

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE MEDICINAL PRODUCT**

ZOLSKETIL pegylated liposomal 2 mg/mL concentrate for dispersion for infusion

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

One mL of ZOLSKETIL pegylated liposomal contains 2 mg doxorubicin hydrochloride in a pegylated liposomal formulation.

ZOLSKETIL pegylated liposomal, a liposome formulation, is doxorubicin hydrochloride encapsulated in liposomes with surface-bound methoxypolyethylene glycol (MPEG). This process is known as pegylation and protects liposomes from detection by the mononuclear phagocyte system (MPS), which increases blood circulation time.

### Excipients with known effect

Contains fully hydrogenated soy phosphatidylcholine (from soyabean) - see section 4.3

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Concentrate for dispersion for infusion

A translucent red coloured dispersion filled in a clear glass vial. When examined under suitable conditions of visibility it should be practically free from particles.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

ZOLSKETIL pegylated liposomal is indicated:

- As monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk.
- For treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen.
- 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 are unsuitable for bone marrow transplant.
- For treatment of AIDS-related Kaposi's sarcoma (KS) in patients with low CD4 counts ( $< 200$  CD4 lymphocytes/mm<sup>3</sup>) and extensive mucocutaneous or visceral disease.

ZOLSKETIL pegylated liposomal 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 anthracycline).

ZOLSKETIL pegylated liposomal is indicated in adults.

### **4.2 Posology and method of administration**

ZOLSKETIL pegylated liposomal should only be administered under the supervision of a qualified oncologist specialised in the administration of cytotoxic agents.

ZOLSKETIL pegylated liposomal exhibits unique pharmacokinetic properties and must not be used interchangeably with other formulations of doxorubicin hydrochloride.

## Posology

### Breast cancer/Ovarian cancer

ZOLSKETIL pegylated liposomal is administered intravenously at a dose of 50 mg/m<sup>2</sup> once every 4 weeks for as long as the disease does not progress and the patient continues to tolerate treatment.

### Multiple myeloma

ZOLSKETIL pegylated liposomal is administered at 30 mg/m<sup>2</sup> on day 4 of the bortezomib 3 week regimen as a 1 hour infusion administered immediately after the bortezomib infusion. The bortezomib regimen consists of 1.3 mg/m<sup>2</sup> on days 1, 4, 8, and 11 every 3 weeks. The dose should be repeated as long as patients respond satisfactorily and tolerate treatment. 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.

### AIDS-related KS

ZOLSKETIL pegylated liposomal is administered intravenously at 20 mg/m<sup>2</sup> every two-to-three weeks. Avoid intervals shorter than 10 days as medicinal product accumulation and increased toxicity cannot be ruled out. Treatment of patients for two-to-three months is recommended to achieve a therapeutic response. Continue treatment as needed to maintain a therapeutic response.

### For all patients

If the patient experiences early symptoms or signs of infusion reaction (see sections 4.4 and 4.8), immediately discontinue the infusion, give appropriate premedications (antihistamine and/or short acting corticosteroid) and restart at a slower rate.

### Guidelines for ZOLSKETIL pegylated liposomal dose modification

To manage adverse reaction such as palmar-plantar erythrodysesthesia (PPE), stomatitis or haematological toxicity, the dose may be reduced or delayed. Guidelines for ZOLSKETIL pegylated liposomal 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 1) and stomatitis (Table 2) 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 haematological toxicity (Table 3) 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 provided following Table 4..

**Table 1. Palmar-Plantar erythrodysesthesia**

Toxicity grade at current assessment	Week after prior Doxorubicin pegylated liposomal dose		
	Week 4	Week 5	Week 6
<b>Grade 1</b> (mild erythema, swelling, or desquamation not interfering with daily activities)	<b>Redose unless</b> patient has experienced a previous grade 3 or 4 skin toxicity, in which case wait an additional week	<b>Redose unless</b> patient has experienced a previous grade 3 or 4 skin toxicity, in which case wait an additional week	<b>Decrease dose by 25%; return to 4 week interval</b>
<b>Grade 2</b> (erythema, desquamation, or swelling interfering)	<b>Wait an additional week</b>	<b>Wait an additional week</b>	<b>Decrease dose by 25%; return to 4 week interval</b>

with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter)			
<b>Grade 3</b> (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing)	<b>Wait an additional week</b>	<b>Wait an additional week</b>	<b>Withdraw patient</b>
<b>Grade 4</b> (diffuse or local process causing infectious complications, or a bedridden state or hospitalisation)	<b>Wait an additional week</b>	<b>Wait an additional week</b>	<b>Withdraw patient</b>

**Table 2. Stomatitis**

<b>Toxicity grade at current assessment</b>	<b>Week after prior Doxorubicin pegylated liposomal dose</b>		
	<b>Week 4</b>	<b>Week 5</b>	<b>Week 6</b>
<b>Grade 1</b> (painless ulcers, erythema, or mild soreness)	<b>Redose unless patient has experienced a previous grade 3 or 4 stomatitis in which case wait an additional week</b>	<b>Redose unless patient has experienced a previous grade 3 or 4 stomatitis in which case wait an additional week</b>	<b>Decrease dose by 25%; return to 4 week interval or withdraw patient per physician's assessment</b>
<b>Grade 2</b> (painful erythema, oedema, or ulcers, but can eat)	<b>Wait an additional week</b>	<b>Wait an additional week</b>	<b>Decrease dose by 25%; return to 4 week interval or withdraw patient per physician's assessment</b>
<b>Grade 3</b> (painful erythema, edema, or ulcers, but cannot eat)	<b>Wait an additional week</b>	<b>Wait an additional week</b>	<b>Withdraw patient</b>
<b>Grade 4</b> (requires parenteral or enteral support)	<b>Wait an additional week</b>	<b>Wait an additional week</b>	<b>Withdraw patient</b>

**Table 3. Haematological toxicity (ANC or platelets) - Management of patients with breast or ovarian cancer**

<b>GRADE</b>	<b>ANC</b>	<b>PLATELETS</b>	<b>MODIFICATION</b>
<b>Grade 1</b>	1,500 – 1,900	75,000 – 150,000	Resume treatment with no dose reduction.
<b>Grade 2</b>	1,000 – < 1,500	50,000 – < 75,000	Wait until ANC $\geq$ 1,500 and platelets $\geq$ 75,000; redose with no dose reduction.
<b>Grade 3</b>	500 – < 1,000	25,000 – < 50,000	Wait until ANC $\geq$ 1,500 and platelets $\geq$ 75,000; redose with no dose reduction.
<b>Grade 4</b>	< 500	< 25,000	Wait until ANC $\geq$ 1,500 and platelets $\geq$ 75,000; decrease dose by 25% or continue full dose with growth factor support.

For multiple myeloma patients treated with doxorubicin pegylated liposomal in combination with bortezomib who experience PPE or stomatitis, the doxorubicin pegylated liposomal dose should be modified as described in Table 1 and 2 above respectively. Table 4, below provides the schedule

followed for other dose modifications in the clinical trial in the treatment of patients with multiple myeloma receiving doxorubicin pegylated liposomal and bortezomib combination therapy. For more detailed information on bortezomib dosing and dosage adjustments, see the SmPC for bortezomib.

**Table 4. Dosage adjustments for doxorubicin pegylated liposomal + bortezomib combination therapy - patients with multiple myeloma**

Patient status	Doxorubicin pegylated liposomal	Bortezomib
Fever $\geq 38^{\circ}\text{C}$ and ANC $< 1,000/\text{mm}^3$	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 $< 25,000/\text{mm}^3$ Haemoglobin $< 8 \text{ g/dl}$ ANC $< 500/\text{mm}^3$	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 haematologic 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-haematologic 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 SmPC for bortezomib.

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

For AIDS-KS patients treated with ZOLSKETIL pegylated liposomal, haematological toxicity may require dose reduction or suspension or delay of therapy. Temporarily suspend ZOLSKETIL pegylated liposomal treatment in patients when the ANC count is  $< 1,000/\text{mm}^3$  and/or the platelet count is  $< 50,000/\text{mm}^3$ . G-CSF (or GM-CSF) may be given as concomitant therapy to support the blood count when the ANC count is  $< 1,000/\text{mm}^3$  in subsequent cycles.

### Special populations

#### Hepatic impairment

Doxorubicin pegylated liposomal pharmacokinetics determined in a small number of patients with elevated total bilirubin levels do not differ from patients with normal total bilirubin; however, until further experience is gained, the doxorubicin pegylated liposomal dosage in patients with impaired hepatic function should be reduced based on the experience from the breast and ovarian clinical trial programs as follows: at initiation of therapy, if the bilirubin is between 1.2-3.0 mg/dl, the first dose is reduced by 25%. If the bilirubin is  $> 3.0 \text{ mg/dl}$ , the first dose is reduced by 50%. If the patient tolerates the first dose without an increase in serum bilirubin or liver enzymes, the dose 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. The dosage can be increased to full dose for subsequent cycles if tolerated. Doxorubicin pegylated liposomal can be administered to patients with liver metastases with concurrent elevation of bilirubin and liver enzymes up to 4 x the upper limit of the normal range. Prior to doxorubicin pegylated liposomal administration, evaluate hepatic function using conventional clinical laboratory tests such as ALT/AST, alkaline phosphatase, and bilirubin.

#### Renal impairment

As doxorubicin is metabolised by the liver and excreted in the bile, dose modification should not be required. Population pharmacokinetic data (in the range of creatinine clearance tested of 30-156 mL/min) demonstrate that doxorubicin clearance is not influenced by renal function. No pharmacokinetic data are available in patients with creatinine clearance of less than 30 mL/min.

#### AIDS-related KS patients with splenectomy

As there is no experience with ZOLSKETIL pegylated liposomal in patients who have had splenectomy, treatment with ZOLSKETIL pegylated liposomal is not recommended.

#### Paediatric population

The experience in children is limited ZOLSKETIL pegylated liposomal is not recommended in patients below 18 years of age.

#### Elderly

Population based analysis demonstrates that age across the range tested (21–75 years) does not significantly alter the pharmacokinetics of doxorubicin.

#### Method of administration

ZOLSKETIL pegylated liposomal is administered as an intravenous infusion. For further instructions on preparation and special precautions for handling (see section 6.6).

Doxorubicin pegylated liposomal must not be administered as a bolus injection or undiluted solution. It is recommended that the doxorubicin pegylated liposomal infusion line be connected through the side port of an intravenous infusion of glucose 50 mg/mL (5%) solution to achieve further dilution and minimise the risk of thrombosis and extravasation. The infusion may be given through a peripheral vein. Do not use with in-line filters. Doxorubicin pegylated liposomal must not be given by the intramuscular or subcutaneous route (see section 6.6).

For doses < 90 mg: dilute doxorubicin pegylated liposomal in 250 mL glucose 50 mg/mL (5%) solution for infusion.

For doses ≥ 90 mg: dilute doxorubicin pegylated liposomal in 500 mL glucose 50 mg/mL (5%) solution for infusion.

#### Breast cancer/Ovarian cancer/Multiple myeloma

To minimise 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 doxorubicin pegylated liposomal infusions may be administered over a 60-minute period.

In those patients who experience an infusion reaction, the method of infusion should be modified as follows:

5% of the total dose should be infused slowly over the first 15 minutes. If tolerated without reaction, the infusion rate may then be doubled for the next 15 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes.

#### AIDS-related KS

The dose of doxorubicin pegylated liposomal is diluted in 250 mL glucose 50 mg/mL (5%) solution for infusion and administered by intravenous infusion over 30 minutes.

### **4.3 Contraindications**

Hypersensitivity to the active substance, peanut or soya, or to any of the excipients listed in section 6.1.

Doxorubicin pegylated liposomal must not be used to treat AIDS-KS that may be treated effectively with local therapy or systemic alpha-interferon.

### **4.4 Special warnings and precautions for use**

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

#### Cardiac toxicity

It is recommended that all patients receiving doxorubicin pegylated liposomal routinely undergo frequent ECG monitoring. Transient ECG changes such as T-wave flattening, S-T segment depression and benign arrhythmias are not considered mandatory indications for the suspension of doxorubicin pegylated liposomal therapy. However, reduction of the QRS complex is considered more indicative of cardiac toxicity. If this change occurs, the most definitive test for anthracycline myocardial injury, i.e., endomyocardial biopsy, must be considered.

More specific methods for the evaluation and monitoring of cardiac functions as compared to ECG are a measurement of left ventricular ejection fraction by echocardiography or preferably by Multigated Angiography (MUGA). These methods must be applied routinely before the initiation of doxorubicin pegylated liposomal therapy and repeated periodically during treatment. The evaluation of left ventricular function is considered to be mandatory before each additional administration of doxorubicin pegylated liposomal that exceeds a lifetime cumulative anthracycline dose of 450 mg/m<sup>2</sup>.

The evaluation tests and methods mentioned above concerning the monitoring of cardiac performance during anthracycline therapy are to be employed in the following order: ECG monitoring, measurement of left ventricular ejection fraction, endomyocardial biopsy. If a test result indicates possible cardiac injury associated with doxorubicin pegylated liposomal therapy, the benefit of continued therapy must be carefully weighed against the risk of myocardial injury.

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

Exercise caution in patients with impaired cardiac function who receive doxorubicin pegylated liposomal.

Whenever cardiomyopathy is suspected, i.e., the left ventricular ejection fraction has substantially decreased relative to pre-treatment values and/or left ventricular ejection fraction is lower than a prognostically relevant value (e.g., < 45%), endomyocardial biopsy may be considered and the benefit of continued therapy must be carefully evaluated against the risk of developing irreversible cardiac damage.

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 must be observed in patients who have received other anthracyclines. The total dose of doxorubicin hydrochloride must also take into account any previous (or concomitant) therapy with cardiotoxic compounds such as other anthracyclines/anthraquinones or e.g., 5-fluorouracil. Cardiac toxicity also may occur at cumulative anthracycline doses lower than 450 mg/m<sup>2</sup> in patients with prior mediastinal irradiation or in those receiving concurrent cyclophosphamide therapy.

The cardiac safety profile for the dosing schedule recommended for both breast and ovarian cancer (50 mg/m<sup>2</sup>) is similar to the 20 mg/m<sup>2</sup> profile in patients with AIDS-KS (see section 4.8).

### Myelosuppression

Many patients treated with doxorubicin pegylated liposomal have baseline myelosuppression due to such factors as their pre-existing HIV disease or numerous concomitant or previous medicines, or tumours involving bone marrow. In the pivotal trial in patients with ovarian cancer treated at a dose of 50 mg/m<sup>2</sup>, myelosuppression was generally mild to moderate, reversible, and was not associated with episodes of neutropaenic infection or sepsis. Moreover, in a controlled clinical trial of doxorubicin pegylated liposomal vs. topotecan, the incidence of treatment related sepsis was substantially less in the doxorubicin pegylated liposomal-treated ovarian cancer patients as compared to the topotecan treatment group. A similar low incidence of myelosuppression was seen in patients with metastatic breast cancer receiving doxorubicin pegylated liposomal in a first-line clinical trial. In contrast to the experience in patients with breast cancer or ovarian cancer, myelosuppression appears to be the dose-limiting adverse reaction in patients with AIDS-KS (see section 4.8). Because of the potential for bone marrow suppression, periodic blood counts must be performed frequently during the course of

doxorubicin pegylated liposomal therapy, and at a minimum, prior to each dose of doxorubicin pegylated liposomal.

Persistent severe myelosuppression, may result in superinfection or haemorrhage.

In controlled clinical studies in patients with AIDS-KS against a bleomycin/vincristine regimen, opportunistic infections were apparently more frequent during treatment with doxorubicin pegylated liposomal. Patients and doctors must be aware of this higher incidence and take action as appropriate.

#### Secondary haematological malignancies

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

#### Secondary oral neoplasms

Very rare cases of secondary oral cancer have been reported in patients with long-term (more than one year) exposure to doxorubicin pegylated liposomal or those receiving a cumulative doxorubicin pegylated liposomal dose greater than 720 mg/m<sup>2</sup>. Cases of secondary oral cancer were diagnosed both, during treatment with doxorubicin pegylated liposomal, and up to 6 years after the last dose. Patients should be examined at regular intervals for the presence of oral ulceration or any oral discomfort that may be indicative of secondary oral cancer.

#### Infusion-associated reactions

Serious and sometimes life-threatening infusion reactions, which are characterised by allergic-like or anaphylactoid-like reactions, with symptoms including asthma, flushing, urticarial rash, chest pain, fever, hypertension, tachycardia, pruritus, sweating, shortness of breath, facial oedema, chills, back pain, tightness in the chest and throat and/or hypotension may occur within minutes of starting the infusion of doxorubicin pegylated liposomal. Very rarely, convulsions also have been observed in relation to infusion reactions (see section 4.8). Temporarily stopping the infusion usually resolves these symptoms without further therapy. However, medicines to treat these symptoms (e.g., antihistamines, corticosteroids, adrenaline, and anticonvulsants), as well as emergency equipment should be available for immediate use. In most patients treatment can be resumed after all symptoms have resolved, without recurrence. Infusion reactions rarely recur after the first treatment cycle. To minimise the risk of infusion reactions, the initial dose should be administered at a rate no greater than 1 mg/minute (see section 4.2).

#### Palmar plantar erythrodysesthesia syndrome (PPE)

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 1-2 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, however, these therapies have not been evaluated in phase III trials. Other strategies to prevent and treat PPE 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 (see section 4.2). However, this reaction can be severe and debilitating in some patients and may require discontinuation of treatment (see section 4.8).

#### Interstitial lung disease (ILD)

Interstitial lung disease (ILD), which may have an acute onset, has been observed in patients receiving pegylated liposomal doxorubicin, including fatal cases (see section 4.8). If patients experience worsening of respiratory symptoms such as dyspnoea, dry cough, and fever, ZOLSKETIL pegylated liposomal should be interrupted and the patient should be promptly investigated. If ILD is confirmed, ZOLSKETIL pegylated liposomal should be discontinued and the patient treated appropriately.

#### Extravasation



Although local necrosis following extravasation has been reported very rarely, doxorubicin pegylated liposomal is considered to be an irritant. Animal studies indicate that administration of doxorubicin hydrochloride as a liposomal formulation reduces the potential for extravasation injury. If any signs or symptoms of extravasation occur (e.g., stinging, erythema) terminate the infusion immediately and restart in another vein. The application of ice over the site of extravasation for approximately 30 minutes may be helpful in alleviating the local reaction. Doxorubicin pegylated liposomal must not be given by the intramuscular or subcutaneous route.

#### Diabetic patients

Doxorubicin pegylated liposomal contains sucrose and the dose is administered in glucose 50 mg/mL (5%) solution for infusion.

#### Excipients

This medicine contains less than 1 mmol sodium (23 mg) per dose and is essentially 'sodium-free'.

For common adverse reaction which required dose modification or discontinuation see section 4.8.

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

No formal medicinal product interaction studies have been performed with doxorubicin pegylated liposomal, although phase II combination trials with conventional chemotherapy agents have been conducted in patients with gynaecological malignancies. Exercise caution in the concomitant use of medicinal products known to interact with standard doxorubicin hydrochloride. Doxorubicin pegylated liposomal, like other doxorubicin hydrochloride preparations, may potentiate the toxicity of other anti-cancer therapies. During clinical trials in patients with solid tumours (including breast and ovarian cancer) who have received concomitant cyclophosphamide or taxanes, no new additive toxicities were noted. In patients with AIDS, exacerbation of cyclophosphamide-induced haemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported with standard doxorubicin hydrochloride. Caution must be exercised when giving any other cytotoxic agents, especially myelotoxic agents, at the same time.

### **4.6 Fertility, pregnancy and lactation**

#### Women of child-bearing potential/contraception in men and women

Due to the genotoxic potential of doxorubicin hydrochloride (see section 5.3), women of child-bearing potential should use effective contraceptive measures while being treated with doxorubicin pegylated liposomal and for 8 months following completion of treatment.

Men are recommended to use effective contraceptive measures and to not father a child while receiving doxorubicin pegylated liposomal and for 6 months following completion of treatment.

#### Pregnancy

Doxorubicin hydrochloride is suspected to cause serious birth defects when administered during pregnancy. Therefore, doxorubicin pegylated liposomal should not be used during pregnancy unless clearly necessary.

#### Breast-feeding

It is not known whether doxorubicin pegylated liposomal is excreted in human milk. Because many medicinal products, including anthracyclines, are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, therefore mothers must discontinue nursing prior to beginning doxorubicin pegylated liposomal treatment. Health experts recommend that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

#### Fertility

The effect of doxorubicin hydrochloride on human fertility has not been evaluated (see section 5.3).

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

Doxorubicin pegylated liposomal has no or negligible influence on the ability to drive and use machines. However, in clinical studies to date, dizziness and somnolence were associated infrequently (< 5%) with the administration of doxorubicin pegylated liposomal. Patients who suffer from these effects must avoid driving and operating machinery.

#### 4.8 Undesirable effects

##### Summary of the safety profile

The most frequent adverse reactions ( $\geq 20\%$ ) were neutropaenia, nausea, leukopaenia, anaemia, and fatigue.

Severe adverse reactions (Grade 3/4 adverse reactions occurring in  $\geq 2\%$  of patients) were neutropaenia, PPE, leukopaenia, lymphopaenia, anaemia, thrombocytopaenia, stomatitis, fatigue, diarrhoea, vomiting, nausea, pyrexia, dyspnoea, and pneumonia. Less frequently reported severe adverse reactions included *Pneumocystis jirovecii* pneumonia, abdominal pain, cytomegalovirus infection including cytomegalovirus chorioretinitis, asthenia, cardiac arrest, cardiac failure, cardiac failure congestive, pulmonary embolism, thrombophlebitis, venous thrombosis, anaphylactic reaction, anaphylactoid reaction, toxic epidermal necrolysis, and Stevens-Johnson syndrome.

##### Tabulated list of adverse reactions

Table 5 summarises the adverse drug reactions that occurred in patients receiving doxorubicin pegylated liposomal in 4,231 patients for the treatment of breast cancer, ovarian cancer, multiple myeloma, and AIDS-related KS. Post-marketing adverse reactions are also included, as indicated by “b”. Frequencies are defined as very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ) and not known (frequency cannot be estimated from the available data). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness

**Table 5: Adverse reactions in patients treated with doxorubicin pegylated liposomal**

System Organ	Frequency all grades	Adverse drug reaction
Infections and infestations	Common	Sepsis
		Pneumonia
		<i>Pneumocystis jirovecii</i> pneumonia
		Cytomegalovirus infection including cytomegalovirus chorioretinitis
		<i>Mycobacterium avium</i> complex infection
		Candidiasis
		Herpes zoster
		Urinary tract infection
		Infection
		Upper respiratory tract infection
		Oral candidiasis
		Folliculitis
		Pharyngitis
		Nasopharyngitis
	Uncommon	Herpes simplex
		Fungal infection
	Rare	Opportunistic infection (including <i>Aspergillus</i> , <i>Histoplasma</i> , <i>Isospora</i> , <i>Legionella</i> , <i>Microsporidium</i> , <i>Salmonella</i> , <i>Staphylococcus</i> , <i>Toxoplasma</i> , <i>Tuberculosis</i> ) <sup>a</sup>
	Not known	Acute myeloid leukaemia <sup>b</sup>

Neoplasms benign, malignant and unspecified (including cysts and		Myelodysplastic syndrome <sup>b</sup>
		Oral neoplasm <sup>b</sup>
Blood and lymphatic disorders	Very common	Leukopaenia
		Neutropaenia
		Lymphopaenia
		Anaemia (including hypochromic)
	Common	Thrombocytopaenia
		Febrile neutropaenia
	Uncommon	Pancytopaenia
		Thrombocytosis
Immune system disorders	Rare	Bone marrow failure
	Uncommon	Hypersensitivity
Metabolism and nutrition disorders	Very common	Anaphylactic reaction
		Anaphylactoid reaction
		Decreased appetite
		Cachexia
		Dehydration
	Common	Hypokalaemia
		Hyponatraemia
		Hypocalcaemia
		Hyperkalaemia
		Hypomagnesaemia
Psychiatric disorders	Uncommon	Hypomagnesaemia
		Confusional state
		Anxiety
		Depression
Nervous system disorders	Common	Insomnia
		Neuropathy peripheral
		Peripheral sensory neuropathy
		Neuralgia
		Paraesthesia
		Hypoesthesia
		Dysgeusia
		Headache
		Lethargy
		Dizziness
	Uncommon	Polyneuropathy
		Convulsion
		Syncope
		Dysaesthesia
Eye disorders	Somnolence	Somnolence
		Conjunctivitis
		Vision blurred
	Uncommon	Lacrimation increased
Cardiac disorders <sup>a</sup>	Rare	Retinitis
	Common	Tachycardia
		Palpitations
		Cardiac arrest
		Cardiac failure
	Uncommon	Cardiac failure congestive
		Cardiomyopathy

	Rare	Cardiotoxicity
		Ventricular arrhythmia
		Bundle branch block right
		Conduction disorder
		Atrioventricular block
		Cyanosis
Vascular	Common	Hypertension
		Hypotension

	Uncommon	Flushing
		Pulmonary embolism
		Infusion site necrosis (including soft tissue necrosis and skin necrosis)
		Phlebitis
	Rare	Orthostatic hypotension
		Thrombophlebitis
		Venous thrombosis
		Vasodilatation
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
		Dyspnoea exertional
		Epistaxis
		Cough
	Uncommon	Asthma
		Chest discomfort
	Rare	Throat tightness
	Not Known	Interstitial lung disease
Gastrointestinal disorders	Very common	Stomatitis
		Nausea
		Vomiting
		Diarrhoea
		Constipation
	Common	Gastritis
		Aphthous stomatitis
		Mouth ulceration
		Dyspepsia
		Dysphagia
		Oesophagitis
		Abdominal pain
		Abdominal pain upper
		Oral pain
		Dry mouth
	Uncommon	Flatulence
		Gingivitis
	Rare	Glossitis
		Lip ulceration
Skin and subcutaneous tissue disorders	Very common	Palmar plantar erythrodysesthesia syndrome <sup>a</sup>
		Rash (including erythematous, maculo-papular, and papular)
		Alopecia
	Common	Skin exfoliation
		Blister
		Dry skin
		Erythema
		Pruritus
		Hyperhidrosis
		Skin hyperpigmentation
	Uncommon	Dermatitis
		Dermatitis exfoliative
		Acne
		Skin ulcer
		Dermatitis allergic

		Urticaria
		Skin discolouration
		Petechiae
		Pigmentation disorder
		Nail disorder
	Rare	Toxic epidermal necrolysis
		Erythema multiforme
		Dermatitis bullous
		Lichenoid keratosis
	Not known	Stevens-Johnson syndrome <sup>b</sup>
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain (including musculoskeletal chest pain, back pain, pain in extremity)
	Common	Muscle spasms
		Myalgia
		Arthralgia
		Bone pain
	Uncommon	Muscular weakness
Renal and urinary disorders	Common	Dysuria
Reproductive disorders	Uncommon	Breast pain
	Rare	Vaginal infection
		Scrotal erythema
General disorders and administration site conditions	Very common	Pyrexia
		Fatigue
	Common	Infusion-related reaction
		Pain
		Chest pain
		Influenza-like illness
		Chills
		Mucosal inflammation
		Asthenia
		Malaise
		Oedema
		Oedema peripheral
	Uncommon	Administration site extravasation
		Injection site reaction
		Face oedema
		Hyperthermia
	Rare	Mucous membrane disorder
Investigations	Common	Weight decreased
	Uncommon	Ejection fraction decreased
	Rare	Liver function test abnormal (including Blood bilirubin increased, Alanine aminotransferase increased and Aspartate aminotransferase increased)
		Blood creatinine increased
Injury, poisoning and procedural complications	Uncommon	Radiation recall phenomenon <sup>a</sup>

<sup>a</sup> See [Description of selected adverse reactions](#)

<sup>b</sup> Post-marketing adverse reaction

## Description of selected adverse reactions

### *Palmar plantar erythrodysesthesia*

The most common undesirable effect reported in breast/ovarian clinical trials was palmar-plantar erythrodysesthesia (PPE). The overall incidence of PPE reported was 41.3% and 51.1% in the ovarian and breast clinical trials, respectively. These effects were mostly mild, with severe (grade 3) cases reported in 16.3% and 19.6% of patients. The reported incidence of life-threatening (grade 4) cases was < 1%. PPE infrequently resulted in permanent treatment discontinuation (1.9% and 10.8%). PPE was reported in 16% of multiple myeloma patients treated with doxorubicin pegylated liposomal plus bortezomib combination therapy. Grade 3 PPE was reported in 5% of patients. No grade 4 PPE was reported. The rate of PPE was substantially lower in the AIDS-KS population (1.3% all grade, 0.4% grade 3 PPE, no grade 4 PPE). See section 4.4.

### *Opportunistic infections*

Respiratory undesirable effects commonly occurred in clinical studies of doxorubicin pegylated liposomal and may be related to opportunistic infections (OI's) in the AIDS population. Opportunistic infections are observed in KS patients after administration with doxorubicin pegylated liposomal, and are frequently observed in patients with HIV induced immunodeficiency. The most frequently observed OI's in clinical studies were candidiasis, cytomegalovirus, herpes simplex, Pneumocystis jirovecii pneumonia, and mycobacterium avium complex.

### *Cardiac toxicity*

An increased incidence of congestive heart failure is associated with doxorubicin therapy at cumulative lifetime doses > 450 mg/m<sup>2</sup> or at lower doses for patients with cardiac risk factors. Endomyocardial biopsies on nine of ten AIDS-KS patients receiving cumulative doses of doxorubicin pegylated liposomal greater than 460 mg/m<sup>2</sup> indicate no evidence of anthracycline-induced cardiomyopathy. The recommended dose of doxorubicin pegylated liposomal for AIDS-KS patients is 20 mg/m<sup>2</sup> every two-to-three weeks. The cumulative dose at which cardiotoxicity would become a concern for these AIDS-KS patients (> 400 mg/m<sup>2</sup>) would require more than 20 courses of doxorubicin pegylated liposomal therapy over 40 to 60 weeks.

In addition, endomyocardial biopsies were performed in 8 solid tumour patients with cumulative anthracycline doses of 509 mg/m<sup>2</sup>-1,680 mg/m<sup>2</sup>. The range of Billingham cardiotoxicity scores was grades 0-1.5. These grading scores are consistent with no or mild cardiac toxicity.

In the pivotal phase III trial versus doxorubicin, 58/509 (11.4%) randomised subjects (10 treated with doxorubicin pegylated liposomal at a dose of 50 mg/m<sup>2</sup>/every 4 weeks versus 48 treated with doxorubicin at a dose of 60 mg/m<sup>2</sup>/every 3 weeks) met the protocol-defined criteria for cardiac toxicity during treatment and/or follow-up. Cardiac toxicity was defined as a decrease of 20 points or greater from baseline if the resting LVEF remained in the normal range or a decrease of 10 points or greater if the LVEF became abnormal (less than the lower limit for normal). None of the 10 doxorubicin pegylated liposomal subjects who had cardiac toxicity by LVEF criteria developed signs and symptoms of CHF. In contrast, 10 of 48 doxorubicin subjects who had cardiac toxicity by LVEF criteria also developed signs and symptoms of CHF.

In patients with solid tumours, including a subset of patients with breast and ovarian cancers, treated at a dose of 50 mg/m<sup>2</sup>/cycle with lifetime cumulative anthracycline doses up to 1,532 mg/m<sup>2</sup>, the incidence of clinically significant cardiac dysfunction was low. Of the 418 patients treated with doxorubicin pegylated liposomal 50 mg/m<sup>2</sup>/cycle, and having a baseline measurement of left ventricular ejection fraction (LVEF) and at least one follow-up measurement assessed by MUGA scan, 88 patients had a cumulative anthracycline dose of > 400 mg/m<sup>2</sup>, an exposure level associated with an increased risk of cardiovascular toxicity with conventional doxorubicin. Only 13 of these 88 patients (15%) had at least one clinically significant change in their LVEF, defined as an LVEF value less than 45% or a decrease of at least 20 points from baseline. Furthermore, only 1 patient (cumulative

anthracycline dose of 944 mg/m<sup>2</sup>), discontinued study treatment because of clinical symptoms of congestive heart failure.

#### Radiation recall phenomenon

Recall of skin reaction due to prior radiotherapy has occurred uncommonly with doxorubicin pegylated liposomal administration.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

### **4.9 Overdose**

Acute overdosing with doxorubicin hydrochloride worsens the toxic effects of mucositis, leukopaenia and thrombocytopaenia. Treatment of acute overdose of the severely myelosuppressed patient consists of hospitalisation, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Cytotoxic agents (anthracyclines and related substances), ATC code: L01DB01.

#### Mechanism of action

The active ingredient is doxorubicin hydrochloride, a cytotoxic anthracycline antibiotic obtained from *Streptomyces peucetius* var. *caesius*. The exact mechanism of the antitumour 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 effects. This is probably the result of intercalation of the anthracycline between adjacent base pairs of the DNA double helix thus preventing their unwinding for replication.

#### Clinical efficacy and safety

A phase III randomised study of doxorubicin pegylated liposomal versus doxorubicin in patients with metastatic breast cancer was completed in 509 patients. The protocol-specified objective of demonstrating non-inferiority between doxorubicin pegylated liposomal and doxorubicin was met, the hazard ratio (HR) for progression-free survival (PFS) was 1.00 (95% Confidence interval (CI) for HR=0.82-1.22). The treatment HR for PFS when adjusted for prognostic variables was consistent with PFS for the ITT population.

The primary analysis of cardiac toxicity showed the risk of developing a cardiac event as a function of cumulative anthracycline dose was significantly lower with doxorubicin pegylated liposomal than with doxorubicin (HR=3.16,  $p < 0.001$ ). At cumulative doses greater than 450 mg/m<sup>2</sup> there were no cardiac events with doxorubicin pegylated liposomal.

A phase III comparative study of doxorubicin pegylated liposomal versus topotecan in patients with epithelial ovarian cancer following the failure of first-line, platinum-based chemotherapy was completed in 474 patients. There was a benefit in overall survival (OS) for doxorubicin pegylated liposomal-treated patients over topotecan-treated patients as indicated by a hazard ratio (HR) of 1.216 (95% CI: 1.000; 1.478),  $p=0.050$ . The survival rates at 1, 2 and 3 years were 56.3%, 34.7% and 20.2% respectively on doxorubicin pegylated liposomal, compared to 54.0%, 23.6% and 13.2% on topotecan.



For the sub-group of patients with platinum-sensitive disease the difference was greater: HR of 1.432 (95% CI: 1.066; 1.923),  $p=0.017$ . The survival rates at 1, 2 and 3 years were 74.1%, 51.2% and 28.4% respectively on doxorubicin pegylated liposomal, compared to 66.2%, 31.0% and 17.5% on topotecan.

The treatments were similar in the sub-group of patients with platinum-refractory disease: HR of 1.069 (95% CI: 0.823; 1.387),  $p=0.618$ . The survival rates at 1, 2 and 3 years were 41.5%, 21.1% and 13.8% respectively on doxorubicin pegylated liposomal, compared to 43.2%, 17.2% and 9.5% on topotecan.

A phase III randomised, parallel-group, open-label, multicentre study comparing the safety and efficacy of doxorubicin pegylated liposomal plus bortezomib combination therapy with bortezomib monotherapy in patients with multiple myeloma who have received at least 1 prior therapy and who did not progress while receiving anthracycline-based therapy, was conducted in 646 patients. There was a significant improvement in the primary endpoint of time to progression (TTP) for patients treated with combination therapy of doxorubicin pegylated liposomal plus bortezomib compared to patients treated with bortezomib monotherapy as indicated by a risk reduction (RR) of 35% (95% CI: 21-47%),  $p < 0.0001$ , based on 407 TTP events. The median TTP was 6.9 months for the bortezomib monotherapy patients compared with 8.9 months for the doxorubicin pegylated liposomal plus bortezomib combination therapy patients. A protocol-defined interim analysis (based on 249 TTP events) triggered early study termination for efficacy. This interim analysis showed a TTP risk reduction of 45% (95% CI: 29-57%),  $p < 0.0001$ . The median TTP was 6.5 months for the bortezomib monotherapy patients compared with 9.3 months for the doxorubicin pegylated liposomal plus bortezomib combination therapy patients. These results, though not mature, constituted the protocol defined final analysis. The final analysis for overall survival (OS) performed after a median follow-up of 8.6 years showed no significant difference in OS between the two treatment arms. The median OS was 30.8 months (95% CI; 25.2-36.5 months) for the bortezomib monotherapy patients and 33.0 months (95% CI; 28.9-37.1 months) for the doxorubicin pegylated liposomal plus bortezomib combination therapy patients.

## **5.2 Pharmacokinetic properties**

Doxorubicin pegylated liposomal is a long-circulating pegylated liposomal formulation of doxorubicin hydrochloride. Pegylated liposomes contain surface-grafted segments of the hydrophilic polymer methoxypolyethylene glycol (MPEG). These linear MPEG groups extend from the liposome surface creating a protective coating that reduces interactions between the lipid bilayer membrane and the plasma components. This allows the doxorubicin pegylated liposomal liposomes to circulate for prolonged periods in the blood stream. Pegylated liposomes are small enough (average diameter of approximately 100 nm) to pass intact (extravasate) through defective blood vessels supplying tumours. Evidence of penetration of pegylated liposomes from blood vessels and their entry and accumulation in tumours has been seen in mice with C-26 colon carcinoma tumours and in transgenic mice with KS-like lesions. The pegylated liposomes also have a low permeability lipid matrix and internal aqueous buffer system that combine to keep doxorubicin hydrochloride encapsulated during liposome residence time in circulation.

The plasma pharmacokinetics of doxorubicin pegylated liposomal in humans differ significantly from those reported in the literature for standard doxorubicin hydrochloride preparations. At lower doses ( $10 \text{ mg/m}^2$ – $20 \text{ mg/m}^2$ ) doxorubicin pegylated liposomal displayed linear pharmacokinetics. Over the dose range of  $10 \text{ mg/m}^2$ – $60 \text{ mg/m}^2$  doxorubicin pegylated liposomal displayed non-linear pharmacokinetics. Standard doxorubicin hydrochloride displays extensive tissue distribution (volume of distribution:  $700$  to  $1,100 \text{ l/m}^2$ ) and a rapid elimination clearance ( $24$  to  $73 \text{ l/h/m}^2$ ). In contrast, the pharmacokinetic profile of doxorubicin pegylated liposomal indicates that doxorubicin pegylated liposomal is confined mostly to the vascular fluid volume and that the clearance of doxorubicin from the blood is dependent upon the liposomal carrier. Doxorubicin becomes available after the liposomes are extravasated and enter the tissue compartment.

At equivalent doses, the plasma concentration and AUC values of doxorubicin pegylated liposomal which represent mostly pegylated liposomal doxorubicin hydrochloride (containing 90% to 95% of the

measured doxorubicin) are significantly higher than those achieved with standard doxorubicin hydrochloride preparations. Doxorubicin pegylated liposomal should not be used interchangeably with other formulations of doxorubicin hydrochloride.

#### Population pharmacokinetics

The pharmacokinetics of doxorubicin pegylated liposomal was evaluated in 120 patients from 10 different clinical trials using the population pharmacokinetic approach. The pharmacokinetics of doxorubicin pegylated liposomal over the dose range of 10 mg/m<sup>2</sup> to 60 mg/m<sup>2</sup> was best described by a two compartment non-linear model with zero order input and Michaelis-Menten elimination. The mean intrinsic clearance of doxorubicin pegylated liposomal was 0.030 l/h/m<sup>2</sup> (range 0.008 to 0.152 l/h/m<sup>2</sup>) and the mean central volume of distribution was 1.93 l/m<sup>2</sup> (range 0.96-3.85 l/m<sup>2</sup>) approximating the plasma volume. The apparent half-life ranged from 24-231 hours, with a mean of 73.9 hours.

#### Breast cancer patients

The pharmacokinetics of doxorubicin pegylated liposomal determined in 18 patients with breast carcinoma were similar to the pharmacokinetics determined in the larger population of 120 patients with various cancers. The mean intrinsic clearance was 0.016 l/h/m<sup>2</sup> (range 0.008-0.027 l/h/m<sup>2</sup>), the mean central volume of distribution was 1.46 l/m<sup>2</sup> (range 1.10-1.64 l/m<sup>2</sup>). The mean apparent half-life was 71.5 hours (range 45.2-98.5 hours).

#### Ovarian cancer patients

The pharmacokinetics of doxorubicin pegylated liposomal determined in 11 patients with ovarian carcinoma were similar to the pharmacokinetics determined in the larger population of 120 patients with various cancers. The mean intrinsic clearance was 0.021 l/h/m<sup>2</sup> (range 0.009–0.041 l/h/m<sup>2</sup>), the mean central volume of distribution was 1.95 l/m<sup>2</sup> (range 1.67–2.40 l/m<sup>2</sup>). The mean apparent half-life was 75.0 hours (range 36.1–125 hours).

#### AIDS-related KS patients

The plasma pharmacokinetics of doxorubicin pegylated liposomal were evaluated in 23 patients with KS who received single doses of 20 mg/m<sup>2</sup> administered by a 30-minute infusion. The pharmacokinetic parameters of doxorubicin pegylated liposomal (primarily representing pegylated liposomal doxorubicin hydrochloride and low levels of unencapsulated doxorubicin hydrochloride) observed after the 20 mg/m<sup>2</sup> doses are presented in Table 10.

**Table 10. Pharmacokinetic parameters in doxorubicin pegylated liposomal-treated AIDS-KS patients**

Parameter	Mean ± standard error 20 mg/m <sup>2</sup> (n=23)
Maximum plasma concentration* (µg/mL)	8.34 ± 0.49
Plasma clearance (l/h/m <sup>2</sup> )	0.041 ± 0.004
Volume of distribution (l/m <sup>2</sup> )	2.72 ± 0.120
AUC (µg/mL•h)	590.00 ± 58.7
λ <sub>1</sub> half-life (hours)	5.2 ± 1.4
λ <sub>2</sub> half-life (hours)	55.0 ± 4.8

\* Measured at the end of a 30-minute infusion

### **5.3 Preclinical safety data**

In repeat dose studies conducted in animals, the toxicity profile of doxorubicin pegylated liposomal appears very similar to that reported in humans who receive long-term infusions of standard doxorubicin hydrochloride. With doxorubicin pegylated liposomal, the encapsulation of doxorubicin hydrochloride in pegylated liposomes results in these effects having a differing strength, as follows.

#### Cardiotoxicity

Studies in rabbits have shown that the cardiotoxicity of doxorubicin pegylated liposomal is reduced compared with conventional doxorubicin hydrochloride preparations.

#### Dermal toxicity

In studies performed after the repeated administration of doxorubicin pegylated liposomal to rats and dogs, serious dermal inflammations and ulcer formations were observed at clinically relevant dosages. In the study in dogs, the occurrence and severity of these lesions was reduced by lowering the dose or prolonging the intervals between doses. Similar dermal lesions, which are described as palmar-plantar erythrodysesthesia were also observed in patients after long-term intravenous infusion (see section 4.8).

#### Anaphylactoid response

During repeat dose toxicology studies in dogs, an acute response characterised by hypotension, pale mucous membranes, salivation, emesis and periods of hyperactivity followed by hypoactivity and lethargy was observed following administration of pegylated liposomes (placebo). A similar, but less severe response was also noted in dogs treated with doxorubicin pegylated liposomal and standard doxorubicin. The hypotensive response was reduced in magnitude by pretreatment with antihistamines. However, the response was not life-threatening and the dogs recovered quickly upon discontinuation of treatment.

#### Local toxicity

Subcutaneous tolerance studies indicate that doxorubicin pegylated liposomal, as against standard doxorubicin hydrochloride, causes slighter local irritation or damage to the tissue after a possible extravasation.

#### Mutagenicity and carcinogenicity

Although no studies have been conducted with doxorubicin pegylated liposomal, doxorubicin hydrochloride, the pharmacologically active ingredient of doxorubicin pegylated liposomal, is mutagenic and carcinogenic. Pegylated placebo liposomes are neither mutagenic nor genotoxic.

#### Reproductive toxicity

Doxorubicin pegylated liposomal resulted in mild to moderate ovarian and testicular atrophy in mice after a single dose of 36 mg/kg. Decreased testicular weights and hypospermia were present in rats after repeat doses  $\geq 0.25$  mg/kg/day and diffuse degeneration of the seminiferous tubules and a marked decrease in spermatogenesis were observed in dogs after repeat doses of 1 mg/kg/day (see section 4.6).

#### Nephrotoxicity

A study has shown that doxorubicin pegylated liposomal at a single intravenous dose of over twice the clinical dose produces renal toxicity in monkeys. Renal toxicity has been observed with even lower single doses of doxorubicin HCl in rats and rabbits. Since an evaluation of the post-marketing safety database for doxorubicin pegylated liposomal in patients has not suggested a significant nephrotoxicity liability of doxorubicin pegylated liposomal, these findings in monkeys may not have relevance to patient risk assessment.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

N-(carbonyl-methoxypolyethylene glycol-2000)-1,2-distearoyl- sn-glycero-3-phosphoethanolamine, sodium salt (MPEG 2000-DSPE)

Hydrogenated soy phosphatidylcholine (HSPC)

Cholesterol

Ammonium sulphate (E 517)

Sucrose (E 473)

Histidine

Hydrochloric acid concentrated (E 507) (for pH adjustment)

Sodium hydroxide (E-524) (for pH adjustment)  
Water for injections

## **6.2 Incompatibilities**

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

## **6.3 Shelf life**

Unopened vial  
18 months.

### After dilution

- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C.
- From a microbiological point of view, the product should be used immediately. 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.
- Partially used vials must be discarded.

## **6.4 Special precautions for storage**

Store in a refrigerator (2°C - 8°C).  
Do not freeze.

For storage conditions of the diluted medicinal product, see section 6.3.

## **6.5 Nature and contents of container**

Type I glass vial with a siliconised grey bromobutyl stopper, and an aluminium seal, containing a deliverable volume of 10 mL (20 mg) or 25 mL (50 mg).

ZOLSKETIL pegylated liposomal is supplied as a single pack or packs of ten vials.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal and other handling**

Do not use material that shows evidence of precipitation or any other particulate matter.

Caution must be exercised in handling ZOLSKETIL pegylated liposomal dispersion. The use of gloves is required. If ZOLSKETIL pegylated liposomal comes into contact with skin or mucosa, wash immediately and thoroughly with soap and water. ZOLSKETIL pegylated liposomal must be handled and disposed of in a manner consistent with that of other anticancer medicinal products in accordance with local requirements.

Determine the dose of ZOLSKETIL pegylated liposomal to be administered (based upon the recommended dose and the patient's body surface area). Take the appropriate volume of ZOLSKETIL pegylated liposomal up into a sterile syringe. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in ZOLSKETIL pegylated liposomal. The appropriate dose of ZOLSKETIL Pegylated Liposomal must be diluted in glucose 50 mg/mL (5%) solution for infusion prior to administration. For doses < 90 mg, dilute ZOLSKETIL pegylated liposomal in 250 mL, and for doses ≥ 90 mg, dilute ZOLSKETIL pegylated liposomal in 500 mL. This can be infused over 60 or 90 minutes as detailed in 4.2.

The use of any diluent other than 50 mg/mL (5%) glucose solution for infusion, or the presence of any bacteriostatic agent such as benzyl alcohol may cause precipitation of ZOLSKETIL pegylated liposomal.

It is recommended that the ZOLSKETIL pegylated liposomal infusion line be connected through the side port of an intravenous infusion of glucose 50 mg/mL (5%). Infusion may be given through a peripheral vein. Do not use with in-line filters.

**7. MARKETING AUTHORISATION HOLDER**

Accord Healthcare S.L.U.  
World Trade Center,  
Moll de Barcelona, s/n,  
Edifici Est 6<sup>a</sup> planta,  
08039, Barcelona,  
Spain

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/22/1629/001  
EU/1/22/1629/002  
EU/1/22/1629/003  
EU/1/22/1629/004

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 31 May 2022.

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

## **ANNEX II**

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer(s) responsible for batch release

Accord Healthcare Polska Sp. z o.o.,  
ul. Lutomska 50, Pabianice, 95-200  
Poland

Accord Healthcare B.V.  
Winthontlaan 200, Utrecht, 3526 KV,  
Netherlands

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

### **• Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

### **• Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**



## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON 20 mg/10 mL****1. NAME OF THE MEDICINAL PRODUCT**

ZOLSKETIL pegylated liposomal 2 mg/mL concentrate for dispersion for infusion  
doxorubicin hydrochloride

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One mL of ZOLSKETIL pegylated liposomal contains 2 mg doxorubicin hydrochloride.

**3. LIST OF EXCIPIENTS**

Excipients: hydrogenated soy phosphatidylcholine, N-(carbonylmethoxypolyethylene glycol-2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine, sodium salt (MPEG 2000-DSPE), cholesterol, ammonium sulphate, histidine, sucrose, water for injections, hydrochloric acid concentrated, sodium hydroxide

**4. PHARMACEUTICAL FORM AND CONTENTS**

1 vial  
10 vials  
20 mg/10 mL

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Intravenous use after dilution.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Do not use interchangeably with other formulations of doxorubicin hydrochloride

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator. Do not freeze.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Cytotoxic  
Partially used vials should be discarded.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Accord Healthcare S.L.U.  
World Trade Center,  
Moll de Barcelona, s/n,  
Edifici Est 6<sup>a</sup> planta,  
08039 Barcelona,  
Spain

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/22/1629/001 (1 vial)  
EU/1/22/1629/002 (10 vials)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN

NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON 50 mg/25 mL****1. NAME OF THE MEDICINAL PRODUCT**

ZOLSKETIL pegylated liposomal 2 mg/mL concentrate for dispersion for infusion  
doxorubicin hydrochloride

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One mL of ZOLSKETIL pegylated liposomal contains 2 mg doxorubicin hydrochloride.

**3. LIST OF EXCIPIENTS**

Excipients: hydrogenated soy phosphatidylcholine, N-(carbonylmethoxypolyethylene glycol-2000)-1,2- distearoyl- sn-glycero-3- phosphoethanolamine, sodium salt (MPEG 2000-DSPE), cholesterol, ammonium sulphate, histidine, sucrose, water for injections, hydrochloric acid concentrated, sodium hydroxide

**4. PHARMACEUTICAL FORM AND CONTENTS**

1 vial  
10 vials  
50 mg/25 mL

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Intravenous use after dilution.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Do not use interchangeably with other formulations of doxorubicin hydrochloride

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator. Do not freeze.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Cytotoxic  
Partially used vials should be discarded.

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Accord Healthcare S.L.U.  
World Trade Center,  
Moll de Barcelona, s/n,  
Edifici Est 6<sup>a</sup> planta,  
08039 Barcelona,  
Spain

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/22/1629/003 (1 vial)  
EU/1/22/1629/004 (10 vials)

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS****VIAL LABEL 20 mg/10 mL****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

ZOLSKETIL pegylated liposomal 2 mg/mL sterile concentrate  
doxorubicin hydrochloride  
IV after dilution

**2. METHOD OF ADMINISTRATION****3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

20 mg/10 mL

**6. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**  
**(VIAL LABEL) 50 mg/25 mL**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

ZOLSKETIL pegylated liposomal 2 mg/mL sterile concentrate  
doxorubicin hydrochloride  
IV after dilution

**2. METHOD OF ADMINISTRATION**

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

50 mg/25 mL

**6. OTHER**



## **B. PACKAGE LEAFLET**

## **Package leaflet: Information for the user**

### **ZOLSKETIL pegylated liposomal 2 mg/mL concentrate for dispersion for infusion** doxorubicin hydrochloride

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What ZOLSKETIL pegylated liposomal is and what it is used for
2. What you need to know before you use ZOLSKETIL pegylated liposomal
3. How to use ZOLSKETIL pegylated liposomal
4. Possible side effects
5. How to store ZOLSKETIL pegylated liposomal
6. Contents of the pack and other information

#### **1. What ZOLSKETIL pegylated liposomal is and what it is used for**

ZOLSKETIL pegylated liposomal is an antitumour agent.

ZOLSKETIL pegylated liposomal is used to treat cancer of the breast in patients at risk for heart problems. ZOLSKETIL pegylated liposomal is also used to treat cancer of the ovary. It is used to kill cancer cells, shrink the size of the tumour, delay the growth of the tumour, and extend your survival.

ZOLSKETIL pegylated liposomal is also used in combination with another medicine, bortezomib, to treat multiple myeloma (a cancer of the blood) in patients who have received at least 1 prior therapy.

ZOLSKETIL pegylated liposomal is also used to produce an improvement in your Kaposi's sarcoma including flattening, lightening and even shrinkage of the cancer. Other symptoms of Kaposi's sarcoma, such as swelling around the tumour, may also improve or disappear.

ZOLSKETIL pegylated liposomal contains a medicine which is able to interact with cells in such a way as to selectively kill cancer cells. The doxorubicin hydrochloride in ZOLSKETIL pegylated liposomal is enclosed in tiny spheres called pegylated liposomes which help to deliver the medicinal product from the blood stream to the cancerous tissue rather than healthy normal tissue.

#### **2. What you need to know before you use ZOLSKETIL pegylated liposomal**

##### **Do not use ZOLSKETIL pegylated liposomal**

- if you are allergic to doxorubicin hydrochloride, peanut or soya, or any of the other ingredients of this medicine (listed in section 6).

##### **Warnings and precautions**

You should tell your doctor about any of the following:

- if you are receiving any treatment for heart disease or liver disease;
- if you are diabetic, because ZOLSKETIL pegylated liposomal contains sugar which may require an adjustment to the treatment of your diabetes;
- if you have Kaposi's sarcoma and have had your spleen removed;

- if you notice sores, discolouration or any discomfort in your mouth.
- if you have bone marrow bone marrow is not making enough blood cells
- if you have cancer where bone marrow makes abnormal blood cells
- if you have painful, macular reddening skin rash
- if you have leakage of vesicant fluids or medicines from the vein into the surrounding tissue
- if you have hand-foot syndrome (redness, swelling and blistering (a pocket of fluid between the upper layers of skin) on the palms of the hands and soles of the feet)

Strategies to prevent and treat hand-foot syndrome include:

- soaking hands and/or feet in basins of cold water when possible (e.g., while watching television, reading, or listening to the radio);
- keeping hands and feet uncovered (no gloves, socks, etc.);
- staying in cool places;
- taking cool baths during hot weather;
- avoiding vigorous exercise that might cause trauma to the feet (e.g., jogging);
- avoiding exposure of skin to very hot water (e.g., jacuzzis, saunas);
- avoiding tight fitting footwear or high-heeled shoes.

**Pyridoxine (Vitamin B6):**

- vitamin B6 is available without prescription;
- take 50-150 mg daily beginning at the first signs of redness or tingling.

The cases of Interstitial lung diseases have been observed in patients receiving pegylated liposomal doxorubicin including fatal cases. The symptoms of Interstitial lung disease are cough and shortness of breath sometimes with fever which are not caused by physical activity. Seek immediate medical attention, if you experience symptoms that may be signs of Interstitial lung disease.

**Children and adolescents**

ZOLSKETIL pegylated liposomal should not be used in children and adolescents, because it is not known how the medicine will affect them.

**Other medicines and ZOLSKETIL pegylated liposomal**

Tell your doctor or pharmacist

- if you are taking or have recently taken any other medicines, including medicines obtained without a prescription;
- about any other cancer treatments you are on or have been taking, as particular care needs to be taken with treatments which reduce the number of white blood cells, as this may cause further reduction in the number of white blood cells. If you are unsure about what treatments you have received or any illnesses you have had, discuss these with your doctor.

**Pregnancy and breast-feeding**

Ask your doctor or pharmacist for advice before taking this medicine.

Because the active ingredient doxorubicin hydrochloride in ZOLSKETIL pegylated liposomal may cause birth defects, it is important to tell your doctor if you think you are pregnant.

Women must avoid becoming pregnant and use contraception while taking ZOLSKETIL pegylated liposomal and in the eight months following discontinuation of ZOLSKETIL pegylated liposomal treatment. Men must use contraception while taking ZOLSKETIL pegylated liposomal and in the six months following discontinuation of ZOLSKETIL pegylated liposomal, so that their partner does not become pregnant.

Because doxorubicin hydrochloride may be harmful to nursing infants, women must discontinue breast-feeding before starting treatment with ZOLSKETIL pegylated liposomal. Health experts recommend that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

**Driving and using machines**

Do not drive or use any tools or machines if you feel tired or sleepy from treatment with ZOLSKETIL pegylated liposomal.

**ZOLSKETIL pegylated liposomal contains soya oil and sodium**

ZOLSKETIL pegylated liposomal contains soya oil. If you are allergic to peanut or soya, do not use this medicine.

ZOLSKETIL pegylated liposomal contains less than 1 mmol sodium (23 mg) per dose, that is to say 'essentially sodium-free'.

**3. How to use ZOLSKETIL pegylated liposomal**

ZOLSKETIL pegylated liposomal is a unique formulation. It must not be used interchangeably with other formulations of doxorubicin hydrochloride.

**How much ZOLSKETIL pegylated liposomal is given**

If you are being treated for breast cancer or ovarian cancer, ZOLSKETIL pegylated liposomal will be administered at a dose of 50 mg per square metre of your body surface area (based on your height and weight). The dose is repeated every 4 weeks for as long as the disease does not progress and you are able to tolerate the treatment.

If you are being treated for multiple myeloma, and have already received at least 1 prior therapy, ZOLSKETIL pegylated liposomal will be administered at a dose of 30 mg per square metre of your body surface area (based on your height and weight) as a 1 hour intravenous infusion on day 4 of the bortezomib 3 week regimen immediately after the bortezomib infusion. The dose is repeated as long as you respond satisfactorily and tolerate treatment.

If you are being treated for Kaposi's sarcoma, ZOLSKETIL pegylated liposomal will be administered at a dose of 20 mg per square metre of your body surface area (based on your height and weight). The dose is repeated every 2 to 3 weeks for 2-3 months, then as often as necessary to maintain an improvement in your condition.

**How ZOLSKETIL pegylated liposomal is given**

ZOLSKETIL pegylated liposomal will be given to you by your doctor in a drip (infusion) into a vein. Depending on the dose and indication, this may take from 30 minutes to more than one hour (i.e., 90 minutes).

**If you use more ZOLSKETIL pegylated liposomal than you should**

Acute overdosing worsens side effects like sores in the mouth or decreases the number of white blood cells and platelets in the blood. Treatment will include administration of antibiotics, platelet cell transfusions, use of factors which stimulate production of white blood cells and symptomatic treatment of mouth sores.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

**4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

During the infusion of ZOLSKETIL pegylated liposomal, the following reactions may occur:

- severe allergic reaction that may include a swollen face, lips, mouth, tongue or throat; difficulty swallowing or breathing; itchy rash (hives)
- inflamed and narrowed airways in the lungs, causing coughing, wheezing and shortness of breath (asthma)
- flushing, sweating, chills or a fever

- chest pain or discomfort
- back pain
- high or low blood pressure
- fast heart beat
- fits (seizures)

Leaking of the injection fluid from the veins into the tissues under the skin may occur. If the drip stings or hurts while you are receiving a dose of ZOLSKETIL pegylated liposomal, tell your doctor immediately

Your doctor should be contacted immediately if any of the following serious side effects are noticed

- you develop fever, feel tired, or if you have signs of bruising or bleeding (very common)
- redness, swelling, peeling or tenderness, mainly on the hands or feet ('hand-foot' syndrome). These effects have been seen very commonly and are sometimes severe. In severe cases, these effects may interfere with certain daily activities, and may last for 4 weeks or longer before resolving completely. The doctor may wish to delay the start and/or reduce the dose of the next treatment (see Strategies to prevent and treat hand foot syndrome, below)
- sores in mouth, severe diarrhoea or vomiting or nausea (very common)
- infections (common), including lung infections (pneumonia) or infections that may affect your vision
- being short of breath (common)
- severe stomach pain (common)
- severe weakness (common)
- severe allergic reaction that may include a swollen face, lips, mouth, tongue or throat; difficulty swallowing or breathing; itchy rash (hives) (uncommon)
- cardiac arrest (heart stops beating); heart failure, in which the heart does not pump enough blood to the rest of the body, which makes you short of breath and may lead to swollen legs (uncommon)
- blood clot that moves to the lungs, causes chest pain and makes you short of breath (uncommon)
- swelling, warmth, or tenderness in the soft tissues of your leg, sometimes with pain which gets worse when you stand or walk (rare)
- severe or life-threatening rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome) or over most of the body (toxic epidermal necrolysis) (rare)

### **Other side effects**

Between infusions, the following may occur:

#### **Very common side effects** (may affect more than 1 in 10 people)

- decrease in the number of white blood cells, which can increase the chances of infections. In rare cases, having low white blood cells may lead to severe infection. Anaemia (reduction in red blood cells) may cause tiredness, and decreased platelets in the blood may increase the risk of bleeding. It is because of the potential changes in your blood cells that you will have regular blood tests.
- decreased appetite;
- constipation;
- skin rashes, including redness of the skin, allergic skin rash, red or raised rash on the skin
- hair loss
- pain including in the muscles and chest muscle, joint, arm, or leg
- feeling very tired

#### **Common side effects** (may affect up to 1 in 10 people)

- infections, including severe infection throughout the body (sepsis), lung infections, herpes zoster virus infections (shingles), a type of bacterial infection (mycobacterium avium complex infection), urinary tract infection, fungal infections (including thrush and oral thrush in the

- mouth) infection of the hair roots, infected or irritated throat, infected nose, sinuses or throat (cold)
- low number of a type of white blood cell (neutrophils), with a fever
  - severe weight loss and muscle wasting, not enough water in the body (dehydration), low level of potassium, sodium, or calcium in the blood
  - feeling confused, feeling anxious, depression, difficulty sleeping
  - nerve damage that may cause tingling, numbness, pain or loss of pain sensation, nerve pain, unusual feeling in the skin (such as tingling or a crawling feeling), decreased feeling or sensitivity, especially in the skin
  - change in sense of taste, headache, feeling very sleepy with low energy, feeling dizzy;
  - inflamed eyes (conjunctivitis)
  - fast heart beat
  - high or low blood pressure, flushing
  - shortness of breath that may be brought on by physical activity, nose bleeds, cough
  - inflamed stomach lining or foodpipe, ulcers (sores) in the mouth, indigestion, difficulty swallowing, mouth pain, dry mouth
  - skin problems, including flaky or dry skin, redness of the skin, blister or ulcer (sore) on the skin, itching, dark skin patches
  - excessive sweating
  - muscle spasms or aches
  - pain including in the muscles, bone, or back
  - pain when passing urine
  - allergic reaction to infusion of the medicine, flu-like illness, chills, inflamed lining of the cavities and passages in the body, such as the nose, mouth or windpipe, feeling weak, generally feeling unwell, swelling caused by fluid build up in the body, swollen hands, ankles or feet
  - weight loss

When ZOLSKETIL pegylated liposomal is used alone, some of these effects are less likely to occur, and some have not occurred at all.

**Uncommon side effects** (may affect up to 1 in 100 people)

- herpes simplex virus infections (cold sores or genital herpes), fungal infection
- low number of all types of blood cells, increased number of 'platelets' (cells that help blood to clot)
- allergic reaction
- high level of potassium in the blood, low level of magnesium in the blood
- nerve damage affecting more than one area of the body
- fits (seizures), fainting
- unpleasant or painful sensation, especially to touch, feeling sleepy
- blurred vision, watery eyes
- heart beat feels fast or uneven (palpitations), heart muscle disease, heart damage
- tissue damage (necrosis) where the injection is given, inflamed veins that cause swelling and pain, feeling dizzy upon sitting up or standing up
- chest discomfort
- passing wind, inflamed gums (gingivitis)
- skin problems or rashes, including flaky or peeling skin, allergic skin rash, ulcer (sore) or hives on the skin, discoloured skin, change in the natural colour (pigment) of the skin, small red or purple spots caused by bleeding under the skin, nail problems, acne
- muscle weakness
- breast pain
- irritation or pain where the injection is given
- swollen face, high body temperature
- symptoms (such as inflammation, redness or pain) come back at a part of the body that previously received radiation therapy or was previously damaged by a chemotherapy injection into a vein

### **Rare side effects (may affect up to 1 in 1,000 people)**

- infection that occurs in people with a weak immune system
- low number of blood cells made in the bone marrow
- inflamed retina, which may cause changes in vision or blindness
- abnormal heart rhythm, abnormal heart tracing on an ECG (electrocardiogram) and may be with a slow heart beat, problem with the heart that affects the heart beat and rhythm, blue colour to the skin and mucosa caused by low oxygen in the blood
- widening of blood vessels
- tight feeling in the throat
- sore and swollen tongue, ulcer (sore) on the lip
- skin rash with fluid-filled blisters
- vaginal infection, redness of the scrotum
- problems with the lining of the cavities and passages in the body, such as the nose, mouth or windpipe
- abnormal liver blood test results, increased level of 'creatinine' in the blood

### **Not known (frequency cannot be estimated from the available data)**

- cancer of the blood that develops quickly and affects the blood cells (acute myeloid leukaemia), bone marrow disease that affects the blood cells (myelodysplastic syndrome), cancer of the mouth or lip
- coughing and shortness of breath, possibly accompanied by fever, that is not brought on by physical activity (Interstitial lung disease)

### **Reporting of side effects**

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## **5. How to store ZOLSKETIL pegylated liposomal**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and carton.

Store in a refrigerator (2°C – 8°C). Do not freeze.

After dilution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C. From a microbiological point of view, the product should be used immediately. 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. Partially used vials must be discarded.

Do not use this medicine if you notice that it shows evidence of precipitation or any other particulate matter.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What ZOLSKETIL pegylated liposomal contains**

- The active substance is doxorubicin hydrochloride. One mL of ZOLSKETIL pegylated liposomal contains 2 mg of doxorubicin hydrochloride in a pegylated liposomal formulation.
- The other ingredient(s) are hydrogenated soy phosphatidylcholine, N-carboxymethoxypolyethylene glycol-2000)-1,2- distearoyl- sn-glycero-3-phosphoethanolamine, sodium salt (MPEG 2000-DSPE), cholesterol, ammonium sulphate, histidine, sucrose, water for injections, hydrochloric acid, concentrated (for pH-adjustment), sodium hydroxide (for pH-adjustment). See section 2.

ZOLSKETIL pegylated liposomal: vials which provide 10 mL (20 mg) or 25 mL (50 mg).

### **What ZOLSKETIL pegylated liposomal looks like and contents of the pack**

This medicine is a translucent red coloured dispersion filled in a clear glass vial. ZOLSKETIL pegylated liposomal is available in glass vials as a single pack or packs of ten vials. Not all pack sizes may be marketed.

### **Marketing Authorisation Holder**

Accord Healthcare S.L.U.  
World Trade Center, Moll de Barcelona, s/n,  
Edifici Est 6<sup>a</sup> planta,  
08039, Barcelona,  
Spain

### **Manufacturer**

Accord Healthcare Polska Sp. z o.o.  
ul. Lutomska 50, Pabianice, 95-200  
Poland

Accord Healthcare B.V.  
Winthontlaan 200, Utrecht, 3526KV,  
Netherlands

**This leaflet was last revised in {MM/YYYY}.**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.

The following information is intended for medical or healthcare professionals only (see section 3):

Caution must be exercised in handling ZOLSKETIL pegylated liposomal solution. The use of gloves is required. If ZOLSKETIL pegylated liposomal comes into contact with skin or mucosa, wash immediately and thoroughly with soap and water. ZOLSKETIL pegylated liposomal must be handled and disposed of in a manner consistent with that of other anticancer medicinal products.

Determine the dose of ZOLSKETIL pegylated liposomal to be administered (based upon the recommended dose and the patient's body surface area). Take the appropriate volume of ZOLSKETIL pegylated liposomal up into a sterile syringe. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in ZOLSKETIL pegylated liposomal. The appropriate dose of ZOLSKETIL pegylated liposomal must be diluted in glucose 50 mg/mL (5%) solution for infusion prior to administration. For doses < 90 mg, dilute ZOLSKETIL pegylated liposomal in 250 mL, and for doses ≥ 90 mg, dilute ZOLSKETIL pegylated liposomal in 500 mL.

To minimise 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 ZOLSKETIL pegylated liposomal 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.

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.

The use of any diluent other than glucose 50 mg/mL (5%) solution for infusion, or the presence of any bacteriostatic agent such as benzyl alcohol may cause precipitation of ZOLSKETIL pegylated liposomal.

It is recommended that the ZOLSKETIL pegylated liposomal infusion line be connected through the side port of an intravenous infusion of glucose 50 mg/mL (5%) solution. Infusion may be given through a peripheral vein. Do not use with in-line filters.

**ANNEX IV**  
**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS**  
**OF THE MARKETING AUTHORISATION(S)**

### **Scientific conclusions**

Taking into account the PRAC Assessment Report on the PSUR(s) for doxorubicin, the scientific conclusions of CHMP are as follows:

In view of available data on interstitial lung disease from the literature and spontaneous reports including in some cases a close temporal relationship, the PRAC considers a causal relationship between pegylated liposomal doxorubicin and interstitial lung disease is at least a reasonable possibility. The PRAC concluded that the product information of products containing pegylated liposomal doxorubicin should be amended accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

### **Grounds for the variation to the terms of the marketing authorisation(s)**

On the basis of the scientific conclusions for doxorubicin the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing doxorubicin is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.