This material is intended for Healthcare Professionals in one of the following markets where QARZIBA® (dinutuximab beta) is currently approved: EU, EEA, UK, China, Hong Kong, Australia or Brazil.

Qarziba®
Dinutuximab beta

Long-term survival with QARZIBA® (dinutuximab beta) in high-risk neuroblastoma: An historical control analysis

Ladenstein R, *et al.* Investigation of the role of dinutuximab beta-based immunotherapy in the SIOPEN high-risk neuroblastoma 1 trial (HR-NBL1). *Cancers*. 2020; 12: 309. doi:10.3390/cancers12020309

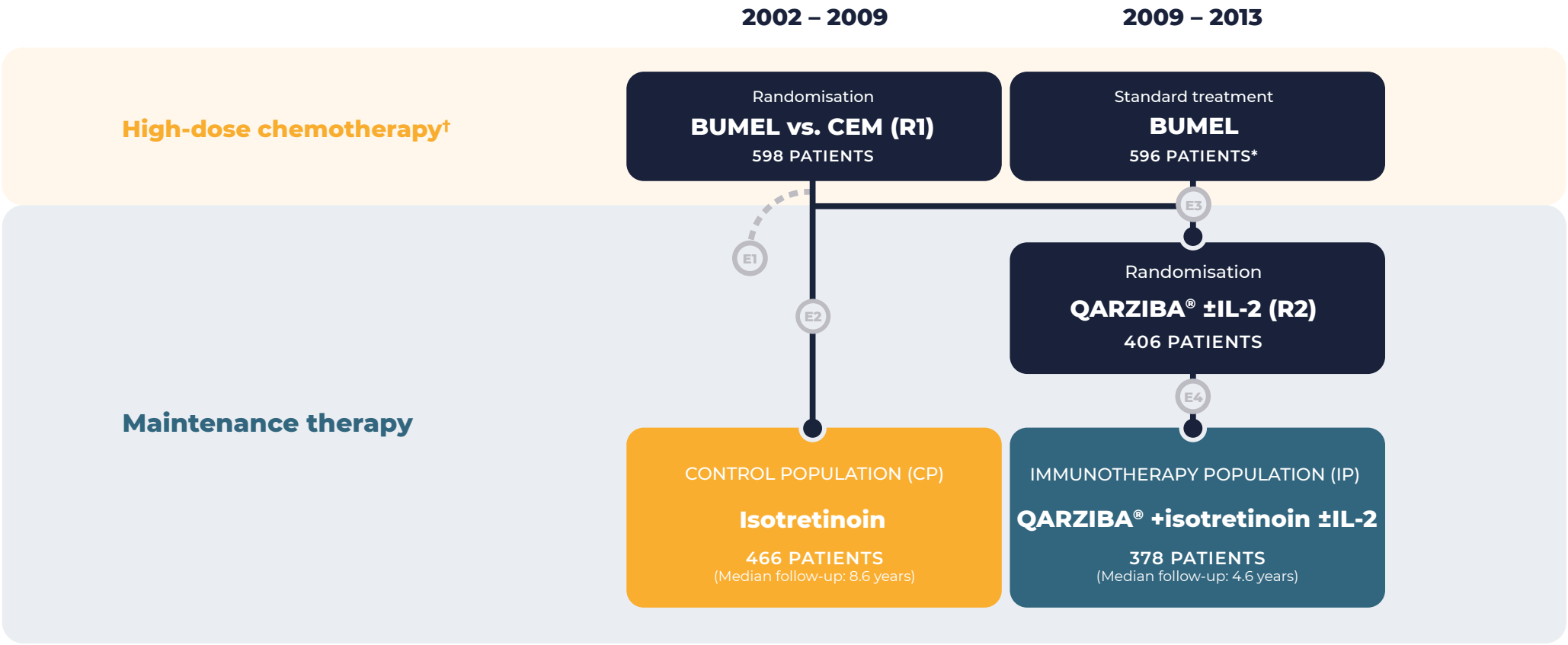
This medicine is subject to additional monitoring. Adverse events related to this product should be reported as per local regulatory authority requirements. Adverse events should also be reported to E: safety@eusapharma.com

Methodology[1]

Objective

To explore the effects of dinutuximab beta in the International Society of Paediatric Oncology Europe Neuroblastoma Group SIOPEN HR-NBL1 trial.

Analysis cohorts



*70 patients received CEM, †After sufficient response with rapid COJEC ±TVD.

E1: 7 patients excluded who did not receive HDT, **E2:** 61 patients excluded who had progression before day 109, **E3:** 46 R1 patients included in R2. 18 patients excluded who were part of initial R2, **E4:** Exclusions included, 1 patient with protocol violation, 18 patients with disease progression before immunotherapy, 8 patients who did not receive immunotherapy and 1 patient without follow-up

Reference: 1. Ladenstein R, *et al. Cancers.* 2020; 12: 309.

Methodology[1]

The use of an historical control analysis is key to illustrating the survival benefit offered by QARZIBA® (dinutuximab beta)

In 2007, the initial results of the Clinical Oncology Group, ANBL0032 trial were communicated – providing the first demonstration of a survival benefit in high-risk neuroblastoma with immunotherapy and cytokines.[2] From this date, it has been deemed unethical to withhold anti-GD2 immunotherapy from high-risk patients.

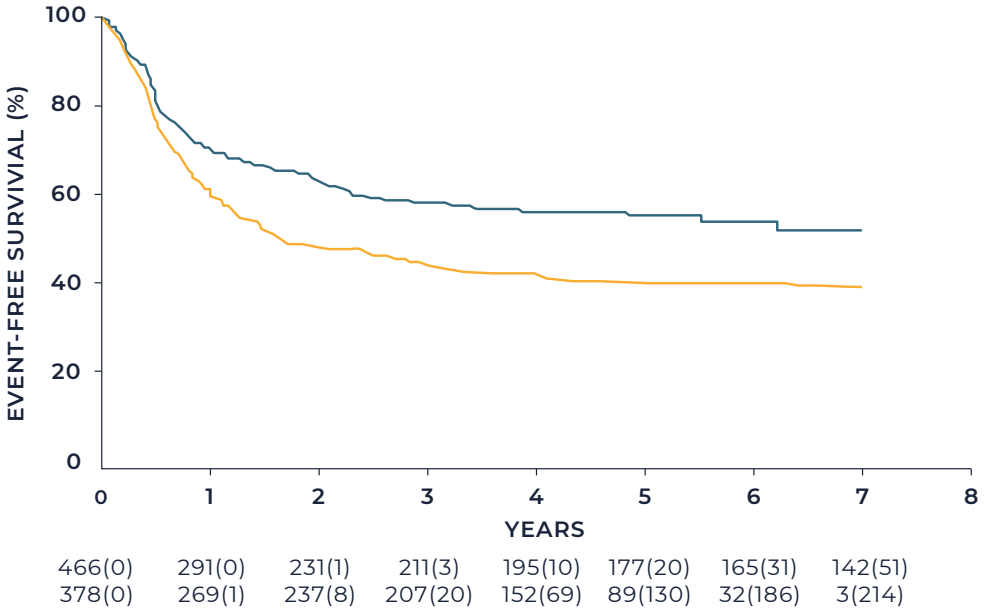
> **"A randomised trial of dinutuximab beta and isotretinoin compared to isotretinoin alone would have produced more robust data, but this was believed not to be ethically feasible within the SIOPEN community"**

- Both populations were balanced for sex, stage 4, MYCN amplification and response prior to HDT
- Both populations are derived from the same trial and received similar treatment up until the maintenance phase
- The control population received isotretinoin alone in the maintenance setting – reflective of clinical practice in the era prior to immunotherapy

References: 1. Ladenstein R, *et al. Cancers.* 2020; 12: 309. 2. Yu AL, *et al. N Engl J Med.* 2010; 363(14): 1324–34.

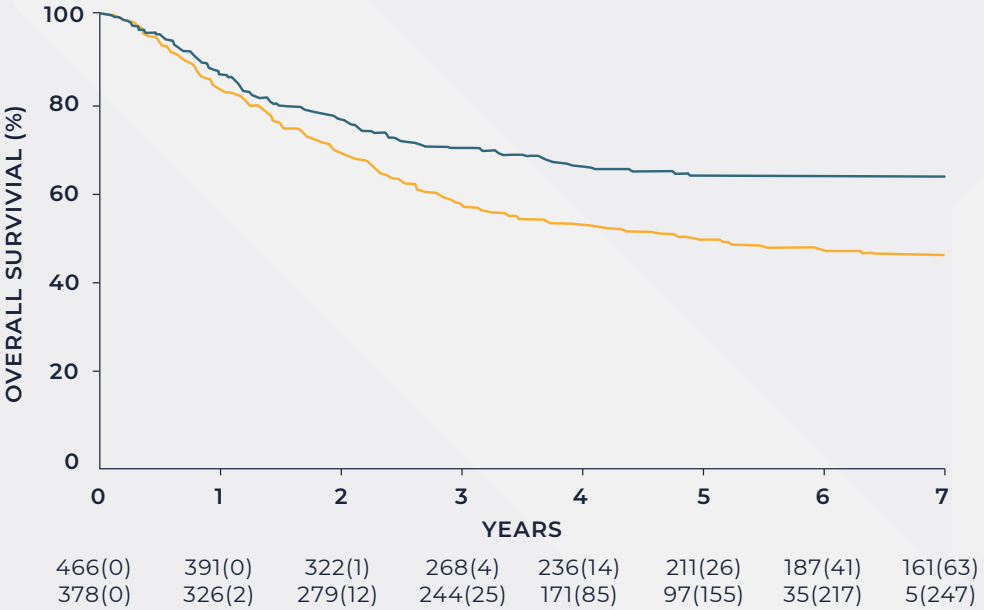
Results[1]

5-year EFS with QARZIBA® ±IL-2 was 57% (95% CI, 51-62%) vs. 42% (95% CI, 38-47%), P<0.001



	CP	IP
Patients	466	378
Events	276	161
2-Year EFS	50% (95% CI: 45-54%)	65% (95% CI: 60-69%)
5-Year EFS	42% (95% CI: 38-47%)	57% (95% CI: 51-62%)
P-value	<0.001	

5-year OS with QARZIBA® ±IL-2 was 64% (95% CI, 59-69%) vs. 50% (95% CI, 46-55%), P<0.001

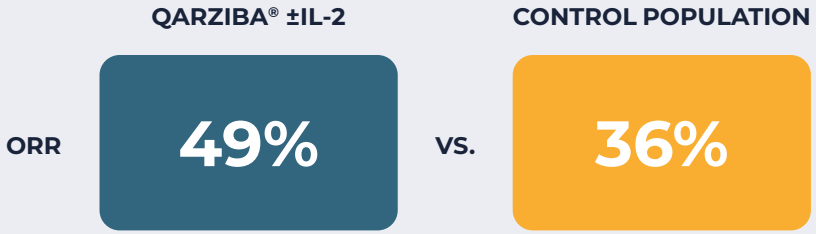


	CP	IP
Patients	466	378
Events	245	127
2-Year OS	69% (95% CI: 65-73%)	77% (95% CI: 72-81%)
5-Year OS	50% (95% CI: 46-55%)	64% (95% CI: 59-69%)

Reference: 1. Ladenstein R, *et al. Cancers.* 2020; 12: 309.

Results[1]

Of patients with a PR or VGPR (i.e. residual disease) prior to maintenance treatment, 49% (64/130) responded to QARZIBA® ±IL-2 vs. 36% (39/108) in the control population, P=0.226



Response was assessed in patients with evaluable disease prior to maintenance therapy. Response was defined as CR + VGPR. Patients had full disease evaluations prior to and after 2 and 5 courses of maintenance treatment. See full publication for details of evaluation.

Of patients with a CR (i.e. no residual disease) prior to maintenance treatment, 61% (95% CI, 53-67%) achieved 5-year EFS with QARZIBA® ±IL-2 vs. 46% (95% CI, 39-52%) in the control population*

*Statistical analysis not performed. 81 events seen with QARZIBA® ±IL-2 and 144 seen in the control population.

Risk factors significantly increasing likelihood of relapse

The following risk factors significantly increased likelihood of relapse in the total population:

- No immunotherapy (P<0.0001)
- HDT with CEM (P=0.0345)
- Partial remission prior to maintenance therapy (P=0.0103)
- >1 metastatic compartment at diagnosis (P<0.001)
- Aged more than 5 years (P=0.0138)

Reference: 1. Ladenstein R, *et al. Cancers.* 2020; 12: 309.

Results[1]

Tolerability

Toxicity tended to be higher in the immunotherapy population, particularly in patients receiving IL-2. Four patients had non-relapse-related mortality in both populations.

Combined Grade 3+4 adverse events seen in more than 10% of patients in any group

TOXICITIES	CONTROL POPULATION	QARZIBA®	QARZIBA® +IL-2
Non-Haem Tox.	15% (46/317)	66% (122/186)	86% (166/192)
General condition	2% (7/314)	16% (30/185)	41% (78/192)
Haemoglobin	4% (12/313)	42% (79/186)	66% (126/191)
WBC	6% (18/313)	26% (48/186)	36% (69/191)
Granulocytes	7% (21/313)	33% (62/186)	58% (111/191)
Platelets	9% (28/313)	34% (64/186)	61% (117/191)
Infection	6% (20/315)	26% (48/185)	34% (64/191)
Fever	2% (5/314)	14% (25/185)	40% (76/190)
Diarrhoea	1% (3/313)	7% (13/185)	21% (41/192)
Skin	3% (11/315)	5% (9/185)	10% (19/192)
Allergy	0% (0/314)	10% (19/185)	20% (39/191)
Hypotension	0% (0/298)	7% (13/182)	17% (32/191)
SGOT/SGPT	2% (6/311)	17% (31/185)	23% (44/192)
Capillary leak syndrome	0% (0/19)	4% (5/119)	15% (19/124)
Pain related to ch14.18/CHO	-	16% (19/122)	26% (32/124)

See full publication for a detailed breakdown of toxicities.

Reference: 1. Ladenstein R, *et al. Cancers.* 2020; 12: 309.

Summary[1]

COMPARABLE PATIENT POPULATIONS

QARZIBA® ±IL-2 has been compared to an historical control cohort, receiving isotretinoin alone, which was derived from the same trial and experienced similar pre-treatment

SIGNIFICANT INCREASE IN 5-YEAR EFS & OS

- **5-year EFS:** 57% (95% CI, 51-62) vs. 42% (95% CI, 38-47), P<0.001
- **5-year OS:** 64% (95% CI, 59-69) vs. 50% (95% CI, 46-55), P<0.001

RESPONSE RATES

Of patients with a PR or VGPR (i.e. residual disease) prior to maintenance treatment, 49% (64/130) responded to QARZIBA® ±IL-2 vs. 36% (39/108) in the control population, P=0.226 (NS)

QARZIBA® (dinutuximab beta) + isotretinoin is the SIOPEN recommended treatment for high-risk neuroblastoma in the maintenance phase.[1]

QARZIBA® is indicated for the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be stabilised by other suitable measures.

In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first line therapy, QARZIBA® should be combined with interleukin-2 (IL-2).[2]

Reference: 1. Ladenstein R, *et al. Cancers. 2020*; 12: 309. 2. QARZIBA® (dinutuximab beta). Summary of Product Characteristics. Available at: https://www.ema.europa.eu/documents/product-information/qarziba-epar-product-information_en-0.pdf. Last accessed: March 2022.

The materials provided for QARZIBA® (dinutuximab beta) are approved according to the EU label, and the UK and EFPIA codes of practice. Prescribing information may vary depending on local approval in each country. Please refer to local prescribing information and/or the Summary of Product Characteristics (SPC).

Abbreviations:

BUMEL; high-dose chemotherapy with busulfan and melphalan, **CEM**; high-dose chemotherapy with carboplatin, etoposide and melphalan, **COG**; Children's Oncology Group, **COJEC**; high-dose chemotherapy with cisplatin, vincristine, carboplatin, etoposide and cyclophosphamide, **CR**; complete response, **EFS**; event-free survival, **GD2**; disialoganglioside, **HDT**; high-dose chemotherapy, **IL-2**; interleukin-2, **MYCN**; MYCN gene, **ORR**; overall response rate, **OS**; overall survival, **PD**; progressed disease, **PR**; partial response, **R1**; high-dose chemotherapy randomisation, **R2**; immunotherapy randomisation, **SD**; stable disease, **SGOT/SGPT**; serum-glutamate-oxalacetate-transaminase/serum-glutamate-pyruvate-transaminase, **TVD**; topotecan, vincristine and doxorubicin, **VGPR**; very good partial response, **WBC**; white blood cells.

ABBREVIATED PRESCRIBING INFORMATION – QARZIBA▼(dinutuximab beta).

Before prescribing Qarziba please refer to full Summary of Product Characteristics.

Presentation: Concentrate for solution for infusion containing 20 mg dinutuximab beta. **Indication:** For the treatment of high-risk neuroblastoma in patients aged 12 months and above, who have previously received induction chemotherapy and achieved at least a partial response, followed by myeloablative therapy and stem cell transplantation, as well as patients with history of relapsed or refractory neuroblastoma, with or without residual disease. Prior to the treatment of relapsed neuroblastoma, any actively progressing disease should be stabilised by other suitable measures. In patients with a history of relapsed/refractory disease and in patients who have not achieved a complete response after first line therapy, dinutuximab beta should be combined with interleukin 2 (IL 2). **Dosage & Administration:** Restricted to hospital-use only and must be administered under the supervision of a physician experienced in the use of oncological therapies. Treatment consists of 5 consecutive courses, each course comprising 35 days. The individual dose is determined based on the body surface area and should be a total of 100 mg/m² per course. Two modes of administration are possible: 1) continuous infusion over the first 10 days of each course (a total of 240 hours) at the daily dose of 10 mg/m² or 2) five daily infusions of 20 mg/m² administered over 8 hours, on the first 5 days of each course. When IL 2 is combined with dinutuximab beta, it should be administered as subcutaneous injections of 6×10^6 IU/m²/day, for 2 periods of 5 consecutive days, resulting in an overall dose of 60×10^6 IU/m² per course. The first 5 day course should start 7 days prior to the first infusion of dinutuximab beta and the second 5 day course should start concurrently with dinutuximab beta infusion (days 1 to 5 of each dinutuximab beta course). ***Paediatric population:*** The safety and efficacy of Qarziba in children aged less than 12 months have not yet been established. No data are available. ***Renal impairment:*** No data are available. ***Hepatic impairment:*** No data are available. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Acute grade 3 or 4, or extensive chronic graft-versus-host disease (GvHD). **Special warnings and precautions for use:** ***Traceability:*** In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. ***Pain:*** Neuropathic pain usually occurs at the beginning of the treatment and premedication with analgesics, including intravenous opioids, prior to each infusion of dinutuximab beta is required. A triple therapy, including nonopioid analgesics (according to WHO guidelines), gabapentin and opioids, is recommended for pain treatment. The individual dose may vary widely. ***Hypersensitivity reactions:*** Severe infusion-related reactions, including cytokine release syndrome (CRS), anaphylactic and hypersensitivity reactions, may occur despite the use of premedication. Occurrence of a severe infusion related reaction (including CRS) requires immediate discontinuation of dinutuximab beta therapy and may necessitate emergency treatment. CRS frequently manifests itself within minutes to hours of initiating the first infusion and is characterised by systemic symptoms such as fever, hypotension and urticaria. Anaphylactic reactions may occur as early as within a few minutes of the first infusion with dinutuximab beta and are commonly associated with bronchospasm and urticaria. ***Capillary leak syndrome (CLS):*** Usually develops within hours after initiation of treatment, while clinical symptoms (i.e. hypotension, tachycardia) are reported to occur after 2 to 12 hours. Careful monitoring of circulatory and respiratory function is required. ***Neurological disorders of the eye:*** May occur as dinutuximab beta binds to optic nerve cells. No dose modification is necessary in the case of an impaired visual accommodation that is correctable with eye glasses, as long as this is judged to be tolerable. Treatment must be interrupted in patients who experience Grade 3 vision toxicity. In case of any eye problems, patients should be referred promptly to an ophthalmology specialist. ***Peripheral neuropathy:*** Occasional occurrences of peripheral neuropathy have been reported. Cases of motor or sensory neuropathy lasting more than 4 days must be evaluated and non-inflammatory causes, such as disease progression, infections, metabolic syndromes and concomitant medication, should be excluded. Treatment should be permanently discontinued in patients experiencing any objective prolonged weakness attributable to dinutuximab beta administration. For patients with moderate (Grade 2) neuropathy (motor with or without sensory), treatment should be interrupted and may be resumed after neurologic symptoms resolve. ***Systemic infections:*** Patients are likely to be immunocompromised as a result of prior therapies as they typically have a central venous catheter in situ, they are at risk of developing systemic infection. Patients should have no evidence of systemic infection and any identified infection should be under control before starting therapy. ***Haematologic toxicities:*** Occurrence has been reported with dinutuximab beta, such as erythropenia, thrombocytopenia or neutropenia. Grade 4 haematologic toxicities, improving to at least Grade 2 or baseline values by start of next treatment course, do not require dose modification. ***Laboratory abnormalities:*** Regular monitoring of liver function and electrolytes is recommended. **Interactions:** No studies performed. A risk for indirect reduction of CYP activity due to higher TNF α and IL 6 levels and, therefore, interactions with concomitantly used medicinal products, cannot be excluded. ***Corticosteroids:*** Due to their immunosuppressive activity, concomitant treatment with corticosteroids is not recommended within 2 weeks prior to the first treatment course until 1 week after the last treatment course with dinutuximab beta, except for life-threatening conditions. ***Vaccinations:*** Should be avoided during administration of dinutuximab beta until 10 weeks after the last treatment course, due to immune stimulation through dinutuximab beta and possible risk for rare neurological toxicities. ***Intravenous immunoglobulin:*** Concomitant use of intravenous immunoglobulins is not recommended as they may interfere with dinutuximab beta-dependent cellular cytotoxicity. **Women of childbearing potential/contraception in males and females:** Dinutuximab beta should not be used in women of childbearing potential not using contraception. It is recommended that women of childbearing potential use contraception for 6 months after discontinuation of treatment with dinutuximab beta. ***Pregnancy:*** Dinutuximab beta should not be used during pregnancy. ***Breast feeding*** – No data. Breast-feeding should be discontinued during treatment and for 6 months after the last dose. ***Fertility*** - Unknown. **Effects on ability to drive and use machines:** Dinutuximab beta has major influence on the ability to drive and use machines. Patients should not use or drive machines during treatment with dinutuximab beta. **Side effects:** ***Very common (≥ 1/10)*** - infection (including pneumonia, skin infection, herpes virus infection, myelitis, encephalomyelitis), device related infection, anaemia, leukopenia, neutropenia, thrombocytopenia, hypersensitivity, cytokine release syndrome, fluid retention, headache, mydriasis, pupillotonia, eye oedema (eyelid, periorbital), tachycardia, hypotension, capillary leak syndrome, hypoxia, cough, vomiting, diarrhoea, constipation, stomatitis, pruritus, rash, urticaria, pyrexia, chills, pain (includes abdominal pain, pain in extremity, oropharyngeal pain, and Back pain reported in >10% of patients. In addition, other common pain types reported were arthralgia, injection site pain, musculoskeletal pain, bone pain, chest pain, and neck pain), peripheral oedema, face oedema, increased weight, increased transaminases, increased gamma glutamyltransferase, increased blood bilirubin increased blood creatinine. ***Common (≥ 1/100 to < 1/10)*** – sepsis, lymphopenia, anaphylactic reaction, decreased appetite, hypoalbuminaemia, hyponatraemia, hypokalaemia, hypophosphataemia, hypomagnesaemia, hypocalcaemia, dehydration, agitation, anxiety, peripheral neuropathy, seizure, paraesthesia, dizziness, tremor, ophthalmoplegia, papilloedema, accommodation disorder, blurred vision, photophobia, cardiac failure, left ventricular dysfunction, pericardial effusion, hypertension, bronchospasm, dyspnoea, respiratory failure, lung infiltration, pulmonary oedema, pleural effusion, tachypnoea, laryngospasm, nausea, lip oedema, ascites, abdominal distension, ileus, dry lips, dermatitis (including exfoliative), erythema, dry skin, hyperhidrosis, petechiae, photosensitivity reaction, muscle spasms, oliguria, urinary retention, hyperphosphaturia, haematuria, proteinuria, injection site reaction, decreased weight, decreased glomerular filtration rate, hypertriglyceridaemia, prolonged activated partial thromboplastin time, prolonged prothrombin time, prolonged thrombin time. ***Uncommon (≥ 1/1,000 to < 1/100)*** - disseminated intravascular coagulation, eosinophilia, serum sickness, intracranial pressure increased, posterior reversible encephalopathy syndrome, hypovolaemic shock, veno-occlusive disease, enterocolitis, hepatocellular injury, renal failure. **Packaging, quantity and price:** Glass vial containing 4.5 ml concentrate for solution for infusion. *The pricing of Qarziba and associated reimbursement differs between countries. Please check with your local country for specific details.* **Storage requirements:** ***Unopened vial*** - 3 year shelf-life. Store in a refrigerator (2°C – 8°C). Keep the vial in the outer carton in order to protect from light. ***In-use stability*** - demonstrated for up to 48 hours at 25°C (50 ml syringe) and for up to 7 days at 37°C (250 ml infusion bag), after cumulative storage in a refrigerator (2°C – 8°C) for 72 hours. From a microbiological point of view, the product should be used immediately. **Legal Category:** POM. **Marketing Authorisation Number:** EU/1/17/1191/001. Full prescribing information, including the SmPC, is available from the **Marketing Authorisation Holder:** EUSA Pharma (Netherlands) B.V., Beechavenue 54, 1119PW, Schiphol-Rijk, Netherlands **Date of preparation:** February 2022 – GL-DNB-2200003

Adverse events should be reported as per local regulatory authority requirements.

Adverse events should also be reported to E: safety@eusapharma.com

GL-DNB-2200008

Date of Preparation: March 2022.