Taiwan Food and Drug Administration

Assessment Report

Trade Name：抑佳妥注射劑 / IMJUDO injection 20 mg/ml

Active Ingredient：Tremelimumab

License Number：MOHW-BI 001242

Applicant：臺灣阿斯特捷利康股份有限公司

Approval Date：2023.09.08

Indication：

與 durvalumab 併用，適用於治療未曾接受全身性療法之晚期或無法切除之肝細胞癌成人病人。

說明：本適應症之樞紐試驗(HIMALAYA 試驗)所納入的試驗族群中，在以 Child-Pugh 評分，主要為 Child-Pugh class A 病人，少數為 Child-Pugh class B 病人。

IMJUDO, in combination with durvalumab, is indicated for the treatment of adult patients with advanced or unresectable HCC who have not received prior systemic therapy.

1. Background Information

Trade Name	抑佳妥注射劑 / IMJUDO injection 20 mg/ml
Active Ingredient(s)	Tremelimumab
Applicant	臺灣阿斯特捷利康股份有限公司
Dosage Form & Strengths	注射液劑 20 毫克/毫升 IMJUDO injection 20 mg/ml
Indication	與 durvalumab 併用，適用於治療未曾接受全身性療法之晚期或無法切除之肝細胞癌成人病人。 說明：本適應症之樞紐試驗(HIMALAYA 試驗)所納入的試驗族群中，在以 Child-Pugh 評分，主要為 Child-Pugh class A 病人，少數為 Child-Pugh class B 病人。 IMJUDO, in combination with durvalumab, is indicated for the treatment of adult patients with advanced or unresectable HCC who have not received prior systemic therapy.
Posology	As listed in label
Pharmacological Category **ATC Code**	L01FX20

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance (DS)

General information

Tremelimumab is a fully human anti-human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4 or CD152) monoclonal antibody of the IgG2a isotype. The mechanism is blockade of the interaction between CTLA-4, a cell surface receptor expressed on activated T cells, and the natural B7 ligands (CD80 and CD86) on antigen-presenting cells. As an immunomodulatory agent, tremelimumab blocks CTLA-4 from binding to B7 ligands resulting in enhanced T cell-mediated immune response such as T cell activation, proliferation, and lymphocyte infiltration into tumors leading to tumor cell death.

Manufacture

The manufacturing process was described including the material inputs, critical process parameters, and process outputs (in-process controls, microbial controls, and performance attributes). The manufacturing process was robustness, demonstrated by process validation results. The raw materials used during DS production were either of compendial quality or were tested according to in-house specifications to ensure their quality. No materials of mammalian origin were used during DS manufacturing. The production cell line was tested such as cell line identity determination, genetic characterization and adventitious agent safety. These results demonstrated the cell line had integrity, consistency and safety. Tremelimumab had an extended product development history including five DS processes, two formulations, and several manufacturing sites. The comparability results of release tests, characterization tests, and stability studies demonstrated DS from different manufacturing processes were comparable in terms of product quality, physicochemical and biological properties, as well as stability.

Characterization

Characterization tests were physicochemical and biological properties of DS, including primary structure, carbohydrate structure, higher order structure, charge isoforms, size heterogeneity, and biological properties. Process-related impurities and product-related impurities presented minimal safety risk from assessment results.

Control of DS

The specification of DS was provided and the acceptance criteria was well-justified. All batch results were within acceptable criteria to demonstrate DS quality consistency. In addition, CoAs showed analytical results met specification requirements.

Stability

The stability tests were performed on at least three DS batches. The results demonstrated DS stability in stainless-steel vessels for 48 months at -50 to -30°C, and for 12 months at 2-8°C. In EVA bags, DS was stable for 36 months at 2-8°C.

2.1.2 Drug Product (DP)

Description of DP

DP is a sterile, preservative-free, liquid dosage form intended for intravenous infusion after dilution. The 20 mg/mL DP is provided in two presentations: a 25 mg vial presentation and a 300 mg vial presentation. The 25 mg presentation is aseptically filled into a 2R clear glass vial and closed with an elastomeric stopper. The 300 mg presentation is aseptically filled into a 20R clear glass vial and closed with an elastomeric stopper. The stoppered DP vial is then capped with an aluminum seal and packaged in single-vial cartons. The DP formulation for each presentation contains tremelimumab in histidine/histidine-HCl monohydrate, trehalose dihydrate, disodium

edetate dihydrate, polysorbate 80, pH 5.5.

Pharmaceutical Development

In pharmaceutical development, four manufacturing processes were developed and two formulation compositions (5 mg/ml and 20 mg/mL) were utilized. The comparability studies were analysis based on statistical criteria, direct comparison of lot release and characterization data, and electrophoretic and chromatographic profile comparison. The results showed DP from different manufacturing processes were comparable. The stability results presented that commercial formulation was more stable than original formulation. The manufacturers and batch formula of DP were provided. The process controls and parameters were presented in manufacturing process description. The process validation results met the acceptance criteria to support process consistent quality.

Control of DP

The specification of DP was provided and the acceptance criteria was well-justified. Release results and CoAs were within acceptance criteria.

Stability

The stability studies were performed on at least three lots of 25 mg vial presentation and 300 mg vial presentation. These results supported DP shelf-life of 48 months at 2-8°C under dark.

Overall, the quality results adequately supported the manufacturing of DP was well-controlled and quality consistency.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

In vitro pharmacodynamic studies demonstrated that tremelimumab bound to CTLA-4+ T cells and enhanced activated T cells-mediated release of IFN-γ and IL-2. Of note, Tremelimumab had no impact on Treg functions, platelet counts, or ADCC mediated by activated NK cells. In vivo studies using tumor-bearing mouse models revealed that combining anti-CTLA-4 and anti-PD-L1 antibodies additively inhibited tumor growth and enhanced T-cell function.

Safety pharmacology studies showed that tremelimumab exhibited no significant effects on neurological, cardiovascular, or respiratory systems. Generally, safety margins observed in the safety pharmacology studies with monkeys were sufficient when compared to the exposures associated with the proposed human doses.

2.2.2 Toxicological Studies

Tremelimumab (IV) was evaluated in GLP-compliant toxicity studies of up to 6 months in monkeys. Cynomolgus monkeys were chosen as the most relevant species for non-clinical studies based on their comparable binding affinity; however, tremelimumab binds cCTLA-4 with a 3.5-fold lower affinity than hCTLA-4. Toxicity findings in monkey studies were consistent with the mechanism of CTLA-4 inhibition, exhibiting dose-related incidence and severity of persistent immune-modulatory effects. These findings were partially reversible after a recovery period. The HNSTD was 50 mg/kg/week, providing a safety margin of 15.9 based on Cmax.

Genotoxicity and carcinogenicity studies are not warranted. EFD studies demonstrated that tremelimumab did not significantly impact pregnant monkeys or fetal development during the organogenesis stage. However, due to its mechanism of action, tremelimumab may pose risks such as cytokine release and resulting inflammation from T-cell activation, which could potentially harm the pregnancy or developing fetus. Although lower exposure to tremelimumab resulted from ADA formation, this IgG2-based mAb might cross the placenta or transfer to infants during nursing. Patients should use contraception and avoid breastfeeding while receiving tremelimumab and at least 3 months after the last dose. Lastly, in vitro studies revealed no unexpected cross-reactivity in human or monkey tissues.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Tremelimumab is administered intravenously. The pharmacokinetics of tremelimumab was studied in patients with other solid tumors following administration of doses 1 mg/kg, 3 mg/kg, and 10 mg/kg (1- to 10-times the approved recommended dosage) administered once every 4 weeks for 4 doses. The steady state was achieved at approximately 12 weeks. The pharmacokinetics of tremelimumab as a single dose of 300 mg were evaluated in patients with HCC. Exposures increased generally dose-proportionally with increasing weight-based doses from 1 to 10 mg/kg. Based on population PK analysis, the geometric mean steady-state volume of distribution was 6.33 L.

The primary elimination pathways of tremelimumab are protein catabolism via reticuloendothelial system (RES) or target-mediated disposition. The geometric mean (CV%) terminal half-life of tremelimumab was 16.9 days (19%) after a single dose and 18.2 days (19%) during steady state. The geometric mean (CV%) clearance of tremelimumab was 0.286 L/day (32%) after a single dose and 0.263 L/day (32%) during steady state.

2.3.2 Interaction Studies

No formal drug-drug interaction studies have been conducted with tremelimumab. PK drug-drug interaction of tremelimumab with other therapeutics is not anticipated given that

tremelimumab are not primarily cleared via hepatic or renal pathways; instead, the primary elimination pathways are protein catabolism. Tremelimumab are not expected to induce or inhibit the major drug metabolizing cytochrome P450 pathways.

2.3.3 Special Populations

Based on population PK analysis, the impact of age (< 65 years, between 65 and 75 years, > 75 years) show no clinically relevant effect on tremelimumab exposure. Thus, no dose adjustment is required by age. Body weight (34.0-149 kg) had a statistically significant impact on clearance and central volume of distribution according to population PK analysis. However, the covariate changed tremelimumab population parameter estimates by less than 20% and can thus be regarded of minor clinical relevance. No dose adjustment is required by body weight (>30 kg).

No formal hepatic and renal impairment studies have been conducted with tremelimumab. Based on population PK analysis, mild to moderate renal impairment (CLcr 30 to 89 mL/min) and mild to moderate hepatic impairment (bilirubin < 3 x ULN and any AST) had no clinically significant effect on the PK of tremelimumab. The effect of severe renal impairment (CLcr 15 to 29 mL/min) or severe hepatic impairment (bilirubin > 3 x ULN and any AST) on the PK of tremelimumab is unknown. In summary, no dose adjustment are required by mild to moderate renal and hepatic impairment. Data from patients with severe renal and hepatic impairment are too limited and insufficient to give a dose recommendation in these group.

In the HIMALAYA study, of the 182 patients who were treated with a single dose of tremelimumab in combination with durvalumab once in every 4 weeks therapy and evaluable for the presence of ADAs against tremelimumab at predose week 0 and week 4, 11% (20/182) of patients tested positive for anti-tremelimumab antibodies. Among the 20 patients who tested positive for ADAs 40% (8/20) tested positive for neutralizing antibodies against tremelimumab. The presence of tremelimumab ADA did not impact tremelimumab PK as it was not identified as a significant covariate in the tremelimumab population PK analysis.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The Applicant provided a pivotal study (HIMALAYA) to claim the efficacy of tremelimumab plus durvalumab for treatment in adult patients with advanced HCC.

When comparing efficacy of primary endpoint OS, superior trend was found in T300+D arm (vs S arm), with HR = 0.78, CI = [0.65, 0.93], p-value = 0.0035. When testing NI of D arm (vs S arm), the trend was positive (with upper bound CI of HR = 1.03 < margin = 1.08).

Sensitivity and supportive analyses mostly coincided with the main analysis result.

Note:

1. T300+D arm：tremelimumab as a one-time single intravenous infusion of 300 mg in combination with durvalumab 1,500 mg on the same day, followed by durvalumab every 4 weeks.
2. D arm: durvalumab 1,500 mg every 4 weeks
3. S arm: sorafenib 400 mg given orally twice daily

Therefore, it is statistically evidential for the Applicant to claim the efficacy of treatment for T300+D to unresectable HCC subjects.

2.4.2 Safety Results

In the HCC T300+D pool, the most commonly reported AEs (reported by ≥ 15% patients) were pruritus, diarrhea, rash, fatigue, decreased appetite, and AST increased. The most commonly reported SAEs (reported by ≥ 2% patients) were pneumonia (2.2%), colitis (2.2%) and diarrhea (2.4%). Immune mediated AE (imAE), which may be severe or fatal, are a risk of the T300+D combination regimen. In Study HIMALAYA, imAEs were reported at a higher frequency in the tremelimumab containing treatment arms (T300+D, 35.8% patients) compared with those reported in the D arm (16.5% patients) and S arm (8.0%). Serious imAE related to treatment occurred in 10.6% patients in T300+D arm, 4.9% in D arm and 1.1 % in S arm. Six patients (1.5%) in the HIMALAYA T300+D arm died due to imAEs (pneumonitis, 3 hepatic events [1 hepatitis and 2 immune-mediated hepatitis], myocarditis, and myasthenia gravis); there were no fatal imAEs in the S arm.

Overall, the safety and tolerability of tremelimumab administered in combination with durvalumab was generally consistent with the known safety profile for each agent, and AEs were generally manageable according to toxicity management guidelines.

2.5 Bridging Study Evaluation

PK

A comparison of tremelimumab PK was conducted in the East-Asian region and the non-Asian region within study HIMALAYA and study 22. The results showed that peak and trough tremelimumab concentration distributions between the East-Asian and the non-Asian patients are generally similar. In addition, based on the population PK analysis, the stimulated $AUC_{0\text{-}inf}$ and C_{max} of the East-Asian patients was similar to that of the non-Asian patients.

Besides, according to ICH E5 guideline, the ethnic sensitivity factors of tremelimumab were evaluated. Considering the results of tremelimumab PK comparison between the East-Asian

and the non-Asian patients, and the evaluation of ICH E5 ethnic sensitivity factors, PK characteristics of tremelimumab is considered to be none to minimally ethnically sensitive.

Clinical

In pivotal study HIMALAYA and supportive study 22 pool, 267 East Asian patients (from Taiwan、Hong Kong、Japan、South Korea) are enrolled.

Efficacy:

In East Asian subpopulation in study HIMALAYA, improvement in OS in patients randomized to the T300+D arm compared to those who were randomized to the sorafenib arm was demonstrated, which is consistent with that observed in the entire study population.

Safety:

The safety results in the East Asian subpopulation were generally similar to those in the entire study population.

In summary, the submitted PK, clinical efficacy and safety data can support the proposed dosage of tremelimumab for the claimed indication for Taiwanese patients. No further bridging study was needed.

2.6 Conclusion

This multidisciplinary review recommends approval for IMJUDO Injection 20mg/ml (Tremelimumab) for the indication of:

IMJUDO, in combination with durvalumab, is indicated for the treatment of adult patients with advanced or unresectable HCC who have not received prior systemic therapy.

3. Post-Marketing Requirements

No post marketing requirement is needed.