LIPO-DOX

Liposome Injection 2mg/mL
Concentrate for Infusion
(Doxorubicin hydrochloride)

SINGLE DOSE FOR INTRAVEOUS INFUSION

【DESCRIPTION】

Lipo-Dox Liposome Injection 2mg/ml Concentrate for Infusion (doxorubicin hydrochloride liposome injection) is an antineoplastic agent of the anthracycline topoisomerase inhibitor. This product is supplied as an orange-red to off red injectable solution and delivers 10ml (20mg of doxorubicin hydrochloride) in a concentrate for single dose intravenous infusion.

Lipo-Dox must be diluted in Dextrose 5% in Water prior to administration. Using 250ml or 500ml diluent, which is not provided with Lipo-Dox according to the prescribing dose. The dilution is red, translucent, and clear solution and should be used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are not be longer than 24 hours at 2°C to 8°C.

【Mechanism】

The exact mechanism of the antitumor activity of doxorubicin is not known. It is generally believed that inhibition of DNA, RNA and protein synthesis is responsible for the majority of the cytotoxic effect. This is probably the result of intercalation of the doxorubicin between adjacent base pairs of the DNA double helix thus preventing their unwinding for replication.

【Clinical Pharmacology】

Lipo-Dox is a long-circulating pegylated liposomal formulation of doxorubicin HCl.

Pegylated liposomes contain surface-grafted segments of the hydrophilic polymer methoxypolyethylene glycol (MPEG). These linear MPEG groups extend from the liposome surface forming a protective coating that reduces interactions between the liposomal lipid bilayer membrane and the plasma components, so the circulation time of pegylated liposomal doxorubicin is prolonged in the blood stream.

Pegylated liposomes are small enough (average diameter of approximately 100 nm) to pass intact (extravasate) through defective blood vessels supplying tumors. Evidence of penetration of pegylated liposomes from blood vessels and their entry and accumulation in tumors has been seen in mice with C-26 colon carcinoma tumors and in transgenic mice with Kaposi's sarcoma-like lesions. The doxorubicin HCl could be encapsulated during liposome residence time in circulation, because of low permeability lipid matrix and internal liquid buffer system of the pegylated liposomes.

The plasma pharmacokinetics in humans are significant different between pegylated liposomal doxorubicin and standard doxorubicin HCl preparations. At lower doses (10 mg/m^2 - 20 mg/m^2), pegylated liposomal doxorubicin displayed linear pharmacokinetics. However, the pharmacokinetics are displayed to be non-linear over the dose range of 10mg/ m^2 to 60 mg/m^2.

The standard doxorubicin HCl displays extensive tissue distribution (volume of distribution, 700 to 1100 L/m^2) and a rapid elimination clearance (24-73 L/h/m^2). In contrast the pharmacokinetic profile of pegylated liposomal doxorubicin indicates that pegylated liposomal doxorubicin is confined mostly to the vascular fluid volume and that the clearance of doxorubicin from the blood is dependent upon the liposomal carrier. After the liposomes are extravasated and enter the tissue compartment, doxorubicin becomes available.

At equivalent doses, the plasma concentration and AUC values of pegylated liposomal doxorubicin which mostly exist as encapsulated in liposomeos (containing 90% to 95% of the measured doxorubicin) are significant higher than standard doxorubicin HCl.

【Indications】

Lipo-Dox, as a monotherapy, is indicated for the treatment of metastatic breast cancer.

Lipo-Dox is indicated for the treatment of advanced ovarian cancer in women who have failed a first-line platinum based chemotherapy regimen.

Lipo-Dox is also indicated for AIDS-related Kaposi's sarcoma (KS) in patients with low CD4 counts (<200 CD4 lymphocytes/mm^3) and extensive mucocutaneous or visceral disease.

Lipo-Dox may be used as first-line systemic chemotherapy, or as second line chemotherapy in AIDS-KS patients with disease that has progressed with, or in patients intolerant to, prior combination systemic chemotherapy comprising at least two of the following agents: a vinca alkaloid, bleomycin and standard doxorubicin (or other anthracyclines).

Lipo-Dox is indicated in combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or unsuitable for bone marrow transplant.

【Dosage and Administration】

Lipo-Dox exhibits unique pharmacokinetic properties and must not be used interchangeably with other formulations of doxorubicin hydrochloride. Lipo-Dox should only be administered under the supervision of a qualified oncologist specialized in the administration of cytotoxic agents.

Breast / Ovarian Cancer

Lipo-Dox is administered intravenously at a dose of 50 mg/m^2 once every four weeks for as long as the disease does not progress and the patient continues to tolerate treatment.

For doses <90 mg: dilute Lipo-Dox in 250 ml Dextrose 5 % in Water.

For doses >90 mg: dilute Lipo-Dox in 500 ml Dextrose 5 % in Water

To minimize the risk of infusion reactions, the initial dose is administered at a rate no greater than 1 mg/minute. If no infusion reaction is observed, subsequent Lipo-Dox infusions may be administered over a 60 minute period. In the breast cancer trial program, modification of the infusion was permitted for those patients experiencing an infusion reaction as follows:

5 % of the total dose was infused slowly over the first 15 minutes. If tolerated without reaction, the infusion rate was doubled for the next 15 minutes. If tolerated, the infusion was completed over the next hour for a total infusion time of 90 minutes. Subsequent Lipo-Dox infusions may be administered over a 60 minute period.

AIDS-KS patients

Lipo-Dox should be administered intravenously at 20mg/m^2 every two-to-three weeks. Intervals shorter than 10 days should be avoided as drug accumulation and increased toxicity cannot be ruled out. Patients should be treated for two-to-three months to achieve a therapeutic response. Treatment should be continued as needed to maintain a therapeutic response.

Lipo-Dox, diluted in 250 ml Dextrose 5% in Water, is administered by intravenous infusion over 30 minutes

Multiple Myeloma

Lipo-Dox is administered at 30mg/m^2 on day 4 of the bortezomib 3 week regimen as 1 hour infusion administered immediately after the

bortezomib infusion. The bortezomib regimen consists of 1.3mg/m^2 on days 1, 4, 8, and 11 every 3 weeks. The dose should be repeated as long as patients respond satisfactorily and tolerate treatment.

For doses < 90 mg: dilute Lipo-Dox in 250 ml of 5 % (50 mg/ml) glucose solution for infusion

For doses ≥ 90 mg: dilute Lipo-Dox in 500 ml of 5 % (50 mg/ml) glucose solution for infusion

The intravenous catheter and tubing should be flushed with 5 % glucose solution for infusion between administration of the 2 medicinal products. Day 4 dosing of both medicinal products may be delayed up to 48 hours as medically necessary. Doses of bortezomib should be at least 72 hours apart. The first infusion of Lipo-Dox should be administered over 90 minutes, as follows:

1. 10 ml over first 10 minutes
2. 20 ml over next 10 minutes
3. 40 ml over next 10 minutes
4. then, complete the infusion over a total of 90 minutes.

Subsequent doses of Lipo-Dox will be administered over 1 hour, as tolerated.

If an infusion reaction to Lipo-Dox occurs, stop the infusion and after the symptoms resolve, attempt to administer the remaining Lipo-Dox over 90 minutes, as follows:

1. 10 ml over first 10 minutes
2. 20 ml over next 10 minutes
3. 40 ml over next 10 minutes
4. Then, complete the remaining infusion over a total of 90 minutes.

Infusion may be given through a peripheral vein or a central line.

All patients

If the patient experiences early symptoms or signs of infusion reaction, immediately discontinue the infusion, give appropriate premedications (antihistamine and/or short acting corticosteroid) and restart at a slower rate.

DO NOT administer as a bolus injection or undiluted solution. It is recommended that the Lipo-Dox infusion line be connected through the side port of an intravenous infusion of Dextrose 5% in Water to achieve further dilution and minimize the risk of thrombosis and extravasation. The infusion may be given through a peripheral vein. Lipo-Dox must not be given by the intramuscular or subcutaneous route. Do not use with in-line filters.

To manage adverse events such as palmar-plantar erythrodysesthesia (PPE), stomatitis or hematologic toxicity, the dose may be reduced or delayed. Guidelines for Lipo-Dox dose modification secondary to these adverse effects are provided in the tables below. The toxicity grading in these tables is based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC).

The tables for PPE (Table 2) and stomatitis (Table3) provide the schedule followed for dose modification in clinical trials in the treatment of breast or ovarian cancer (modification of the recommended 4 week treatment cycle): If these toxicities occur in patients with AIDS-related KS, the recommended 2 to 3 week treatment cycle can be modified in a similar manner.

The table for hematologic toxicity (Table 4) provides the schedule followed for dose modification in clinical trials in the treatment of patients with breast or ovarian cancer only. Dose modification in patients with AIDS-KS is addressed in ADVERSE EFFECTS.

Guidelines for Lipo-Dox Dose Modification

Table 2. PALMAR- PLANTAR ERYTHRODYSESTHESIA

	Week After Prior Lipo-Dox Dose		
Toxicity Grade at Current Assessment	Week 4	Week 5	Week 6
Grade 1 (mild erythema, swelling, or desquamation not interfering with daily activities)	Redose unless patient has experienced previous Grade 3 or 4 toxicity, in which case wait an additional week	Redose unless patient has experienced previous Grade 3 or 4 toxicity, in which case wait an additional week	Decrease dose by 25%. Return to 4 weeks dose interval
Grade 2 (erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter)	Wait an additional week.	Wait an additional week.	Decrease dose by 25%. Return to 4-week dose interval
Grade 3 (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing)	Wait an additional week	Wait an additional week	Withdraw patient
Grade 4 (diffuse or local process causing infectious complications, or a bedridden state or hospitalization)	Wait an additional week	Wait an additional week	Withdraw patient

Table 3. STOMATITIS

	Week After Prior Lipo-Dox Dose		
Toxicity Grade at Current Assessment	Week 4	Week 5	Week 6
Grade 1 (painless ulcers, erythema, or mild soreness)	Redose unless patient has experienced a previous Grade 3 or 4 toxicity in which case wait an additional week.	Redose unless patient has experienced a previous Grade 3 or 4 toxicity in which case wait an additional week.	Decrease dose by 25% ; return to 4-week dose interval or withdraw patient per physician's assessment.
Grade 2 (painful erythema, edema, or ulcers, but can eat)	Wait an additional week	Wait an additional week	Decrease dose by 25% ; return to 4-week dose interval or withdraw patient per physician's assessment.
Grade 3 (painful erythema, edema, or ulcers, but cannot eat)	Wait an additional week	Wait an additional week	Withdraw patient
Grade 4 (require parenteral or enteral support)	Wait an additional week	Wait an additional week	Withdraw patient

Table 4. HEAMATOLOGICAL TOXICITY (ANC or PLATELETS) – dose adjustment for breast or ovarian cancer patients

Grade	ANC	PLATELETS	MODIFICATION
Grade 1	1500 – 1900	75,000 – 150,000	Resume treatment with no dose reduction
Grade 2	1000 - < 1500	50,000 - < 75,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; redose with no dose reduction.
Grade 3	500 - < 1000	25,000 - < 50,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; redose with no dose reduction.
Grade 4	< 500	< 25,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; decrease does at 25% or continue full dose with growth factor support.

For multiple myeloma patients treated with Lipo-Dox in combination with bortezomib who experience PPE or stomatitis, the Lipo-Dox dose should be modified as described in Table 2 and 3 above respectively. Table 5, below provides the schedule followed for other dose modifications

in the clinical trial in the treatment of patients with multiple myeloma receiving Lipo-Dox and bortezomib combination therapy. For more detailed information on bortezomib dosing and dosage adjustments, see the SPC for bortezomib.

Table 5. DOSAGE ADJUSTMENTS FOR LIPO-DOX + BORTEZOMIB COMBINATION THERAPY – patients with multiple myeloma		
Patient Status	Lipo-Dox	Bortezomib
Fever ≥38°C and ANC < 1,000/mm^3	Do not dose this cycle if before Day 4; if after Day 4, reduce next dose by 25 %.	Reduce next dose by 25 %.
On any day of medicine administration after Day 1 of each cycle: Platelet count < 25,000/mm^3 Hemoglobin < 8 g/dl ANC < 500/mm^3	Do not dose this cycle if before Day 4; if after Day 4 reduce next dose by 25 % in the following cycles if bortezomib is reduced for hematologic toxicity.*	Do not dose; if 2 or more doses are not given in a cycle, reduce dose by 25 % in following cycles.
Grade 3 or 4 non-hematologic medicine related toxicity	Do not dose until recovered to Grade < 2 and reduce dose by 25 % for all subsequent doses.	Do not dose until recovered to Grade < 2 and reduce dose by 25 % for all subsequent doses.
Neuropathic pain or peripheral neuropathy	No dosage adjustments.	See the SPC for bortezomib.

*for more information on bortezomib dosing and dosage adjustment, see the SPC for bortezomib

Patients with Impaired Hepatic Function

Base on reports, in the small amount of patients with elevated total bilirubin levels, the pharmacokinetics is similar to patients with normal total bilirubin levels. However, until further experience is gained, the pegylated liposomal doxorubicin dosage in patients with impaired hepatic function should be reduced based on the experience from the breast and ovarian cancer clinical trial programs as follows: at initiation of therapy, if the bilirubin is ranged 1.2 to 3.0 mg/dL, the first dose is reduced by 25%. If the bilirubin is more than 3.0 mg/dL, the first dose should be reduced by 50%. If the patient tolerates the first dose without an increase in serum bilirubin or liver enzymes, the dosage for cycle 2 can be increased to the next dose level, i.e., if reduced by 25% for the first dose, increase to full dose for cycle 2; if reduced by 50% for the first dose, increase to 75% of full dose for cycle 2. If the patient well tolerate, the dosage can be increased to full dose for the subsequent cycles. In the liver metastases patients with concurrent elevation of bilirubin and liver enzymes up to 4× the upper limit of the normal range, pegylated liposomal doxorubicin could be administered. Prior to pegylated liposomal doxorubicin administration, evaluate hepatic function using conventional clinical laboratory tests such as ALT/AST, alkaline phosphatase, and bilirubin is necessary.

Patients with Impaired Renal Function

As doxorubicin is metabolized by the liver and excreted in bile, dosage adjustment is not necessary. From the pharmacokinetic analysis of special population, it is confirmed that the pharmacokinetic properties are not different in the patients with the creatinine clearance between 30 - 156 mL/min. No pharmacokinetic data are available in patients with creatinine clearance of less than 30 mL/min.

AIDS-KS Patients with Splenectomy

There is no experience with pegylated liposomal doxorubicin in patients who have had splenectomy, treatment with Lipo-Dox is not recommended.

Pediatric Patients

The experience in children is limited. Lipo-Dox is not recommended in patients below 18 years of age.

Elderly Patients

Base on the Population based analysis demonstrates that age cross the range test (21-75 years) doesn't significantly alter the pharmacokinetics of pegylated liposomal doxorubicin.

【Instructions for use/handling】

Precaution during handling

- Caution must be exercised in handling pegylated liposomal doxorubicin.
- Do not use material that shows evidence of precipitation or any other particulate matter.
- The use of gloves is required.
- If pegylated liposomal doxorubicin comes into contact with skin or mucosa, wash immediately and thoroughly with soap and water.
- Pegylated liposomal doxorubicin should be handled and disposed of in a manner consistent with that of other anticancer products in accordance with local requirements.

Dilution of Lipo-dox

- The appropriate dose of pegylated liposomal doxorubicin must be diluted in Dextrose 5% in Water prior to administration. Do not use any diluent other than Dextrose 5% in Water, or the presence of any bacteriostatic agent, such as benzyl alcohol, which will cause precipitation.
- For doses <90mg, dilute in 250 ml of Dextrose 5% in Water, and for doses ≥90mg, dilute in 500ml of Dextrose 5% in Water. Unless specific compatibility data are available, pegylated liposomal doxorubicin should not be mixed with other drug in the same IV infusion bag, these drugs are incompatible.
- The dilution of pegylated liposomal doxorubicin is red, translucent, and clear solution, and should be used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C to 8°C

Administration

- Do not administer the undiluted solution.
- This can be infused over 60 or 90 minutes as detailed in Dosage and Administration
- It is recommended that the pegylated liposomal doxorubicin infusion line should be connected through the side port of an intravenous infusion of Dextrose 5% in Water.
- The infusion might be given through a peripheral vein. Do not use with in-line filters.

【Incompatibilities】

Do not mix with other drugs.

【Drug Interactions】

Caution should be exercised in the concomitant use of drugs known to interact with standard doxorubicin HCl. Like other doxorubicin HCl preparations, pegylated liposomal doxorubicin may potentiate the toxicity of other anti-cancer therapies.

Pegylated liposomal doxorubicin HCl has been administered to patients with solid tumors (including ovarian cancer or breast cancer) as part of combination therapy regimen (combined with either cyclophosphamide, taxanes or vinorelbine). In AIDS-KS patients, it has been reported that conventional doxorubicin HCl exacerbates the cyclophosphamide-induced hemorrhagic cystitis and enhances the hepatotoxicity of 6-mercaptopurine. Caution must be exercised when giving other cytotoxic agents, especially those may induce bone marrow suppression, at the same time.

【Adverse Reactions】

Summary of the safety profile

The most common undesirable effect reported was palmar-plantar erythrodysesthesia (PPE). The effects of PPE are mostly mild, but in some case, the effects of PPE are severe and life-threatening. PPE infrequently results in permanent treatment discontinuation. PPE is characterised by painful, macular reddening skin

eruptions. In patients experiencing this event, it is generally seen after two or three cycles of treatment. Improvement usually occurs in one - two weeks, and in some cases, may take up to 4 weeks or longer for complete resolution. Pyridoxine at a dose of 50-150 mg per day and corticosteroids have been used for the prophylaxis and treatment of PPE. Other strategies to prevent and treat PPE, which may be initiated for 4 to 7 days after treatment with pegylated liposomal doxorubicin include keeping hands and feet cool, by exposing them to cool water (soaks, baths, or swimming), avoiding excessive heat/hot water and keeping them unrestricted (no socks, gloves, or shoes that are tight fitting). PPE appears to be primarily related to the dose schedule and can be reduced by extending the dose interval 1-2 weeks. However, this reaction can be severe and debilitating in some patients and may require discontinuation of treatment.

Stomatitis/mucositis and nausea were also commonly reported in breast/ovarian cancer patient populations, whereas the AIDS-KS Program (20 mg/m^2 every 2 weeks), myelosuppression (mostly leukopaenia) was the most common side effect. The PPE is also common adverse reaction for patients with multiple myeloma patients treated with pegylated liposomal doxorubicin plus bortezomib combination therapy. The most frequently medicine-related or treatment-emergent adverse events in combination therapy (Pegylated liposomal doxorubicin + bortezomib) are nausea, diarrhoea, neutropaenia, thrombocytopaenia, vomiting, fatigue, and constipation.

For All Patients

During treatment with pegylated liposomal doxorubicin, infusion-associated reaction is common adverse reaction for patients with solid tumor. The infusion-associated reactions are defined as following: allergic reaction, anaphylactoid reaction, asthma, face edema, hypotension, vasodilatation, urticaria, back pain, chest pain, chills, fever, hypertension, tachycardia, dyspepsia, dizziness, dyspnea, pharyngitis, rash, nausea, pruritus, sweating, injection site reaction and drug interactions. For patients with multiple myeloma receiving pegyated liposomal doxorubicin plus bortezomib, the infusion-associated recations are common. And for patients with AIDS-KS the infusion-associated reactions are also common which were characterized by flushing, shortness of breath, facial edema, headache, chills, back pain, tightness in the chest and throat, and/or hypotension. Permanent treatment discontinuation rates infusion-associated reaction are infrequently occurs. Very rarely, convulsions have been observed in relation to infusion reactions.

In all patients, infusion associated reactions occurred primarily during the first infusion. Usually, temporarily stopping the infusion could resolve these symptoms without further therapy. In nearly all patients could resume pegylated liposomal doxorubicin treatment after all symptoms have resolved without recurrence. After the first cycle of pegylated liposomal doxorubicin treatment finished, the infusion reactions rarely recurred. Infusion reactions rarely recur after the first treatment cycle with pegylated liposomal doxorubicin.

Myelosuppression associated with anaemia, thrombocytopaenia, leukopaenia, and rarely febrile neutropaenia, has been reported in pegylated liposomal doxorubicin -treated patients

There was stomatitis reported in patients receiving continuous infusions of conventional doxorubicin HCl and was frequently reported in patients receiving pegylated liposomal doxorubicin. It did not interfere with patients completing therapy and no dosage adjustments are generally required, unless Stomatitis is affecting a patient's ability to eat. In the case, the dose interval by 1 to 2 weeks or reduce the dosage.

Treatment of standard doxorubicin HCl at cumulative doses of lifetime above 450mg/m^2 or at lower doses for patients with cardiac risk factors may increase the incidence of congestive heart failure. However, the incidence of clinically significant cardiac injury was very low in the solid tumor patients (including breast and ovarian cancers) receiving pegylated liposomal doxorubicin.

As with other DNA-damaging antineoplastic agents, secondary acute myeloid leukemias and myelodysplasias have been reported in patients having received combined treatment with doxorubicin. Therefore, any patient treated with doxorubicin should be kept under haematological supervision.

Although local tissue necrosis following extravasation of pegylated liposomal doxorubicin has been reported very rarely, but its irritant reaction should be considered. If any symptoms of extravasation occur (e.g., stinging, erythema), the infusion should be immediately terminated and restarted in another vein. The application of ice over the site of extravasation for approximately 30 minutes may be helpful in alleviating the local reaction. Pegylated liposomal doxorubicin should not be given by the route of intramuscular or subcutaneous.

The recurrence of skin reaction due to prior radiotherapy is very rarely seen in pegylated liposomal doxorubicin administration.

Following the marketing of pegylated liposomal doxorubicin, serious skin conditions including erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis have been reported very rarely.

In patients treated with pegylated liposomal doxorubicin, cases of venous thromboembolism, including thrombophlebitis, venous thrombosis and pulmonary embolism have been seen uncommonly. However, because patients with cancer are at increased risk for thromboembolic disease, a causal relationship cannot be determined.

【Contraindications】

Lipo-Dox is contraindicated in patients who have a history hypersensitivity to doxorubicin HCl or the excipient of Lipo-Dox.

Lipo-Dox should not be administered while breast-feeding.

Lipo-Dox should not be used in AIDS-KS patients, when they were effectively treated by local therapy or systemic α-interferon.

【Warnings and Precaution】

Given the difference in pharmacokinetic profiles and dosing schedules, Lipo-Dox should not be used interchangeably with other formulations of doxorubicin hydrochloride.

Cardiac Toxicity

All patients treating with Lipo-Dox should routinely undergo ECG monitoring. When T-wave flattening, S-T segment depression and arrhythmia occur, therapy discontinuance immediately is not necessary. However, reduction of the QRS complex is considered more indicative of cardiac toxicity. Endomyocardial biopsy should be considered to define for anthracycline induced myocardial injury. (see Adverse Reaction)

Besides ECG, there are many specific methods for monitoring cardiac functions, such as a measurement of LVEF by cardiac echo or preferably by Multigated Angiography (MUGA). These methods should be applied routinely before or during the Lipo-Dox treatment.

The evaluation of left ventricular function is considered to be mandatory before each addition administration of pegylated liposomal doxorubicin which exceeds a lifetime cumulative anthracycline dose of 400 mg/m^2 in patients without prior anthracycline exposure. For patients who have received prior adjuvant anthracyclines (epirubicin or doxorubicin), LVEF assessments should be performed before each additional administration of pegylated liposomal doxorubicin that exceeds a lifetime, doxorubicin-equivalent, cumulative anthracycline dose of 450 mg/m^2 and each time when the accumulated dosage increment of pegylated liposomal doxorubicin is 100mg/m^2, the patients

must receive the evaluation of LVEF.

The evaluation tests and monitoring of cardiac performance during anthracycline therapy should be employed in the following order: ECG monitoring, measurement of left ventricular ejection fraction, endomyocardial biopsy. If the test result indicates possible cardiac injury associated with pegylated liposomal doxorubicin therapy, the benefit of continuance of therapy or not must be carefully evaluated.

In patients with cardiovascular disease requiring treatment, administer pegylated liposomal doxorubicin only when the benefit outweighs the risk to the patient.

Caution should be exercised in patients with impaired cardiac function who receive pegylated liposomal doxorubicin.

If the test results indicate possible cardiac injury, such as the left ventricular ejection fraction lower than pre-treatment baseline and/or LVEF is lower than a prognostically relevant values, endomyocardial biopsy might be considered. The benefit of continuance of therapy must be carefully weighed against the risk of developing irreversible myocardial injury.

Congestive heart failure due to cardiomyopathy may occur suddenly, without prior ECG changes and may also be encountered several weeks after discontinuation of therapy.

Caution should be observed in patients who have received other anthracyclines. The total dose of doxorubicin HCl should be taken into account any previous (or concomitant) therapy with cardiotoxic compounds such as other anthracyclines/anthraquinones or 5-fluorouracil. The cardiac toxicity also may occur at cumulative anthracycline doses lower than 450 mg/m^2 in patients with prior mediastinal irradiation or in those with concurrent cyclophosphamide therapy.

The cardiac safety profile for dosing schedule recommended for both breast and ovarian cancer (50 mg/m^2/every 4 weeks) is similar to the 20mg/m^2/every 2 weeks profile in AIDS-KS patients. (See Adverse Reactions)

Myelosuppression

Many patients treated with pegylated liposomal doxorubicin have baseline myelosuppression due to such factors as their pre-existing HIV disease or concomitant or previous medications, or tumors involving bone marrow.

In contrast to the experience in breast cancer and ovarian cancer patients, the myelosuppression appears to be the dose-limiting adverse event in AIDS-KS patients. Because of the potential for bone marrow suppression, periodic blood counts must be performed during the course of pegylated liposomal doxorubicin, and at least before each dose of pegylated liposomal doxorubicin.

Persistent severe myelosuppression, may result in recurrent infection or hemorrhage.

Due to the different pharmacokinetic properties and dosing schedules, Lipo-Dox should not be interchanged with other doxorubicin HCl formulations. Combination chemotherapy with pegylated liposomal doxorubicin has been studied in solid tumor populations. Pegylated liposomal doxorubicin has been safely co-administered with standard doses of chemotherapeutic agents that are frequently used in the treatment of advanced breast cancer or ovarian cancer; however the efficacy of such combination regimens has not been established.

Diabetic Patients

Each vial of Lipo-Dox contains sucrose and is administered in Dextrose 5% in Water for intravenous infusion, so precaution should be exercised.

Infusion-associated Adverse Reactions

Severe and sometimes life-threatening infusion reactions which are characterized by allergic-like or anaphylactoid-like reactions, with symptoms including asthma, flushing, urticaria, chest pain, fever, hypertension, tachycardia, pruritus, sweating, shortness of breath, facial edema, chills, back pain, tightness in the chest and throat and/or hypotension may occur within minutes of starting the infusion of pegylated liposomal doxorubicin. Temporarily stopping the infusion usually resolved these symptoms without further therapy. However, medications to treat these symptoms (e.g., antihistamines, corticosteroids, and adrenaline), as well as emergency equipment should be available for immediate use. In most patients can be resumed after all symptoms have resolved, without recurrence. Infusion reactions rarely recur after the first treatment cycle. The initial rate of infusion should be not over 1mg/min to help minimize the risk of infusion reactions. (See Adverse Reactions).

Driving and Machine Operations

Pegylated lipoosmal doxorubicin does not affect on patient's driving, but occur dizziness and somnolence on few people. Driving and machine operations should be avoided in patients who suffer from these effects.

Pregnancy and Lactation

Pegylated liposomal doxorubicin is embryotoxic in rats and embryotoxic and abortifacient in rabbits. Teratogenicity cannot be excluded. There is no experience in pregnant women with pegylated liposomal doxorubicin, therefore administration to pregnant women is not recommended. Avoid pregnancy in women of childbearing potential and their male partner within 6 months after discontinuation of Lipo-Dox therapy.

It is not known whether Lipo-Dox is excreted in human milk and because of the potential for severe adverse reactions in nursing infants, mothers should discontinue nursing. Medical experts recommend that HIV-infected women should not nurse infants under any circumstances in order to avoid transmission of HIV.

Overdosage

Acute reaction of overdosage with doxorubicin HCl worsens the effects of mucositis, leukopenia and thrombocytopenia. Treatments of acute reaction of overdosage in the severely myelosuppressed patient include hospitalization, antibiotics, platelet and granulocyte transfusions and symptom relief of mucositis.

【Package】

Each 10 ml Lipo-Dox vial contains 20mg of doxorubicin HCl as a concentration of 2mg/ml. For single dose usage. 1 vial per box.

For the expiration date, please refer to the label in the box and vial.

【Storage】

Refrigerate unopened vials at 2°C to 8°C Avoid freezing.

After dilution with Dextrose 5% in Water, the diluted Lipo-Dox solution should be used immediately or stored at 2°C to 8°C for not longer than 24 hours. Discard the partially used vials.

Please keep out of the reach of children.

Ask your physicians or pharmacists for further information.

【Manufacture】

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