swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Qarziba

International non-proprietary name: dinutuximab beta
Pharmaceutical form: concentrate for solution for infusion
Dosage strength(s): 20.25 mg/4.5 mL,
Route(s) of administration: intravenous use
Marketing authorisation holder: Medius AG
Marketing authorisation no.: 67463
Decision and decision date: approved on 18.04.2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

13-cis RA	13-cis retinoid acid, isotretinoin
1L	First-line
2L	Second-line
ADA	Anti-drug antibody
AE	Adverse event
API	Active pharmaceutical ingredient
CI	Confidence interval
DB	Dinutuximab beta
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HDC/ASCR	High-dose chemotherapy/autologous stem cell rescue
HPLC	High-performance liquid chromatography
HR-NB	High-risk neuroblastoma
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IL-2	Interleukin-2
INSS	International Neuromblastoma Staging System
LoQ	List of Questions
MAH	Marketing Authorisation Holder
MYCN	v-myc myelocytomatosis viral related oncogene
NB	Neuroblastoma
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
R/R	Relapsed/refractory
SAE	Serious adverse event
SCT	Stem cell transplantation
SIOPEN	International Society of Pediatric Oncology Europe Neuroblastoma Group
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for dinutuximab beta in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 11 September 2019.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Article 9a TPA. Within the course of the assessment, the application was switched to an authorisation without special conditions (see section 6.5).

2.2 Indication and dosage

2.2.1 Requested indication

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 a 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).

2.2.2 Approved indication

Neuroblastoma front-line maintenance treatment population
Qarziba is used in combination with isotretinoin for the treatment of high-risk neuroblastoma in paediatric 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 (see "Clinical Efficacy").

Neuroblastoma relapsed or refractory treatment population
Qarziba is used in combination with isotretinoin or as monotherapy for the treatment of paediatric patients aged 12 months and above with a history of relapsed or refractory neuroblastoma, with or without residual disease, who have no actively progressing disease (see "Clinical Efficacy").

2.2.3 Requested dosage

Summary of the requested standard dosage:
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 intravenous infusion over the first 10 days of each course (a total of 240 hours) at the daily dose of 10 mg/m^2 (at a rate of 2 mL per hour (48 mL per day)), or
- 5 daily intravenous infusions of 20 mg/m^2 administered over 8 hours, on the first 5 days of each course (at a rate of approximately 13 mL per hour).

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).

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	11 May 2023
Formal control completed	15 May 2023
List of Questions (LoQ)	19 July 2023
Response to LoQ	17 October 2023
Preliminary decision	7 December 2023
Response to preliminary decision	11 February 2024
Labelling corrections	23 February 2024
Response to labelling corrections	24 February 2024
Final decision	18 April 2024
Decision	approval

3 Medical context

Neuroblastoma (NB) is the most frequently occurring extracranial childhood tumour. It is classified as an embryonal neuroendocrine tumour, originating from neural crest progenitor cells[1].
More than 650 cases are diagnosed each year in the United States (US). The incidence is 10.2 cases per 1 million per year in children younger than 15 years. About 37% of patients are diagnosed as infants, and 90% are younger than 5 years at diagnosis, with a median age at diagnosis of 17 months[2]. Adult-onset neuroblastoma is rare and there is no established therapy for these patients.

Given the wide areas populated by neural crest cells in humans, neuroblastoma can present in the neck, chest, abdomen, or pelvis. As the most frequent site of origin is the adrenal medulla, patients often present with a solid abdominal mass. Tumour behaviour can range from spontaneous regression to widespread dissemination at presentation. With over half of all neuroblastoma patients having hematogenous spread at diagnosis, the disease can involve the bone as well as the bone marrow (56% and 71%, respectively), followed by lymph nodes (31%), and lungs (3%).

The treatment of neuroblastoma is determined based on risk categories. The definition of high-risk neuroblastoma used by the International Society of Pediatric Oncology Europe Neuroblastoma Group (SIOPEN) refers to patients with International Neuroblastoma Staging System (INSS) stage 4 and >12 months of age, and those in INSS stage 2, 3, and 4S with v-myc myelocytomatosis viral related oncogene (MYCN) amplification.
Treatment options for high-risk neuroblastoma (HR-NB) typically include multimodal treatments of surgery, radiation therapy, as well as chemotherapy, including myeloablation followed by stem cell transplantation (SCT), as well as anti-GD2 monoclonal antibodies combined with granulocyte-macrophage colony-stimulating factor (GM-CSF) and 13-cis retinoid acid (13-cis RA, isotretinoin).
SIOPEN recommends that patients with HR-NB in the front-line setting receive maintenance therapy with dinutuximab beta and 13-cis RA following induction chemotherapy, surgery, high-dose chemotherapy/autologous stem cell rescue (HDC/ASCR), and local radiation.
In Switzerland, several chemotherapeutic agents are licensed for the treatment of neuroblastoma. No immunotherapeutic agent is officially authorised in this disease setting and there is an unmet medical need in Switzerland.

[1] Matthay KK et al. Neuroblastoma. Nat Rev Dis Primers. 2016 Nov 10;2:16078
[2] Mahapatra S, Challagundla KB: Neuroblastoma. Treasure Island, FL: StatPearls Publishing LLC, 2022. Available online. Last accessed June 6, 2023; London WB, Castleberry RP, Matthay KK, et al.: Evidence for an age cutoff greater than 365 days for neuroblastoma risk group stratification in the Children's Oncology Group. J Clin Oncol 23 (27): 6459-65, 2005

4 Quality aspects

4.1 Drug substance

Dinutuximab beta is a mouse-human chimeric monoclonal antibody (IgG1,κ) that binds to GD2, a disialoganglioside overexpressed by cells of neuroectodermal origin such as neuroblastoma cells. Dinutuximab beta triggers complement-dependent as well as antibody-dependent cellular cytotoxicity, mediated by recruitment of natural killer cells via the Fc-receptor interaction of the constant region of the heavy chains and finally also leading to target cell lysis. Dinutuximab beta consists of 2 heavy and 2 light chains connected by inter-chain disulfide bonds. Both heavy chains contain 1 oligosaccharide chain in the conserved Fc site (Asn293).
Dinutuximab beta is expressed in a Chinese hamster ovary (CHO) cell line and is manufactured using a fed-batch production process in a production bioreactor. The cell culture fluid is harvested and the antibody is purified by several chromatographic and filtration steps, including virus inactivation and virus removal steps. The drug substance manufacturing process is performed by Rentschler Biopharma SE, Laupheim, Germany. The fermentation and purification process was validated using 4 consecutive batches, demonstrating a consistent manufacturing process that effectively reduces process-related impurities. The characterisation of the physicochemical and biological properties of the drug substance and its impurities were performed using state-of-the-art methods.
The specifications for release include relevant tests and limits, e.g. for description, colour, clarity, identity, several purity/impurity tests (e.g. reduced SDS-PAGE, non-reduced SDS-PAGE, SE-HPLC, CIEX-HPLC), glycan pattern, protein concentration, and potency assays (GD-2-binding activity, CD16-binding activity, and complement dependent cytotoxicity). Specifications are based on clinical data and batch analysis and are in conformance with current compendial or regulatory guidelines. Batch analysis data of development, clinical, and process validation batches were provided. All batch release data comply with the drug product specifications valid at the time of batch release. All specific analytical methods are described and are fully validated.
The drug substance is stored frozen. No changes were observed under the proposed storage conditions. A shelf life of 36 months under long-term (-70±10°C) storage conditions has been accepted.

4.2 Drug product

The finished product Qarziba is available as 20 mg product, which is supplied as sterile liquid in a single-use vial. It is intended for intravenous infusion together with normal saline and 1% human albumin. All excipients used comply with the European Pharmacopoeia.
The finished product manufacturing process consists of aseptic filling, sterile filtration, capping, and inspection steps and is conducted at Patheon Italia S.P.A., Ferentino, Italy. Process validation studies were executed at commercial scale using 4 and 3 validations batches, respectively.
The release and stability specifications include relevant tests and limits, e.g. for appearance, identity, pH, osmolality, purity and impurity tests (reduced SDS-PAGE, non-reduced SDS-PAGE, SE-HPLC, CIEX-HPLC), potency assays (GD-2-binding activity, CD16-binding activity, and complement dependent cytotoxicity), glycan pattern, protein concentration, particles, sterility, and bacterial endotoxins. All specific methods are validated in accordance with ICH guidelines.
Batch analysis data of development, clinical, and process validation batches were provided. All batch release data comply with the drug product specifications valid at the time of batch release.
The drug product is stored in 6 mL Type I clear glass vials at 2-8°C, protected from light. Each vial is closed with a bromobutyl rubber stopper. The stoppered vial is sealed with an aluminium closure with a flip-off button. All components are Ph.Eur. and USP compliant. A shelf life of 48 months has been accepted.

4.3 Quality conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf life of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated and stress

studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk of adventitious agents is minimised.

5 Nonclinical aspects

Regarding the marketing authorisation application for Qarziba (new active substance dinutuximab beta), the Nonclinical Assessment Division conducted an abridged evaluation, which was based on the EMA assessment report of 23 March 2017.
Overall, the submitted nonclinical study package is limited but considered acceptable to support the approval of Qarziba in the proposed indication, also taking into account the clinical experience with the product.
No nonclinical studies to evaluate the potential of dinutuximab beta to cause carcinogenicity, genotoxicity, or developmental and reproductive toxicity have been conducted; this is acceptable based on ICH S6(R1) and ICH S9. Due to its mechanism of action, dinutuximab beta may cause fetal harm and neurotoxic effects. This is mentioned in the information for healthcare professionals; neurotoxic effects were observed with clinical use of dinutuximab beta.

6 Clinical aspects

6.1 Clinical pharmacology

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the EMA. The available assessment reports and associated product information from this authority were used as a basis for the clinical pharmacology evaluation.

For further details concerning clinical pharmacology, see the information for healthcare professionals in the appendix of this report.

6.2 Dose finding and dose recommendation

No proper dose-finding trial was conducted. The first trial (APN-311-101) investigated only 3 treatment cycles (5-day infusion at 10, 20, and 30 mg/m^2/day) in n=15 patients only and without defined timing of efficacy assessments. No concomitant treatment with IL-2 or 13-cis-retinoic acid (13-cis RA) was provided. The second trial (APN311-202) tested only 1 dose of continuous 10-day infusion at 10 mg/m^2/day in n=44 patients.

6.3 Efficacy

The Applicant submitted studies evaluating the use of dinutuximab beta in both patients having received first-line treatment only and patients with relapsed/refractory (R/R) disease.
Since immunotherapy with dinutuximab beta is globally accepted as standard adjuvant immunotherapy for the treatment of paediatric neuroblastoma, controlled studies withholding treatment with dinutuximab beta in the comparator arm were considered ethically not feasible. Thus, no placebo-controlled studies were performed. Historical controls with the known inherent limitations were provided.

Notably, the majority of studies submitted were investigator-initiated trials, in essence representing "research" studies that were not intended to generate confirmatory data for the pursuit of marketing authorisation. The conduct of the studies therefore has limitations in light of the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) standards. The Applicant, however, made an effort to appropriately monitor patient data and collect additional patient information, and has established data quality control for analysis of the data presented in the Marketing Authorisation Application (MAA) and included this information in the submission.

First-line treatment
Study APN311-301/302 is an investigator-initiated, multi-centre, open-label, randomised, controlled Phase 3 trial in high-risk neuroblastoma patients, parts of which are currently still accruing. The study was planned to compare dinutuximab beta (DB) + 13-cis-RA vs. 13-cis-RA monotherapy. Due to upcoming clinical data from study ANBL0032 showing that immunotherapy with dinutuximab together with granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-2, and 13-cis-RA was associated with a significantly improved outcome compared to 13-cis-RA monotherapy in high-risk neuroblastoma patients, the aim of the immunotherapy phase of study APN311-301/302 was revised. The study was amended to the assessment of DB + 13-cis RA + IL-2 vs. DB + 13-cis RA without IL-2. The efficacy analysis included data from 34 patients aged 1.5 years to 11.5 years in the first part of the immunotherapy phase (comparing DB + 13-cis-RA vs. 13-cis-RA mono). The following results for the n=34 patients were considered overall supportive: Event-free survival (EFS), as the primary endpoint, was higher in the concomitant DB treatment arm at 1 year (71% vs 52%), 2 years (64% vs 52%), and 3 years (64% vs 52%). In addition, overall survival (OS) was numerically higher in patients with DB treatment than those without DB treatment at 3 years (71% vs 64%) and at 4 years (48% vs 35%).
The full analysis set of the second part of the immunotherapy phase (comparison of DB + 13-cis-RA +/- IL-2) included 370 patients aged 6-20 years. Three-year EFS in the overall population was 61.2%

in patients receiving IL-2 treatment and slightly lower in patients without IL-2-treatment at 55.4%. No relevant differences between the DB and DB + IL-2 treatment groups were seen for 1-year and 2-year EFS estimates (72.3% vs 72.3% and 63.2 vs 66.3%). The addition of subcutaneous IL-2 to immunotherapy with DB and 13-cis RA did not significantly improve outcomes but increased toxicity (see “Safety”).

Historic control data from an earlier phase of the study were provided for contextualisation. At the start of the high-risk HRNBL1 study, patients were treated with induction and consolidation chemotherapy as well as differentiation therapy with 13-cis-RA, but no DB therapy (period 2002-2009, R1 part). From 2009 onward, patients received immunotherapy with DB in addition to differentiation therapy with 13-cis-RA with or without IL-2 as maintenance therapy (period 2009-2013, R2 part and reported as study APN311-302). Survival data were then compared between patients who were solely part of the R1 randomisation and patients from the more recent part (R2).
In the historic control R1 group, OS was 83% at 1 year, 69% at 2 years, 59% at 3 years, and 50% at 5 years. In the APN311-302 R2 group, OS was 89% at 1 year, 78% at 2 years, 71% at 3 years, and 65% at 5 years. Notably, the historic comparison has inherent limitations so that the true effect size is considered unknown.

Relapsed/refractory treatment
Three main studies were provided for the assessment of patients with relapsed and refractory high-risk neuroblastoma.
Study APN311-202V1/2 was a Phase 1/2 study of dinutuximab beta in combination with subcutaneous aldesleukin (IL-2) in patients with primary refractory or relapsed high-risk neuroblastoma. The first cohort was allocated to receive 10 mg/m² over 10 days (total dose 100 mg/m²) and this dose was considered the suitable dose. Subsequently, only this regimen was tested in the confirmatory phase. Overall, 44 patients (24 dose schedule-finding, 20 confirmatory phase) were analysed. Notably, efficacy parameters were only secondary endpoints.
At the end of treatment, a response was observed in 16/32 patients (50%) with evidence of disease at baseline. Event-free survival (EFS) in the population including relapsed/refractory neuroblastoma was 52.3% at 1 year, 47.4% at 2 years, and 41.1% at 3 years. Overall survival in the population including relapsed/refractory neuroblastoma was 88.6% at 1 year, 62.7% at 2 years, and 54.0% at 3 years. These results were contextualised with historic control data from previous study phases without DB treatment. There was a numerically higher 1 and 2-year OS rate in the APN311-202 cohort compared to the historic cohort.

Additional data were provided for n=54 patients treated within a compassionate use programme (study APN311-303). Prolonged continuous infusion of DB in combination with subcutaneous IL-2 and oral 13-cis-RA was analysed retrospectively. Out of the 54 patients included in the analysis, 30 patients had relapsed disease, 15 patients had refractory disease, and 9 patients were treated with first-line therapy only.
For the total of both studies APN311-303 and 202V1/2, the overall response at the end of treatment was 26/72 (36%; 95%CI [25%, 48%]) in patients with detectable disease, out of whom 9 (13%) had a CR, while disease had progressed in 29/72 patients (40%; 95%CI [19%, 52%]). Overall survival results compared to historic control data provided for contextualisation appeared to be superior in patients treated with DB. However, these results are prone to bias.

Study APN311-202V3 (follow-up study to APN311-202V1/2) was a Phase 1/2 dose schedule-finding study of DB continuous infusion combined with IL-2 in patients with neuroblastoma according to the INSS criteria, who had received at least 1 previous high-dose treatment followed by stem cell rescue after conventional therapy. Patients with actively progressing disease were excluded from the study. Patients were randomly assigned to either the standard arm (IL-2 + DB + 13-cis RA) or the experimental arm (DB + 13-cis RA).
The efficacy population consisted of 150 patients (77 experimental and 73 standard) aged 1-10 years. Only 7.2% of the patients in the standard group completed the 5 cycles without any dose

modifications compared to 52.5% in the experimental group. Refractory disease was reported in 71.6% and 68.3%, respectively.
The hazard ratio of the EFS rates in the experimental group to the standard group was estimated as 1.0666 (90% CI 0.69, 1.56) and no statistically significant difference between the treatment groups could be detected. Kaplan Meier estimated event-free survival after 1 year was 72.7% in the experimental arm and 75.3% in the standard arm. After 3 years, EFS was 59.7% in the experimental arm and 57.1% in the standard arm. No difference was seen in treatment response (complete response/partial response), which was 62.4% (48/77) with DB alone and 57.5% (42/73) with DB + IL-2.
Overall, the study failed to demonstrate superiority for the combination of DB and IL-2. Conversely, however, no non-inferiority can be claimed either, since the study was designed to show superiority.

6.4 Safety

Safety data were presented from 677 patients who received DB treatment in the clinical development programme. The method of adverse event (AE) collection varied across studies.

The most frequent treatment-emergent adverse events (TEAEs) were related to the MedDRA system organ classes gastrointestinal disorders, general disorders and administration site conditions, investigations, skin and subcutaneous tissue disorders, and respiratory, thoracic, and mediastinal disorders. The most frequent TEAE was pyrexia. Please refer to the information for healthcare professionals for further details.
The most frequent severe (grade 3/4) AEs were pain, abnormal haematological and liver function tests, pyrexia, infections, allergic reactions, and capillary leak syndrome.
Five deaths in the safety population were considered to be possibly treatment-related as they occurred as a result of an AE that started under therapy. Two deaths occurred in study APN311-302 due to capillary leak syndrome and acute respiratory distress syndrome, which may have been the result of an anaphylactic reaction. One death occurred in study APN311-201 (herpes encephalitis) and 1 in study APN311-202V1/2 (septic shock). In study APN311-202V3 there was 1 death due to respiratory distress and secondary pulmonary alveolar proteinosis.
The most frequent serious adverse events (SAEs) were infections, pyrexia, hypotension, and thrombocytopenia. Study APN311-302 allowed comparison of the safety profile of DB (+13-cis RA) alone and combined with IL-2. SAEs were reported more frequently in patients receiving IL-2 compared to those not receiving IL-2: 46% vs 27%. In study APN311-202V3, SAEs were less common without IL-2 (DB: 36.3% vs. DB+IL-2: 59.0%). The greatest difference for any preferred term was capillary leak syndrome, with no SAE in the DB group versus 10 subjects with SAE (12.0%) in the DB+IL-2 group.
Please refer to the information for healthcare professionals for further details on adverse events of interest.

6.5 Final clinical benefit-risk assessment

Neuroblastoma (NB) is the most frequently-occurring extracranial childhood tumour. It is classified as an embryonal neuroendocrine tumour, originating from neural crest progenitor cells. The incidence is 10.2 cases per 1 million per year in children younger than 15 years, and 90% of patients are younger than 5 years at diagnosis. The treatment of neuroblastoma is determined based on risk categories. Patients most at risk for disease progression and mortality are older than 18 months, have metastatic disease or localised disease with unfavourable biology such as MYCN amplification, or have unfavourable histology. For children with high-risk neuroblastoma treated with myeloablative chemotherapy and SCT, 5-year EFS and OS rates were 35% and 40% when using a busulfan/melphalan-containing conditioning regimen in the pre-immunotherapy period[3].

[3] Proust-Houdemont S. et al. Busulfan-melphalan in high-risk neuroblastoma: the 30-year experience of a single institution. Bone Marrow Transplant. 2016 Aug;51(8):1076-81

Currently, SIOPEN recommends that patients with HR-NB in the front-line setting receive maintenance therapy with dinutuximab beta (DB) and 13-cis-retinoic acid (13-cis RA) following induction chemotherapy, surgery, HDC/ASCR, and local radiation. Dinutuximab beta is a GD2 inhibitor that binds specifically to the disialoganglioside GD2. This glycolipid is expressed on neuroblastoma cells and induces cell lysis of GD2-expressing cells via complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC).
As anti-GD2 became standard practice after the publication of the ECOG trial in 2009 [4], conducting randomised controlled trials became practically impossible.
The studies submitted investigated the use of DB in the first-line (APN311-301/302) and in the R/R setting (APN311-201, -202V1/2, -202V3, -303). Studies APN311-201 and -301/302 evaluated administration as a short-term (8 hours) infusion for 5 days, and studies APN311-202V1/2 and -303 evaluated DB administered with a novel treatment schedule as a continuous 10-day infusion. No direct comparison of the 2 schedules is available and no superiority can be claimed for either of the schedules. Currently, both administration schedules are included in the label and it is up to the physician to decide which schedule to choose.

None of the submitted studies included a comparative arm with patients not receiving dinutuximab beta, with the exception of the APN311-301 study. In the first-line setting there is preliminary evidence from n=34 patients treated with DB with 13-cis RA compared to 13-cis RA monotherapy (APN311-301), with increased survival rates in the combination arm. However, the study was closed due to emerging scientific evidence of the improved outcome of GD2-directed immunotherapy in high-grade NB, and the interpretability of the results is limited due to the small number of patients.
The subsequent randomised controlled trial (APN311-302) investigating the effect of interleukin-2 (IL-2) in addition to DB and 13-cis RA in the first-line setting showed similar event-free survival (EFS) results in both treatment arms. The results were contextualised with historic control data from an earlier cohort of study HRNBL1, of which study APN311-302 was part, treating patients with induction and consolidation chemotherapy as well as differentiation therapy with 13-cis-RA but no DB therapy. Even though the historic comparison has inherent limitations, the difference in OS is considered clinically meaningful.

The response rates observed in the studies addressing the relapsed/refractory setting varied between 26.5% and 62.4%. EFS at 1 year was about 52-73% and at 3 years 41-60%. Contextualisation with historic control data is prone to bias; however, the comparisons provided pointed at least overall in the same direction, showing a numerically longer overall survival in patients treated additionally with DB.

Overall, while none of these outcomes on its own would be sufficient to establish efficacy, given the totality of the evidence provided (early tumour response to treatment and long-term survival data), the efficacy of dinutuximab beta was considered acceptable for paediatric patients, even though the exact effect size is not fully known.

DB has well-known severe toxicities, the management of which requires a considerable level of medication. Pain, hypersensitivity reactions, and capillary leak syndrome are major adverse events associated with anti-GD2 therapies.
The evaluation of safety was hampered by the absence of control arms without DB in the trials and by the heterogeneity of data collection across the academic trials. However, the safety profile of anti-GD2 monoclonal antibodies is already known to a large extent and the available data are in line with current knowledge.

Overall, the totality of the evidence provided for efficacy of dinutuximab beta is acceptable in the population of paediatric patients with high-grade neuroblastoma, even though the exact effect size is not fully known. There are no studies ongoing, which would provide additional confirmatory data.

[4] Yu AL et al.: Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med 363 (14): 1324-34, 2010

Taking into consideration the existing medical need and the established use as standard treatment in clinical practice, the overall benefit-risk ratio is considered positive for an authorisation of dinutuximab beta for paediatric patients with high-grade neuroblastoma both in the 1L/maintenance setting and the R/R setting. The ongoing PASS study will be required as a post-marketing requirement.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Qarziba was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Qarziba®

Composition

Active substances

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

Excipients

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

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion
1 mL of concentrate contains 4.5 mg dinutuximab beta.
Each vial contains 20.25 mg dinutuximab beta in 4.5 mL.

Indications/Uses

Neuroblastoma Front Line Maintenance Treatment Population

Qarziba is used in combination with isotretinoin in for the treatment of high-risk neuroblastoma in paediatric 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 (see “Clinical Efficacy”).

Neuroblastoma Relapsed or refractory Treatment Population

Qarziba is used in combination with isotretinoin or as monotherapy for the treatment of paediatric patients aged 12 months and above with history of relapsed or refractory neuroblastoma, with or without residual disease, who have no actively progressing disease (see “Clinical Efficacy”).

Dosage/Administration

Qarziba is restricted to hospital-use only. The use of Qarziba must be carried out in a medical facility where resources for effective resuscitation can be immediately utilized, under the direct supervision of a physician experienced in the use of oncological therapies.

Before each administration of Qarziba, premedication with an anti-allergic agent and pretreatment with gabapentin should always be performed. In addition, the instructions for concomitant medication must be observed (see "Dosage/Application - route of administration" and "Warnings and precautions").
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

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

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 adjustment

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%.

Adverse reaction	Severity	Treatment modification
		After resolution, resume infusion at original rate.
Hypersensitivity reaction (including cytokine release syndrome)	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 (including cytokine release syndrome)	e.g. bronchospasm, angioedema	Interrupt infusion immediately and treat appropriately (see section “Warnings and precautions”). Resume treatment for subsequent courses. Permanently discontinue in case of grade 3 or 4 anaphylaxis
Capillary leak syndrome		Interrupt infusion and administer supportive measures. Resume at 50% rate if ADR resolves or improves to Grade 1 – 2. Permanently discontinue in case of recurrent or grade 4 capillary leak syndrome (requires ventilator support).
Central neurotoxicity		Interrupt infusion immediately, rule out other influencing factors and treat appropriately. Treatment with dinutuximab beta should be permanently discontinued following the occurrence of severe neurotoxicity.

Adverse reaction	Severity	Treatment modification
		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.
Neurological disorders of the eye		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 ophthalmology specialist.
Peripheral neuropathy		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.

Moreover, treatment with Qarziba should be permanently discontinued if the following toxicities occur:

- 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

Patients with renal and/or hepatic disorders

There are no data in patients with renal and hepatic impairment (see section “Pharmacokinetics”).

Elderly patients

There are no data in elderly patients (see section “Pharmacokinetics”).

Paediatric population - Children and adolescents

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

Mode 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 “Instructions for handling”).
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 “Warnings and precautions”).

For instructions on dilution of the medicinal product before administration, see section “Instructions for handling”.

Pre- and Co-medication:

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 gabapentin, 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 require 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 continuous 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 tramadol may be administered.

Anti-allergic 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.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section "Composition".
Acute grade 3 or 4, or extensive chronic graft-versus-host disease (GvHD)

Warnings and precautions

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 (see section dosage/administration).

Hypersensitivity reactions (including cytokine release syndrome)

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. 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. 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. (see section dosage/administration)

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 (see section dosage/administration).

Neurological disorders of the eye

Eye disorders (including dilated, unequal or fixed pupils, accommodation disorders, blurred or impaired vision or photophobia) may occur as dinutuximab beta binds to optic nerve cells (see section dosage/administration).

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 (see section dosage/administration).

Central neurotoxicity

Central neurotoxicity has been reported following treatment with Qarziba. The potential reported symptoms are cytotoxic brain stem oedema, demyelination, transverse myelitis, demyelinating neuropathy, PRES (posterior reversible encephalopathy syndrome), seizures, mood disturbances, photophobia, toxic demyelinating encephalopathy (paresis and coma), and CNS inflammatory lesions). 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 (see section dosage/administration).

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. Please monitor patients closely for signs and symptoms of systemic infections.

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. Monitor peripheral blood counts closely during therapy with Qarziba.

Laboratory abnormalities

Treatment with Qarziba leads to decrease in white blood cells, red blood cells and platelets and transient liver toxicity, which fully recover by the end of treatment. Regular monitoring of liver function and electrolytes is recommended.

Interactions

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.

Pregnancy, lactation

Women of childbearing potential / Contraception

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.

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 dinutuximab beta may cross the placenta; therefore, Qarziba may cause fetal harm when administered to pregnant women.
Qarziba should not be used during pregnancy.

Lactation

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 cynomolgus monkey.

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.

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 acid 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 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) and uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The type of adverse reactions seen in the post-

marketing setting is consistent with the reactions seen in clinical trials.

System organ class	Very common	Common	Uncommon
Infections and infestations	infection (including pneumonia, skin infection, herpes virus infection, myelitis, encephalomyelitis) (67%)	sepsis, device related infection	
Blood and lymphatic system disorders	Anaemia (49%), leukopenia (40%), neutropenia (46%), thrombocytopenia (42%)	lymphopenia	disseminated intravascular coagulation, eosinophilia
Immune system disorders	Hypersensitivity (74%), cytokine release syndrome (32%)	anaphylactic reaction	serum sickness
Metabolism and nutrition disorders		decreased appetite, hypoalbuminaemia, hyponatraemia, hypokalaemia, hypophosphataemia, hypomagnesaemia, hypocalcaemia, dehydration, fluid retention	
Psychiatric disorders		agitation, anxiety	
Nervous system disorders	Headache (10%)	peripheral neuropathy, seizure, paraesthesia, dizziness, tremor	intracranial pressure increased, posterior reversible encephalopathy syndrome
Eye disorders		ophthalmoplegia, papilloedema, accommodation disorder, blurred vision, photophobia, mydriasis, pupillotonia, eye oedema (eyelid, periorbital)	
Cardiac disorders	Tachycardia (23%)	cardiac failure, left ventricular dysfunction, pericardial effusion	
Vascular disorders	Hypotension (41%), capillary leak syndrome (36%)	hypertension	hypovolaemic shock, veno-occlusive disease
Respiratory, thoracic and mediastinal disorders	Hypoxia (13%), cough (33%)	bronchospasm, dyspnoea, respiratory failure, lung infiltration, pulmonary oedema, pleural effusion, tachypnoea, laryngospasm	

System organ class	Very common	Common	Uncommon
Gastrointestinal disorders	Vomiting (55%), diarrhoea (52%), constipation (41%),	nausea, lip oedema, ascites, abdominal distension, ileus, dry lips, stomatitis	enterocolitis
Hepatobiliary disorders			hepatocellular injury
Skin and subcutaneous tissue disorders	Pruritus (25%), rash (16%)	dermatitis (including exfoliative), erythema, dry skin, hyperhidrosis, petechiae, photosensitivity reaction, urticaria	
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 (86%), pain* (57%), face oedema (13%)	injection site reaction, peripheral oedema, chills	
Investigations	increased weight (23%), increased transaminases (60%), increased gamma glutamyltransferase (16%), increased blood creatinine (11%)	decreased weight, decreased glomerular filtration rate, hypertriglyceridaemia, prolonged activated partial thromboplastin time, prolonged prothrombin time, prolonged thrombin time, increased blood bilirubin	

* 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 and additional information

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 suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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.

Properties/Effects

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.

Pharmacodynamics

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 males and 37 females, 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 evaluable patients was 36% in Study 1.

Table 1: Event-free survival (EFS) and overall survival (OS) rates

	Study 1 N=54		**Study 2 N=44**	
	1 year	**2 years**	**1 year**	**2 years**

EFS	53%	34%	53%	47%
OS	93%	75%	89%	63%

Relapsed and refractory patients – IL-2 randomisation

In Study 4 (amendment to Study 2, Phase II), 82 patients received 10 mg/m^2/day dinutuximab beta given by continuous 10-day intravenous infusion with subcutaneous IL-2 (6×10^6 IU/m²/day given on days 1-5 and 8-12 of each course) (Standard Arm) and 81 patients received 10 mg/m²/day dinutuximab beta given by continuous 10-day intravenous infusion without IL-2 (Experimental Arm) over a 5-week treatment course. The treatment with dinutuximab beta ± IL-2 was followed by oral 13-cis-RA treatment (160 mg/m²/day for 14 days per course) in both sets of patients.

Patients in both arms had primary refractory or relapsed neuroblastoma. These were 99 male and 64 female, aged 1 to 20 years (mean 5.7 years). Most had an initial diagnosis of INSS stage 4 disease without MYCN amplification (16% of the patients had MYCN amplified tumours and in 14% this information was missing). Treatment of disease before immunotherapy included intensive chemotherapy regimen followed by autologous stem cell transplantation (ASCT), radiotherapy, and surgery. At baseline, 95 patients had evidence of disease (47 in Experimental Arm and 48 in Standard Arm) and 68 (34 in each arm) patients had no evidence of disease.

The primary efficacy endpoint in Study 4 was Event-Free Survival (EFS) with Overall Survival (OS) as a secondary efficacy endpoint. The study was powered to demonstrate superiority of dinutuximab beta vs. dinutuximab beta with IL-2 under a 20% type I error. The Hazard Ratio (HR) of EFS was 1.07 (80% Equal-Tail Interval 0.74 to 1.42) showing no superiority. HR of OS was 1.21 (80% Equal-Tail Interval 0.79 to 1.69**,** however the interpretation is limited due to multiple crossing of the Kaplan-Meier curves.

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.

Table 2: Event-free survival (EFS) and overall survival (OS)

Efficacy	without IL-2 N=104			with IL-2 N=107		
	1 year	2 year	3 year	1 year	2 year	3 year
EFS (95% CI)	72% (65-78%)	63% (55-70%)	57% (47-63%)	72% (65-78%)	66% (59-73%)	61% (53-68%)
OS (95% CI)	86% (80-91%)	76% (69-82%)	64% (55-71%)	88% (82-92%)	75% (68-81%)	69% (61-76%)

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.

Pharmacokinetics

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.

Metabolism

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 Cmax was 1.13 (± 0.54) after 5 LTI courses (mean (±SD)). The apparent terminal elimination t1/2 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 “Properties/Effects”).

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.

Kinetics in specific patient groups

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.

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≤3x ULN.

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.

Preclinical 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 data

No nonclinical 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.

Other information

Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section “Instructions for handling”.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

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), after cumulative storage in a refrigerator (2 °C – 8 °C) for 72 hours (see section “Instructions for handling”).
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 would not normally be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Special precautions for storage

Store in the refrigerator (2-8°C).
Keep the vial in the outer carton in order to protect the contents from light.
Keep out of the reach of children.

Instructions for 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 Dosage/Administration). 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 applied, 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.

Authorisation number

67463 [Swissmedic]

Packs

Vial with 20.25 mg/4.5 mL: 1 [A]

Clear Type I glass vial (6 mL) with a halobutyl rubber stopper and aluminium flip-off cap

Marketing authorisation holder

Medius AG, 4132 Muttenz

Date of revision of the text

December 2023