Taiwan Food and Drug Administration

Assessment Report

Trade Name：寬利安濃縮輸注液 / Qarziba 4.5 mg/mL concentrate for solution for infusion

Active Ingredient：dinutuximab beta

License Number：衛部菌疫輸字第 001175 號；MOHW-BI 001175

Applicant：吉帝藥品股份有限公司

Approval Date：2021.9.11

Indication：

神經母細胞瘤：

- **Qarziba 適用於治療有殘存或沒有殘存疾病的高危險性神經母細胞瘤，年齡 12 個月以上的病人，這些病人以前接受過誘導化學療法並至少達到了部分緩解，隨後進行了清髓治療和幹細胞移植。**
- **Qarziba 適用於治療有殘存或沒有殘存疾病且具復發或難治性病史的神經母細胞瘤患者，年齡 12 個月以上的病人。**

說明:

1. 對於有復發或難治性疾病史的病人以及在一線治療後仍未完全緩解的病人， Qarziba 應該與白介素 interleukin-2 (IL-2) 合併使用。

2. 在治療復發性神經母細胞瘤之前，應透過其他合適的措施來穩定任何正在惡化的疾病。

Background Information

Trade Name	寬利安濃縮輸注液 / Qarziba 4.5 mg/mL concentrate for solution for infusion
Active Ingredient(s)	dinutuximab beta
Applicant	吉帝藥品股份有限公司
Dosage Form & Strengths	注射液劑 20 mg / 4.5ml /vial
Indication	神經母細胞瘤： -Qarziba 適用於治療有殘存或沒有殘存疾病的高危險性神經母細胞瘤，年齡 12 個月以上的病人，這些病人以前接受過誘導化學療法並至少達到了部分緩解，隨後進行了清髓治療和幹細胞移植。 -Qarziba 適用於治療有殘存或沒有殘存疾病且具復發或難治性病史的神經母細胞瘤患者，年齡 12 個月以上的病人。
Posology	Qarzia 的治療包 5 個連續的療程，每一個療程為 35 天。劑量是根據個別體表面積來決定的，每個療程總計應為 100 毫克/平方米。兩種投藥模式都可以： ·每一個療程的第 1-10 天，每天投藥劑量 10 毫克/平方米，連續輸十天(共 240 小時) ·或者每一個療程的第 1-5 天，每天投藥劑量 20 毫克/平方米，輸注 8 小時，連續五天。當 IL-2 與 Qarziba 合併使用時，IL-2 應以每天 $6x10^6$IU/平方米皮下注射劑投與，療程中有兩個連續五天的用藥，療程總劑量為 $60x10^6$IU/平方米。第一個 5 天的療程應在首次輸注 dinutuximab beta 前 7 天開始，第二個 5 天的療程應與 dinutuximab beta 輸注同時開始(每個 dinutuximab beta 療程的第 1 至 5 天)。
Pharmacological Category ATC Code	L01XC

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Dinutuximab beta, the drug substance of brand name Qarziba, is a mouse/human chimeric anti-GD2-mAb, a ganglioside overexpressed by cells of neuroectodermal origin such as neuroblastoma cells. The manufacturer of dinutuximab beta is Rentschler Biopharma SE, Germany.

Dinutuximab beta is produced in CHO cells and contains the IgG-typical fucosylated N-glycans. The relative molecular mass of dinutuximab beta is approximately 150 kDa. Detailed description of the origin, history, and preparations of cell banks including MCB, WCB, and EPC are provided. Adventitious and endogenous agent safety testing, identity, and genetic stability for cell banks were conducted based on the recommendations in ICH guidance. Raw materials of direct and indirect biological origin are also justified.

Characterization studies are presented including primary and higher-order structure, glycosylation, disulfide structure, charge and size variants, and biological activity of target binding, as well as product variants and process-related impurities. The exclusion for some process-related impurities from routine testing is appropriately justified. Manufacturing process with in-process controls, process development histories for 3 process versions, comparability studies, process validation, specification, analytical methods and validation, batch analyses, reference materials, and virus clearance studies, are provided abundantly to demonstrate the quality and consistency of dinutuximab beta using commercial process.

Long-term, accelerated, and stress stability studies have been carried out for Dinutuximab beta batches. The stability studies are derived from Dinutuximab beta batches produced with the commercial process.

2.1.2 Drug product

Qarziba is the clear, colorless liquid in glass vials, containing 4.5 mg/mL per vial, concentrate for solution for infusion. It is intended for intravenous infusion after dilution. The manufacturer for the drug product, Qarziba, is Rentschler Biopharma SE, Germany.

The composition of drug product is listed. The excipients for drug product are complied with Ph. Eur. No novel excipients and no excipients of human or animal origin are used in the formulation.

Drug product manufacturing process and formulation development are described appropriately. Adequate justifications for potential impurities and the container closure integrity are provided to support the suitability of the container closure system. The compatibility data is submitted adequately. Manufacturing process within process controls, process validation, specification, and batch analyses are provided and show that the manufactures of Qarziba are controlled properly and consistently.

The release specification and stability specification for Qarziba include appearance, identity, content, potency, purity and impurities, contaminants, and general tests. The specifications of Qarziba are generally acceptable.

Stability studies, conducted under long-term storage, accelerated, stress conditions, and in-use stability studies could support the storage and on-site usage for Qarziba. The long-term stability study results support the shelf life of Qarziba for 36 months under the storage condition of 5±3°C, protected from light.

In conclusion, information on the drug substance and finished drug product is regarded as appropriate to support the quality of Qarziba.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Dinutuximab beta (anti-GD2 mAb) is a monoclonal, chimeric antibody targeting the disialoganglioside GD2 antigen, which is highly expressed on neuroectodermal tumors such as neuroblastoma and melanoma but also osteosarcoma and soft tissue sarcomas.

Pharmacology data demonstrated dinutuximab beta has two key anti-tumor modes of action: (i) antibody-dependent cellular cytotoxicity (ADCC)-mediated killing of GD2-positive tumor cells and (ii) triggering of complement-dependent cellular cytotoxicity (CDC)-mediated killing of GD2-positive tumor cells. Dinutuximab beta showed strong lysis of the GD2-positive cell lines LAN-1 and M21 via complement-mediated cytotoxicity. In vivo data showed that Dinutuximab beta was effective in syngeneic, neuroblastoma cell, liver metastasis mouse models.

No stand-alone safety pharmacology studies have been performed with Dinutuximab beta in accordance with ICH guidance S9. However, tests of neurological, cardiovascular, and respiratory function parameters included in repeated-dose toxicity studies in Guinea pigs and Cynomolgus monkeys showed no test item-related changes.

2.2.2 Toxicological Studies

In toxicology, dinutuximab beta has been administered to juvenile Guinea pigs and young cynomolgus monkeys as repeated-dose regimens exceeding the recommended clinical dose. Noteworthy findings included changes (decrease) in thymus weight and bone marrow

changes (atrophy affecting myeloid and erythroid precursor cell lines), reduced activity, food consumption, and body weight gain possibly due to pain associated with drug treatment. 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.

The absence of genotoxicity and carcinogenicity studies is reasonable since dinutuximab beta is an antibody that is not expected to interact with DNA or be carcinogenic. No dedicated reproductive organ and developmental toxicity studies have been performed with dinutuximab beta. However, due to its mode of action (induction of CDC/ADCC after binding), the expression of GD2 on neuronal tissues, especially during embryo-fetal development, and the potential of placental transfer of antibodies, Dinutuximab beta has the potential to cause fetal harm when administered to pregnant women.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Dinutuximab beta is dosed via the IV route and therefore is completely bioavailable. Calculations of PK parameters for dinutuximab beta are based upon measurements using non-validated bioanalytical methods. This has to be taken into consideration when interpreting PK parameters. Following a 10-day continuous intravenous infusion of 10 mg/m^2/day (equal to a total dose of 100 mg/m^2/course), peak concentrations were generally reached at the end of the 10-day infusion. The mean C_{max} was approximately 12 µg/mL in Cycle 1. The mean accumulation ratio for $AUC_{0\text{-}504hr}$ increased from Cycle 2 to Cycle 5, but did not exceed 1.61. The volume of distribution is stated to be 5- 6.5 L/m^2 and the terminal half-life is estimated to be 8 days. From the results of study APN311-202, mean AUC_{inf} in Cycle 1 appeared roughly proportional over the dose range of 40 to 100 mg/m^2/cycle. PK of dinutuximab beta has not been evaluated in healthy volunteers. No metabolism or excretion studies have been performed because dinutuximab beta are proteins which are degraded into amino acids that are then recycled into other proteins.

Serum samples from Study 303 were re-analyzed using a validated ECLIA to obtain PK results. Following a 10-day continuous intravenous infusion of 10 mg/m^2/day (equal to a total dose of 100 mg/m^2/course), mean C_{max} was approximately 9.63 µg/mL in Cycle 1. The volume of distribution (V_z) is predicted to be 8.31 L/m^2. The terminal half-life is estimated to be 7.78 days.

2.3.2 Interaction Studies

No interaction studies have been performed. Dinutuximab beta is expected to be catabolized into amino acids by general protein degradation process, not to be metabolized by phase I and II metabolizing enzymes. It has been shown in study APN311-201 that dinutuximab beta induced the release of cytokines, in particularly IL-6 and TNFα. Therefore, interactions with concomitantly used medicinal products, cannot be excluded.

2.3.3 Special Populations

A population PK analysis conducted on the data obtained with the initial non-validated assays was used to investigate the important covariates on dinutuximab beta exposure. Gender and age did not have a significant impact on the PK. The assay for anti-drug antibody is also not considered robust; however, the suggestion is an effect on Vd, but not clearance. Markers of renal and hepatic clearance (eGFR and bilirubin) did not show a relationship with exposure (C_{max} and AUC_{24h} on day 1 and day 10 during a 10-day infusion). Due to poor drug tolerance of the immunogenicity assay, the impact of ADA formation on PK can only be considered exploratory. Overall, there was a trend towards a reduction in C_{max} and AUC in subjects with ADA positive.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The regimen of dinutuximab beta + RA with or without IL-2 may give 3-year survival rates of at least 63% for R/R or high risk neuroblastoma.

2.4.2 Safety Results

Major safety concerns include bone marrow suppression, infusion reactions/hypersensitivity, neurotoxicity (especially pain), visual disturbances, infections, capillary leak syndrome/fluid retention, cytokine release syndrome, elevated liver enzymes, decreased calcium/potassium level and GI symptoms.

Dosing modification schedule for toxicities is provided in label.

2.5 Bridging Study Evaluation

A Phase I bridging study was conducted to evaluate PK parameters to bridge between Japanese and European results. Ch14.18/CHO (100 mg/m^2/cycle; 3.3mg/kg/cycle below 12 kg body weight) was administered over 10 consecutive days every 5 weeks to patients with recurrent/refractory neuroblastoma. The PK of ch14.18/CHO in the Japanese patients was not significantly different from that observed in Caucasian patients.

2.6 Conclusion

There is unmet clinical need for R/R or high risk neuroblastoma. Based on the provided dossier, approval is recommended.

3. Post-Marketing Requirements

(1) Submit the results of APN311-202v3 to evaluate the add-on effect of IL-2 in patients with R/R neuroblastoma.

(2) Submit the 5-year survival data for patients included in Study APN311-202 and APN311.

(3) Routine pharmacovigilance