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FINAL PI APPROVED FOR PRINTING

MA. VICTORIA VILLASIN / 23 JULY 2024
MEGA LIFESCIENCES LIMITED INC.

PACLITAXEL

Rx

BRAVIFO

6 mg / ml (30 mg / 5ml)
6 mg / ml (100 mg / 16.7 ml)
6 mg / ml (300 mg / 50 ml)
Solution for Injection (IV Infusion)
Antineoplastic Agent (Taxane)

MEGA We care MSN

Fomulation
Each mL solution for infusion contains:
Paclitaxel, USP.....6 mg

Pharmaceutical form
A clear colorless to slightly yellow viscous solution free from visible particulate in tubular USP type-I clear glass vial with 20 mm bromobutyl coated rubber stopper and sealed with 20 mm aluminium seal having polypropylene disc and in multidose vials.

Pharmacodynamic properties
Pharmacotherapeutic group: antineoplastic agents (taxanes),
ATC code: L01C D01

Machanism of action
Paclitaxel is a antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganisation 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.

Clinical efficacy and safety
In the first-line chemotherapy of ovarian carcinoma, the safety and efficacy of paclitaxel were evaluated in two major, randomised, controlled (vs. cyclophosphamide 750 mg/m^2/cisplatin 75 mg/m^2) trials. In the Intergroup trial (BMS CA139-209), over 650 patients with stage II_{b-c},III or IV primary ovarian cancer received a maximum of 9 treatment courses of paclitaxel (175 mg/m^2 over 3 hr) followed by cisplatin (75 mg/m^2) or control. The second major trial (GOG-111/BMS CA139-022) evaluated a maximum of 6 courses of either paclitaxel (135 mg/m^2 over 24 hrs) followed by cisplatin (75 mg/m^2) or control in over 400 patients with stage III/IV primary ovarian cancer, with a > 1 cm residualdisease after staging laparotomy, or with distant metastases. While the two different paclitaxel posologies were not compared with each other directly, in both trials patients treated with paclitaxel in combination with cisplatin had a significantly higher response rate, longer time to progression, and longer survival time when compared with standard therapy. Increased neurotoxicity, arthralgia/myalgia but reduced myelosuppression were observed in advanced ovarian cancer patients administered 3-hour infusion paclitaxel/cisplatin as compared to patients who received cyclophosphamide/cisplatin.

Breast carcinoma
In the adjuvant treatment of breast carcinoma, 3121 patients with node positive breast carcinoma were treated with adjuvant paclitaxel therapy or no chemotherapy following four courses of doxorubicin and cyclophosphamide (CALGB 9344, BMS CA 139-223). Median follow-up was 69 months. Overall, paclitaxel patients had a significant reduction of 18% in the risk of disease recurrence relative to patients receiving AC alone (p = 0.0014), and a significant reduction of 19% in the risk of death (p = 0.0044) relative to patients receiving AC alone. Retrospective analyses show benefit in all patient subsets. In patients with hormone receptor negative/ unknown tumours, reduction in risk of disease recurrence was 28% (95%CI: 0.59-0.86). In the patient subgroup with hormone receptor positive tumours, the risk reduction of disease recurrence was 9% (95% CI: 0.78-1.07).

However, the design of the study did not investigate the effect of extended AC therapy beyond 4 cycles. It cannot be excluded on the basis of this study alone that the observed effects could be partly due to the difference in duration of chemotherapy between the two arms (AC 4 cycles; AC + paclitaxel 8 cycles). Therefore, adjuvant treatment with paclitaxel should be regarded as an alternative to extended AC therapy.

In a second large clinical study in adjuvant node positive breast cancer with a similar design, 3060 patients were randomized to receive or not four courses of paclitaxel at a higher dose of 225 mg/m^2 following four courses of AC (NSABP B-28, BMS CA139-270). At a median follow-up of 64 months, paclitaxel patients had a significant reduction of 17% in the risk of disease recurrence relative to patients who received AC alone (p = 0.006) ; paclitaxel treatment was associated with a reduction in the risk of death of 7% (95% CI: 0.78-1.12). All subset analyses favored the paclitaxel arm. In this study patients with hormone receptor positive tumour had a reduction in the risk of disease recurrence of 23% (95% CI: 0.6-0.92); in the patient subgroup with hormone receptor negative tumour the risk reduction of disease recurrence was 10% (95% CI: 0.7-1.11).

In the first-line treatment of metastatic breast cancer, the efficacy and safety of paclitaxel were evaluated in two pivotal, phase III, randomised, controlled open-label trials. In the first study (BMS CA139-278), the combination of bolus doxorubicin (50 mg/m^2) followed after 24 hours by paclitaxel (220 mg/m^2 by 3-hour infusion) (AT), was compared versus standard FAC regimen (5-FU 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2), both administered every three weeks for eight courses. In this randomised study, 267 patients with metastatic breast cancer, who had either received no prior chemotherapy or only non-anthracycline chemotherapy in the adjuvant setting, were enrolled. Results showed a significant difference in time to progression for patients receiving AT compared to those receiving FAC (8.2 vs. 6.2 months; p= 0.029). The median survival was in favour of paclitaxel/doxorubicin vs. FAC (23.0 vs. 18.3 months; p= 0.004). In the AT and FAC treatment arm 44% and 48% respectively received follow-up chemotherapy which included taxanes in 7% and 50% respectively. The overall response rate was also significantly higher in the AT arm compared to the FAC arm (68% vs. 55%). Complete responses were seen in 19% of the paclitaxel/doxorubicin arm patients vs. 8% of the FAC arm patients. All efficacy results have been subsequently confirmed by a blinded independent review.

In the second pivotal study, the efficacy and safety of the paclitaxel and Herceptin®combination was evaluated in a planned subgroup analysis (metastatic breast cancer patients who formerly received adjuvant anthracyclines) of the study HO648g. The efficacy of Herceptin® in combination with paclitaxel in patients who did not receive prior adjuvant anthracyclines has not been proven. The combination of trastuzumab (4 mg/kg loading dose then 2 mg/kg weekly) and paclitaxel (175 mg/m^2) 3-hour infusion, every three weeks was compared to single-agent paclitaxel (175 mg/m^2) 3-hour infusion, every three weeks in 188 patients with metastatic breast cancer overexpressing HER2 (2+ or 3+ as measured by immunohistochemistry), who had previously been treated with anthracyclines. Paclitaxel was administered every three weeks for at least six courses while trastuzumab was given weekly until disease progression. The study showed a significant benefit for the paclitaxel/trastuzumab combination in terms of time to progression (6.9 vs. 3.0 months), response rate (41% vs. 17%), and duration of response (10.5 vs. 4.5 months) when compared to paclitaxel alone. The most significant toxicity observed with the paclitaxel/trastuzumab combination was cardiac dysfunction.

Advanced non-small cell lung carcinoma
In the treatment of advanced NSCLC, paclitaxel 175 mg/m^2 followed by cisplatin 80 mg/m^2 has been evaluated in two phase III trials (367 patients on paclitaxel containing regimens). Both were randomised trials, one compared to treatment with cisplatin 100 mg/m^2, the other used teniposide 100 mg/m^2 followed by cisplatin 80 mg/m^2 as comparator (367 patients on comparator). Results in each trial were similar. For the primary outcome of mortality, there was no significant difference between the paclitaxel containing regimen and the comparator (median survival times 8.1 and 9.5 months on paclitaxel containing regimens, 8.6 and 9.9 months on comparators). Similarly, for progression-free survival there was no significant difference between treatments. There was a significant benefit in terms of clinical response rate. Quality of life results are suggestive of a benefit on paclitaxel containing regimens in terms of appetite loss and provide clear evidence of the inferiority of paclitaxel containing regimens in terms of peripheral neuropathy (p < 0.008) with combination teatment.

AIDS-related Kaposi's sarcoma
In the treatment of AIDS-related KS, the efficacy and safety of paclitaxel were investigated in a non-comparative study in patients with advanced KS, previously treated with systemic chemotherapy. The primary end-point was best tumour response. Of the 107 patients, 63 were considered resistant to liposomal anthracyclines. This subgroup is considered to constitute the core efficacy population. The overall success rate (complete/partial response) after 15 cycles of treatment was 57% (CI 44 - 70%) in liposomal anthracycline-resistant patients. Over 50% of the responses were apparent after the first 3 cycles. In liposomal anthracycline-resistant patients, the response rates were comparable for patients who had never received a protease inhibitor (55.6%) and those who received one at least 2 months prior to treatment with paclitaxel (60.9%). The median time to progression in the core population was 468 days (95% CI 257-NE). Median survival could not be computed, but the lower 95% bound was 617 days in core patients.

Pharmacokinetic properties
Absorption Following intravenous administration, paclitaxel exhibits a biphasic decline in plasma concentrations.
The pharmacokinetics of paclitaxel were determined following 3- and 24-hour infusions at doses of 135 and 175 mg/m^2. The mean half-life was between 3.0 and 52.7 hours, and the mean non-compartmentally derived value for total body clearance was between 11.6 and 24.0 l/hr/m^2. The total body clearance appeared to decrease with higher plasma concentrations. The mean steady-state volume of distribution was between 198 and 688 l/m^2, indicating extensive extravascular distribution and/or tissue binding. Dose increases associated with the 3-hour infusion resulted in non-linear pharmacokinetics. When the dose increased by 30% from 135 mg/m2 to 175 mg/m^2, the maximum plasma concentration (C_{max}) increased by 75% and the area under the plasma concentration time curve ($AUC_{0-\infty}$) by 81%.

The variation of systemic paclitaxel exposure in the same patient was found to be minimal. No signs of cumulative effects were found for paclitaxel in association with multiple treatment courses.

Distribution *In vitro* studies of serum protein binding indicate that 89-98% of paclitaxel is bound to proteins. Cimetidine, ranitidine, dexamethasone or diphenhydramine were not found to affect the protein binding of paclitaxel.

Biotransformation and Elimination The distribution and metabolism of paclitaxel in humans has not been fully investigated. The cumulative excretion of unchanged paclitaxel in the urine has been between 1.3% and 12.6% of the dose on average, which is an indication of extensive non-renal clearance. Hepatic metabolism and biliary clearance are possibly the principal mechanisms for elimination of paclitaxel. Paclitaxel is primarily metabolised by the action of CYP450 enzyme. An average of 26% of the radioactively marked dose of paclitaxel was eliminated in the faeces as a 6α-hydroxypaclitaxel, 2% as 3'p-dihydroxypaclitaxel and 6% as 6α-3'p-dihydroxypaclitaxel. 6α-hydroxypaclitaxel is formed by the effect of CYP2C8, 3'p-hydroxypaclitaxel by CYP3A4 and 6α-3'p-dihydroxypaclitaxel by CYP2C8 and CYP3A4. The effect of renal or hepatic impairment on the elimination of paclitaxel after 3 hour infusions has not been studied. The pharmacokinetic parameters of a patient on haemodialysis were of values similar to those of non-dialysis patients when the administration rate was 135 mg/m^2 of paclitaxel as a 3-hour infusion.

Following an intravenous dose of 100 mg/m^2 given as a 3-hour infusion to 19 KS patients, the mean Cmax was 1,530 ng/ml (range 761 - 2,860 ng/ml) and the mean AUC 5,619 ng.hr/ml (range 2,609 - 9,428 ng.hr/ml). Clearance was 20.6 l/h/m^2 (range 11-38) and the volume of distribution was 291 l/m^2 (range 121-638). The terminal elimination half-life averaged 23.7 hours (range 12 – 33).

In clinical trials where paclitaxel and doxorubicin were administered concomitantly, the distribution and elimination of doxorubicin and its metabolites were prolonged. Total plasma exposure to doxorubicin was 30% higher when paclitaxel immediately followed doxorubicin than when there was a 24-hour interval between drugs.

For use of paclitaxel in combination with other therapies, please consult the Summary of Product Characteristics of cisplatin, doxorubicin or trastuzumab for information on the use of these medicinal products.

Preclinical safety data
Administration prior to or during mating produced impairment of fertility in male and female rats. Additionally, paclitaxel caused reduced fertility and reproductive indices, and increased embryo- and fetotoxicity.
The carcinogenic potential of paclitaxel has not been studied. However, paclitaxel is a potential carcinogenic and genotoxic agent based on its pharmacodynamic mechanism of action. Paclitaxel has been shown to be mutagenic in both in vitro and in vivo mammalian test systems.

Clinical particulars

Therapeutic indications
Ovarian cancer:
In the first-line chemotherapy of ovarian cancer, paclitaxel is indicated for the treatment of patients with advanced disease or with residual disease (> 1 cm) after initial laparotomy, in combination with cisplatin.
In the second-line chemotherapy of ovarian cancer, paclitaxel is indicated in the treatment of metastatic carcinoma of the ovary after failure of standard platinum based therapy.

Breast cancer:
In the adjuvant setting, Paclitaxel is indicated for the treatment of patients with node-positive breast carcinoma following anthracycline and cyclophosphamide (AC) therapy. Adjuvant treatment with Paclitaxel should be regarded as an alternative to extended AC therapy.
Paclitaxel is indicated for the initial treatment of locally advanced or metastatic breast cancer either in combination with an anthracycline in patients for whom anthracycline therapy is suitable, or in combination with trastuzumab, in patients who over-express HER-2 (human epidermal growth factor receptor 2) at a 3+ level as determined by immunohistochemistry and for whom an anthracycline is not suitable.
As a single agent, treatment of metastatic carcinoma of the breast in patients who have failed to respond adequately to standard treament with anthracycline or in whom anthracycline therapy has not been appropriate.

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

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

AIDS-related Kaposi's sarcoma:
Paclitaxel is indicated for the treatment of patients with advanced AIDS-related Kaposi's sarcoma (KS) who have failed prior liposomal anthracycline therapy.
Limited efficacy data supports this indication, a summary of the relevant studies.

Posology and method of administration
Posology
Pre-medication: All patients must be given premedication consisting of corticosteroids, antihistamines, and H_2 receptor antagonists prior to Paclitaxel administartion in order to prevent severe hypersensitivity reactions such as pre-medication may consist of.
pre-medication schedule

Medicinal product	Dose	Administration prior to Paclitaxel
dexamethasone	20 mg oral* or IV**	For oral administration: approximately 12 and 6 hours or for IV administration: 30 to 60 min
diphenhydramine***	50 mg IV	30 to 60 min
Cimetidine or ranitidine	300 mg IV 50 mg IV	30 to 60 min

*8–20 mg for KS patients
**intrveous
*** or an equivalent antihistamine e.g. Chlorpheniramine 10 mg IV administered 30 to 60 minute prior to paclitaxel should be administered using in-line filter with a microporous membrane of ≤0.22 microns.

First-line chemotherapy of ovarian cancer: Although alternative medication regimens for paclitaxel aere 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 treament:175 mg/m^2 paclitaxel is administered as an intravenous infusion over a period of three hours followed thereafter by cisplatin at a dose of 75 mg/m^2 and the therapy repeated at every three week intervals or paclitaxel 135 mg/m^2, in a 24-hour infusion, followed by cisplatin 75 mg/m^2, with a 3 week interval between courses.

Second-line chemotherapy of ovarian 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.

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.

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 betwwen courses.

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

The 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 adjustament: Subsequent doses of paclitaxel should be administered according to individual patient tolerance. Paclitaxel should not be readministered until the neutrophil count is ≥1.5x10^9/l (≥ 1x10^9/l for KS patients) and the platelet count is ≥ 100,000/mm^3 (≥ 75,000/mm^3 for KS patients).

Patients who experience severe neutropenia (neutrophil count < 500/mm^3 for a week or longer) 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 should 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.

Method of administration
Precautions to be taken before handling or administering the medicinal product.
The concentrate for solution for infusion must be diluted before use and should only be administered intravenously.

Contraindications
Paclitaxel is contraindicated in patients with severe hypersensitivity reactions to paclitaxel macrogolglycerol ricinoleate (polyoxyl castor oil). or to any excipients listed in Pharmaceutical particulars.

Paclitaxel should not be used in patients with baseline neutrophils < 1,500/mm^3 (< 1,000/mm^3 for KS patients) <100 x 10^9/l (<75 x 10^9/l Ks patients)

Paclitaxel is contraindicated during lactation.
In KS, Paclitaxel is also contraindicated in patients with concurrent, serious, uncontrolled infections.
patients with severe hepatic impairment must not be treated with paclitaxel.

Special warnings and precautions for use
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.
Patients must be pretreated with corticosteroids, antihistamines and H_2 antagonists.
Paclitaxel should be given before cisplatin when used in combination.
Significant hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angioedema and generalised urticaria have occurred in < 1% of patients receiving paclitaxel after adequate premedication. These reactions are probably histamine-mediated. In the case of severe hypersensitivity reactions, paclitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be rechallenged with paclitaxel.macrogoglycerol ricinoleate(ployoxy0l castor oil),an excipient in this medicinal product, can cause these reactions.

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 ≥1,500/mm^3 (≥ 1,000/mm^3 for KS patients) and platelets recover to ≥100,000/mm^3 (≥ 75,000/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 paclitaxel is increased when given as a 3-hour infusion to patients with mildly abnormal liver function. When paclitaxel 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. Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments.

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 paclitaxel. If patients develop significant cardiac 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 sign monitoring, particularly during the first hour of paclitaxel 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 paclitaxel is used in combination with doxorubucin 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, 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^2) of anthracycline administered when making decisions regarding frequency of ventricular function assessment. When testing indicates deterioration in cardiac function, even asymptomatic, treating physicians should carefully assess the clinical benefits of further therapy against the potential for producing cardiac damage, including potentially irreversible damage. If further treatment is 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 paclitaxel is recommended. In NSCLC patients and in ovarian cancer patients treated in the first-line setting, the administration of paclitaxel as a three hour infusion in combination with cisplatin, resulted in a greater incidence of severe neurotoxicity than both single agent paclitaxel and cyclophosphamide followed by 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. When paclitaxel 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. 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%.

Fertility, pregnancy and lactation
Pregnancy
Paclitaxel has been shown to be both embryotoxic and foetotoxic in rabbits.
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.

Paclitaxel 6 mg/ml Concentrate for Solution for Infusion should not be used during pregnancy unless the clinical condition of the woman requires treatment with paclitaxel.
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.

Breast-feeding
It is not known whether paclitaxel is excreted in human milk. Paclitaxel is contraindicated during lactation. Breast-feeding should be discontinued for the duration of therapy with paclitaxel.
Fertility
Paclitaxel has been shown to reduce fertility in rats. Male patients should seek advice regarding cryoconservation of sperm prior to treatment with paclitaxel because of the possibility of infertility.

Interaction with other medicinal products and other forms of interaction
Paclitaxel clearance is not affected by cimetidine premedication.
Cisplatin: paclitaxel is recommended to be administered before cisplatin. When given before cisplatin, the
safety profile of paclitaxel is consistent with that reported for single agent use. 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.

Active substances metabolised 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.

Studies in KS patients, who were taking multiple concomitant medications, 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, 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 paclitaxel 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 paclitaxel 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/m^2 3-hour infusion (85% neurotoxicity, 15% severe) than with a 135 mg/m^2 24-hour infusion (25% peripheral neuropathy, 3% severe) when paclitaxel was combined with cisplatin. In NSCLC patients and in ovarian cancer patients treated with paclitaxel 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 paclitaxel. Peripheral neuropathy was the cause of paclitaxel 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 paclitaxel 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 paclitaxel 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 paclitaxel 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 paclitaxel administered as a three hour infusion in the metastatic setting (812 patients treated in clinical studies) and asreported in the post-marketing surveillance* of paclitaxel.

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 (paclitaxel + cisplatin: over 1050 patients); two phase III trials in the first line treatment of metastatic breast cancer: one investigating the combination with doxorubicin (paclitaxel + doxorubicin: 267 patients), another one investigating the combination with trastuzumab (planned subgroup analysis paclitaxel + trastuzumab: 188 patients) and two phase III trials for the treatment of advanced NSCLC (paclitaxel + 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 paclitaxel followed by cisplatin than patients treated with cyclophosphamide followed by cisplatin. Myelosuppression appeared to be less frequent and severe with paclitaxel as a three hour infusion followed by cisplatin compared with cyclophosphamide followed by cisplatin.

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 paclitaxel (220 mg/m^2) was administered as a 3-hour infusion 24 hours following doxorubicin (50 mg/m^2) when compared to standard FAC therapy (5-FU 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2). Nausea and vomiting appeared to be less frequent and severe with the paclitaxel (220 mg/m^2) / doxorubicin (50 mg/m^2) 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 paclitaxel/doxorubicin arm.

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

When doxorubicin was administered in combination with paclitaxel 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 paclitaxel/doxorubicin and standard FAC arms. Administration of trastuzumab in combination with paclitaxel in patients previously treated with anthracyclines resulted in an increased frequency and severity of cardiac dysfunction in comparison with patients treated with paclitaxel 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^3) 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^3) in 9%. Only 14% experienced a drop in their platelet count < 75,000 cells/mm^3, 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.

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 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.

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
Paclitaxel (Bravifo) 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 Paclitaxel (Bravifo), the bottle should be swirled gently to disperse the Paclitaxel (Bravifo). DO NOT SHAKE.
Avoid contact of Paclitaxel (Bravifo) solutions with plasticized polyvinyl chloride (PVC) equipment, infusion lines or devices used when preparing infusion solutions. Prepare and store diluted Paclitaxel (Bravifo) 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. Paclitaxel (Bravifo) solutions should be administered through polyethylene lined administration sets (e.g., Gemini 20 giving set), using an IMED® pump.
Although solutions of Paclitaxel (Bravifo) 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 Paclitaxel (Bravifo) 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 Paclitaxel (Bravifo). 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 Paclitaxel (Bravifo).
Paclitaxel (Bravifo) is a cytotoxic anticancer drug and as with other potentially toxic compounds, caution should be exercised in handling Paclitaxel (Bravifo). The use of gloves is recommended. Following topical exposure, tingling, burning, redness have been observed. If Paclitaxel (Bravifo) solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If Paclitaxel (Bravifo) 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 Paclitaxel should be administered according to individual patient tolerance. Repetition of a course of Paclitaxel (Bravifo) 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 Paclitaxel (Bravifo) therapy, the dose of Paclitaxel (Bravifo) 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:
Bravifo 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)
Bravifo 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)
Bravifo 6 mg/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: paclitaxel is a cytotoxic anticancer medicinal product and caution should be exercised in handling paclitaxel. Dilution should be carried out under aseptic conditions, by trained personnel in a designated area. Appropriate gloves should be used. Contact of paclitaxel with skin and mucous membranes should be avoided.

If paclitaxel 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 paclitaxel 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 paclitaxel since they can cause the stopper to collapse resulting in loss of sterile integrity of the solution.
Prior to infusion, paclitaxel 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 paclitaxel infusions, with precipitation usually taking place towards the end of a 24-hour infusion period. To reduce the risk of precipitation, paclitaxel 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 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 preparation, administration, infusion, or otherwise coming into contact with paclitaxel 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.

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