Taiwan Food and Drug Administration

Assessment Report

Trade Name：埃宗力注射液 / Elzonris Injection

Active Ingredient：Tagraxofusp

License Number：MOHW-BI-001240

Applicant：新加坡商美納里尼醫藥有限公司台灣分公司

Approval Date：112/11/13

Indication：
用於治療芽球性胞漿性樹突狀細胞瘤(Blastic plasmacytoid dendritic cell neoplasm, BPDCN)成人病人。

Indicated for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adult patients

1. Background Information

Trade Name	埃宗力注射液 / Elzonris Injection
Active Ingredient(s)	Tagraxofusp
Applicant	
Dosage Form & Strengths	Concentrate for solution for infusion 1000 mcg/mL
Indication	用於治療芽球性胞漿性樹突狀細胞瘤(Blastic plasmacytoid dendritic cell neoplasm, BPDCN)成人病人。 Indicated for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adult patients
Posology	詳如仿單
Pharmacological Category **ATC Code**	L01XX67

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance (DS)

General information

Tagraxofusp, a Diphtheria Toxin (DT) Interleukin-3 (IL-3) Fusion Protein (DT388IL3), is a 524 amino acid recombinant fusion protein expressed in *Escherichia coli* from a hybrid gene comprised of a deoxyribonucleic acid (DNA) sequence of IL-3 contiguous with a truncated version of DT intentionally engineered without its receptor binding domain (i.e., IL-3 replaces the receptor binding domain).

Manufacture

Tagraxofusp is produced by recombinant DNA technology in *Escherichia coli* competent cells. The manufacturing process is described with raw materials, critical process parameters, and process controls (in-process controls, microbial controls) and process characterization. The results of process validation support the consistency of the quality of drug substance. Tagraxofusp is manufactured without using human- or animal-derived components with potential risks. The raw materials used during the production of tagraxofusp comply with compendial standards or are tested according to in-house specifications to ensure their quality.

There are a few DS process changes in the manufacturing process history throughout development to commercial manufacturing. Comparability studies were conducted to

evaluate and to monitor those product attributes by vast analytical procedures for primary structure and higher order structure, product- and process- related impurities, and degradation profiles in stability study. The comparability results demonstrate the process changes have no significant changes on the quality of drug substance.

Characterization

Physicochemical and biological properties of tagraxofusp are shown. Primary structure, higher order structure, charge and size heterogeneity are determined by analytical procedures. Process-related impurities and product-related impurities were within the set specification.

Control of DS

The specification of DS was provided and the acceptance criteria is well-justified. All batch results were within acceptable criteria to demonstrate DS quality consistency. In addition, Certification of Analysis (CoA) shows that test results meet specification criteria.

2.1.2 Drug product (DP)

Description of DP

Tagraxofusp, injection (drug product) is a non-preserved, sterile, liquid dosage form containing an aqueous solution. The finished product is presented as concentrate for solution for infusion containing 1 mg/mL of tagraxofusp as active substance.

Other ingredients are trometamol, sodium chloride, sorbitol (E420) and water for injections. The product is available in type I glass single dose vial with a butyl rubber stopper and an aluminium/plastic flipoff seal, containing 1 mL concentrate.

Pharmaceutical Development

There are two major modifications were introduced throughout the manufacturing development. Comparability between process A batches and process B batches is provided and batches are demonstrated to be comparable. The manufacturers and batch formula are presented. The process controls and parameters are stated in manufacturing process description. The process validation results meet the acceptance criteria to support process consistent quality. A compatibility study was performed with the finished product after dilution in 0.9% NaCl solution to a concentration of 0.1 mg/mL. The aim of the in-use study was to demonstrate compatibility of the product with the diluent, an intravenous tubing set, syringes, and a terminal in-line filter used in the clinical administration of this product during 4 hours at ambient temperature.

Control of DP

The specification of DP is provided and the acceptance criteria is well-justified. Release

results and CoAs are within acceptance criteria.

Stability

The results of accelerated stability and long-term stability data are provided and supported 36 months of shelf-life for DP stored at -20 ±5 °C.

Overall, the quality results include the manufacturing process, control of materials, in-process controls, characterization, specifications, container closure system, and stability. These results adequately support that the manufacturing of DP is well-controlled and quality consistency.

2.2 Preclinical Pharmacology/Toxicology Evaluation

Tagraxofusp is a recombinant fusion protein composed of truncated diphtheria toxin (DT) and human interleukin-3 (IL-3). Based on surface plasmon resonance data, tagraxofusp bound human IL-3Rα, but not mouse IL-3Rα, with a comparable Kd to recombinant human IL-3 binding to human IL-3Rα. Mechanism-wise, tagraxofusp showed similar activity to DT to inactivate EF-2 through ADP-ribosylation and induce apoptosis in CD123-expressing cells. In vitro cytotoxic activity of tagraxofusp against both BPDCN and AML cell lines and primary cells derived from the patients was demonstrated, with IC50 values against BPDCN cells in the femtomolar to picomolar range. In the human BPDCN and AML cell lines- and patient cells-derived mouse xenograft models, tagraxofusp reduced tumor burden from the blood and/or multiple organ compartments and extended survival of the treated animals.

The cynomolgus monkey was chosen as the most relevant species for toxicological assessment based on a greater amino acid sequence homology to humans. In the 1-month and 3-month GLP toxicity studies in cynomolgus monkeys, IV administration of tagraxofusp for 5 consecutive days in a 21-day cycle for 1 or 3 cycles in monkeys identified the kidneys, liver, thymus, and choroid plexus of the brain as the major target organs of toxicity. Pre-term mortality/euthanasia occurred at the high dose tested, 60 and 45 mcg/kg/day, in 1-month and 3-month studies, respectively. The NOAELs could not be determined in these two studies. The HNSTD determined in the 1-month study was approximately 0.8-fold the recommended clinical dose based on body surface area (BSA), but the HNSTD could not be determined in the 3-month study. In these two monkey studies, severe renal cortical tubules degeneration/necrosis and degeneration/necrosis of the choroid plexus in the brain were observed at doses providing approximately 1.6- and 0.8-fold the recommended clinical dose based on BSA, respectively.

No stand-alone safety pharmacology studies were conducted. ECG was assessed as part of the GLP repeated-dose toxicity studies in cynomolgus monkeys and found no tagraxofusp-related

effects. No special issues of the effects on the vital organs have been noted in the context of these studies; however, it is noteworthy that potentially tagraxofusp-related neurological clinical signs, including tremors, were observed in the 3-cycle study in monkeys.

Immunohistochemistry with tagraxofusp in Urieto 2004 showed no meaningful reactivity in a panel of normal human tissues. However, because CD123 expression in normal tissues is not limited to hematopoietic lineage cells, the risk of on-target off-tumor toxicity associated with tagraxofusp can not be ruled out. In line with the applicant's response to the reviewer, tagraxofusp-related effects in monkeys, such as microscopic changes in the brain, kidneys, and female reproductive tissues, as well as tagraxofusp-related capillary leak syndrome (CLS) observed in the clinic, might be considered as potential on-target off-tumor effects of tagraxofusp.

In line with ICH S9 and ICH S6(R1), genotoxicity and carcinogenicity studies have not been conducted. Regarding development and reproductive toxicity, a weight of evidence-based risk assessment suggested that potential teratogenic and embryotoxic effects could be expected based on the mechanism of action of tagraxofusp. No non-clinical safety evaluation in juvenile animals was performed to inform the risk of using tagraxofusp in child patients.

Lastly, local tolerance for the administration of tagraxofusp via IV routes was evaluated in the toxicity studies in cynomolgus monkeys. Signs of dry skin and local irritation/inflammation at the injection sites have been reported.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Following administration of tagraxofusp 12 μg/kg in patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN), the mean (StD) AUC was 231 (123) hr·μg/L and C_{max} was 162 (58.1) μg/L. In BPDCN patients, with no detectable ADA in the C1D1 baseline (pre-treatment) sample, following administration of 12 μg/kg, tagraxofusp was eliminated rapidly with a mean (StD) $t_{1/2}$ of 0.714 (0.337) hours. The tagraxofusp V_z was estimated at 5.11 (1.85) L and CL was 7.14 (7.16) L/h. In addition, free tagraxofusp exposure demonstrated a titer-dependent reduction with increasing ADA measured at baseline. Overall, the presence of ADA is a major determinant of exposure to free tagraxofusp.

Tagraxofusp is a 524-amino acid recombinant fusion protein, it is expected to be degraded into peptides and its constituent amino acids through proteolysis and then further recycled for use in general protein synthesis. Furthermore, tagraxofusp is administered by intravenous infusion, thus food effect is not a concern.

2.3.2 Interaction Studies

No drug-drug interaction studies have been conducted with tagraxofusp.

2.3.3 Special Populations

No clinically significant differences in the pharmacokinetics of tagraxofusp were observed based on age (22 to 84 years), sex or body weight after adjusting dose by body weight.

No clinically significant differences in the pharmacokinetics of tagraxofusp were observed based on mild to moderate renal impairment and mild to moderate hepatic impairment. The effect of severe renal impairment and severe hepatic impairment on tagraxofusp pharmacokinetics is unknown.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The main efficacy data of tagraxofusp in patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) are derived from Study STML-401-0114, a multicenter, open-label, single-arm study of tagraxofusp in patients with BPDCN and acute myeloid leukemia (AML).

Sixty-five subjects received tagraxofusp at 12 μg/kg/day, the proposed dose, as first-line therapy and were evaluable for efficacy. The median age was 68.0 (range: 22-84) years. The complete response (CR) rate was 56.9% (95% confidence interval [CI]: 44.0%, 69.2%). The median duration of CR was 24.9 (range: 1.0-57.4^{+}) months. Nineteen of the 37 responders had duration of CR > 6 months, including 16 responders with duration of CR > 12 months. The median progression free survival (PFS) was 4.4 (95% CI: 3.2, 7.3) months, and the median overall survival (OS) was 15.8 (95% CI: 9.7, 25.8) months. Twenty-one (32.3%) subjects were successfully bridged to hematopoietic stem cell transplantation (HSCT) including 19 subjects experienced CR and 2 subjects experienced partial response (PR) to tagraxofusp before HSCT. A prespecified formal statistical hypothesis test for CR was performed in the 13 subjects enrolled in Stage 3. The CR rate of these subjects was 53.8% (95% CI: 25.1%, 80.8%) exceeded the prespecified rate of 10%.

Nineteen subjects received tagraxofusp at 12 μg/kg/day as second- or more line therapy and were evaluable for efficacy. The median age was 72.0 (range: 44-87) years. Eleven (57.9%) subjects received one line prior therapy, 3 (15.8%) subjects received two lines prior therapy, and 4 (19.0%) subjects received more than three lines prior therapy. Six (31.6%) subjects received prior HSCT. The CR rate was 15.8% (95% CI: 3.4%, 39.6%). The median duration of CR was 3.6 (range: 3.0-13.9^{+}) months. The median PFS was 2.2 (95% CI: 0.7, 3.6) months, and the median OS was 8.2 (95% CI: 4.1, 11.9) months. Only 1 subject who achieved CR to tagraxofusp before HSCT was bridged to HSCT.

2.4.2 Safety Results

The main efficacy data of tagraxofusp in patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) are derived from Study STML-401-0114, a multicenter, open-label, single-arm study of tagraxofusp in patients with BPDCN and acute myeloid leukemia (AML). Overall, 86 subjects with BPDCN and 36 subjects with AML received tagraxofusp at 12 μg/kg/day. The median relative dose intensity was 94.9%. The median duration of exposure was 68.0 (range: 1-1622) days for subjects with BPDCN and only 6.0 (range 2-201) days for subjects with AML.

The most common adverse events (AEs) included liver enzyme elevation, hypoalbuminemia, edema events, body weight increased, capillary leak syndrome (CLS), hematologic AEs, constitutional symptoms, gastrointestinal (GI) symptoms, and hyperglycemia.

Overall, 62.3% and 60.7% subjects reported alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased. Grade ≥ 3 ALT increased and Grade ≥ 3 AST increased were reported for 27.9% and 28.7% subjects, respectively. Most subjects experienced these AEs in the first cycle and most of these AEs were non-serious. There were no cases fulfilled the Hy's Law. Only 1 subject discontinued tagraxofusp because of AST increased.

Twenty-four (19.7%) subjects experienced CLS, including 3 Grade 3, 2 Grade 4, and 2 Grade 5 events. CLS was also the most common (11.5%) serious AE (SAE) and led to tagraxofusp discontinuation for 2 (1.6%) subjects. Risk mitigation strategies were provided after the occurrence of a Grade 5 CLS, and the incidence of Grade ≥ 3 CLS decreased after implementation. The time to onset of CLS was short with a median time to onset of 5.5 (range: 3-51) days, and all but 2 subjects experienced the event in the first cycle. The course of CLS ranged from 3-69 days, with a median duration of 6.5 days.

Hematologic AEs included thrombocytopenia (35.2%), anemia (23.0%), febrile neutropenia (18.9%), neutropenia (16.4%), and leukopenia (11.5%). Grade ≥ 3 hematologic AEs were also common, including thrombocytopenia (27.9%), febrile neutropenia (15.6%), anemia (13.1%), and neutropenia (11.5%). These events were generally non-serious except febrile neutropenia (7.4%).

Thirty-three (27.0%) subjects experienced hyperglycemia, and 12 (9.8%) subjects experienced Grade ≥ 3 hyperglycemia. All events of hyperglycemia were non-serious.

The AEs of hypoalbuminemia, edema, weight increased, constitutional symptoms (fatigue, pyrexia, chills), and gastrointestinal (GI) symptoms (nausea, constipation, diarrhea and

vomiting) were generally Grade 1 or 2 in intensity and non-serious.

2.5 Bridging Study Evaluation

Currently, all Asian subjects in the clinical development program of tagraxofusp were enrolled in the study center in the United States.

In order to evaluate the effect of ethnic on PK, pharmacokinetic data is based on Studies 0114, 0214, 0314, and 0414 and includes PK data from Cycle 1 for 14 Asian and 209 non-Asian patients with hematological diseases: namely acute myeloid leukemia (AML) (n=65), BPDCN (n=88), relapsed or refractory multiple myeloma (MM) (n=8), or advanced, high risk myeloproliferative neoplasm (HRMPN) (n=62). The tagraxofusp population PK model (STM0112F) was used to derive individual PK parameters and to compare the PK of tagraxofusp between both subpopulations (Asian vs. non-Asian). Overall, no significant differences in PK of tagraxofusp were observed between Asian and non-Asian patients. Specifically, tagraxofusp AUC_{0-24} and C_{max} distributions for Asian patients were contained within the respective distributions for non-Asian patients, therefore indicating similar plasma exposures between both sub-populations. In conclusion, race is not considered a sensitive factor on tagraxofusp PK.

Clinically, it is difficult to draw conclusion based on the limited data in Asian subjects. Ongoing Study NS401-P1-02 evaluating the safety, pharmacokinetics, and safety of tagraxofusp in Japanese subjects with BPDCN will provide more relevant clinical data in East Asian subjects. The clinical study report should be submitted after study completion.

2.6 Conclusion

Considering the rarity of BPDCN, unmet medical need, and the data submitted, CDE review team leader recommends approval of tagraxofusp.

The recommended indication is “treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adult patients.”

The recommended dosage is “12 μg/kg intravenously over 15 minutes once daily on days 1 to 5 of a 21-day cycle. The dosing period may be extended for dose delays up to day 10 of the cycle. Continue treatment until disease progression or unacceptable toxicity.”

3. Post-Marketing Requirements

Submit the final clinical study report of NS401-P1-02