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SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

RUBEXET LIPOSOMAL 20 mg/10 ml (Concentrate for solution for infusion)

RUBEXET LIPOSOMAL 50 mg/25 ml (Concentrate for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RUBEXET 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.

Each RUBEXET LIPOSOMAL vial contains 2 mg/ml doxorubicin hydrochloride in a pegylated liposomal formulation and delivers 10 ml (20 mg) or 25 ml (50 mg) in a concentrate for infusion for single intravenous use and is presented as a sterile, translucent, red coloured dispersion. The active ingredient of RUBEXET LIPOSOMAL is doxorubicin HCl, a cytotoxic anthracycline antibiotic obtained from *Streptomyces peucetius* var. *caesius*.

Contains hydrogenated soy phosphatidylcholine (made from soyabean) – see section 4.3 and 4.4

Contains sugar: sucrose 100 mg/ml

For the full list of excipients, see section 6.1.

Initials:

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3. PHARMACEUTICAL FORM

Concentrate for solution 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

RUBEXET LIPOSOMAL is indicated:

- As monotherapy for patients with metastatic breast cancer.
- For the 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 AIDS-related Kaposi's sarcoma (KS) in patients with low CD_4 counts (< 200 CD_4 lymphocytes/mm^3) and extensive mucocutaneous or visceral disease.

4.2 Posology and method of administration

RUBEXET LIPOSOMAL should only be administered under the supervision of a qualified medical practitioner specialised in the administration of cytotoxic medicines.

RUBEXET LIPOSOMAL exhibits unique pharmacokinetic properties and must not be used interchangeably with other formulations of doxorubicin hydrochloride.

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Posology

Breast cancer / Ovarian cancer

RUBEXET LIPOSOMAL is administered intravenously at a dose of 50 mg/m^2 once every 4 weeks for as long as the disease does not progress and the patient continues to tolerate treatment.

Multiple myeloma

RUBEXET LIPOSOMAL is administered at 30 mg/m^2 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^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.

Day 4 dosing of both medicines may be delayed up to 48 hours as medically necessary.

Doses of bortezomib should be at least 72 hours apart. The first infusion of RUBEXET LIPOSOMAL should be administered over 90 minutes (see “Method of Administration”).

AIDS-KS patients

RUBEXET LIPOSOMAL should be administered intravenously at 20 mg/m^2 every 2 to 3 weeks. Avoid intervals shorter than 10 days as medicine accumulation and increased toxicity cannot be ruled out. Patients should be treated for 2 to 3 months to achieve a therapeutic response. Treatment should be continued as needed to maintain a therapeutic response.

All patients

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

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Guidelines for RUBEXET LIPOSOMAL dose modification

To manage adverse events such as palmar-plantar erythrodysaesthesia (PPE), stomatitis or haematological toxicity, the dose may be reduced or delayed. Guidelines for RUBEXET 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 and stomatitis 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 addressed under section 4.8.

Table 1: Palmar-Plantar Erythrodysaesthesia

	Week after prior RUBEXET LIPOSOMAL dose		
Toxicity Grade after prior RUBEXET LIPOSOMAL dose	**Week 4**	**Week 5**	**Week 6**
Grade 1 (mild erythema, swelling, or	Re-dose unless patient has experienced a	Re-dose unless patient has experienced a	Decrease dose by 25 %; return to 4-week interval

desquamation not interfering with daily activities)	previous Grade 3 or 4 skin toxicity, in which case wait an additional week.	previous Grade 3 or 4 skin toxicity, in which case wait an Additional week.	
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 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.	Discontinue RUBEXET LIPOSOMAL

Grade 4 (diffuse or local process causing infectious complications, or a bedridden state or hospitalisation)	Wait an additional week.	Wait an additional week.	Discontinue RUBEXET LIPOSOMAL

Table 2: Stomatitis

	Week after prior RUBEXET LIPOSOMAL dose		
Toxicity Grade after prior RUBEXET LIPOSOMAL dose	**After Week 4**	**After Week 5**	**After Week 6**
Grade 1 (painless ulcers, erythema, or mild soreness)	Re-dose unless patient has experienced a previous Grade 3 or 4 stomatitis, in which case wait an additional week.	Re-dose unless patient has experienced a previous Grade 3 or 4 stomatitis, in which case wait an additional week.	Decrease dose by 25 %; return to 4-week interval or withdraw patient per physician's assessment.
Grade 2 (painful erythema, oedema or ulcers, but can eat)	Wait an additional week.	Wait an additional week.	Decrease dose by 25 %; return to 4-week interval or withdraw patient

			per physician's assessment.
Grade 3 (painful erythema, oedema, or ulcers, but cannot eat)	Wait an additional week.	Wait an additional week.	Discontinue RUBEXET LIPOSOMAL
Grade 4 (requires parenteral or enteral support)	Wait an additional week.	Wait an additional week.	Discontinue RUBEXET LIPOSOMAL

Table 3: Haematological toxicity (ANC or platelets) – management of patients with breast or ovarian cancer

GRADE	**Absolute neutrophil count (ANC)/mm^3**	**Platelets/mm^3**	**Modification**
1	1500 - 1900	75 000 – 150 000	Resume treatment with no dose reduction
2	1000 - <1500	50 000 - <75 000	Wait until ANC ≥ 1500 and platelets ≥ 75 000; re-dose with no dose reduction

3	500 - <1000	25 000 - <50 000	Wait until ANC ≥ 1500 and platelets ≥ 75 000; re-dose with no dose reduction
4	<500	<25 000	Wait until ANC ≥ 1500 and platelets ≥ 75 000; decrease dose by 25 % or continue full dose with growth factor support

For multiple myeloma patients treated with RUBEXET LIPOSOMAL in combination with bortezomib who experience PPE or stomatitis, the RUBEXET LIPOSOMAL dose should be modified as described in the Table 1 and 2 above respectively. For more detailed information on bortezomib dosing and dosage adjustments, refer to the professional information insert for bortezomib.

Table 4: Dosage adjustments for RUBEXET LIPOSOMAL + bortezomib combination therapy – patients with multiple myeloma

Patient status	**RUBEXET LIPOSOMAL**	**Bortezomib**
Fever ≥ 38 °C and ANC <1000/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 Haemoglobin < 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 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	Refer to the professional information insert for bortezomib.

* For more information on bortezomib dosing and dosage adjustment, refer to the professional information insert for bortezomib.

Special populations

Patients with impaired hepatic function:

RUBEXET LIPOSOMAL pharmacokinetics determined in a small number of patients with elevated total bilirubin levels do not differ from patients with normal total bilirubin; however, the RUBEXET 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 20,5 to 51,3 µmol/L the first dose is reduced by 25 %. If the bilirubin is > 51,3 µmol/L, 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. RUBEXET LIPOSOMAL can be administered to patients with liver metastases with concurrent elevation of bilirubin and liver enzymes up to 4 times the upper limit of the normal range. Prior to RUBEXET LIPOSOMAL administration, evaluate hepatic function using conventional clinical laboratory tests such as Alanine transaminase (ALT), Aspartate transaminase (AST), alkaline phosphatase and bilirubin.

Patients with impaired renal function:

As doxorubicin is metabolised by the liver and excreted in the bile, dose modification should not be required with RUBEXET LIPOSOMAL. Population-based analysis confirms that changes in the renal function over the range tested (estimated creatinine clearance 30 to 156 mL/min) do not alter the pharmacokinetics of RUBEXET LIPOSOMAL. No pharmacokinetic data are available for patients with creatinine clearance of less than 30 mL/min.

AIDS-KS patients with splenectomy

As there is no experience with RUBEXET LIPOSOMAL in patients with splenectomy, treatment with RUBEXET LIPOSOMAL is not recommended.

Elderly patients

Population-based analysis demonstrates that age across the range tested (21 to 75 years) does not significantly alter the pharmacokinetics of RUBEXET LIPOSOMAL.

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Method of administration

RUBEXET LIPOSOMAL is administered as an intravenous infusion. Caution is advised in handling RUBEXET LIPOSOMAL and the use of gloves is required. For further instructions on dilution and special precautions for handling, see section 6.6.

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

For doses <90 mg: dilute RUBEXET LIPOSOMAL in 250 ml Dextrose 5 % in Water
For doses ≥90 mg: dilute RUBEXET LIPOSOMAL in 500 ml Dextrose 5 % in Water.

Breast cancer / Ovarian cancer

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 RUBEXET LIPOSOMAL infusions may be administered over a 60-minute period.
In those patients who experienced 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.

Multiple myeloma

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The intravenous catheter and tubing should be flushed with 5 % glucose for infusion between administration of RUBEXET LIPOSOMAL and bortezomib. Day 4 dosing of both medicines may be delayed up to 48 hours as medically necessary. Doses of bortezomib should be at least 72 hours apart.

The first infusion of RUBEXET LIPOSOMAL 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 RUBEXET LIPOSOMAL will be administered over 1 hour, as tolerated. If an infusion reaction to RUBEXET LIPOSOMAL occurs, stop the infusion. After the symptoms resolve, attempt to administer the remaining RUBEXET LIPOSOMAL over 90 minutes, as follows:

5. 10 mL over first 10 minutes
6. 20 mL over next 10 minutes
7. 40 mL over next 10 minutes
8. then complete the infusion over a total of 90 minutes.

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

AIDS-KS patients

RUBEXET LIPOSOMAL diluted in 250 mL Dextrose 5 % in Water is administered by intravenous infusion over 30 minutes.

4.3 Contraindications

- Hypersensitivity to the active substance, doxorubicin hydrochloride or to any of the excipients listed in section 6.1.
- RUBEXET LIPOSOMAL should not be administered during pregnancy and breastfeeding (see section 4.6).
- RUBEXET LIPOSOMAL must not be used to treat AIDS-related KS that may be treated effectively with local therapy or systemic alpha-interferon.
- The safety and effectiveness in patients less than 18 years of age have not been established.

4.4 Special warnings and precautions for use

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

Combination therapy with pegylated liposomal doxorubicin hydrochloride has been extensively studied in solid tumour populations however the efficacy of pegylated liposomal doxorubicin hydrochloride combination chemotherapy has not been established in the treatment of ovarian cancer.

Cardiac risk

All patients receiving RUBEXET LIPOSOMAL should routinely undergo frequent electrocardiogram (ECG) monitoring. Transient ECG changes such as T-wave flattening, S-T segment depression and benign dysrhythmias are not considered mandatory indications for the suspension of RUBEXET LIPOSOMAL therapy.

However, reduction of the QRS complex is considered more indicative of cardiac toxicity. If this change occurs, the most definitive test for RUBEXET LIPOSOMAL myocardial injury i.e. endomyocardial biopsy, should be considered.

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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 should be applied routinely before the initiation of RUBEXET LIPOSOMAL therapy and should be repeated periodically during treatment.

The evaluation of left ventricular function is considered to be mandatory before each additional administration of RUBEXET LIPOSOMAL that exceeds a lifetime cumulative anthracycline dose of 450 mg/m^2.

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 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 RUBEXET LIPOSOMAL only when the benefit outweighs the risk to the patient.
Exercise caution in patients with impaired cardiac function who receive RUBEXET LIPOSOMAL.

Whenever cardiomyopathy is suspected i.e. the left ventricular ejection fraction has decreased relatively as compared to pre-treatment values and/or (at the same time) left ventricular ejection is lower than a prognostically relevant value (e.g. < 45 %), endomyocardial biopsies should be performed and the benefit of continued therapy with RUBEXET LIPOSOMAL must be carefully evaluated against the risk of producing irreversible cardiac damage.

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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 hydrochloride should 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^2 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^2) is similar to the 20 mg/m^2 profile in patients with AIDS-KS (see section 4.8).

Myelosuppression

Many patients treated with RUBEXET LIPOSOMAL have baseline myelosuppression due to such factors as their pre-existing HIV disease or numerous concomitant medications, or tumours involving bone marrow. In studies of patients with ovarian cancer treated at a dose of 50 mg/m^2, myelosuppression was generally mild to moderate, reversible, and was not associated with episodes of neutropenic infection or sepsis.

In contrast to the experience in patients with breast or ovarian cancer, myelosuppression appears to be the dose-limiting adverse event in patients with AIDS-KS (see section 4.8). Because of the potential for bone marrow suppression, periodic blood counts should be performed frequently during the course of RUBEXET LIPOSOMAL therapy, and at a minimum, prior to each dose of RUBEXET LIPOSOMAL.

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Persistent severe myelosuppression, although not seen in patients with ovarian cancer, may result in super-infection or haemorrhage.

Study data indicate that in patients with AIDS-KS against a bleomycin/vincristine regimen, opporutnistic infections were more frequent during treatment with pegylated liposomal doxorubicin hydrochloride. Patients and doctors must be aware of this higher incidence so that appropriate action can be taken.

Secondary haematological malignancies

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.

Secondary oral neoplasms

Cases of secondary oral cancer have been reported in patients with long-term (more than one year) exposure to pegylated liposomal doxorubicin hydrochloride or those receiving a cumulative pegylated liposomal doxorubicin hydrochloride dose greater than 720 mg/m^2. Cases of secondary oral cancer were diagnosed both, during treatment with pegylated liposomal doxorubicin hydrochloride, 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 RUBEXET LIPOSOMAL. Convulsions have been observed in relation to infusion reactions. Temporarily stopping the infusion usually resolves these symptoms without further therapy. However, medications 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 erythrodysaesthesia 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 fully evaluated.

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).

Extravasation

Although local necrosis following extravasation has been reported infrequently, pegylated liposomal doxorubicin hydrochloride 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. RUBEXET LIPOSOMAL must not be given by the intramuscular or subcutaneous route.

Diabetic patients

It should be noted that RUBEXET LIPOSOMAL contains sucrose (100 mg/ml) and is administered in Dextrose 5 % in Water for intravenous infusion. An adjustment to diabetic treatment may be required.

Excipients

RUBEXET LIPOSOMAL contains hydrogenated soy phosphatidylcholine. If you are allergic to peanut or soya, do not use this medicine.

4.5 Interaction with other medicines and other forms of interaction

No formal medicine interaction studies have been conducted with pegylated liposomal doxorubicin hydrochloride, although combination trials with conventional chemotherapy medicines have been conducted in patients with gynaecological malignancies. Caution should be exercised in the concomitant use of medicines known to interact with doxorubicin hydrochloride. RUBEXET LIPOSOMAL, may potentiate the toxicity of other anti-cancer therapies. In studies of patients with solid tumours (including ovarian cancer) who have received concomitant cyclophosphamide or taxanes, no new additive toxicities were noted.

In patients with AIDS-KS, exacerbation of cyclophosphamide-induced haemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported with doxorubicin hydrochloride. Caution must be exercised when giving any other cytotoxic medicines, especially myelotoxic medicines, at the same time.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Women of child-bearing potential must be advised to avoid pregnancy while they or their male partner is receiving RUBEXET LIPOSOMAL and in the six months following discontinuation of RUBEXET LIPOSOMAL therapy.

Pregnancy

RUBEXET LIPOSOMAL is teratogenic in animals. There is no experience in pregnant women with RUBEXET LIPOSOMAL. Teratogenicity cannot be ruled out. Therefore, RUBEXET LIPOSOMAL should not be administered during pregnancy.

Breastfeeding

It is not known whether doxorubicin is excreted in human milk and because of the potential for serious adverse reactions in breastfeeding infants, RUBEXET LIPOSOMAL should not be administered in women breastfeeding their infants.

Fertility

The effect of doxorubicin hydrochloride on human fertility has not been established.

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4.7 Effects on ability to drive and use machines

Patients may experience dizziness and somnolence during RUBEXET LIPOSOMAL treatment. Patients who experience these effects must avoid driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were neutropenia, nausea, leucopaenia, anaemia and fatigue.

Severe adverse reactions (Grade 3/4 adverse reactions) were neutropaenia, PPE, leucopaenia, 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

The table below summarises the adverse reactions experienced in patients receiving treatment for breast cancer, ovarian cancer, multiple myeloma and AIDS-related KS.

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION

Infections and infestations	Frequent	Sepsis, pneumonia, Pneumocystis jirovecii pneumonia, cytomegalovirus infection including cytomegalovirus chorioretinitis, Mycobacterium avium complex infection, candidiasis, Herpes zoster, urinary tract infection, infection, upper respiratory tract infection, oral candidiasis, folliculitis, pharyngitis, nasopharyngitis
	Less frequent	Herpes simplex, fungal infection, opportunistic infection (including *Aspergillus, Histoplasma, Isospora, Legionella, Microsporidium, Salmonella, Staphylococcus, Toxoplasma, Tuberculosis)*
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Frequency unknown	Acute myeloid leukaemia, myelodysplastic syndrome, oral neoplasm
Blood and lymphatic system disorders	Frequent	Leucopaenia, neutropaenia, lymphopaenia, anaemia (including hypochromic),

		thrombocytopaenia, febrile neutropaenia
	Less frequent	Pancytopaenia, thrombocytosis, bone marrow failure
Immune system disorders	Less frequent	Hypersensitivity, anaphylactic reaction, anaphylactoid reaction
Metabolism and nutrition disorders	Frequent	Decreased appetite, anorexia cachexia, dehydration, hypokalaemia, hyponatraemia, hypocalcaemia
	Less frequent	Hyperkalaemia, hypomagnesemia
Psychiatric disorders	Frequent	Confusional state, anxiety, depression, insomnia
Nervous system disorders	Frequent	Neuropathy peripheral, peripheral sensory neuropathy, neuralgia, paraesthesia, hypoaesthesia, dysgeusia, headache, lethargy, dizziness, hypertonia
	Less frequent	Polyneuropathy, convulsion, syncope, dysaesthesia, somnolence
Eye disorders	Frequent	Conjunctivitis
	Less frequent	Vision blurred, lacrimation increased, retinitis
Cardiac disorders	Frequent	Tachycardia

	Less frequent	Palpitations, cardiac arrest, cardiac failure, cardiac failure congestive, cardiomyopathy, cardiotoxicity, ventricular dysrhythmia, bundle branch block right, conduction disorder, atrioventricular block, cyanosis
Vascular disorders	Frequent	Hypertension, hypotension, flushing
	Less frequent	Pulmonary embolism, infusion site necrosis (including soft tissue necrosis and skin necrosis), phlebitis, orthostatic hypotension, thrombophlebitis, venous thrombosis, vasodilation
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea, dyspnoea exertional, epistaxis, cough
	Less frequent	Asthma, chest discomfort, throat tightness
Gastrointestinal disorders	Frequent	Stomatitis, nausea, vomiting, diarrhoea, constipation, gastritis, aphthous stomatitis, mouth ulceration, dyspepsia, dysphagia, oesophagitis, abdominal pain,

		abdominal pain upper, oral pain, dry mouth
	Less frequent	Flatulence, gingivitis, glossitis, lip ulceration
Skin and subcutaneous tissue disorders	Frequent	Palmar plantar erythrodysaesthesia syndrome, rash (including erythematous, maculo-papular, and papular), alopecia, skin exfoliation, blister, dry skin, erythema, pruritus, hyperhidrosis, skin hyperpigmentation
	Less frequent	Dermatitis, dermatitis exfoliative, acne, skin ulcer, dermatitis allergic, urticaria, skin discolouration, petechiae, pigmentation disorder, nail disorder, toxic epidermal necrolysis, erythema multiforme, dermatitis bullous, lichenoid keratosis
	Frequency unknown	Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders	Frequent	Musculoskeletal pain (including musculoskeletal chest pain, back pain, pain in extremity), muscle

		spasms, myalgia, arthralgia, bone pain
	Less frequent	Muscular weakness
Renal and urinary disorders	Frequent	Dysuria
Reproductive system and breast disorders	Less frequent	Breast pain, vaginal infection, scrotal erythema
General disorders and administration site conditions	Frequent	Pyrexia, fatigue, infusion-related reaction, pain, chest pain, influenza-like illness, chills, mucosal inflammation, asthenia, malaise, oedema, oedema peripheral
	Less frequent	Administration site extravasation, injection site reaction, face oedema, hyperthermia, mucous membrane disorder
Investigations	Frequent	Weight decreased
	Less frequent	Ejection fraction decreased, liver function test abnormal (including Blood bilirubin increased, Alanine aminotransferase increased and Aspartate aminotransferase increased),blood creatinine increased

Injury, poisoning and procedural complications	Less frequent	Radiation recall phenomenon

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety App (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Acute overdosage with doxorubicin hydrochloride worsens the toxic effects of mucositis, leukopenia and thrombocytopenia. Treatment of acute overdosage 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

Pharmacological classification: A.26 Cytostatic agents

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

Mechanism of action

The exact mechanism of the anti-tumour 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 anthracycline between adjacent base pairs of the DNA double helix, thus preventing their unwinding for replication.

5.2 Pharmacokinetic properties

RUBEXET 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 RUBEXET 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 pegylated liposomal doxorubicin hydrochloride in humans differ significantly from those reported in the literature for standard doxorubicin hydrochloride preparations. At lower doses (10 mg/m^2-20 mg/m^2) pegylated liposomal doxorubicin hydrochloride displayed linear pharmacokinetics. Over the dose range of 10 mg/m^2–60 mg/m^2 pegylated liposomal doxorubicin hydrochloride displayed non-linear pharmacokinetics. Standard doxorubicin hydrochloride displays extensive tissue distribution (volume of distribution: 700 to 1 100 l/m^2) and a rapid elimination clearance (24 to 73 l/h/m^2). In contrast, the pharmacokinetic profile of pegylated liposomal doxorubicin hydrochloride indicates that it 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 pegylated liposomal doxorubicin hydrochloride (containing 90 % to 95 % of the measured doxorubicin) are significantly higher than those achieved with standard doxorubicin hydrochloride preparations.

Pegylated liposomal doxorubicin hydrochloride should not be used interchangeably with other formulations of doxorubicin hydrochloride.

Breast cancer patients

The pharmacokinetics of pegylated liposomal doxorubicin hydrochloride in 18 patients with breast carcinoma were similar to the pharmacokinetics determined in a larger population of 120 patients with various cancers. The mean intrinsic clearance was 0,016 l/h/m^2 (range 0,008-0,027 l/h/m^2), the mean central volume of distribution was 1,46 l/m^2 (range 1,10-1,64 l/m^2). The mean apparent half-life was 71,5 hours (range 45,2-98,5 hours).

Ovarian cancer patients

The pharmacokinetics of pegylated liposomal doxorubicin hydrochloride in 11 patients with ovarian carcinoma were similar to the pharmacokinetics determined in a larger population of 120 patients with various cancers. The mean intrinsic clearance was 0,021 l/h/m^2 (range 0,009-0,041 l/h/m^2), the mean central volume of distribution was 1,95 l/m^2 (range 1,67-2,40 l/m^2). The mean apparent half-life was 75 hours (range 36,1-125 hours).

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Pegylated liposomal doxorubicin hydrochloride displayed linear pharmacokinetics in the dose range 10 to 20 mg/m^2. Disposition occurred in 2 phases after pegylated liposomal doxorubicin hydrochloride administration, with a relatively short first phase (approximately 5 hours) and a prolonged second phase (approximately 55 hours) that

accounted for the majority of the area under the curve (AUC).

AIDS-related KS patients

The plasma pharmacokinetics of pegylated liposomal doxorubicin hydrochloride was evaluated in 23 patients with KS who received single doses of 20 mg/m^2 administered by a 30-minute infusion. The pharmacokinetic parameters of, primarily pegylated liposomal doxorubicin hydrochloride and low levels of unencapsulated doxorubicin hydrochloride, as in RUBEXET LIPOSOMAL, observed after the 20 mg/m^2 dose are presented below:

Pharmacokinetic parameters of AIDS-KS patients treated with pegylated liposomal doxorubicin hydrochloride	
	Mean ± standard error
Parameter	**20 mg/m^2 (n=23)**
Maximum plasma concentration* (µg/ml)	8,34 ± 0,49
Plasma clearance (l/h/m^2)	0,041 ± 0,004
Volume of distribution (l/m^2)	2,72 ± 0,120
AUC (µg/ml * h)	590,00 ± 58,7
λ_1 half-life (hours)	5,2 ± 1,4
λ_2 half-life (hours)	55,0 ± 4,8

*Measured at the end of a 30-minute infusion

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrogenated soy phosphatidylcholine

N-(carbonyl-methoxypolyethylene glycol-2000)-1,2-distearoyl-*sn*-glycero3 phosphoethanolamine, sodium salt (MPEG-DSPE)

Cholesterol

Ammonium sulphate

Histidine

Sucrose

Ethanol anhydrous

Hydrochloric acid, concentrated (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injection

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial:

18 months

After dilution:

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- 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

Unopened vial:

Store in a refrigerator (2 ºC – 8 ºC). Do not freeze. Store in the original package.

For storage conditions after dilution, see section 6.3.

6.5 Nature and contents of container

RUBEXET LIPOSOMAL 20 mg/10 ml: 10 ml clear tubular glass vial (type I) with a 20 mm grey bromobutyl rubber stopper and a 20 mm aluminium blue coloured flip off seal.

RUBEXET LIPOSOMAL 50 mg/25 ml: 30 ml clear moulded glass vial (type I) with a 20 mm grey bromobutyl rubber stopper and a 20 mm aluminium red coloured flip off seal.

Pack sizes: Single vial or packs of ten.

Not all pack sizes may be marketed.

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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 RUBEXET LIPOSOMAL dispersion. The use of gloves is required. If RUBEXET LIPOSOMAL comes into contact with skin or mucosa, wash immediately and thoroughly with soap and water. RUBEXET LIPOSOMAL must be handled and disposed of in a manner consistent with that of other anticancer medicines in accordance with local requirements.

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

The use of any diluent other than Dextrose 5 % in water for infusion, or the presence of any bacteriostatic agent such as benzyl alcohol may cause precipitation of RUBEXET LIPOSOMAL. It is recommended that the RUBEXET LIPOSOMAL infusion line be connected through the side port of an intravenous infusion of Dextrose 5 % in water. Infusion may be given through a peripheral vein. Do not use with in-line filters.

7. HOLDER OF CERTIFICATE OF REGISTRATION

11.08.2025

PROFESSIONAL INFORMATION

Accord Healthcare (Pty) Ltd

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8. REGISTRATION NUMBER(S)

RUBEXET LIPOSOMAL 20 mg/10 ml: 58/26/0250.248

RUBEXET LIPOSOMAL 50 mg/25 ml: 58/26/0251.249

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08 July 2025

10. DATE OF REVISION OF THE TEXT

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