







*Signature*

Interaction with other medicinal products and other forms of interaction

Paditaxel clearance is not affected by cimetidine premedication.  
Cisplatin: paditaxel is recommended to be administered before cisplatin. When given before cisplatin, the safety profile of paditaxel is consistent with that reported for single agent use. Administration of paditaxel after cisplatin treatment leads to greater myelosuppression and about a 20% decrease in paditaxel clearance. Patients treated with paditaxel and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynecological cancers.

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

Active substances metabolised in the liver: The metabolism of paditaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, in the absence of a PK drug drug interaction study, caution should be exercised when administering paditaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paditaxel may be increased due to higher paditaxel exposure. Administering paditaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paditaxel exposures.

Studies in KS patients, who were taking multiple concomitant medications, suggest that the systemic clearance of paditaxel was significantly lower in the presence of nelfinavir and ritonavir, but not with indinavir. Insufficient information is available on interactions with other protease inhibitors. Consequently, paditaxel should be administered with caution in patients receiving protease inhibitors as concomitant therapy.

Effects on ability to drive and use machines

This medicinal product contains alcohol, which may impair the ability to drive or operate machines.

Adverse drug reaction

Unless otherwise noted, the following discussion refers to the overall safety database of 812 patients with solid tumors treated with single-agent paditaxel in clinical studies. As the KS population is very specific, a special chapter based on a clinical study with 107 patients, is presented at the end of this section. The frequency and severity of undesirable effects, unless otherwise mentioned, are generally similar between patients receiving paditaxel for the treatment of ovarian carcinoma, breast carcinoma, or NSCLC. None of the observed toxicities were clearly influenced by age. The most frequent significant undesirable effect was bone marrow suppression. Severe neutropenia (<0.5 x 109/l) occurred in 28% of patients, but was not associated with febrile episodes. Only 1% of patients experienced severe neutropenia for ≥7 days. Thrombocytopenia was reported in 11% of patients. Three percent of patients had a platelet count nadir <50 x 109/l at least once while on study. Anaemia was observed in 64% of patients, but was severe (Hb <8.1 g/dl) in only 6% of patients. Incidence and severity of anaemia is related to baseline haemoglobin status.

Neurotoxicity, mainly peripheral neuropathy, appeared to be more frequent and severe with a 175 mg/m² 3-hour infusion (85% neurotoxicity, 15% severe) than with a 135 mg/m² 24-hour infusion (25% peripheral neuropathy, 3% severe) when paditaxel was combined with cisplatin. In NSCLC patients and in ovarian cancer patients treated with paditaxel over 3 hours followed by cisplatin, there is an apparent increase in the incidence of severe neurotoxicity. Peripheral neuropathy can occur following the first course and can worsen with increasing exposure to paditaxel. Peripheral neuropathy was the cause of paditaxel discontinuation in a few cases. Sensory symptoms have usually improved or resolved within several months of paditaxel discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for paditaxel therapy.

Arthralgia or myalgia affected 60% of patients and was severe in 13% of patients.

A significant hypersensitivity reaction with possible fatal outcome (defined as hypotension requiring therapy, angioedema, respiratory distress requiring bronchodilator therapy, or generalised urticaria) occurred in two (< 1%) patients. Thirty-four percent of patients (17% of all courses) experienced minor hypersensitivity reactions. These minor reactions, mainly flushing and rash, did not require therapeutic intervention nor did they prevent continuation of paditaxel therapy.

Injection site reactions during intravenous administration may lead to localised oedema, pain, erythema, and induration; on occasion, extravasation can result in cellulitis. Skin sloughing and/or peeling has been reported, sometimes related to extravasation. Skin discoloration may also occur. Recurrence of skin reactions at a site of previous extravasation following administration of paditaxel at a different site, i.e., "recall", has been reported rarely. A specific treatment for extravasation reactions is unknown at this time.

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.

Disseminated intravascular coagulation (DIC), often in association with sepsis or multi-organ failure, has been reported.

Alopecia: Alopecia was observed in 87% of patients and was abrupt in onset. Pronounced hair loss of ≥50% is expected for the majority of patients who experience alopecia. The table below lists undesirable effects regardless of severity associated with the administration of single agent paditaxel administered as a three hour infusion in the metastatic setting (812 patients treated in clinical studies) and asreported in the post-marketing surveillance" of paditaxel.

The frequency of undesirable effects listed below is defined using the following convention:

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000)

System Organ Class	Frequency /Adverse Reactions
Infections and infestations:	Very common: infection (mainly urinary tract and upper respiratory tract infections), with reported cases of fatal outcome Uncommon: septic shock Rare*: sepsis, peritonitis, pneumonia Very rare*: Pseudomembranous colitis
Blood and the lymphatic system disorders:	Very common: myelosuppression, neutropenia, anaemia, thrombocytopenia, leucopenia, bleeding Rare*: febrile neutropenia Very rare*:acute myeloid leukaemia, myelodysplastic syndrome Not known: disseminated intravascular coagulation
Immune system disorders:	Very common: minor hypersensitivity reactions (mainly excessive flushing and rash) Uncommon: significant hypersensitivity reactions requiring therapy (e.g., hypotension, angioneurotic oedema, respiratory distress, generalised urticaria, chills, back pain, chest pain, tachycardia, abdominal pain, pain in extremities, diaphoresis and hypertension) Rare*: anaphylactic reactions Very rare*: anaphylactic shock Not known*: Bronchospasm
Metabolism and nutrition disorders:	Rare*: Dehydration Very rare*: anorexia Not known*: tumour lysis syndrome
Psychiatric disorders:	Very rare*: confusional state
Nervous system disorders:	Very common: neurotoxicity (mainly: peripheral neuropathy) Rare*: motor neuropathy (with resultant minor distal weakness) Very rare*: grand mal seizures, autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), encephalopathy, convulsions, dizziness, ataxia, headache
Eye disorders:	Very rare*: optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended Not known*: macular oedema, photopsia, vitreous floaters
Ear and labyrinth disorders:	Very rare*: hearing loss, ototoxicity, tinnitus, vertigo
Cardiac disorders:	Common: bradycardia Uncommon: myocardial infarction, AV block and syncope, cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy Rare: heart failure Very rare*: atrial fibrillation, supraventricular tachycardia
Vascular disorders:	Very common: hypotension Uncommon: thrombosis, hypertension, thrombophlebitis Very rare*: shock Not known*: phlebitis
Respiratory, thoracic and mediastinal disorders:	Rare*: respiratory failure, pulmonary embolism, lung fibrosis, interstitial pneumonia, dyspnoea, pleural effusion Very rare*: cough
Gastrointestinal disorders:	Very common: diarrhoea, vomiting, nausea Rare*: bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis Very rare*: mesenteric thrombosis, neutropenic colitis, ascites, oesophagitis, constipation
Hepatobiliary disorders:	Very rare*: hepatic necrosis, hepatic encephalopathy (both with reported cases of fatal outcome)
Skin and subcutaneous tissue disorders:	Very common: alopecia Common: transient and mild nail and skin changes Rare*: pruritus, rash, erythema Very rare*: Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet) Not known*: scleroderma
Musculoskeletal and connective tissue disorders:	Very common: arthralgia, myalgia Not known*: systemic lupus erythematosus, scleroderma
General disorders and administration site conditions:	Very common: Mucosal inflammation Common: injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis) Rare*: pyrexia, asthenia, oedema, malaise
Investigations:	Common: severe elevation in AST (SGOT), severe elevation in alkaline phosphatase Uncommon: severe elevation in bilirubin Rare*: increase in blood creatinine

Breast cancer patients who received paditaxel in the adjuvant setting following AC experienced more neurosensory toxicity, hypersensitivity reactions, arthralgia/myalgia, anaemia, infection, fever, nausea/vomiting and diarrhoea than patients who received AC alone. However, the frequency of these events was consistent with the use of single agent paditaxel, as reported above.

Combination treatment

The following discussion refers to two major trials for the first-line chemotherapy of ovarian carcinoma (paditaxel + cisplatin: over 1050 patients); two phase III trials in the first line treatment of metastatic breast cancer: one investigating the combination with doxorubicin (paditaxel + doxorubicin: 267 patients), another one investigating the combination with trastuzumab (planned subgroup analysis paditaxel + trastuzumab: 188 patients) and two phase III trials for the treatment of advanced NSCLC (paditaxel + cisplatin: over 360 patients).

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 paditaxel followed by cisplatin than patients treated with cyclophosphamide followed by cisplatin. Myelosuppression appeared to be less frequent and severe with paditaxel as a three hour infusion followed by cisplatin compared with cyclophosphamide followed by cisplatin.

For the first line chemotherapy of metastatic breast cancer, neutropenia, anaemia, peripheral neuropathy, arthralgia/myalgia, asthenia, fever, and diarrhoea were reported more frequently and with greater severity when paditaxel (220 mg/m²) was administered as a 3-hour infusion 24 hours following doxorubicin (50 mg/m²) when compared to standard FAC therapy (5-FU 500 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m²). Nausea and vomiting appeared to be less frequent and severe with the paditaxel (220 mg/m²) / doxorubicin (50 mg/m²) regimen as compared to the standard FAC regimen. The use of corticosteroids may have contributed to the lower frequency and severity of nausea and vomiting in the paditaxel/doxorubicin arm.

When paditaxel was administered as a 3-hour infusion in combination with trastuzumab for the first line treatment of patients with metastatic breast cancer, the following events (regardless of relationship to paditaxel or trastuzumab) were reported more frequently than with single agent paditaxel: heart failure (8% vs. 1%), infection (46% vs. 27%), chills (42% vs. 4%), fever (47% vs. 23%), cough (42% vs. 22%), rash (39% vs. 18%), arthralgia (37% vs. 21%), tachycardia (12% vs. 4%), diarrhoea (45% vs. 30%), hypertonia (11% vs. 3%), epistaxis (18% vs. 4%), acne (11% vs. 3%), herpes simplex (12% vs. 3%), accidental injury (13% vs. 3%), insomnia (25% vs. 13%), rhinitis (22% vs. 5%), sinusitis (21% vs. 7%), and injection site reaction (7% vs. 1%).

Some of these frequency differences may be due to the increased number and duration of treatments with paditaxel/trastuzumab combination vs. single agent paditaxel. Severe events were reported at similar rates for paditaxel /trastuzumab and single agent paditaxel.

When doxorubicin was administered in combination with paditaxel in metastatic breast cancer, cardiac contraction abnormalities (≥ 20% reduction of left ventricular ejection fraction) were observed in 15% of patients vs. 10% with standard FAC regimen. Congestive heart failure was observed in < 1% in both paditaxel/doxorubicin and standard FAC arms. Administration of trastuzumab in combination with paditaxel in patients previously treated with anthracyclines resulted in an increased frequency and severity of cardiac dysfunction in comparison with patients treated with paditaxel single agent (NYHA Class I/II 10% vs. 0%; NYHA Class III/IV 2% vs. 1%) and rarely has been associated with death (see trastuzumab Summary of Product Characteristics). In all but these rare cases, patients responded to appropriate medical treatment. Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

AIDS-related Kaposi's sarcoma

Except for haematologic and hepatic undesirable effects (see below), the frequency and severity of undesirable effects are generally similar between KS patients and patients treated with paditaxel monotherapy for other solid tumours, based on a clinical study including 107 patients.

Blood and the lymphatic system disorders : bone marrow suppression was the major dose-limiting toxicity. Neutropenia is the most important haematological toxicity. During the first course of treatment, severe neutropenia (< 500 cells/mm³) occurred in 20% of patients. During the entire treatment period, severe neutropenia was observed in 39% of patients. Neutropenia was present for > 7 days in 41% and for 30-35 days in 8% of patients. It resolved within 35 days in all patients who were followed. The incidence of Grade 4 neutropenia lasting ≥7 days was 22%. Neutropenic fever related to paditaxel was reported in 14% of patients and in 1.3% of treatment cycles. There were 3 septic episodes (2.8%) during paditaxel administration related to the medicinal product that proved fatal. Thrombocytopenia was observed in 50% of patients, and was severe (< 50,000 cells/mm³) in 9%. Only 14% experienced a drop in their platelet count < 75,000 cells/mm³, at least once while on treatment. Bleeding episodes related to paditaxel were reported in < 3% of patients, but the haemorrhagic episodes were localised. Anaemia (Hb < 11 g/dL) was observed in 61% of patients and was severe (Hb < 8 g/dL) in 10%. Red cell transfusions were required in 21% of patients.

Hepato-biliary disorders : Among patients (> 50% on protease inhibitors) with normal baseline liver function, 28%, 43% and 44% had elevations in bilirubin, alkaline phosphatase and AST (SGOT), respectively. For each of these parameters, the increases were severe in 1% of cases.

Overdose and treatment

There is no known antidote for paditaxel overdose. In case of overdose, the patient should be closely monitored. Treatment should be directed at the primary anticipated toxicities, which consist of bone marrow suppression, peripheral neurotoxicity and mucositis.

Pharmacological properties

Pharmaceutical particulars

List of excipients

Polyoxyl 35 castor oil, Citric acid anhydrous, Dehydrated Alcohol (Ethanol, anhydrous).

Incompatibilities

Not applicable.

Preparation of Intravenous fluid:

Dilution

Paditaxel (Bravivo) MUST BE DILUTED PRIOR TO INTRAVENOUS INFUSION. It should be diluted in 5% glucose or 0.9% sodium chloride intravenous infusion.

Dilution should be made to a final concentration of 0.3 to 1.2 mg/mL.

After the final dilution of Paditaxel (Bravivo), the bottle should be swirled gently to disperse the Paditaxel (Bravivo). DO NOT SHAKE.

Avoid contact of Paditaxel (Bravivo) solutions with plasticized polyvinyl chloride (PVC) equipment, infusion lines or devices used when preparing infusion solutions. Prepare and store diluted Paditaxel (Bravivo) solutions in glass bottles or non-PVC infusion bags. These precautions are to avoid leaching of the plasticizer DEHP (di-[2-ethylhexyl] phthalate) from PVC infusion bags or sets. Paditaxel (Bravivo) solutions should be administered through polyethylene lined administration sets (e.g., Gemini 20 giving set), using an IMED® pump.

Although solutions of Paditaxel (Bravivo) for infusion prepared as outlined above are chemically stable for 3 days at room temperature (25°C) and 14 days at 2°C to 8°C, it is recommended that the solution for infusion should be administered immediately after preparation as it does not contain an antimicrobial agent. The infusion should be completed within 24 hours of preparation of the solution and any residue discarded, according to the guidelines for the disposal of cytotoxic drugs (see Section 6.4 Special Precautions for Handling and Disposal). Use in one patient on one occasion only.

Table 1:

Diluent	Stored Below 25°C		Stored at 2°C to 8°C (Refrigerate, Do not freeze)	
	Non-PVC Infusion Bag	Glass Bottle	Non-PVC Infusion Bag	Glass Bottle
0.9% Sodium Chloride for Intravenous Infusion	7 days	3 days	28 days	14 days
5% Glucose for Intravenous Infusion	7 days	3 days	14 days	14 days

Solutions prepared this way have been shown to be chemically stable for these periods. Administration should be completed within 24 hours of the start of the infusion and any residue discarded according to the guidelines for the disposal of cytotoxic drugs. Do not use Paditaxel (Bravivo) if any precipitation forms or if the diluted solution appears cloudy.

Filtration

A microporous membrane of 0.22 microns or less in size is recommended as the in-line filter for all infusions of Paditaxel (Bravivo). The IMED® 0.2 micron add on filter set composed of polysulfone and the IVEX™ II 0.2-micron filter composed of cellulose have both been found to be suitable for Paditaxel (Bravivo).

Paditaxel (Bravivo) is a cytotoxic anticancer drug and as with other potentially toxic compounds, caution should be exercised in handling Paditaxel (Bravivo). The use of gloves is recommended. Following topical exposure, tingling, burning, redness have been observed. If Paditaxel (Bravivo) solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If Paditaxel (Bravivo) contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnea, chest pain, burning eyes, sore throat and nausea have been reported. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. The published guidelines related to procedures for the proper handling and disposal of cytotoxic drugs should be followed. Care must be taken whenever handling cytostatic products. Always take steps to prevent exposure. This included appropriate equipment, such as wearing gloves and washing hands with soap and water after handling such products.

Dosage Adjustment

Subsequent doses of Paditaxel should be administered according to individual patient tolerance. Repetition of a course of Paditaxel (Bravivo) is not recommended until the patient's neutrophil count is at least 1,5 x 109 cells/L (1,500 cells/mm3) and the platelet count is at least 100 x 109 cells/L (100,000 cells/mm3). If there is severe neutropenia (neutrophil count less than 0.5 x 109 cells/L) or severe peripheral neuropathy or severe mucositis during Paditaxel (Bravivo) therapy, the dose of Paditaxel (Bravivo) in subsequent courses should be reduced by 20% (see Section 4.4 Special Warnings and Precautions for Use). The incidence of neurotoxicity and the severity of neutropenia increase with dose within a regime.

Storage condition

Store at temperatures not exceeding 30°C.

Protect from light.

Retain in the carton until time of use only.

Nature and contents of container

A clear tubular glass vial (5mL, 20mL, 50mL) with 20 mm bromobutyl serum coated rubber stopper with 20mm aluminium flip off seals in multidose vials.

Packaging:

Bravivo 6 mg/mL (30 mg/5 mL): USP Type 1 clear glass vial with dark gray bromobutyl rubber stopper and blue aluminum flip off seal in 5 mL (Box of 1 Vial)

Bravivo 6 mg/mL (100 mg/16.7 mL): 20 mL-capacity USP Type 1 clear glass vial with dark gray bromobutyl rubber stopper and yellow aluminum flip off seal in 16.7 mL (Box of 1 Vial)

Bravivo 6 mg/50 mL (300 mg/50 mL): USP Type 1 clear glass vial with dark gray bromobutyl rubber stopper and green aluminum flip off seal in 50 mL (Box of 1 Vial)

Special precautions for disposal and other handling

Handling: paditaxel is a cytotoxic anticancer medicinal product and caution should be exercised in handling paditaxel. Dilution should be carried out under aseptic conditions, by trained personnel in a designated area. Appropriate gloves should be used. Contact of paditaxel with skin and mucous membranes should be avoided.

If paditaxel solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning, and redness. If paditaxel contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnoea, chest pain, burning throat, and nausea have been reported.

Preparation for IV Administration: During dilution of the concentrate for infusion, cytostatic dispensing needles or similar devices with spikes should not be used with vials of paditaxel since they can cause the stopper to collapse resulting in loss of sterile integrity of the solution.

Prior to infusion, paditaxel must be diluted to a ready-to-use solution for infusion (0.3 to 1.2 mg/ml) using aseptic techniques with one of the following solutions:

- 9 mg/ml (0.9%) sodium chloride solution for infusion and 50 mg/ml (5%) dextrose solution for infusion,
- Ringer's solution containing 50 mg/ml dextrose.

Storage of the ready-to-use infusion.

The ready-to-use infusion should be visually inspected for particulate matter and discoloration.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle, and is not removed by filtration. However haziness does not affect the potency of the product. The solution for infusion should be administered through an in-line filter with microporous membrane not greater than 0.22 microns. No significant losses in potency have been noted following simulated delivery of the solution through I.V. tubing containing an in-line (0.22 micron) filter.

There have been some reports of precipitation during paditaxel infusions, with precipitation usually taking place towards the end of a 24-hour infusion period. To reduce the risk of precipitation, paditaxel should be used as soon as possible after dilution and excessive shaking or agitation should be avoided. The infusion solution should be regularly inspected during infusion and the infusion should be discontinued if precipitation occurs.

To minimise patient exposure to DEHP which may be leached from plasticised PVC infusion bags, sets, or other medical instruments, diluted paditaxel 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 preparation, administration, infusion, or otherwise coming into contact with paditaxel should be placed in an appropriate safety container and disposed according to local guidelines for the handling of cytotoxic compounds.

Caution: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR Reporting Statement.

For suspected adverse drug reaction, report to the FDA: www.fda.gov/ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

Manufactured by:

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(Formulations Division) Unit-II,

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Nandigama (Village & Mandal),

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