Taiwan Food and Drug Administration

Assessment Report

Trade Name：
隆保注射劑 20 毫克/毫升/ OMVOH Injection 20mg/mL
隆保注射劑 100 毫克/毫升/ OMVOH Injection 100mg/mL

Active Ingredient：Mirikizumab

License Number：MOHW-BI 001247/ MOHW-BI 001246

Applicant：台灣禮來股份有限公司

Approval Date：112.11.17

Indication：
對傳統治療或生物製劑治療反應不佳、失去反應、或無法耐受的中度至重度活動性潰瘍性結腸炎成人病人。

Treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or biological treatment.

Background Information

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Active Ingredient(s)	Mirikizumab
Applicant	台灣禮來股份有限公司
Dosage Form & Strengths	注射液劑
Indication	對傳統治療或生物製劑治療反應不佳、失去反應、或無法耐受的中度至重度活動性潰瘍性結腸炎成人病人。 Treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or biological treatment.
Posology	詳見仿單
Pharmacological Category **ATC Code**	L04AC24

Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

General information

DS, Mirikizumab is a humanized, immunoglobulin G4 (IgG4) isotype monoclonal antibody against the p19 subunit of human interleukine 23 (IL-23), which is an important driver of mucosal inflammation in ulcerative colitis.

Drug product (DP), OMVOH^{TM} has two strengths, 300 mg/15 mL and 100 mg/mL, in respective glass vial and pre-filled syringe packages for *i.v.* and *s.c.* administration use, which is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis.

2.1.1 Drug substance (DS)

Manufacturing

Mirikizumab DS manufacturing process involves cell culture and harvest, detergent and pH virus inactivation, purifications, virus filtration, and DS formulation. The resulting DS bulk is then filtered into plastic containers with appropriate storage.

Controls

Overall, the safety of mirikizumab in relation to adventitious agents demonstrated by the strategies including raw material control and the down-scale viral clearance studies, is considered adequate.

Process validation

The validation of the mirikizumab DS manufacturing process was carried and focused on process consistency, especially in impurities removal, and viral clearance.

The additional analytical comparison data supports that batches manufactured by commercial processes are consistent to the historical records.

Characterization

Extensive characterization studies are conducted in physicochemical (primary sequences, PTM, size variants, charge variants and higher-order immunoglobin structure etc.), as well as biological and immunochemical characterization. The biological activity of mirikizumab is tested by dose-response inhibition curve.

DS specification

The proposed release specifications of DS including general appearance, identity, purity, impurities, potency, quantity, and microbiological tests, are considered adequate.

Reference materials

A two-tiered reference standards (RS) consisting of a primary/working standards (PRSs/WRSs), have been established for release testing.

Stability

Stability has been demonstrated by real-time data from primary stability batches made by commercial process. It revealed that DS is stable under long-term condition, which supports the proposed 48 months of shelf-life, when stored at the recommended temperature.

2.1.2 Drug product

Drug product, OMVOH^{TM} injection, contains two different presentations, namely, 300 mg/15 mL Vial and 100 mg/mL Semi-filled syringe (SFS).

Manufacturing process and controls

Both Vial and SFS presentations for OMVOHTM DP, are manufactured and released at Eli Lilly. The critical process parameters, key process parameters, in-process control tests that control the critical steps were provided.

Process validation and/or evaluation

Consecutive DP batches each of presentation are used for the manufacturing process validation. Overall, the validation studies have demonstrated that the manufacturing process of OMVOH^{TM} injection DP batches are robust.

DP Specification

The release specifications for OMVOH DPs include general tests, identity, quantity, purity/impurities, size and charge variants, potency, endotoxins, sterility, container closure integrity and device dosing accuracy.

Stability of the DP

The long-term stability data for primary stability DP batches and supportive batches, are provided. In addition, the photo stability studies have also been performed on respective DP batches according to specified ICH guideline.

The stability data provided could support the proposed shelf-life of 24 months when the DP (including the vial, and SFS DP assembled in devices, e.g., PFS and pre-filled Pen) are stored at the recommend condition (2 - 8°C) and protected from light. The stability data also could support the claim that, after SFS DP was once taken out of long-term storage condition, the permit storage period at room temperature (not more than 30°C) is two weeks or up to the expiration date.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

In vitro pharmacodynamic studies revealed that mirikizumab specifically bound to human IL-23 and neutralized IL-23-induced IL-17 release and Th17 proliferation with IC_{50} values in the low picomolar range. In vivo neutralization assays showed that mirikizumab inhibited the pro-inflammatory mRNA expression in rhIL-23-induced psoriasis-like mice models. Moreover, mirikizumab inhibited the ex vivo mIL-17 production in the hIL-23/IL-2-primed rodent splenocytes upon CD3/CD28-restimulation. The potential effect of mirikizumab on cardiovascular, neurological, and respiratory systems has been investigated in monkeys, and no significant liabilities were identified.

2.2.2 Toxicological Studies

Mirikizumab (IV and SC) was evaluated in GLP-compliant toxicity studies for up to 6 months in monkeys. Cynomolgus monkey is the only relevant species of mirikizumab, although the mirikizumab has a 2.6-fold lower binding affinity for cynomolgus monkey IL-23 than that for human IL-23. The toxicity finding was noted in 1 female monkey, which was sporadic, idiosyncratic, non-dose responsive immune-mediated hemolytic effect at 300 mg/kg/twice weekly. Genotoxicity and carcinogenicity studies are not warranted. Enhanced PPND study showed that

mirikizumab had no significant effect on pregnant monkeys and fetal development during the organogenesis and parturition stage. Known or suspected ADA formation caused lower exposure in some animals in repeat-dose toxicology studies, but did not impact interpretation. This IgG based bsAb may cross the placenta, resulting in fetal exposure during pregnancy, or may be transmitted to a nursing infant. The patients should implement contraception and avoid breastfeeding while receiving mirikizumab. Mirikizumab had no unexpected cross-reactivity in human or monkey tissues, and no evidence of potential risk of cytokine release syndrome was identified in non-clinical studies.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

OMVOH is indicated for the treatment of moderately to severely active ulcerative colitis in adult. OMVOH contains the active substance mirikizumab, which is a humanized immunoglobulin G4 (IgG4) variant monoclonal antibody (mAb) that is directed against the p19 subunit of IL-23 and does not bind IL-12.

OMVOH has two dosage strengths, one is an intravenous (IV) infusion solution with 20 mg/ml (300 mg/15 ml) strength in a single-dose vial, and the other one is 100 mg/ml strength in a single-dose prefilled autoinjector (AI; also called prefilled pens) for subcutaneous (SC) injection. The recommended induction dosage of OMVOH is 300 mg administered by intravenous infusion over at least 30 minutes at Week 0, Week 4 and Week 8, and the recommended maintenance dosage of OMVOH is 200 mg administered by subcutaneous injection at Week 12 and every 4 weeks thereafter.

The SC absolute bioavailability was about 47.6%, and T_{max} was achieved approximately 3 days following SC administration. Although the exposure ($C_{max,ss}$ and AUC_{ss}) between SC and IV administration were extremely different, the $C_{trough,ss}$ was comparable between them. The exposure of mirikizumab increased proportionally over a dose range of 60 to 2400 mg given as an IV injection or over a dose range of 120 to 400 mg given as a SC injection. There was no apparent accumulation when administered mirikizumab via SC injection route every 4 weeks. The total volume of distribution in subjects with ulcerative colitis was 4.83 L. The estimated systemic clearance and $T_{1/2}$ were 0.0229 L/h and 9.33 days, respectively, in UC patients. Clearance was independent of dose.

2.3.2 Interaction Studies

No dedicated DDI study was conducted. Mirikizumab is not anticipated to be eliminated intact in the urine or to be metabolized by the CYP450 enzymes. Thus, the potential of DDI was low. The DDI between mirikizumab (250 mg, SC Q4W, for 5 doses) and CYP probe substrates (CYP 3A4, CYP 2C9, CYP 2D6, CYP 2C19 and CYP 1A2) in patients with

moderate-to-severe psoriasis showed that mirikizumab did not have impact on the PK of probe substrates.

2.3.3 Special Populations

Since mirikizumab is a monoclonal antibody, it is expected to be degraded into small peptides and amino acids via catabolic pathways and is not excretion via renal route. Thus, it is not necessary to adjust dose in hepatic or renal impairment patients. Although the exposure of mirikizumab decreased with increasing body weight (BW), and vice versa. However, considering the exposure-response relationship and the extent of exposure difference, it is acceptable that not necessary adjust dose based on body weight.

Overall, the pharmacokinetic studies conducted were satisfactory met the minimum requirements to support the marketing authorization of OMVOH. It is recommended to approve the NDA of OMVOH from the PK/PD perspective.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

Two pivotal Phase III, randomized, placebo-controlled studies, one 12-week induction trial I6T-MC-AMAN and one 40-week maintenance trial I6T-MC-AMBG, supported the efficacy OMVOH® (Mirikizumab) for the treatment of adult patients with moderately to severely active ulcerative colitis.

Study AMAN had demonstrated that mirikizumab induction dosing (300 mg mirikizumab IV Q4W) was superior to placebo for the primary endpoint, clinical remission at Week 12 (24.2% vs. 13.3%; p=0.00006), and all major secondary endpoints, alternate clinical remission at Week 12 (25.6% vs. 14.6%; p=0.00007), clinical response at Week 12 (63.5% vs. 42.2%; p <0.00001), clinical response in biologic-failed population at Week 12 (54.6% vs. 29.7%; p<0.001), endoscopic remission at Week 12 (36.3% vs. 21.1%; p<0.00001), symptomatic remission at Weeks 4 and 12 (Week 4: 21.8% vs. 12.9%; p=0.00064. Week 12: 45.5% vs. 27.9%; p<0.00001), histologic-endoscopic mucosal improvement at Week 12 (27.1% vs. 13.9%; p<0.00001), and Bowel Movement Urgency NRS at Week 12 (LSMean change (SE): -2.59 (0.083) vs. -1.63 (0.141); p<0.00001).

Study AMBG had demonstrated, among mirikizumab induction responders in Study AMAN, that mirikizumab maintenance dosing (200 mg SC Q4W) was superior to placebo for the primary endpoint, clinical remission at Week 40 (49.9% vs. 25.1%; p<0.001), and all major secondary endpoints, alternate clinical remission at Week 40 (51.8% vs. 26.3%; p<0.001), endoscopic remission at Week 40 (58.6% vs. 29.1%; p<0.001), histologic-endoscopic mucosal remission at Week 40 (43.3% vs. 21.8%; p<0.001), Bowel Movement Urgency NRS at Week

40 (LSMean change (SE): -3.80 (0.139) vs. -2.74 -(0.202); p<0.001), corticosteroid-free remission without surgery at Week 40 (44.9% vs. 21.8%; p<0.001), Urgency Remission at Week 40 (with Urgency NRS ≥3 at induction baseline) (42.9% vs. 25.0%; p<0.001), and clinical remission at Week 40 among clinical remitters at AMAN Week 12 (63.6% vs. 36.9%; p<0.001).

2.4.2 Safety Results

Two pivotal Phase III, randomized, placebo-controlled studies, one 12-week induction trial 16T-MC-AMAN and one 40-week maintenance trial 16T-MC-AMBG, supported the safety of mirikizumab (OMVOH™) for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment.

The overall safety profiles were similar between the mirikizumab and the placebo group. The majority of treatment-emergent adverse events (TEAEs) were mild or moderate in intensity. The frequency of severe TEAEs, serious adverse events (SAEs) or TEAEs leading to study treatment discontinuation was lower in the mirikizumab group compared with the placebo group.

During the 12-week induction treatment period, TEAE clusters of upper respiratory tract infection, headache, herpes simplex infection, and rash were reported more commonly in the mirikizumab group compared to the placebo group.

During the 40-week maintenance treatment period, TEAE clusters of upper respiratory tract infection, headache, fatigue, hypertension, herpes simplex infection, rash, diarrhea, and tinea infection were reported more commonly in the mirikizumab group compared to the placebo group.

There were 5 deaths in the mirikizumab UC clinical studies. Three deaths occurred after discontinuation of mirikizumab treatment, one death occurred during the maintenance treatment period with placebo, and one death of COVID-19 occurred during the maintenance treatment period with mirikizumab.

The incidence of opportunistic infections was slightly higher in the mirikizumab group compared to the placebo group. The most frequently reported event was herpes zoster infection.

Hypersensitivity reactions were another more commonly reported TEAE with mirikizumab. Injection site reaction was also more commonly reported with mirikizumab administered by subcutaneous injection.

One subject who was a non-responder to the initial induction therapy and received additional one additional induction dose of mirikizumab met Hy's Law and was considered as having a drug-induced liver injury (DILI) associated with mirikizumab. This event resolved after treatment discontinuation without specific treatment.

Among the 378 evaluable subjects across the two placebo-controlled studies through 52 weeks, 88 (23.3%) were treatment-emergent anti-drug antibody (TE ADA) positive, and the majority were neutralizing antibody. No clinically meaningful differences in the frequency of hypersensitivity, injection site, and infusion site reactions were observed in TE ADA positive patients compared with TE ADA negative patients.

2.5 Bridging Study Evaluation

There were 185 (15.9%) East Asian subjects among the 1162 subjects enrolled in the 12-week induction trial 16T-MC-AMAN, and 92 (16.9%) East Asian subjects among the 544 subjects enrolled in the 40-week maintenance trial 16T-MC-AMBG.

The pharmacokinetics, efficacy and safety of mirikizumab were similar between East Asian and Western subjects. The incidence of immunogenicity in East Asian patients was higher than that in non-East Asian patients. The data showed that patients with postbaseline treatment emergent antidrug antibody positive (TE ADA+) in East Asian patients was 50% (30 of 60), but it was only 18.6% (60 of 329) in non-East Asian patients. Besides, these TE ADA+ East Asian patients almost belonged to neutralizing antidrug antibodies (46.7%; 28 of 60). When evaluating the impact of TE ADA+ on PK of mirikizumab, it was observed that higher ADA titer (> 1:160) could cause lower mirikizumab exposure. And, it was more been seen in Asian subjects.

Overall, there was sufficient data to investigate the ethnic difference. Thus, bridging study can be waive from PK and clinical point of view.

2.6 Conclusion

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

1. Recommended indication: Mirikizumab is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment.
2. Recommended posology:
   (1) Induction dose: 300 mg by intravenous infusion for at least 30 minutes at Week 0, 4, and 8.

Patients should be evaluated after the 12-week induction dosing and if there is adequate therapeutic response, transition to maintenance dosing. For patients who do not achieve adequate therapeutic benefit at week 12 of induction dosing, mirikizumab 300 mg by intravenous infusion may be continued at weeks 12, 16 and 20 (extended induction therapy). If therapeutic benefit is achieved with the additional intravenous therapy, patients may initiate mirikizumab subcutaneous maintenance dosing every 4 weeks, starting at week 24. Mirikizumab should be discontinued in patients who do not show evidence of therapeutic benefit to extended induction therapy by week 24.

(2) Maintenance dose: 200 mg by subcutaneous injection every 4 weeks after completion of induction dosing.

Patients with loss of therapeutic response during maintenance treatment may receive 300 mg mirikizumab by intravenous infusion every 4 weeks, for a total of 3 doses (re-induction). If clinical benefit is achieved from this additional intravenous therapy, patients may resume mirikizumab subcutaneous dosing every 4 weeks. The efficacy and safety of repeated re-induction therapy have not been evaluated.

3. Shelf-life: 24 months stored at the recommend condition (2-8℃) and protected from light.

3. Post-Marketing Requirements

1. Taiwan Risk Management Plan
2. Submit the complete clinical study report of extension trial 16T-MC-AMAP.