Pacli®

Paclitaxel

Concentrated solution for IV Infusion

Description

Pacli® is a preparation of paclitaxel Injection which is a clear, colorless to slightly yellow viscous solution. It is supplied as a concentrated solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion.

Mode of Action

Paclitaxel is a novel anti-microtubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerisation. This stability results in the inhibition of the 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.

Following intravenous administration of Pacli®, paclitaxel plasma concentrations declined in a biphasic manner. 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.

Indication and usage

Pacli® Injection is a microtubule inhibitor indicated for:

- **Ovarian Carcinoma:** Pacli® is indicated as first line and subsequent therapy for the treatment of advanced carcinoma of the ovary. As first line therapy, Pacli® is indicated in combination with cisplatin.
- **Breast Carcinoma:** Pacli® is indicated for the adjuvant treatment of node positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy.

Pacli® is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracline unless clinically contraindicated.

Pacli® is indicated for the first line therapy of advanced or metastatic breast cancer either in combination with an anthracycline in patients for whom anthracline therapy is suitable or in combination with trastuzumab in patients who over express HER2 at a 2+ or 3+ level as determined by immuno-histochemistry.

- **Gemcitabine, in combination of Pacli®,** is indicated in the treatment of patients with unresectable, locally recurrent or metastatic breast cancer who have relapsed following adjuvant/neoadjuvant chemotherapy. Prior chemotherapy should have included an anthracycline unless clinically contraindicated.
- **Pacli® is indicated for the treatment of metastatic cancer of the breast,** in combination with trastuzumab, in patients who have tumors that over-express HER2 and who have not received previous chemotherapy for their metastatic disease.

Non-Small Cell Lung Carcinoma

- **Pacli®, in combination with cisplatin, is indicated for the first line treatment of non-small cell lung cancerin patients** who are not candidates for potential curative surgery and/or radiation therapy.
- **Kaposi's Sarcoma:** Pacli® is indicated for the second line treatment of AIDS related Kaposi's Sarcoma.
- **Gastric Carcinoma:** Pacli® is indicated for the treatment of Gastric Carcinoma.

Dosage & Administration

All patients should be premedicated prior to Pacli® administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before Pacli®, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to Pacli®, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before Pacli®.

Preparation for Intravenous Infusion

Pacli® (paclitaxel) Injection must be diluted prior to infusion. Pacli® should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/ml. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (below 30° C) and room lighting conditions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

First-line treatment of ovarian cancer: Although alternative medication regimens for paclitaxel are under investigation at present, a combination therapy of paclitaxel and cisplatin is recommended.

Depending on the duration of infusion, two different dosages are recommended for paclitaxel treatment: 175 mg/m^2 of paclitaxel is administered as an intravenous infusion over a period of three hours followed thereafter by 75 mg/m^2 of cisplatin and the therapy is repeated at 3-week intervals, or 135 mg/m^2 of paclitaxel is administered as an intravenous infusion over a period of 24 hours followed thereafter by 75 mg/m^2 of cisplatin and the therapy is repeated at 3-week intervals

Second-line treatment of ovarian cancer: The recommended dose of paclitaxel is 175 mg/m^2 administered over 3 hours, with a 3-week interval between courses.

Adjuvant chemotherapy in breast carcinoma: The recommended dose of paclitaxel is 175 mg/m^2 administered over a period of 3 hours every 3 weeks for four courses, following AC therapy.

First-line chemotherapy of breast carcinoma: When used in combination with doxorubicin (50 mg/m^2), paclitaxel should be administered 24 hours after doxorubicin. The recommended dose of paclitaxel is 220 mg/m^2 administered intravenously over a period of 3 hours, with a 3-week interval between courses.

When used in combination with trastuzumab, the recommended dose of paclitaxel is 175 mg/m^2 administered intravenously over a period of 3 hours, with a 3-week interval between courses. Paclitaxel 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.

Second-line chemotherapy of breast carcinoma: The recommended dose of paclitaxel is 175 mg/m^2 administered over a period of 3 hours, with a 3-week interval between courses.

Advanced non-small cell lung cancer: The recommended dose of paclitaxel is 175 mg/m^2 administered over 3 hours followed by 80 mg/m^2 of cisplatin, with a 3-week interval between courses.

Treatment of AIDS-related KS: The recommended dose of paclitaxel is 100 mg/m^2 administered as a 3-hour intravenous infusion every two weeks.

Dose adjustment: Subsequent doses of paclitaxel should be administered according to individual patient tolerance. Paclitaxel should not be re-administered until the neutrophil count is ≥1.5 x 109/l (≥1 x 109/l for KS patients) and the platelet count is ≥100 x 109/l (≥75 x 109/l for KS patients).

Patients who experience severe neutropenia (neutrophil count <0.5 x 109/l for a minimum of 7 days) or severe peripheral neuropathy, should receive a dose reduction of 20% for subsequent courses (25% for KS patients).

Patients with hepatic impairment: Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments. Patients with severe hepatic impairment must not be treated with paclitaxel.

Paediatric use: Paclitaxel is not recommended for use in children below 18 years due to lack of data on safety and efficacy.

Precautions

Paclitaxel 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. Paclitaxel should be given before cisplatin when used in combination.

Significant hypersensitivity reactions, as characterised by dyspnoea and hypotension requiring treatment, angioedema, and generalised urticaria have occurred in <1% of patients receiving paclitaxel after adequate premedication. Fatal hypersensitivity reactions have occurred in patients despite premedication. These reactions are probably histamine-mediated. In the case of severe hypersensitivity reactions, paclitaxel infusion should be discontinued immediately.

Bone marrow suppression, primarily neutropenia, is the dose-limiting toxicity. Neutrophil nadirs occurred at a median of 11 days. Frequent monitoring of blood counts should be instituted. Patients should not be retreated until the neutrophil count is ≥1.5 x 109/l (≥1 x 109/l for KS patients) and the platelets recover to ≥100 x 109/l (≥75 x 109/l for KS patients).

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

Hypotension, hypertension, and bradycardia have been observed during paclitaxel administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital signs monitoring, particularly during the first hour of paclitaxel infusion, is recommended. Severe cardiovascular events were observed more frequently in patients with non-small cell lung cancer than in those with breast or ovarian carcinoma. A single case of heart failure related to paclitaxel was seen in the AIDS-KS clinical study.

When paclitaxel 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 paclitaxel in these combinations, they should undergo baseline cardiac assessment including history, physical examination, electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (MUGA) scan. Cardiac function should be further monitored during treatment (e.g. every three months. 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).

Peripheral neuropathy: 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) is recommended for all subsequent courses of paclitaxel. In non-small cell lung cancer patients, the administration of paclitaxel in combination with cisplatin resulted in a greater incidence of severe neurotoxicity than administration of single agent paclitaxel. In first-line ovarian cancer patients, administration of paclitaxel as a 3-hour infusion combined with cisplatin resulted in a greater incidence of severe neurotoxicity than administration of a combination of cyclophosphamide and cisplatin.

Impaired hepatic function: Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III-IV myelosuppression. There is no evidence that the toxicity of paclitaxel is increased when given as a 3-hour infusion to patients with mildly abnormal liver function. No data are available for patients with severe baseline cholestasis. Patients should be monitored closely for the development of profound myelosuppression. Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments. Patients with severe hepatic impairment must not be treated with paclitaxel.

Ethanol: This product contains 49.7% vol ethanol (alcohol), i.e. up to 21 g per average dose, equivalent to 740 ml of a 3.5% vol beer, 190 ml of a 14% vol 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. The amount of alcohol in this medicinal product may alter the effects of other medicines.

Intra-arterial: Special care should be taken to avoid intra-arterial administration of paclitaxel. In animal studies investigating local tolerance, severe tissue reactions occurred following intra-arterial administration.

Pseudomembranous colitis has also been reported, rarely, including cases in patients who have not received concurrent antibiotic treatment. This reaction should be considered in the differential diagnosis of severe or persistent cases of diarrhoea occurring during or shortly after treatment with paclitaxel.

A combination of pulmonary radiotherapy and paclitaxel treatment (irrespective of the order of the treatments) may promote the development of interstitial pneumonitis.

Paclitaxel has been shown to be a teratogen, embryotoxic and a mutagen in several experimental systems. Therefore, female and male patients of reproductive age must take contraceptive measures for themselves and/or their sexual partners during and for at least 6 months after therapy. Male patients are advised to seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with paclitaxel.

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

There have been reports of reduced visual acuity due to cystoid macular oedema (CME) during treatment with paclitaxel as well as with other taxanes. Patients with visual impairment during paclitaxel treatment should seek a prompt and complete ophthalmologic examination.

Preparation for Intravenous Infusion

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Contraindications

- Paclitaxel is contraindicated in patients with severe hypersensitivity reactions to paclitaxel, macrogolglycerol ricinoleate (polyoxyl castor oil.)
- Paclitaxel is contraindicated during lactation.
- Paclitaxel should not be used in patients with baseline neutrophils <1.5 x 109/l (<1 x 109/l for KS patients) or platelets <100 x 109/l (<75 x 109/l for KS patients).
- In KS, paclitaxel is also contraindicated in patients with concurrent, serious, uncontrolled infections.
- Patients with severe hepatic impairment must not be treated with paclitaxel.

Side Effects

Common: Low blood counts leading to increased risk for infection, anemia and/or bleeding, hair loss, arthralgias and myalgias, pain in the joints and muscles, peripheral neuropathy, nausea, vomiting (usually mild), diarrhea, Mouth sores, hypersensitivity reaction, fever, facial flushing, chills, shortness of breath, or hives after paclitaxel is given.

Rare: Swelling of the feet or ankles (edema), liver problems, low blood pressure, darkening of the skin where previous radiation treatment has been given.

Use in Specific Population

- ***Pregnancy:*** Category 'D'. There is no adequate data from the use of paclitaxel in pregnant women, however as with other cytotoxic medicinal products, paclitaxel may cause foetal harm when administered to pregnant women.
- ***Nursing Mothers:*** Paclitaxel is contraindicated during lactation.
- ***Hepatic Impairment Patients:*** Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments. Patients with severe hepatic impairment must not be treated with paclitaxel.
- ***Pediatric Use:*** Paclitaxel is not recommended for use in children below 18 years due to lack of data on safety and efficacy.

Drug Interaction

Paclitaxel clearance is not affected by cimetidine premedication.

Cisplatin: Administration of paclitaxel after cisplatin treatment leads to greater myelosuppression and about a 20% decrease in paclitaxel clearance. Patients treated with paclitaxel 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 paclitaxel and doxorubicin are given closer in time, paclitaxel for initial treatment of metastatic breast cancer should be administered 24 hours after 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 over 48 hours).

Active substances metabolized in the liver: The metabolism of paclitaxel 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 paclitaxel 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 paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel 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 paclitaxel exposures.

Overdose

There is no known antidote for paclitaxel 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.

Pharmaceutical Precautions

Keep in a dry place and store below 30° C. Protect from light and keep out of the reach of children. Use only freshly prepared solution.

Commercial Pack

Pacli® 30 mg/5 ml concentrated solution for IV infusion: Each box contains one vial. Each vial of 5 ml contains Paclitaxel USP 30 mg.

Pacli® 100 mg/16.7 ml concentrated solution for IV infusion: Each box contains one vial. Each vial of 16.7 ml contains Paclitaxel USP 100 mg.

Pacli® 300 mg/50 ml concentrated solution for IV infusion: Each box contains one vial. Each vial of 50 ml contains Paclitaxel USP 300 mg.

BEXIMCO PHARMA

Manufactured by

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