclitaxel in patients with hepatic and renal infusion impairment. The pharmacokinetic parameters of a patient who received 135 mg/m^2 of paclitaxel as a three-hour infusion were similar to the values exhibited in non-dialysis patients.

5.3 Preclinical Safety Data

Studies on the carcinogenic potential of paclitaxel have not been performed. Due to its pharmacodynamic reaction mechanism, however, paclitaxel is regarded as potentially carcinogenic and genotoxic.

Both *in vitro* and *in vivo* studies demonstrate that paclitaxel has a mutagenic effect on mammalian cells.

In animal studies paclitaxel was shown to be embryotoxic and foetotoxic and to decrease fertility in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Macrogolglycerol ricinoleate, anhydrous ethanol, anhydrous citric acid.

6.2 Incompatibilities

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

6.3 Shelf Life

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

After opening before dilution

Chemical and physical in-use stability has been demonstrated for 28 days below 25°C following multiple needle entries and withdrawal.

From a microbiological point of view, after first opening the concentrated solution for infusion may be stored for a maximum of 28 days below 25°C. Other in-use storage times and conditions are the responsibility of the user.

After dilution

Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated for 27 hours at 25°C when diluted in a mixture of 9 mg/ml (0.9%) sodium chloride solution for infusion and 50 mg/ml (5%) glucose solution for infusion, or Ringer's solution for infusion containing 50 mg/ml (5%) glucose.

Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 5°C and at 25°C for 14 days when diluted in 50 mg/ml (5%) glucose solution for infusion or in 9 mg/ml (0.9%) sodium chloride solution for infusion.

Microbiological in-use stability of the solution prepared for infusion has been demonstrated for 27 hours at 25°C. Other in-use storage times and conditions are the responsibility of the user.

6.4 Special Precautions for Storage

Store below 25ºC. Do not refrigerate. Do not freeze.

Store in the original package.

Diluted solutions: see section "Shelf Life".

6.5 Nature and Contents of Container

Presentations

Each carton contains one colourless glass vial (type I) with bromobutyl rubber stopper Teflon coating, with aluminium seal and plastic snap-cap:
5 ml vial: 30 mg paclitaxel
16.7 ml vial: 100 mg paclitaxel
50 ml vial: 300 mg paclitaxel
Not all pack sizes may be marketed.

6.6 Special Precautions for Disposal

Instructions for Use and Handling

Handling

As with other antineoplastic agents, caution should be exercised when handling Paclitaxel Teva. Pregnant women should not handle cytotoxic agents (see also section "Pregnancy and Lactation"). Dilution should be carried out under aseptic conditions by trained personnel in a designated area. Adequate protective gloves should be worn. Precautions should be taken to avoid contact with the skin or mucous membranes. In the event of contact with the skin, the area should be washed with soap and water. Following topical exposure, tingling, burns and redness have been observed. In the event of contact with the mucous membranes, these should be flushed thoroughly with water. Upon inhalation, dyspnoea, chest pain, burning throat and nausea have been reported.

If unopened vials are refrigerated or frozen, a precipitation may form, that redissolves with little or no agitation upon reaching room temperature. Product quality is not affected. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded.

Following multiple needle entries and product withdrawals, the vials maintain microbial, chemical and physical stability for up to 28 days at 25°C. Other in-use storage times and conditions are the responsibility of the user.

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.

Preparation of an intravenous administration

Prior to infusion, Paclitaxel Teva must be diluted using aseptic techniques in 9 mg/ml (0.9%) sodium chloride solution for infusion, or 50 mg/ml (5%) glucose solution for infusion, or a mixture of 9 mg/ml (0.9%) sodium chloride solution for infusion and 50 mg/ml (5%) glucose solution for infusion**,** or Ringer's solution for infusion containing 50 mg/ml (5%) glucose, to a final concentration of 0.3 to 1.2 mg/ml.

For microbial, chemical and physical in-use stability of the diluted solutions see section "Shelf Life".

Upon preparation, solutions may show some haziness, which is attributed to the formulation vehicle, and is not removed by filtration. Paclitaxel Teva 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.

There have been rare reports of precipitation during paclitaxel infusions, usually towards the end of a 24-hour infusion period. Although the cause of this precipitation has not been elucidated, it is probably linked to the supersaturation of the diluted solution. To reduce the precipitation risk, Paclitaxel Teva 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.

To minimise patient exposure to DEHP [di-(2-ethylhexyl)phthalate] which may be leached from plasticised PVC infusion materials, diluted paclitaxel solutions should be stored in non-PVC bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets. Use of filter devices which incorporate short inlet

and/or outlet plasticised PVC tubing has not resulted in significant leaching of DEHP.

Disposal
All items used for the preparation, administration or otherwise coming into contact with Paclitaxel Teva should undergo disposal according to local guidelines for the handling of cytotoxic compounds.

7. LICENCE HOLDER AND MANUFACTURER

Manufacturer:
Pharmachemie B.V. (Teva Group),
Haarlem, The Netherlands.

License Holder:
Abic Marketing Ltd.,
P.O.Box 8077, Netanya.

8. REGISTRATION NUMBER

136.41.31278

The content of this leaflet was approved by the Ministry of Health in June 2016 and updated according to the guidelines of the Ministry of Health in November 2018.