Taiwan Food and Drug Administration

Assessment Report

Trade Name：癌適求注射液 40 毫克/毫升 /
ELREXFIO 40mg/mL solution for injection

Active Ingredient：Elranatamab

License Number：MOHW-BI-001261

Applicant：輝瑞大藥廠股份有限公司

Approval Date：2024.07.03

Indication：
適用於治療先前曾接受至少四線療法(包括一種蛋白酶體抑制劑、一種免疫調節劑和一種抗 CD38 單株抗體)並在最後治療顯示疾病惡化的復發性或難治性多發性骨髓瘤成人病人。

此適應症係依據腫瘤整體反應率及反應持續時間加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。

The treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Background Information

Trade Name	癌適求注射液 40 毫克/毫升 / ELREXFIO 40mg/mL solution for injection
Active Ingredient(s)	Elranatamab
Applicant	輝瑞大藥廠股份有限公司
Dosage Form & Strengths	注射液劑 40mg/mL
Indication	適用於治療先前曾接受至少四線療法(包括一種蛋白酶體抑制劑、一種免疫調節劑和一種抗 CD38 單株抗體)並在最後治療顯示疾病惡化的復發性或難治性多發性骨髓瘤成人病人。 此適應症係依據腫瘤整體反應率及反應持續時間加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。 The treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
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Pharmacological Category **ATC Code**	L01FX32

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance

General Information of Drug Substance (DS)

Elranatamab, the active substance of Elrexfio, is a heterodimeric humanized full-length bispecific IgG2 kappa antibody derived from two monoclonal antibodies (mAbs), directed against cluster of differentiation 3 (CD3) and B-cell maturation antigen (BCMA). The CD3 and BCMA monoclonal antibodies are separately produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology, and 4-chain bispecific antibody is covalently linked via inter-chain disulfide bonds.

Manufacture

Elranatamab DS is manufactured at Wyeth BioPharma, USA. All sites involved in manufacture and control of the elranatamab DS are in accordance with Good Manufacturing Practice (GMP). The details of manufacturing process, including the material inputs, critical process parameters, and process outputs (in-process controls, microbial controls, and performance attributes) are provided in the dossier. The process parameters and critical controls are considered appropriately. No human or animal derived materials are used in the manufacturing process, and all raw materials meet the compendial requirements or in-house specifications. The production recombinant cell lines are no adventitious contaminants and genotypic consistency. Process validation results can demonstrate control, effectiveness and consistency of the manufacturing process. During the elranatamab DS development, there are two main processes at two manufacturing sites and at two different scales. The comparability evaluations conclude that elranatamab DS manufactured at all sites and scales throughout development are comparable.

Characterization

Characterization study of elranatamab DS is conducted for its primary structure, posttranslational modifications, charge and size heterogeneity, purity, high order structure, and biological activity. Process-related impurities, product-related impurities, and potential contaminants is analyzed comprehensively. The analytical techniques/ methodologies performed in the studies are considered suitable for their intended use. Overall, the results can demonstrate that elranatamab DS has the expected structure, relative biological activity, and the impurities are well controlled.

Control of DS

The specification of elranatamab DS is provided and the acceptance criteria is well justified. Compendial and non-compendial analytical procedures used for release and stability testing have been appropriately validated. All batch results and Certification of Analysis (CoA) are within acceptable criteria to demonstrate elranatamab DS quality consistency.

Stability

The proposed self-life is 30 months at ≤ -20 ± 5 °C (long-term storage condition). The long-term stability results of at least three elranatamab DS batches can demonstrate that all quality attributes are expected to remain within the acceptance criteria at the recommended storage condition.

2.1.2 Drug Product

Description of Drug Product (DP)

Elranatamab DP is supplied as two presentations 44 mg/1.1 mL and 76 mg/1.9 mL for injection in a single-dose vial. The finished product contains 40 mg/mL elranatamab, L-histidine, L-histidine hydrochloride monohydrate, edetate disodium dihydrate, polysorbate 80, sucrose, and water for injection.

Pharmaceutical Development and Manufacture

Elranatamab DP is manufactured at Pharmacia and Upjohn Company LLC, USA. All sites involved in manufacture, control and storage of elranatamab DP are in accordance with GMP. In pharmaceutical development, clinical and commercial elranatamab DP were manufactured at different sites. A comparability study is provided to demonstrate the comparability of lots derived from the commercial process to lots manufactured from the other site used in clinical trials. The manufacturer process, process controls and parameters are described in details, and process validation results can further demonstrate robustness and consistency of the elranatamab DP manufacturing process.

Control of DP

The specification of elranatamab DP is provided, the analytical procedures is validated and the acceptance criteria is well-justified. Batch release results and CoAs meet acceptance criteria to demonstrate quality consistency.

Stability

The long-term stability data from 76 mg/1.9 mL and from 44 mg/1.1 mL presentation s can support elranatamab DP shelf-life of 24 months at 2~8℃.

Overall, the CMC quality data, including the manufacturing process, control of materials, in-process controls, characterization, specifications, container closure system, and stability, can adequately support that the manufacturing of Elrexfio is well-controlled and quality consistency.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

In vitro pharmacodynamic studies revealed that elranatamab bound to BCMA+ and CD3+ cells and induced T cell-dependent activation, cytotoxicity, and various cytokines release with EC_{50} values in the low picomolar range. *In vivo* tumor-bearing mice studies showed that elranatamab induced healthy donors' PBMC- or T cell-mediated elimination of MM tumor compared with control groups. Cardiovascular, neurological, and respiratory system safety has been investigated for elranatamab and revealed no major liabilities in monkeys.

2.2.2 Toxicological Studies

Elranatamab was evaluated in toxicity studies for up to 3-month duration in monkeys. Cynomolgus monkeys were the only relevant species for elranatamab based on sequence similarity and cross-reactivity. In monkeys undergoing SC administrations, elranatamab decreased BCMA+ cells, antibody-secreting cells, immunoglobulins, and lymphocyte cellularity in lymphoid organs in all treated groups, leading to the loss of humoral immunity, immunosuppression, and secondary infections involving multiple organs. Subsequently, a moribund condition caused by the continued progression of exaggerated pharmacology was found. In addition, transient and reversible cytokine release without neurological-related toxicity was observed mainly after the first dosing. Of note, recovery was not conducted in any toxicity studies. The LOAEL was 0.3 mg/kg/week, providing a margin of <1 in both genders.

According to ICH S6(R1) and S9, genotoxicity and carcinogenicity studies are not warranted to support marketing for biotechnology-derived drugs that are not cross-reactive with rodents. Developmental and reproductive toxicity studies have not been conducted but a weight-of-evidence risk assessment was provided which is considered acceptable. Although lower exposure of elranatamab resulted from ADA formation was noted, this IgG-based bsAb may transfer across the placenta to the fetus or through nursing to the infants. The patients should implement contraception and avoid breastfeeding while receiving elranatamab. Elranatamab had no unexpected cross-reactivity in human or monkey tissues and spiked impurities did not alter the cytokine profile of elranatamab.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Elranatamab is an IgG2 kappa bispecific antibody derived from two monoclonal antibodies (mAbs), an anti-BCMA mAb and an anti-CD3 mAb. The absolute bioavailability of elranatamab following subcutaneous (SC) administration is estimated to be 56.2%. The median T_{max} after elranatamab SC administration of a single dose or after multiple doses ranged from 3 to 7 days. Population PK (PopPK) analyses estimate for free elranatamab central and peripheral volume of distribution were 4.78 L and 2.83 L, respectively.

The major elimination pathway of elranatamab in humans is expected to be via non-specific catabolic degradation. Total and free elranatamab exposure for the overall population increased with dose in approximately dose-proportional manner over the dose range of 80 to 1000 μg/kg (fixed doses of 6 to 76 mg) evaluated via SC route. The predicted geometric mean half-life of elranatamab is 22 days at week 24 following doses of 76 mg weekly. The estimated free elranatamab clearance (CL) from the PopPK analysis was 0.324 L/day. Apparent clearance of total elranatamab (CL/F) was 0.44 L/day calculated as dose/simulated AUC_{tau} after multiple weekly doses on week 24.

2.3.2 Interaction Studies

No formal drug interaction studies have been conducted with elranatamab.

The initial release of cytokines associated with the start of elranatamab treatment could suppress activity of cytochrome P450 (CYP) enzymes, resulting in increased exposure of CYP substrates. The highest risk of interaction is expected to be during the step-up dosing schedule as the increases in cytokine levels (eg, IL-6) in vivo in monkeys and humans were transient. During the step-up dosing period, toxicity or drug concentrations should be monitored in patients who are receiving concomitant CYP450 substrates with a narrow therapeutic index. The dose of the concomitant medicinal product should be adjusted as needed.

2.3.3 Special Populations

No clinically relevant differences in the pharmacokinetics of elranatamab were observed based on age, sex, race and body weight.

No studies of elranatamab in patients with renal impairment or hepatic impairment have been conducted. The results of the PopPK analysis indicated no clinically meaningful differences in the PK of total or free elranatamab in participants with mild renal impairment or moderate renal impairment compared to participants with normal renal function. The results of the population PK analysis indicated no clinically meaningful differences in the total or free PK of elranatamab in participants with mild hepatic impairment compared to participants with normal hepatic function. The effects of severe renal impairment, end-stage renal disease, or moderate to severe hepatic impairment on the PK of elranatamab are unknown.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this submission, a phase 2, multinational, multicenter, open-label, non-randomized study (C1071003) was provided to support the efficacy of elranatamab as monotherapy for the treatment of adult patients with RRMM, who were refractory to at least one PI, one IMiD, and

one anti-CD38 monoclonal antibody and have demonstrated disease progression or did not respond to the last therapy.

A total of 123 subjects who were naïve to BCMA-directed therapies were enrolled. Most subjects had received at least 4 prior lines of therapies. At the data cutoff date of October 14, 2022, the confirmed ORR determined by BICR per IMWG was 61.0% (95% CI: 51.8%, 69.6%). The study met its primary endpoint as the null hypothesis of ORR by BICR ≤ 30% was rejected. the median duration of response by BICR was not yet reached (95% CI: 12.0, NE), and the Kaplan-Meier probability of maintaining response at 9 months was 84.4% (95% CI: 72.7%, 91.4%).

The updated efficacy data based on the data cutoff date of April 16, 2023 demonstrated consistent results.

2.4.2 Safety Results

The safety data were based on 265 subjects with relapsed or refractory MM who received a 76 mg full dose or equivalent dose calculated on a body weight base (1000 μg/kg) which included 183 subjects who received the 2 step-up priming regimen.

The majority of subjects experienced Grade ≥ 3 treatment-emergent adverse events (TEAEs). Approximate 70% subjects experienced serious TEAEs. A total of 41 (15.5%) subjects had TEAEs leading to treatment discontinuation.

The most frequently reported TEAEs were cytokine release syndrome (CRS), anemia, neutropenia, diarrhea, thrombocytopenia, fatigue, decreased appetite, lymphopenia, injection site reaction, pyrexia, nausea, hypokalemia, and headache.

The most frequently reported Grade 3/4 TEAEs were hematological toxicities, including neutropenia, anemia, lymphopenia, thrombocytopenia and leukopenia. Fifty (18.9%) subjects had Grade 5 TEAEs, mainly related to underlying disease or infections. The most frequently reported serious TEAEs were CRS, COVID-19 pneumonia, pneumonia and disease progression.

The incidence and severity of CRS or immune effector cell-associated neurotoxicity syndrome (ICANS) decreased with the use of pre-medication and 2 step-up priming regimen. All CRS or ICANS events resolved.

2.5 Bridging Study Evaluation

The distributions of the individual population PK (PopPK) parameters (CL, V, and Ka) for Taiwanese, Japanese and Other-Asian participants were similar and were all within the range for non-Asian participants.

Moreover, the PopPK parameters CL, V and ka were compared between East Asian participants in Study C1071002, East Asian participants in other studies, and non-East Asian participants via a cross study comparison. The results indicate similar distribution of all parameters in all subgroups. Furthermore, PopPK model derived estimates for total and free elranatamab PK parameters $C_{avg, Day 28}$ and $C_{trough, Day 28}$ were similar between East Asian and non-East Asian participants via a cross study comparison.

Although the geometric mean PK parameters are approximately 20% higher in East Asian participants. Such increase in exposure is not considered clinically relevant given the relatively flat exposure safety relationship for all safety endpoints evaluated. No significant differences in PK of elranatamab were observed between Asian and non-Asian patients.

Study C1071003 enrolled 12 (9.8%) Japanese subjects. The clinical efficacy and safety of these subjects were generally consistent with the overall population. The ongoing confirmatory Study C1071005 will enroll more East Asian subjects. The clinical study report and East Asian subgroup analysis will provide more comprehensive data.

In conclusion, no adjustment of dose nor a bridging study is warranted for East Asian patients.

2.6 Conclusion

Based on the above multidiscipline review, CDE review team recommends approval of elranatamab.

1. Recommended indication:
   Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody and have demonstrated disease progression on the last therapy.
   This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval of indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).
2. The recommended dose:
   For subcutaneous injection, step-up dose 1 of 12 mg on Day 1, step-up dose 2 of 32 mg on Day 4, followed by the first treatment dose of 76 mg on Day 8, and then 76 mg weekly thereafter through week 24.
   For patients who have received at least 24 weeks of treatment with ELREXFIO and have

achieved a response [partial response (PR) or better] and maintained this response for at least 2 months, the dose interval should transition to an every two-week schedule.

3. Post-Marketing Requirements

1. Submit the clinical study report (CSR) of the following trials once available or after completion:
   (1) Confirmatory Study C1071005, including East Asian subgroup analysis
   (2) Study C1071003
2. Taiwan Risk Management Plan.