Barcode area

EBUNAT

(Eribulin Mesylate Solution for Injection 0.5 mg/mL) (2mL/Vial)

1. NAME OF THE MEDICINAL PRODUCT
EBUNAT (Eribulin Mesylate Solution for Injection 0.5mg/mL)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 2 ml vial contains: eribulin mesylate 1 mg equivalent to eribulin 0.88 mg.

3. PHARMACEUTICAL FORM
Solution for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast cancer
EBUNAT monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.

EBUNAT is indicated as monotherapy for the treatment of locally advanced or metastatic HER2 negative breast cancer after failure of one chemotherapeutic regimen for advanced disease. Patients should have received an anthracycline and a taxane unless these treatments were not suitable.

Soft Tissue Sarcoma (Liposarcoma)
EBUNAT is indicated for the treatment of inoperable liposarcoma after progression following prior chemotherapy for advanced or metastatic disease in adults. Patients should have received two previous chemotherapy treatments, one of which should have included an anthracycline, unless this treatment is unsuitable.

4.2 Posology and method of administration
EBUNAT should only be prescribed by a qualified physician experienced in the appropriate use of anti-cancer therapy. It should be administered by an appropriately qualified healthcare professional only.

Posology
The recommended dose of eribulin mesylate as the ready to use solution is 1.4 mg/m2 which should be administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle.
Please note: In the EU the recommended dose refers to the base of the active substance (eribulin). Calculation of the individual dose to be administered to a patient must be based on the strength of the ready to use solution that contains 0.44 mg/ml eribulin and the dose recommendation of 1.23 mg/m2 . The dose reduction recommendations shown below are also shown as the dose of eribulin to be administered based on the strength of the ready to use solution.
In the pivotal trials, the corresponding publication and in some other regions e.g. the US and Switzerland, the recommended dose is based on the salt form (eribulin mesylate).
Patients may experience nausea or vomiting. Antiemetic prophylaxis including corticosteroids should be considered.

Dose delays during therapy
The administration of EBUNAT should be delayed on Day 1 or Day 8 for any of the following:
- Absolute neutrophil count (ANC) < 1 x 10^9/l
- Platelets < 75 x 10^9/l
- Grade 3 or 4 non-hematological toxicities.

Dose reduction during therapy
Dose reduction recommendations for retreatment are shown in the following table.

Dose reduction recommendations

Adverse reaction after previous EBUNAT administration	**Recommended dose of Eribulin Mesylate**
Haematological:	
ANC < 0.5 x 10^9/l lasting more than 7 days	1.1 mg/m^2
ANC < 1 x 10^9/l neutropenia complicated by fever or infection	
Platelets < 25 x 10^9/l thrombocytopenia	
Platelets < 50 x 10^9/l thrombocytopenia complicated by haemorrhage or requiring blood or platelet transfusion	
Non-haematological:	
Any Grade 3 or 4 in the previous cycle	
Reoccurrence of any haematological or non-haematological adverse reactions as specified above	
Despite reduction to 1.1 mg/m^2	0.7 mg/m^2
Despite reduction to 0.7 mg/m^2	Consider discontinuation

The dose of eribulin should not be re-escalated after it has been reduced.

Patients with hepatic impairment
Impaired liver function due to metastases
The recommended dose of eribulin mesylate in patients with mild hepatic impairment (Child-Pugh A) is 1.1 mg/m2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. The recommended dose of eribulin mesylate in patients with moderate hepatic impairment (Child-Pugh B) is 0.7 mg/m2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.

Severe hepatic impairment (Child-Pugh C) has not been studied but it is expected that a more marked dose reduction is needed if eribulin is used in these patients.

Impaired liver function due to cirrhosis
This patient group has not been studied. The doses above may be used in mild and moderate impairment, but close monitoring is advised as the doses may need readjustment.

Patients with renal impairment
Some patients with moderately or severely impaired renal function (creatinine clearance <50 ml/min) may have increased eribulin exposure and may need a reduction of the dose. For all patients with renal impairment, caution and close safety monitoring is advised.

Elderly patients
No specific dose adjustments are recommended based on the age of the patient.

Paediatric population
There is no relevant use of EBUNAT in children and adolescents for the indication of breast cancer.
The safety and effectiveness of EBUNAT in pediatric patients below the age of 18 years have not been established.

4.3 Contraindications
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Breast-feeding

4.4 Special warnings and precautions for use

Haematology
Myelosuppression is dose dependent and primarily manifested as neutropenia. Monitoring of complete blood counts should be performed on all patients prior to each dose of eribulin. Treatment with eribulin should only be initiated in patients with ANC values ≥ 1.5 x 10^9/l and platelets > 100 x 10^9/l.

Febrile neutropenia occurred in < 5% of patients treated with eribulin. Patients experiencing febrile neutropenia, severe neutropenia or thrombocytopenia, should be treated according to the recommendations.

Patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x upper limit of normal (ULN) experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia. Although data are limited, patients with bilirubin >1.5 x ULN also have a higher incidence of Grade 4 neutropenia and febrile neutropenia.

Fatal cases of febrile neutropenia, neutropenic sepsis, sepsis and septic shock have been reported.

Severe neutropenia may be managed by the use of granulocyte colony-stimulating factor (G-CSF) or equivalent at the physician's discretion in accordance with relevant guidelines.

Peripheral neuropathy
Patients should be closely monitored for signs of peripheral motor and sensory neuropathy. The development of severe peripheral neurotoxicity requires a delay or reduction of dose.
In clinical trials, patients with pre-existing neuropathy greater than Grade 2 were excluded. However, patients with pre-existing neuropathy Grade 1 or 2 were no more likely to develop new or worsening symptoms than those who entered the study without the condition.

QT prolongation
In an uncontrolled open-label ECG study in 26 patients, QT prolongation was observed on Day 8, independent of eribulin concentration, with no QT prolongation observed on Day 1. ECG monitoring is recommended if therapy is initiated in patients with congestive heart failure, bradyarrhythmias or concomittant treatment with medicinal products known to prolong the QT interval, including Class Ia and III antiarrhythmics, and electrolyte abnormalities. Hypokalaemia, hypocalcaemia or hypomagnesaemia should be corrected prior to initiating EBUNAT and these electrolytes should be monitored periodically during therapy. Eribulin should be avoided in patients with congenital long QT syndrome.

Excipients
This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per dose.

4.5 Interaction with other medicinal products and other forms of interaction
Eribulin is mainly (up to 70%) eliminated through biliary excretion. The transport protein involved in this process is unknown. Eribulin is not a substrate of breast cancer resistance protein (BCRP), organic anion (OAT1, OAT3, OATP1B1, OATP1B3), multi-drug resistance-associated protein (MRP2, MRP4) and bile salt export pump (BSEP) transporters.

No drug-drug interactions are expected with CYP3A4 inhibitors and inducers. Eribulin exposure (AUC and C_{max}) was unaffected by ketoconazole, a CYP3A4 and P glycoprotein (Pgp) inhibitor, and rifampicin, a CYP3A4 inducer.

Effects of eribulin on the pharmacokinetics of other medicines
In vitro data indicate that eribulin is a mild inhibitor of the important drug metabolising enzyme CYP3A4. No *in vivo* data are available. Caution and monitoring for adverse events is recommended with concomitant use of substances that have a narrow therapeutic window and that are eliminated mainly via CYP3A4-mediated metabolism (eg alfentanil, cyclosporine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus).
Eribulin does not inhibit the CYP enzymes CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 2E1 at relevant clinical concentrations. At relevant clinical concentrations, eribulin did not inhibit BCRP, OCT1, OCT2, OAT1, OAT3, OATP1B1 and OATP1B3 transporter-mediated activity

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of eribulin in pregnant women. Eribulin is embryotoxic, foetotoxic, and teratogenic in rats. EBUNAT should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus.
Women of childbearing potential must be advised to avoid becoming pregnant whilst they are receiving EBUNAT and must use highly effective contraception during treatment with EBUNAT and for 7 months after treatment.

Men with partners of child-bearing potential should be advised not to father a child while receiving EBUNAT and must use effective contraception during EBUNAT treatment and for 4 months after treatment.

Breast-feeding
It is unknown whether eribulin/metabolites are excreted in human or animal breast milk. A risk to newborns/infants cannot be excluded and therefore EBUNAT must not be used during breast-feeding.

Fertility
Testicular toxicity has been observed in rats and dogs. Male patients should seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with EBUNAT.

4.7 Effects on ability to drive and use machines
EBUNAT may cause adverse reactions such as tiredness and dizziness which may lead to minor or moderate influence on the ability to drive or use machines. Patients should be advised not to drive or use machines if they feel tired or dizzy.

4.8 Undesirable effects

Summary of safety profile
The most commonly reported adverse reactions related to EBUNAT, are bone marrow suppression manifested as neutropenia, leucopenia, anaemia, thrombocytopenia with associated infections. New onset or worsening of pre-existing peripheral neuropathy has also been reported. Gastrointestinal toxicities, manifested as anorexia, nausea, vomiting, diarrhoea, constipation, and stomatitis are among reported undesirable effects. Other undesirable effects include fatigue, alopecia, increased liver enzymes, sepsis and musculoskeletal pain syndrome.

Tabulated list of adverse reactions
Unless otherwise noted, the table shows the incidence rates of adverse reactions observed in breast cancer and soft tissue sarcoma patients who received the recommended dose in Phase 2 and Phase 3 studies.
Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).
Within each frequency grouping, undesirable effects are presented in order of decreasing frequency. Where Grade 3 or 4 reactions occurred, the actual total frequency and the frequency of Grade 3 or 4 reactions are given.

System Organ Class	**Adverse Reactions – all Grades**			
	Very Common (Frequency %)	**Common (Frequency %)**	**Uncommon (Frequency %)**	**Rare or not known**
Infections and infestations		Urinary tract infection (8.5%) (G3/4: 0.7%) Pneumonia (1.6%) (G3/4: 1.0%) Oral candidiasis Oral herpes Upper respiratory tract infection Nasopharyngitis Rhinitis Herpes zoster	Sepsis (0.5%) (G3/4: 0.5%)a Neutropenic sepsis (0.2%) (G3/4: 0.2%)a Septic Shock (0.2%) (G3/4:0.2%)a	
Blood and lymphatic system disorders	Neutropenia (53.6%) (G3/4: 46.0%) Leukopenia (27.9%) (G3/4: 17.0%) Anaemia (21.8%) (G3/4: 3.0%)	Lymphopenia (5.7%) (G3/4: 2.1%) Febrile neutropenia (4.5%) (G3/4: 4.4%)a Thrombocytopenia (4.2%) (G3/4: 0.7%)		*Disseminated intravascular coagulation[b]
Metabolism and nutrition disorders	Decreased appetite (22.5%) (G3/4: 0.7%)d	Hypokalaemia (6.8%) (G3/4: 2.0%) Hypomagnesaemia (2.8%) (G3/4: 0.3%) Dehydration (2.8 %) (G3/4: 0.5%)d Hyperglycaemia Hypophosphataemia Hypocalcaemia		
Psychiatric disorders		Insomnia Depression		
Nervous system disorders	Peripheral neuropathyc (35.9%) (G3/4: 7.3%) Headache (17.5%) (G3/4: 0.7%)	Dysgeusia Dizziness (9.0%) (G3/4: 0.4%)d Hypoaesthesia Lethargy Neurotoxicity		
Eye disorders		Lacrimation increased (5.8%) (G3/4: 0.1%)d Conjunctivitis		
Ear and labyrinth disorders		Vertigo Tinnitus		
Cardiac disorders		Tachycardia		
Vascular disorders		Hot flush Pulmonary embolism (1.3%) (G3/4: 1.1%)a	Deep vein thrombosis	
Respiratory, thoracic and mediastinal disorders	Dyspnoea (15.2%)a (G3/4: 3.5%)a Cough (15.0%) (G3/4: 0.5%)d	Oropharyngeal pain Epistaxis Rhinorrhoea	Interstitial lung disease (0.2%) (G3/4: 0.1%)	
Gastrointestinal disorders	Nausea (35.7%) (G3/4: 1.1%)d Constipation (22.3%) (G3/4: 0.7%)d Diarrhoea (18.7%) (G3/4: 0.8%) Vomiting (18.1%) (G3/4: 1.0%)	Abdominal pain Stomatitis (11.1%) (G3/4: 1.0%)d Dry mouth Dyspepsia (6.5%) (G3/4: 0.3%)d Gastrooesophageal reflux disease Abdominal distension	Mouth ulceration Pancreatitis	
Hepatobiliary disorders		Aspartate aminotransferase increased (7.7%) (G3/4: 1.4%)d Alanine aminotransferase increased (7.6%) (G3/4: 1.9%)d Gamma glutamyl transferase increased (1.7%) (G3/4: 0.9%)d Hyperbilirubinaemia (1.4%) (G3/4: 0.4%)	Hepatotoxicity (0.8%) (G3/4: 0.6%)	

Skin and subcutaneous tissue disorders	Alopecia	Rash (4.9%) (G3/4: 0.1%) Pruritus (3.9%) (G3/4: 0.1%)d Nail disorder Night sweats Dry skin Erythema Hyperhidrosis Palmar plantar erythrodysaesthesia (1.0%) (G3/4: 0.1%)d	Angioedema	**Stevens-Johnson syndrome/ Toxic epidermal necrolysisb
Musculoskeletal and connective tissue disorders	Arthralgia and myalgia (20.4%) (G3/4: 1.0%) Back pain (12.8%) (G3/4: 1.5%) Pain in extremity (10.0%) (G3/4: 0.7%)d	Bone pain (6.7%) (G3/4: 1.2%) Muscle spasms (5.3%) (G3/4: 0.1%)d Musculoskeletal pain Musculoskeletal chest pain Muscular weakness		
Renal and urinary disorders		Dysuria	Haematuria Proteinuria Renal failure	
General disorders and administration site conditions	Fatigue/Asthenia (53.2%) (G3/4 : 7.7%) Pyrexia (21.8%) (G3/4: 0.7%)	Mucosal Inflammation (6.4%) (G3/4: 0.9%)d Peripheral oedema Pain Chills Chest pain Influenza like illness		
Investigations	Weight decreased (11.4%) (G3/4: 0.4%)d			

[a] Includes Grade 5 events.
[b] From spontaneous reporting
[c] Includes preferred terms of peripheral neuropathy, peripheral motor neuropathy, polyneuropathy, paraesthesia, peripheral sensory neuropathy, peripheral sensorimotor neuropathy and demyelinating polyneuropathy
[d] No Grade 4 events
* Rare
** Frequency not known

Overall, the safety profiles in the breast cancer and soft tissue sarcoma patient populations were similar.

Description of selected adverse reactions

Neutropenia

The neutropenia observed was reversible and not cumulative; the mean time to nadir was 13 days and the mean time to recovery from severe neutropenia (< 0.5 x 109/l) was 8 days.

Neutrophil counts of < 0.5 x 109/l that lasted for more than 7 days occurred in 13% of breast cancer patients treated with eribulin in the EMBRACE study.

Neutropenia was reported as a Treatment Emergent Adverse Event (TEAE) in 151/404 (37.4% for all grades) in the sarcoma population, compared with 902/1559 (57.9% for all grades) in the breast cancer population. The combined grouped TEAE and neutrophil laboratory abnormality frequencies were 307/404 (76.0%) and 1314/1559 (84.3%), respectively. The median duration of treatment was 12.0 weeks for sarcoma patients and 15.9 weeks for breast cancer patients.

Fatal cases of febrile neutropenia, neutropenic sepsis, sepsis and septic shock have been reported. Out of 1963 breast cancer and soft tissue sarcoma patients who received eribulin at the recommended dose in clinical trials there was one fatal event each of neutropenic sepsis (0.1%) and febrile neutropenia (0.1%). In addition there were 3 fatal events of sepsis (0.2%) and one of septic shock (0.1%).

Severe neutropenia may be managed by the use of G-CSF or equivalent at the physician's discretion in accordance with relevant guidelines. 18% and 13% of eribulin treated patients received G-CSF in the two phase 3 breast cancer studies (Studies 305 and 301, respectively). In the phase 3 sarcoma study (Study 309), 26% of the eribulin treated patients received G-CSF. Neutropenia resulted in discontinuation in < 1% of patients receiving eribulin.

Disseminated intravascular coagulation

Cases of disseminated intravascular coagulation have been reported, typically in association with neutropenia and/or sepsis.

Peripheral neuropathy

In the 1559 breast cancer patients the most common adverse reaction resulting in discontinuation of treatment with eribulin was peripheral neuropathy (3.4%). The median time to Grade 2 peripheral neuropathy was 12.6 weeks (post 4 cycles). Out of the 404 sarcoma patients, 2 patients discontinued treatment with eribulin due to peripheral neuropathy. The median time to Grade 2 peripheral neuropathy was 18.4 weeks.

Development of Grade 3 or 4 peripheral neuropathy occurred in 7.4% of breast cancer patients and 3.5% of sarcoma patients. In clinical trials, patients with pre-existing neuropathy were as likely to develop new or worsening symptoms as those who entered the study without the condition.

In breast cancer patients with pre-existing Grade 1 or 2 peripheral neuropathy the frequency of treatment-emergent Grade 3 peripheral neuropathy was 14%.

Hepatotoxicity

In some patients with normal/abnormal liver enzymes prior treatment with eribulin, increased levels of liver enzymes have been reported with initiation of eribulin treatment. Such elevations appeared to have occurred early with eribulin treatment in cycle 1 – 2 for the majority of these patients and whilst thought likely to be a phenomenon of adaptation to eribulin treatment by the liver and not a sign of significant liver toxicity in most patients, hepatotoxicity has also been reported.

Special populations

Elderly population

Of the 1559 breast cancer patients treated with the recommended dose of eribulin, 283 patients (18.2%) were ≥ 65 years of age. In the 404 sarcoma patient population, 90 patients (22.3%) treated with eribulin were ≥ 65 years of age. The safety profile of eribulin in elderly patients (≥ 65 years of age) was similar to that of patients <65 years of age except for asthenia/ fatigue which showed an increasing trend with age. No dose adjustments are recommended for the elderly population.

Patients with hepatic impairment

Patients with ALT or AST > 3 x ULN experienced a higher incidence of Grade 4 neutropenia and febrile neutropenia. Although data are limited, patients with bilirubin > 1.5 x ULN also have a higher incidence of Grade 4 neutropenia and febrile neutropenia (see also sections 4.2 and 5.2).

Paediatric population

Three open-label studies, Studies 113, 213 and 223, were conducted in paediatric patients with refractory or recurrent solid tumours and lymphomas, but excluding central nervous system (CNS) tumours.

The safety of eribulin monotherapy was evaluated in 43 paediatric patients who received up to 1.58 mg/m2 on Days 1 and 8 of a 21-day cycle (Studies 113 and 223). The safety of eribulin in combination with irinotecan was also evaluated in 40 paediatric patients who received eribulin 1.23 mg/m2 on Days 1 and 8 and irinotecan 20 or 40 mg/m2 on Days 1 to 5 of a 21-day cycle, or 100 or 125 mg/m2 on Days 1 and 8 of a 21-day cycle (Study 213).

In Study 113 (Phase 1), the most frequently reported adverse drug reactions were white blood cell count decreased, lymphocyte count decreased, anaemia and neutrophil count decreased.

In Study 213 (Phase 1/2), the most frequently reported adverse drug reactions were neutropenia (Phase 1) and diarrhoea and neutrophil count decreased (Phase 2).

In Study 223 (Phase 2), the most frequently reported adverse drug reactions were neutrophil count decreased, anaemia, and white blood cell count decreased.

The safety profile of eribulin as monotherapy or in combination with irinotecan hydrochloride in this paediatric population was consistent with the known safety profile of either study drug in the adult population.

4.9 Overdose

In one case of overdose the patient inadvertently received 8.6 mg of Eribulin mesylate (approximately 4 times the planned dose) and subsequently developed a hypersensitivity reaction (Grade 3) on Day 3 and neutropenia (Grade 3) on Day 7. Both adverse reactions resolved with supportive care.

There is no known antidote for eribulin overdose. In the event of an overdose, the patient should be closely monitored. Management of overdose should include supportive medical interventions to treat the presenting clinical manifestations.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Eribulin mesylate is a microtubule dynamics inhibitor belonging to the halichondrin class of antineoplastic agents. It is a structurally simplified synthetic analogue of halichondrin B, a natural product isolated from the marine sponge Halichondria okadai.

Eribulin inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into non-productive aggregates. Eribulin exerts its effects via a tubulin-based antimitotic mechanism leading to G2/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged and irreversible mitotic blockage.

In addition, eribulin treatment of human breast cancer cells caused changes in morphology and gene expression as well as decreased migration and invasiveness in vitro. In mouse xenograft models of human breast cancer, eribulin treatment was associated with increased vascular perfusion and permeability in the tumor cores, resulting in reduced tumor hypoxia, and changes in the expression of genes in tumor specimens associated with a change in phenotype.

5.2 Pharmacokinetic properties

Distribution

The pharmacokinetics of eribulin are characterized by a rapid distribution phase followed by a prolonged elimination phase, with a mean terminal half-life of approximately 40 h. It has a large volume of distribution (range of means 43 to 114 l/m^2).

Eribulin is weakly bound to plasma proteins. The plasma protein binding of eribulin (100-1000 ng/ml) ranged from 49% to 65% in human plasma.

Biotransformation

Unchanged eribulin was the major circulating species in plasma following administration of ^{14}C-eribulin to patients. Metabolite concentrations represented <0.6% of parent compound, confirming that there are no major human metabolites of eribulin.

Elimination

Eribulin has a low clearance (range of means 1.16 to 2.42 l/h/m^2). No significant accumulation of eribulin is observed on weekly administration. The pharmacokinetic properties are not dose or time dependent in the range of eribulin doses of 0.22 to 3.53 mg/m^2.

Eribulin is eliminated primarily by biliary excretion. The transport protein involved in the excretion is presently unknown. Preclinical in vitro studies indicate that eribulin is transported by Pgp. However, it has been shown that at clinically relevant concentrations eribulin is not a Pgp inhibitor in vitro. Additionally, in vivo, concomitant administration of ketoconazole, a Pgp inhibitor, has no effect on eribulin exposure (AUC and C_{max}). In vitro studies have also indicated that eribulin is not a substrate for OCT1.

After administration of ^{14}C-eribulin to patients, approximately 82% of the dose was eliminated in faeces and 9% in urine indicating that renal clearance is not a significant route of eribulin elimination.

Unchanged eribulin represented most of the total radioactivity in faeces and urine.

Hepatic impairment

A study evaluated the pharmacokinetics of eribulin in patients with mild (Child-Pugh A; n=7) and moderate (Child-Pugh B; n=4) hepatic impairment due to liver metastases. Compared to patients with normal hepatic function (n=6), eribulin exposure increased 1.8-fold and 3-fold in patients with mild and moderate hepatic impairment, respectively. Administration of EBUNAT at a dose of 0.97 mg/m^2 to patients with mild hepatic impairment and 0.62 mg/m^2 to patients with moderate hepatic impairment resulted in a somewhat higher exposure than after a dose of 1.23 mg/m^2 to patients with normal hepatic function. EBUNAT was not studied in patients with severe hepatic impairment (Child-Pugh C). There is no study in patients with hepatic impairment due to cirrhosis.

Renal impairment

Increased eribulin exposure was seen in some patients with moderately or severely impaired renal function, with high between-subject variability. The pharmacokinetics of eribulin were evaluated in a Phase 1 study in patients with normal renal function (Creatinine clearance: ≥ 80 ml/min; n=6), moderate (30-50 ml/min; n=7) or severe (15-<30 ml/min; n=6) renal impairment. Creatinine clearance was estimated with the Cockcroft-Gault formula. A 1.5-fold (90% CI: 0.9-2.5) higher dose-normalised $AUC_{(0\text{-}inf)}$ was observed in patients with moderate and severe renal impairment.

Paediatric population

Eribulin plasma concentrations were collected from 83 paediatric patients (age range: 2 to 17 years), with refractory/relapsed and recurrent solid tumours and lymphomas, who received eribulin in Studies 113, 213 and 223. Eribulin PK in paediatric patients was comparable to adult patients with STS and patients with other types of tumour. Eribulin exposure in paediatric patients was similar to exposure in adult patients. Concomitant irinotecan did not have an effect on eribulin PK in paediatric patients with refractory/relapsed and recurrent solid tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dehydrated Alcohol
Hydrochloric acid
Sodium hydroxide
Nitrogen
Water for injection

6.2 Shelf life

Refer Outer carton

In-use shelf life

If not used immediately EBUNAT as the undiluted solution in a syringe should not normally be stored longer than 4 hours at 25°C and ambient lighting, or 24 hours at 2°C - 8°C.

Diluted solutions of EBUNAT (0.018 mg/ml to 0.18 mg/ml eribulin in sodium chloride 9 mg/ml (0.9%)) solution for injection should not be stored longer than 24 hours at 2°C -.8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Expiration data

EBUNAT should be used before the expiration date indicated on the package

From a microbiological point of view unless the method of opening precludes the risk of microbial contamination the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.3 Special precautions for storage

Store below 30°C

This medicinal product does not require any special storage conditions.

For storage conditions after first opening or dilution of the medicinal product, see section 6.2.

6.4 Nature and contents of container <and special equipment for use, administration or implantation>

Clear colorless solution filled in 5ml Type-I clear glass vials, stoppered with 20mm chlorobutyl rubber stopper and sealed with 20 mm blue matte color flip-off seal.

Each pack contain one vial

6.5 Special precautions for disposal <and other handling>

No special handling instructions.

7. MANUFACTURER

Natco Pharma Limited
Pharma Division, Kothur Village,
Kothur Mandal Rangareddy District,
Telangana 509228 India.

8. DATE OF REVISION OF THE TEXT

03/2026