

## Paclitaxel

### Core Safety Profile

#### 4.3 Contraindications

Hypersensitivity to paclitaxel or to any excipient, especially polyoxyethylated castor oil (see section 4.4).

TAXOL should not be used in patients with baseline neutrophils  $< 1,500/\text{mm}^3$  ( $< 1,000/\text{mm}^3$  for KS patients).

TAXOL is contraindicated during lactation (see section 4.6).

In KS, TAXOL is also contraindicated in patients with concurrent, serious, uncontrolled infections.

#### 4.4 Special warnings and precautions for use

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

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Patients must be pretreated with corticosteroids, antihistamines and  $\text{H}_2$  antagonists (see section 4.2).

TAXOL should be given before cisplatin when used in combination (see section 4.5).

*Significant hypersensitivity reactions* characterised by dyspnoea and hypotension requiring treatment, angioedema and generalised urticaria have occurred in  $< 1\%$  of patients receiving TAXOL after adequate premedication. These reactions are probably histamine-mediated. In the case of severe hypersensitivity reactions, TAXOL infusion should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be rechallenged with the medicinal product.

*Bone marrow suppression* (primarily neutropenia) is the dose-limiting toxicity. Frequent monitoring of blood counts should be instituted. Patients should not be retreated until neutrophils recover to  $\geq 1,500/\text{mm}^3$  ( $\geq 1,000/\text{mm}^3$  for KS patients) and platelets recover to  $\geq 100,000/\text{mm}^3$  ( $\geq 75,000/\text{mm}^3$  for KS patients). In the KS clinical study, the majority of patients were receiving granulocyte colony stimulating factor (G-CSF).

*Patients with hepatic impairment* may be at increased risk of toxicity, particularly Grade 3-4 myelosuppression. There is no evidence that the toxicity of TAXOL is increased when given as a 3-hour infusion to patients with mildly abnormal liver function. When TAXOL is given as a longer infusion, increased myelosuppression may be seen in patients with moderate to severe hepatic impairment. Patients should be monitored closely for the development of profound myelosuppression (see section 4.2). Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments (see section 5.2).

No data are available for patients with severe baseline cholestasis. Patients with severe hepatic impairment must not be treated with paclitaxel.

*Severe cardiac conduction abnormalities* have been reported rarely with single agent TAXOL. If patients develop significant conduction abnormalities during TAXOL administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with TAXOL. Hypotension, hypertension, and bradycardia have been observed during TAXOL administration, patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of TAXOL infusion, is recommended. Severe cardiovascular events were observed more frequently in patients with NSCLC than breast or ovarian carcinoma. A single case of heart failure related to paclitaxel was seen in the AIDS-KS clinical study.

When TAXOL is used in combination with doxorubicin or trastuzumab for initial treatment of metastatic breast cancer, attention should be placed on the monitoring of cardiac function. When patients are candidates for treatment with TAXOL in these combinations, they should undergo baseline cardiac assessment including history, physical examination, ECG, echocardiogram, and/or MUGA scan. Cardiac function should be further monitored during treatment (e.g. every three months). Monitoring may help to identify patients who develop cardiac dysfunction and treating physicians should carefully assess the cumulative dose (mg/m<sup>2</sup>) 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 administered, monitoring of cardiac function should be more frequent (e.g. every 1-2 cycles). For more details see Summary of Product Characteristics of Herceptin or doxorubicin.

Although the occurrence of *peripheral neuropathy* is frequent, the development of severe symptoms is rare. In severe cases, a dose reduction of 20% (25% for KS patients) for all subsequent courses of TAXOL is recommended. In NSCLC patients and in ovarian cancer patients treated in the first-line setting, the administration of TAXOL as a three hour infusion in combination with cisplatin, resulted in a greater incidence of severe neurotoxicity than both single agent TAXOL and cyclophosphamide followed by cisplatin.

Special care should be taken to avoid *intra-arterial* application of TAXOL, since in animal studies testing for local tolerance severe tissue reactions were observed after intra-arterial application.

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

Since TAXOL contains *ethanol* (396 mg/ml), consideration should be given to possible CNS and other effects.

*Pseudomembranous colitis* has been rarely reported including cases in patients who have not been concomitantly treated with antibiotics. This reaction should be considered in the differential diagnosis of cases of severe or persistent diarrhoea occurring during or shortly after treatment with paclitaxel.

In KS patients, *severe mucositis* is rare. If severe reactions occur, the paclitaxel dose should be reduced by 25%.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

The recommended regimen of TAXOL administration for the first-line chemotherapy of ovarian carcinoma is for TAXOL to be given before cisplatin. When TAXOL is given before cisplatin, the safety profile of TAXOL is consistent with that reported for single-agent use. When TAXOL was given after cisplatin, patients showed a more profound myelosuppression and an approximately 20% decrease in paclitaxel clearance. Patients treated with TAXOL and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynecological cancers.

Since the elimination of doxorubicin and its active metabolites can be reduced when paclitaxel and doxorubicin are given closer in time, TAXOL for initial treatment of metastatic breast cancer should be administered 24 hours after doxorubicin (see 5.2).

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and 3A4 (see 5.2). Clinical studies have demonstrated that CYP2C8-mediated metabolism of paclitaxel, to 6 $\alpha$ -hydroxypaclitaxel, is the major metabolic pathway in humans. Concurrent administration of ketoconazole, a known potent inhibitor of CYP3A4, does not inhibit the elimination of paclitaxel in patients; thus, both medicinal products may be administered together without dosage adjustment. Further data on the potential of drug interactions between paclitaxel and other CYP3A4 substrates/inhibitors are limited. Therefore, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g. erythromycin, fluoxetine, gemfibrozil) or induce (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) either CYP2C8 or 3A4.

Paclitaxel clearance is not affected by cimetidine premedication.

Studies in KS patients, who were taking multiple concomitant medicinal products, suggest that the systemic clearance of paclitaxel 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, paclitaxel should be administered with caution in patients receiving protease inhibitors as concomitant therapy.

#### **4.6 Pregnancy and lactation**

There is no adequate data from the use of paclitaxel in pregnant women. Paclitaxel has been shown to be both embryotoxic and foetotoxic in rabbits, and to reduce fertility in rats. As with other cytotoxic medicinal products, paclitaxel may cause foetal harm when administered to pregnant women. Therefore, paclitaxel should not be used during pregnancy unless clearly necessary. Women of childbearing potential receiving paclitaxel should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur. Female and male patients of fertile age, and/or their partners should use contraceptions for at least 6 months after treatment with paclitaxel.

Male patients should seek advice regarding cryoconservation of sperm prior to treatment with paclitaxel because of the possibility of infertility.

Paclitaxel is contraindicated during lactation (see section 4.3). It is not known whether paclitaxel is excreted in human milk. Breastfeeding should be discontinued for the duration of therapy.

#### **4.7 Effects on ability to drive and use machines**

TAXOL has not been demonstrated to interfere with the ability to drive and use machines. However, it should be noted that TAXOL does contain alcohol (see sections 4.4 and 6.1).

#### **4.8 Undesirable effects**

Unless otherwise noted, the following discussion refers to the overall safety database of 812 patients with solid tumours treated with single-agent TAXOL 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 adverse reactions, unless otherwise mentioned, are generally similar between patients receiving TAXOL for the treatment of ovarian carcinoma, breast carcinoma, or NSCLC. None of the observed toxicities were clearly influenced by age.

*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 TAXOL therapy.

The most frequent significant adverse event was *bone marrow suppression*. Severe neutropenia (< 500 cells/mm<sup>3</sup>) occurred in 28% of patients, but was not associated with febrile episodes. Only 1% of patients experienced severe neutropenia for  $\geq 7$  days. Thrombocytopenia was reported in 11% of patients. Three percent of patients had a platelet count nadir < 50,000/mm<sup>3</sup> at least once while on study. Anaemia was observed in 64% of patients, but was severe (Hb < 5 mmol/l) 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/m<sup>2</sup> 3-hour infusion (85% neurotoxicity, 15% severe) than with a 135 mg/m<sup>2</sup> 24-hour infusion (25% peripheral neuropathy, 3% severe) when TAXOL was combined with cisplatin. In NSCLC patients and in ovarian cancer patients treated with TAXOL 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 TAXOL. Peripheral neuropathy was the cause of TAXOL discontinuation in a few cases. Sensory symptoms have usually improved or resolved within several months of TAXOL discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for TAXOL therapy.

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

*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 TAXOL 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.

The table below lists adverse reactions associated with the administration of single agent TAXOL administered as a three hour infusion in the metastatic setting (812 patients treated in clinical studies) and as reported in the postmarketing surveillance\* of Taxol.

The frequency of adverse reactions listed below is defined using the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$ , < 1/10); uncommon

( $\geq 1/1,000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ); very rare ( $< 1/10,000$ ). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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*
Blood and lymphatic system disorders	very common	myelosuppression, neutropenia, anaemia, thrombocytopenia, leucopenia, bleeding

	rare	febrile neutropenia*
	very rare	acute myeloid leukaemia,* myelodysplastic syndrome*
Immune system disorders	very common	minor hypersensitivity reactions (mainly 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*
Metabolism and nutrition disorders	very rare	anorexia*
	not known	tumor 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	cardiac 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, mucosal inflammation
	rare	bowel obstruction,* bowel perforation,* ischaemic colitis,* pancreatitis*
	very rare	mesenteric thrombosis,* pseudomembranous colitis,* 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*
General disorders and administration site conditions	common	injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis)
	rare	pyrexia,* dehydration,* 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 TAXOL 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 TAXOL, as reported above.

### Combination treatment

The following discussion refers to two major trials for the first-line chemotherapy of ovarian carcinoma (TAXOL + cisplatin: over 1050 patients); two phase III trials in the first line treatment of metastatic breast cancer: one investigating the combination with doxorubicin (TAXOL + doxorubicin: 267 patients), another one investigating the combination with trastuzumab (planned subgroup analysis TAXOL + trastuzumab: 188 patients) and two phase III trials for the treatment of advanced NSCLC (TAXOL + cisplatin: over 360 patients) (see section 5.1).

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 TAXOL followed by cisplatin than patients treated with cyclophosphamide followed by cisplatin. Myelosuppression appeared to be less frequent and severe with TAXOL 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 TAXOL (220 mg/m<sup>2</sup>) was administered as a 3-hour infusion 24 hours following doxorubicin (50 mg/m<sup>2</sup>) when compared to standard FAC therapy (5-FU 500 mg/m<sup>2</sup>, doxorubicin 50 mg/m<sup>2</sup>, cyclophosphamide 500 mg/m<sup>2</sup>). Nausea and vomiting appeared to be less frequent and severe with the TAXOL (220 mg/m<sup>2</sup>) / doxorubicin (50 mg/m<sup>2</sup>) 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 TAXOL/doxorubicin arm.

When TAXOL 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 TAXOL or trastuzumab) were reported more frequently than with single agent TAXOL: 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 TAXOL/trastuzumab combination vs. single agent TAXOL. Severe events were reported at similar rates for TAXOL/trastuzumab and single agent TAXOL.

When doxorubicin was administered in combination with TAXOL in metastatic breast cancer, *cardiac contraction abnormalities* ( $\geq 20\%$  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 TAXOL/doxorubicin and standard FAC arms. Administration of trastuzumab in combination with TAXOL in patients previously treated with anthracyclines resulted in an increased frequency and severity of *cardiac dysfunction* in comparison with patients treated with TAXOL 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 paclitaxel 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/mm<sup>3</sup>) 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 paclitaxel was reported in 14% of patients and in 1.3% of treatment cycles. There were 3 septic episodes (2.8%) during paclitaxel administration related to the medicinal product that proved fatal.

Thrombocytopenia was observed in 50% of patients, and was severe (< 50,000 cells/mm<sup>3</sup>) in 9%. Only 14% experienced a drop in their platelet count < 75,000 cells/mm<sup>3</sup>, at least once while on treatment. Bleeding episodes related to paclitaxel 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.

*Hepatobiliary 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.

## **4.9 Overdose**

There is no known antidote for TAXOL 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.

Overdoses in paediatric patients may be associated with acute ethanol toxicity.