SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Qarziba
4.5 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL of concentrate contains 4.5 mg dinutuximab beta.
Each vial contains 20 mg dinutuximab beta in 4.5 mL.

Dinutuximab beta is a mouse-human chimeric monoclonal IgG1 antibody produced in a mammalian cell line (CHO) by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion
Colourless to slightly yellow liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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).

4.2 Posology and method of administration

Qarziba is restricted to hospital-use only and must be administered under the supervision of a physician experienced in the use of oncological therapies. It must be administered by a healthcare professional prepared to manage severe allergic reactions including anaphylaxis in an environment where full resuscitation services are immediately available.

Posology
Treatment with Qarziba 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/m^2 per course.

Two modes of administration are possible:

- a continuous infusion over the first 10 days of each course (a total of 240 hours) at the daily dose of 10 mg/m^2
- or five daily infusions of 20 mg/m^2 administered over 8 hours, on the first 5 days of each course

When IL-2 is combined with Qarziba, it should be administered as subcutaneous injections of 6×10^6 IU/m^2/day, for 2 periods of 5 consecutive days, resulting in an overall dose of 60×10^6 IU/m^2 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).

Prior to starting each treatment course, the following clinical parameters should be evaluated and treatment should be delayed until these values are reached:

- pulse oximetry > 94% on room air
- adequate bone marrow function: absolute neutrophil count ≥ 500/µL, platelet count ≥ 20,000/µL, haemoglobin > 8.0 g/dL
- adequate liver function: alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) < 5 times upper limit of normal (ULN)
- adequate renal function: creatinine clearance or glomerular filtration rate (GRF) > 60 mL/min/1.73 m^2

Dose modification of dinutuximab beta

Based on the physician's evaluation of the severity of adverse drug reactions to dinutuximab beta, patients may undergo a dose reduction of 50% or a temporary interruption of the infusion. As a consequence, either the infusion period is prolonged or, if tolerated by the patient, the infusion rate may be increased up to 3 mL/h (continuous infusion), in order to administer the total dose.

Recommended dose modifications for dinutuximab beta

Adverse reaction	**Severity**	**Treatment modification**
Any	**Grade 1 – 2**	Decrease infusion rate to 50%, After resolution, resume infusion at original rate
Hypersensitivity reaction	e.g. hypotension	Interrupt infusion and administer supportive measures, After resolution, resume infusion at original rate
Dilated pupils with sluggish light reflex +/- photophobia		Interrupt infusion, After resolution, resume infusion at 50% rate
Any	**Grade ≥ 3**	Interrupt infusion and administer supportive measures, Resume infusion at 50% rate if ADR resolves or improves to Grade 1 – 2, After resolution, increase to original rate
	Recurrent	Discontinue infusion, Resume next day if ADR resolves
Hypersensitivity reaction	e.g. bronchospasm, angioedema	Interrupt infusion immediately and treat appropriately (see section 4.4), Resume treatment for subsequent courses
Capillary leak syndrome		Interrupt infusion and administer supportive measures, Resume at 50% rate if ADR resolves or improves to Grade 1 – 2
Central neurotoxicity		Interrupt infusion immediately, rule out other influencing factors and treat appropriately. There is limited data available on resuming treatment and no recommendations can be made

Treatment with dinutuximab beta should be permanently discontinued if the following toxicities occur:

- grade 3 or 4 anaphylaxis
- prolonged grade 2 peripheral motor neuropathy
- grade 3 peripheral neuropathy
- grade 3 vision eye toxicity
- grade 4 hyponatremia (< 120 mEq/L) despite appropriate fluid management
- recurrent or grade 4 capillary leak syndrome (requires ventilator support)
- severe central neurotoxicity that includes grade 3 or 4 with substantial prolonged neurological deficit without any detectable reason, recurrent grade 1-3 neurotoxicity, and permanent neurological deficit
- all grades of posterior reversible encephalopathy syndrome and transverse myelitis

Renal and hepatic impairment
There are no data in patients with renal and hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of Qarziba in children aged less than 12 months have not yet been established. No data are available.

Method of administration
Qarziba is for intravenous infusion. The solution should be administered via a peripheral or central intravenous line. Other intravenously co-administered agents should be delivered via a separate infusion line (see section 6.6).

For continuous infusions, the solution is administered at a rate of 2 mL per hour (48 mL per day) using an infusion pump.

For 8-hour daily infusions, the solution is administered at a rate of approximately 13 mL per hour.

Pre-medication should always be considered before starting each infusion (see section 4.4).

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

Acute grade 3 or 4, or extensive chronic graft-versus-host disease (GvHD)

4.4 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.

Nonopioid analgesics
Nonopioid analgesics should be used permanently during the treatment, e.g. paracetamol or ibuprofen.

Gabapentin
The patient should be primed with 10 mg/kg/day, starting 3 days prior to dinutuximab beta infusion. The daily dose of gabapentin is increased to 2×10 mg/kg/day orally, the next day and to 3×10 mg/kg/day orally, the day before the onset of dinutuximab beta infusion and thereafter. The maximum single dose of gabapentin is 300 mg. This dosing schedule should be maintained for as long as required by the patient.
Oral gabapentin should be tapered off after weaning off intravenous morphine infusion, at the latest after dinutuximab beta infusion therapy has stopped.

Opioids
Treatment with opioids is standard with dinutuximab beta. The first infusion day and course usually requires a higher dose than subsequent days and courses.

- Before initiation of a continuous intravenous morphine infusion, a bolus infusion of 0.02 to 0.05 mg/kg/hour morphine should be started 2 hours before dinutuximab beta infusion.
- Subsequently, a dosing rate of 0.03 mg/kg/hour is recommended concomitantly with dinutuximab beta infusion.
- With daily infusions of dinutuximab beta, morphine infusion should be continued at a decreased rate (e.g. 0.01 mg/kg/h) for 4 hours after the end of dinutuximab beta infusion.
- With continuous infusion, in response to the patient's pain perception, it may be possible to wean off morphine over 5 days by progressively decreasing its dosing rate (e.g. to 0.02 mg/kg/hour, 0.01 mg/kg/hour, 0.005 mg/kg/hour).

- If continous morphine infusion is required for more than 5 days, treatment should be gradually reduced by 20% per day after the last day of dinutuximab beta infusion.

After weaning off intravenous morphine, in case of severe neuropathic pain, oral morphine sulphate (0.2 to 0.4 mg/kg every 4 to 6 hours) can be administered on demand. For moderate neuropathic pain, oral tramodol may be administered.

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.

Cytokine release syndrome 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.

Premedication
Antihistamine premedication (e.g. diphenhydramine) should be administered by intravenous injection approximately 20 minutes before starting each dinutuximab beta infusion. It is recommended that antihistamine administration be repeated every 4 to 6 hours as required during dinutuximab infusion.

Patients should be closely monitored for anaphylaxis and allergic reactions, particularly during the first and second treatment course.

Treatment of hypersensitivity reactions
Intravenous antihistamine, epinephrine (adrenaline) and prednisolone for intravenous administration should be immediately available at the bedside during administration of dinutuximab beta to manage life-threatening allergic reactions. It is recommended that treatment for such reactions include prednisolone administered by intravenous bolus, and epinephrine administered by intravenous bolus every 3 to 5 minutes as necessary, according to clinical response. In case of bronchial and/or pulmonary hypersensitivity reaction, inhalation with epinephrine (adrenaline) is recommended and should be repeated every 2 hours, according to clinical response.

Capillary leak syndrome (CLS)
CLS is characterised by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. 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
Eye disorders 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 (i.e. subtotal vision loss per toxicity scale). In case of any eye problems, patients should be referred promptly to an ophtalmology specialist.

Peripheral neuropathy
Occasional occurrences of peripheral neuropathy have been reported with Qarziba. 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.

Central neurotoxicity
Central neurotoxicity has been reported following treatment with Qarziba. If central neurotoxicity occurs the infusion should be interrupted immediately and the patient treated symptomatically, other influencing factors such as active infection, metastatic spread of neuroblastoma to CNS, neurotoxic concomitant medications should be ruled out.

Treatment with dinutuximab beta should be permanently discontinued following the occurrence of severe neurotoxicity that includes grade 3 or 4 central neurotoxicity with substantial prolonged neurological deficit without any detectable reason, recurrent grade 1-3 neurotoxicity and/or permanent neurological deficit and all grades of posterior reversible encephalopathy syndrome and transverse myelitis.

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 of haematologic toxicities has been reported with Qarziba, 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.

Atypical haemolytic uraemic syndrome
Atypical haemolytic uraemic syndrome (aHUS) has been reported in patients who received dinutuximab beta, in some cases with fatal outcome. Signs and symptoms of aHUS should be monitored for. If aHUS is diagnosed, prompt treatment is required and dinutuximab beta should be permanently discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been 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
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.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data on pregnant women. No animal data are available on teratogenicity or embryotoxicity. Dinutuximab beta target (GD2) is expressed on neuronal tissues, especially during embryofetal development, and may cross the placenta; therefore, Qarziba may cause fetal harm when administered to pregnant women.

Qarziba should not be used during pregnancy.

Breast-feeding
There are no data on lactating women. It is unknown whether dinutuximab beta is excreted in human milk. Breast-feeding should be discontinued during treatment with Qarziba and for 6 months after the last dose.

Fertility
The effects of dinutuximab beta on fertility in humans are unknown. In animals, dedicated fertility studies have not been conducted, but no adverse effects on reproductive organs were observed in toxicity studies performed in Guinea pig and cynomolgous monkey.

Qarziba 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.

4.7 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.

4.8 Undesirable effects

Summary of the safety profile
The safety of dinutuximab beta has been evaluated in 791 patients with high-risk and relapsed/refractory neuroblastoma, who received it as a continuous infusion (212) or as repeated daily infusions (416). It was combined with 13-cis retinoic in most patients and with IL-2 in 307 patients.

The most common adverse reactions were pyrexia (86%) and pain (57%) that occurred despite analgesic treatment. Other frequent adverse reactions were hypersensitivity (74.1%), vomiting (55%), diarrhoea (52%), capillary leak syndrome (36%), anaemia (49%), neutropenia (46%), thrombocytopenia (42%) and hypotension (41%).

Tabulated list of adverse reactions
Adverse reactions reported in clinical trials and post-marketing are listed by system organ class and by frequency and summarised in the table below. These adverse reactions are presented by MedDRA system organ class and frequency. Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Not known
Infections and infestations	infection (including pneumonia, skin infection, herpes virus infection, myelitis, encephalomyelitis), device related infection	sepsis		
Blood and lymphatic system disorders	anaemia, leukopenia, neutropenia, thrombocytopenia	lymphopenia	disseminated intravascular coagulation, eosinophilia	Atypical haemolytic uraemic syndrome
Immune system disorders	hypersensitivity, cytokine release syndrome	anaphylactic reaction	serum sickness	
Metabolism and nutrition disorders	fluid retention	decreased appetite, hypoalbuminaemia, hyponatraemia, hypokalaemia, hypophosphataemia, hypomagnesaemia, hypocalcaemia, dehydration		
Psychiatric disorders		agitation, anxiety		
Nervous system disorders	headache	peripheral neuropathy, seizure, paraesthesia, dizziness, tremor	intracranial pressure increased, posterior reversible encephalopathy syndrome	
Eye disorders	mydriasis, pupillotonia, eye oedema (eyelid, periorbital)	ophthalmoplegia, papilloedema, accommodation disorder, blurred vision, photophobia		
Cardiac disorders	tachycardia	cardiac failure, left ventricular dysfunction, pericardial effusion		
Vascular disorders	hypotension, capillary leak syndrome	hypertension	hypovolaemic shock, veno-occlusive disease	
Respiratory, thoracic and mediastinal disorders	hypoxia, cough	bronchospasm, dyspnoea, respiratory failure, lung infiltration, pulmonary oedema, pleural effusion, tachypnoea, laryngospasm		

System organ class	Very common	Common	Uncommon	Not known
Gastrointestinal disorders	vomiting, diarrhoea, constipation, stomatitis	nausea, lip oedema, ascites, abdominal distension, ileus, dry lips	enterocolitis	
Hepatobiliary disorders			hepatocellular injury	
Skin and subcutaneous tissue disorders	pruritus, rash, urticaria	dermatitis (including exfoliative), erythema, dry skin, hyperhidrosis, petechiae, photosensitivity reaction		
Musculoskeletal and connective tissue disorders		muscle spasms		
Renal and urinary disorders		oliguria, urinary retention, hyperphosphaturia, haematuria, proteinuria	renal failure	
General disorders and administration site conditions	pyrexia, chills, pain*, peripheral oedema, face oedema	injection site reaction		
Investigations	increased weight, increased transaminases, increased gamma glutamyltransferase, increased blood bilirubin, increased blood creatinine	decreased weight, decreased glomerular filtration rate, hypertriglyceridaemia, prolonged activated partial thromboplastin time, prolonged prothrombin time, prolonged thrombin time		

*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.

Description of selected adverse reactions

Hypersensitivity
The most frequent hypersensitivity reactions included hypotension (42.2%), urticaria (7%) and bronchospasm (1%). Cytokine release syndrome was also reported in 32% of the patients. Serious anaphylactic reactions occurred in 3.5% of the patients.

Pain
Pain typically occurs during the first infusion of dinutuximab beta and decreases over the treatment courses. Most commonly, patients reported abdominal pain, pain in the extremities, back pain, chest pain, or arthralgia.

Capillary leak syndrome (CLS)
Overall, 10% of CLS were severe (grade 3-4) and their frequency decreased over the treatment courses.

Eye problems
These included impaired visual accommodation that is correctable with eye glasses, as well as mydriasis (2%), periorbital oedema and eyelid oedema (3%), blurred vision (3%) or photophobia (3%), which were usually reversible after treatment discontinuation. Severe eye disorders were also reported including ophthalmoplegia (2%) and optic atrophy.

Peripheral neuropathy
Both motor and sensory peripheral neuropathies have been reported, overall in 9% of the patients. Most events were of grade 1-2 and resolved.

Central Neurotoxicity
Reports of central neurotoxicity and severe neurotoxicity have been received including posterior reversible encephalopathy syndrome (0.7%) and seizures (1.7%).

Safety profile with and without IL-2
The combination of Qarziba with IL-2 increases the risk of adverse drug reactions compared to Qarziba without IL-2, especially for pyrexia (94% vs. 80%), CLS (45% vs. 20%), pain related to dinutuximab beta (70% vs. 62%), hypotension (44% vs. 27%), and peripheral neuropathy (9% vs. 5%), respectively.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose

No cases of dinutuximab beta overdose have been reported.
In the case of overdose, patients should be carefully observed for signs or symptoms of adverse reactions and supportive care administered, as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01FX06

Mechanism of action
Dinutuximab beta is a chimeric monoclonal IgG1 antibody that is specifically directed against the carbohydrate moiety of disialoganglioside 2 (GD2), which is overexpressed on neuroblastoma cells.

Pharmacodynamic effects
Dinutuximab beta has been shown *in vitro* to bind to neuroblastoma cell lines known to express GD2 and to induce both complement dependent cytoxicity (CDC) and antibody dependent cell-mediated cytoxicity (ADCC). In the presence of human effector cells, including peripheral blood nuclear cells and granulocytes from normal human donors, dinutuximab beta was found to mediate the lysis of human neuroblastoma and melanoma cell lines in a dose-dependent manner. Additionally, *in vivo* studies demonstrated that dinutuximab beta could suppress liver metastasis in a syngeneic liver metastasis mouse model.

Neurotoxicity associated to dinutuximab beta is likely due to the induction of mechanical allodynia that may be mediated by the reactivity of dinutuximab beta with the GD2 antigen located on the surface of peripheral nerve fibres and myelin.

Clinical efficacy

The efficacy of dinutuximab beta has been evaluated in a randomised controlled trial comparing the administration of dinutuximab beta with or without IL-2 in the first-line treatment of patients with high-risk neuroblastoma and in two single-arm studies in the relapsed/refractory setting.

Relapsed and refractory patients

In a compassionate use programme (study 1), 54 patients received 10 mg/m^2/day dinutuximab beta given by continuous 10-day intravenous infusion in a 5-week treatment course, concurrently with subcutaneous IL-2 (6×10^6 IU/m^2/day given on days 1-5 and 8-12 of each course) and followed by oral 13-cis-RA treatment (160 mg/m^2/day for 14 days per course). The same treatment regimen was used in a Phase II study (study 2), which enrolled 44 patients.

Overall, these 98 patients had primary refractory neuroblastoma (40) or relapsed neuroblastoma (49) with an additional 9 patients enrolled after first-line therapy. These were 61 boys and 37 girls, aged 1 to 26 years (median 5 years). Most had an initial diagnosis of INSS stage 4 disease without MYCN amplification (16% of the subjects had MYCN amplified tumours and in 14% this information was missing). Most patients with relapsed disease were enrolled after their first relapse and the median time from diagnosis to first relapse was about 14 months. Treatment of disease before immunotherapy included intensive chemotherapy regimen followed by autologous stem cell transplantation (ASCT), radiotherapy, and surgery. At baseline, 72 patients had measurable disease and 26 patients had no detectable disease.

Survival rates (event-free survival, overall survival) are presented by type of disease in Table 1. The overall response rate (complete response plus partial response) in patients with evidence of disease at baseline was 36% (95% confidence interval [25; 48]) and was more favourable in patients with refractory disease (41% [23; 57]) than in patients with relapsed disease (29% [15; 46]).

Table 1: Event-free survival (EFS) and overall survival (OS) rates in relapsed and refractory patients

		Study 1 N=29	**Study 2 N=19**	**Study 1 N=15**	**Study 2 N=25**
		Relapsed patients		**Refractory patients**	
EFS	1 year	45%	42%	58%	60%
	2 years	31%	37%	29%	56%
OS	1 year	90%	74%	93%	100%
	2 years	69%	42%	70%	78%

First-line patients who received autologous stem cell transplantation

In study 3, patients with high-risk neuroblastoma were enrolled after they had received induction chemotherapy and achieved at least a partial response, then myeloablative therapy and stem cell transplantation. Patients with progressive disease were excluded. Dinutuximab beta was administered at a dose of 20 mg/m^2/day on 5 consecutive days, given by 8-hour intravenous infusion in a 5-week treatment course, and was combined with 13-cis-RA and with or without additional subcutaneous IL-2 at the same posologies as in the previous studies.

A total of 370 patients were randomised and received treatment. These included 64% male and 36% female patients with a median age of 3 years (0.6 to 20); 89% had a tumour INSS stage 4 and MYCN amplification was reported in 44% of the cases. The primary efficacy endpoint was 3-year EFS and secondary endpoint was OS. EFS and OS rates are presented in Tables 2 and 3 according to the evidence of disease at baseline.

For patients without evidence of disease at baseline, addition of IL-2 did not improve EFS and OS.

Table 2: Event-free survival (EFS) and overall survival (OS) rates [95% confidence interval] in patients without evidence of disease at baseline (complete response to initial treatment)

Efficacy	**without IL-2 N=104**			**with IL-2 N=107**		
	1 year	**2 year**	**3 year**	**1 year**	**2 year**	**3 year**
EFS	77% [67; 84]	67% [57; 75]	62% [51; 71]	73% [63; 80]	70% [60; 77]	66% [56; 75]
OS	89% [81; 94]	78% [68; 85]	71% [60; 80]	89% [81; 93]	78% [68; 85]	72% [61; 80]

Table 3: Event-free survival (EFS) and overall survival (OS) rates [95% confidence interval] in patients with evidence of disease at baseline (no complete response to initial treatment)

Efficacy	**without IL-2 N=73**			**with IL-2 N=76**		
	1 year	**2 year**	**3 year**	**1 year**	**2 year**	**3 year**
EFS	67% [55; 76]	58% [45; 69]	46% [33; 58]	72% [60; 81]	62% [49; 72]	54% [41; 65]
OS	83% [72; 90]	73% [61; 82]	54% [40; 66]	86% [75; 92]	71% [58; 80]	63% [50; 74]

Immunogenicity

In 3 clinical studies the appearance of ADA was 57.1% (112/196) in subjects being classed as ADA positive on the basis of having at least one measurable ADA response over the course of treatment. Neutralising antibody activity was observed in 63.5% (54/85) of the ADA-positive subjects in 2 studies. There was an overall trend of lower dinutuximab beta concentration with increasing ADA titre, (low, medium and high). In 16.8% of subjects (33/196) with a high ADA titre, the reduction in dinutuximab beta concentration impacted on pharmacodynamic responses. Based on the available data it is not possible to determine a quantitative association between ADA titre and impact on efficacy.

No clear associations between ADA response and relevant Selected Safety Events were observed.

From an efficacy and safety perspective, there is no rationale for adjusting or stopping treatment on the basis of measured ADA responses.

5.2 Pharmacokinetic properties

Dinutuximab beta has been investigated using short-term infusions (STI - five days of eight-hour infusions at 20 mg/m^2/day) and long-term infusions (LTI - ten days of continuous infusion at 100 mg/m^2).

Absorption

Dinutuximab beta is administered as an intravenous infusion. The maximum concentration (mean (± SD)) at the end of the long-term infusion was 11.2 (± 3.3) mg/L. Other routes of administration have not been investigated.

Distribution

The population mean (±SD) estimate for the central volume of distribution was 2.04 (± 1.05) L and for the peripheral volume of distribution 2.65 (±1.01) L.

Biotransformation
The metabolism of dinutuximab beta has not been investigated. As a protein, dinutuximab beta is expected to be metabolised to small peptides and individual amino acids by ubiquitous proteolytic enzymes.

Elimination
The clearance after the LTI was 0.72 (± 0.24) L/d/m^2. The accumulation ratio for C_{max} was 1.13 (± 0.54) after 5 LTI courses (mean (±SD)). The apparent terminal elimination $t_{1/2}$ was 8.7 (± 2.6) days (mean (± SD)). The clearance of dinutuximab beta increased in the presence of high anti-drug antibody titres regardless of neutralising activity. (See Immunogenicity in Section 5.1).

Linearity/non-linearity
Variations in dose of the first infusion in Study 2 revealed a dose-proportional increase in exposure (AUC∞) up to the recommended dose of 100 mg/m^2 per course for 10 days.

Specific populations
The age of patients ranged from 1 to 27 years (median 6 years). Body weight ranged from 9 to 75 kg (median 18.5 kg) and body-surface area ranged from 0.44 to 1.94 m^2 (median 0.75 m^2). A two-compartment population-PK model with first-order elimination from the central compartment was developed using the data from 224 patients in four studies (STI 30 patients, LTI 194 patients). Volume and clearance parameters increased across the ranges with increasing body size. Body weight and ADA titre were covariates for clearance while body weight, age and IL-2 co-administration were covariates for volume of distribution.

Age
The population pharmacokinetic analyses showed comparable exposure to dinutuximab beta in patients of all ages studied when dosed at 100 mg/m^2.

Gender
The population pharmacokinetic analysis with 89 female (40%) and 135 male (60%) patients showed no clinically meaningful effect of gender on dinutuximab beta pharmacokinetics.

Race
Since the PK analysis population was predominantly Caucasian (92.9%) race was not formally examined as a potential PK covariate.

Weight
Dosing on the basis of body surface area provides consistent exposure across populations.

Renal impairment
No formal studies have been conducted in patients with renal impairment. Renal function was not a significant covariate in population pharmacokinetic analyses that included patients with normal renal function and mild renal impairment.

Hepatic impairment
No formal studies have been conducted in patients with hepatic impairment. Subjects with ALT >3x ULN had comparable pharmacokinetics as subjects with ALT≤3xULN.

5.3 Preclinical safety data

General toxicology
Dinutuximab beta has been administered to male and female juvenile Guinea pigs, as well as male and female young cynomolgus monkeys, as repeat-dose regimens that exceeded the recommended clinical dose. Findings of note included changes (decrease) in thymus weight as well as bone marrow changes (atrophy affecting myeloid and erythroid precursor cell lines). The bone marrow changes were slight to severe and recovered after cessation of dosing. No effects on cardiovascular functions (ECG, blood pressure) were observed in monkeys.

Other
No non-clinical studies to evaluate the potential of dinutuximab beta to cause carcinogenicity, genotoxicity or developmental and reproductive toxicity have been conducted. In the repeat-dose toxicity studies in Guinea pigs and cynomolgus monkeys, no adverse effects of dinutuximab beta were observed on reproductive organs at exposure levels above clinical levels.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Histidine
Polysorbate 20
Water for injections
Hydrochloric acid (for pH adjustment)

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
The expiry date of the product is indicated on the packaging materials.

Diluted solution (solution for infusion)
Chemical and physical in-use stability has been demonstrated for up to 48 hours at 25 °C (50 mL syringe) and for up to 7 days at 37 ºC (250 mL infusion bag).

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.

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

Clear Type I glass vial (6 mL) with a bromobutyl rubber stopper, containing a minimum extractable volume of 4.5 mL concentrate for solution for infusion.

Each carton contains 1 vial.

6.6 Special precautions for disposal and other handling

The solution for infusion must be prepared under aseptic conditions. The solution must not be exposed to direct sunlight or heat.

The patient specific daily dose of Qarziba is calculated based on body surface area (see section 4.2). Qarziba should be diluted aseptically to the patient specific concentration/dose with sodium chloride 9 mg/mL (0.9%) solution for infusion containing 1% human albumin (e.g. 5 mL of human albumin 20% per 100 mL sodium chloride solution).

For continuous infusions, the solution for infusion can be prepared freshly on a daily basis, or sufficient for up to 5 days of continuous infusion. The daily dose is 10 mg/m^2. The amount of solution to be infused per day (within a treatment course of 10 consecutive days) should be 48 mL; with 240 mL for a 5-day dose. It is recommended to prepare 50 mL solution in a 50 mL syringe, or 250 mL in an infusion bag suitable for the employed infusion pump, i.e. an overfill of 2 mL (syringe) or 10 mL (infusion bag) to allow for dead volumes of the infusion systems.

For repeated daily 8-hour infusions, the daily dose is 20 mg/m^2 and the calculated dose should be diluted in 100 mL sodium chloride 9 mg/mL (0.9%) containing 1% human albumin.

The solution for infusion should be administered via a peripheral or central intravenous line. Other intravenously co-administered agents should be delivered via a separate infusion line. The container should be inspected visually for particulates prior to administration. It is recommended that a 0.22 micrometre in-line filter is used during infusion.

For continuous infusions, any medical device suitable for infusion at a rate of 2 mL per hour can be used, e.g. syringe infusion pumps/infusors, electronic ambulatory infusion pumps. Note that elastomeric pumps are not considered suitable in combination with in-line filters.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Recordati Netherlands B.V.
Beechavenue 54,
1119PW Schiphol-Rijk
Netherlands

8. LICENSE HOLDER

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Revised in December 2025

Qarziba-SPC-1225-V1