swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Omvoh

International non-proprietary name: mirikizumab
Pharmaceutical form: concentrate for solution for infusion
Dosage strength(s): 300 mg
Route(s) of administration: intravenous
Marketing authorisation holder: Eli Lilly (Suisse) SA
Marketing authorisation no.: 68950
Decision and decision date: approved on 30 November 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
IV	Intravenous
LoQ	List of Questions
mAB	Monoclonal antibody
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MMS	Modified Mayo Score
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SC	Subcutaneous
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
UC	Ulcerative colitis

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for mirikizumab in the above-mentioned medicinal product.

Work-sharing procedure
The applicant requested a work-sharing procedure with Australia.
The Access NAS (new active substance) work-sharing initiative is a collaboration between regulatory authorities – specifically Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA) and Swissmedic - and the pharmaceutical industry.
The work-sharing initiative involves the coordinated assessment of NAS applications that have been filed in at least two jurisdictions.

2.2 Indication and dosage

2.2.1 Requested indication

Omvoh 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 conventional therapy or a biologic treatment or a Janus kinase (JAK) inhibitor, or have medical contraindications to such therapies.

2.2.2 Approved indication

Omvoh 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, or have medical contraindications to such therapies (see "Properties/Effects").

2.2.3 Requested dosage

Summary of the requested standard dosage:

The recommended induction dose of Omvoh is 300 mg administered as an intravenous infusion for at least 30 min. at weeks 0, 4, and 8.

The recommended maintenance dose of Omvoh is 200 mg administered as 2 subcutaneous injections of 100 mg at week 12 and every 4 weeks thereafter.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	27 June 2022
Formal objection	29 June 2022
Response to formal objection	6 July 2022
Formal control completed	28 July 2022
List of Questions (LoQ)	25 November 2022
Response to LoQ	24 January 2023
Preliminary decision	10 March 2023
Response to preliminary decision	10 April 2023
2nd Preliminary decision	8 June 2023
Response to 2nd preliminary decision	17 July 2023
Labelling corrections	12 October 2023
Response to labelling corrections	13 November 2023
Final decision	30 November 2023
Decision	approval

3 Medical context

Ulcerative colitis (UC) is a chronic inflammatory condition characterised by relapsing and remitting episodes of inflammation of the colon's mucosa, almost always involving the rectum. Onset is typically between 15 and 30 years of age with a second smaller peak between 50 and 70 years of age. UC is characterised by a balanced gender ratio.

Diarrhoea is the main symptom of UC. It may be associated with blood in the stool. Other symptoms include frequent bowel movements, abdominal pain, urgency, tenesmus, and incontinence. The onset of symptoms is usually gradual and may be self-limiting. The severity of symptoms ranges from mild (defined as up to 4 bowel movements per day) to severe (defined as more than 10 bowel movements per day with cramps and bleeding). Systemic symptoms may occur, such as fever, fatigue, and weight loss.

The severity of UC can be estimated using the Mayo Score. In the clinical development programme for mirikizumab, a modified version of the Mayo Score (Modified MS (MMS)) was used with 0 points indicating no active disease and 9 points indicating severe disease.

The treatment goals of UC depend on the severity of symptoms. Important criteria of clinical efficacy refer to the induction of clinical remission, the maintenance of steroid-free remission, the prevention of hospitalisation and/or surgery, and improved quality of life. In most cases, mesalazine and corticosteroids represent the backbone of treatment. Novel treatment strategies include antibodies targeted against tumour necrosis factors (TNF), interleukin-12/-23, or integrin.

Mirikizumab is a humanised IgG4 antibody with high affinity and specificity to interleukin-23, offering a therapeutic alternative to well-established anti-TNF antibodies and the already-approved interleukin-12/-23 antibody ustekinumab. Mirikizumab treatment is initiated with a 12-week intravenous induction phase followed by a subcutaneous maintenance phase.

4 Quality aspects

4.1 Drug substance

Mirikizumab is a recombinant humanised monoclonal antibody (IgG4,κ) that binds to the p19 subunit of human IL-23 cytokine, inhibits its interaction with the IL-23 receptor, and thus affects the production of pro-inflammatory cytokines. Mirikizumab consists of 2 heavy and 2 light chains connected by inter-chain disulfide bonds. Both heavy chains contain 1 oligosaccharide chain in the conserved Fc site (Asn292).

Mirikizumab is expressed in a Chinese hamster ovary (CHO) cell line and is manufactured using a fed-batch production process in a production bioreactor. The cell culture fluid is harvested and the antibody is purified by several chromatographic and filtration steps, including virus inactivation and virus removal steps. The drug substance manufacturing process is performed by Eli Lilly Kinsale Ltd, Kinsale, Ireland. The fermentation and purification process was validated using 3 consecutive batches, demonstrating a consistent manufacturing process that effectively reduces process-related impurities. The characterisation of the physicochemical and biological properties of the drug substance and its impurities were performed using state-of-the-art methods.

The specifications for release include relevant tests and limits, e.g. for description, colour, clarity, identity, several purity/impurity tests (e.g. SEC-HPLC, non-reduced CE-SDS), imaged capillary isoelectric focusing, protein concentration, and a potency assay (cell-based bioassay). Specifications are based on clinical data and batch analysis and are in conformance with current compendial or regulatory guidelines. Batch analysis data from development, clinical, and process validation batches were provided. All batch release data comply with the drug product specifications, which were valid at the time of batch release. All specific analytical methods are described and are fully validated.

The drug substance is stored frozen. No changes were observed within the proposed storage conditions. A shelf life of 36 months at long-term (≤-65°C) storage has been accepted.

4.2 Drug product

Three different presentations of the finished product are offered. The product Omvoh is available as 300 mg product solution for injection/infusion, which is supplied as a sterile liquid in a single-use vial. Furthermore, Omvoh is available as 100 mg solution for injection in a pre-filled syringe or pre-filled autoinjector. All excipients used comply with the European Pharmacopoeia.

The finished product manufacturing process consists of pooling and mixing of the drug substance, sterile filtration, aseptic filling, stoppering/capping or plungering, respectively, and inspection steps, and is conducted at Eli Lilly and Company, Indianapolis, IN, USA. Process validation studies were executed at commercial scale using 3 validations batches each for vials and syringes.

The release and stability specifications include relevant tests and limits, e.g. for appearance, identity, pH, osmolality, purity and impurities tests (SEC, non-reduced CE-SDS, icIEF), a potency assay (cell-based bioassay), protein concentration, particles, sterility, and bacterial endotoxins. All specific methods are validated in accordance with ICH guidelines. Batch analysis data from development, clinical, and process validation batches were provided. All batch release data comply with the drug product specifications valid at the time of batch release.

The drug product is stored in 20 mL Type I glass vials or 1 mL syringes at 2-8°C, protected from light. Each vial is closed with a chlorobutyl rubber stopper which is secured in place with a 2-piece flip-top aluminium seal. Each syringe or autoinjector contains a bromobutyl, laminated, coated elastomer plunger. All primary components are Ph.Eur. and USP-compliant. A shelf-life of 24 months at 2-8°C has been accepted.

4.3 Quality conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf life of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk of adventitious agents is minimised.

5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant’s request / Work-sharing procedure).

6 Clinical aspects

6.1 Clinical pharmacology

ADME

The PK of mirikizumab was assessed following single IV doses over a range of 5 to 2400 mg and single SC doses over a range of 120 to 400 mg in healthy subjects and patients with psoriasis and following multiple doses up to 600 mg every 4 weeks (Q4W; IV) and up to 200 mg Q4W (SC) in UC patients.

Absorption

Following SC administration of mirikizumab in patients with UC, peak concentrations were achieved within 2 to 3 days. The absolute bioavailability following SC administration of 200 mg of mirikizumab in patients with UC was 42%.

Exploratory comparisons of the bioavailability following administration into the upper arm, abdomen, or thigh indicated only small (max. 22%) differences in mean exposure values. These differences are regarded as not clinically relevant and administration at all these sites is acceptable.

Distribution

In a PopPK analysis, the mean central and peripheral volume of distribution were 3.1 L and 1.7 L, respectively, in patients with UC, which are typical values for a monoclonal antibody (mAB).

Metabolism and excretion

The metabolism of mirikizumab was not studied specifically, which is acceptable considering the biologic nature of the molecule. Mirikizumab is expected to be degraded into small peptides and amino acids via standard protein catabolic pathways.

In a PopPK analysis, the mean systemic clearance was estimated at 0.0229 L/h in patients with UC and the elimination half-life was estimated at 9.3 days. This is consistent with a half-life of approximately 10 days observed across the various Phase 1 studies.

Dose proportionality

Mirikizumab exposure increased proportionally with increasing dose over a dose range of 5 to 2400 mg IV or over a dose range of 120 to 400 mg SC.

PK after multiple doses

No considerable accumulation of mirikizumab after administration of multiple doses (Q4W or every 12 weeks (Q12W)) could be observed.

Special populations

Comparison of the PK parameters between healthy subjects and patients with UC, across studies, indicated a comparable PK of mirikizumab.

Potential effects of intrinsic factors on the PK of mirikizumab in UC patients were assessed in the PopPK analysis. The PopPK model of mirikizumab in patients with UC was a 2-compartment model with first order absorption following SC administration and linear clearances.

Body weight

The overall range of body weights in the Phase 3 PopPK dataset was 34 to 152 kg. As expected for an mAB drug, body weight had a significant effect on clearance and volume of distribution. Both parameters increased with increasing body weights, but the impact on the mirikizumab exposure was limited. The median AUC in patients in the highest (83 to 152 kg) and lowest (38 to 60.4 kg) body weight quartiles was 16% lower and 19% higher than the median AUC in the overall population, respectively.

Albumin (disease state)

Albumin is understood to reflect disease severity, which is linked to general metabolic turnover (patients with more severe disease tend to have lower albumin concentrations, and patients with

lower albumin concentrations tend to have a higher clearance). This effect is physiologically plausible and has been observed previously for other antibody drugs. The effect of varying albumin on mirikizumab exposure was limited (<10% difference in AUC in the lowest and highest albumin level quartiles compared to the overall mean).

BMI on bioavailability

In addition to the effect of BW on the clearance and volume terms, a significant covariate effect of body mass index (BMI) on bioavailability was found: patients with a lower BMI had higher bioavailability following SC administration. The median $AUC_{tau,SS}$ following SC administration in patients in the highest (26.8-53.5 kg/m^2) and lowest (13.8-21.3 kg/m^2) BMI quartiles was 30% lower and 33% higher than the median AUC in the overall population, respectively.

Race

The PK of mirikizumab in Japanese or Chinese subjects was assessed in dedicated studies and compared to the PK in Caucasian subjects as part of the PopPK analysis. No significant effect of race (74.7% Caucasian, 22.2% Asian, others <2% each) was found.

Age and sex

The PopPK dataset included 60.9% male and 39.1% female patients. 1,045 (92.6%) patients in the dataset were <65 years, 73 (6.5%) were 65-<75 years, and 11 (1.0%) were >75 years of age. No significant covariate effects of age or sex were identified.

Renal and hepatic impairment

No specific studies to evaluate the effects of renal and hepatic impairment on the PK of mirikizumab have been conducted. This is acceptable considering the biologic nature of the molecule.

Potential effects of creatinine clearance (range of 36.2 to 291 mL/min) and baseline bilirubin (range of 1.5 to 29 µmol/L) on mirikizumab clearance were assessed as part of the PopPK analysis. No significant effects were identified.

Immunogenicity

No significant covariate effect for ADAs on mirikizumab clearance was identified. However, the lack of statistical significance may be due to low power as only a low number of patients (n=10) developed a high titre ADA response. In this subgroup of patients with high ADA titre, the clearance tended to be lower than in ADA negative patients.

Interactions

Drugs that modulate proinflammatory cytokines have the potential to indirectly affect CYP activity. The potential of mirikizumab for this type of DDI has been assessed in a dedicated cocktail DDI study in patients with moderate to severe psoriasis. Following concomitant administration of CYP probe substrates with multiple doses of mirikizumab, the exposure (AUC and C_{max}) of midazolam (CYP3A substrate), S-warfarin (CYP2C9 substrate), dextromethorphan (CYP2D6 substrate), and caffeine (CYP1A2 substrate) were similar to exposures in the absence of mirikizumab. The geometric mean ratio (GMR) and corresponding 90% CIs were contained within 0.80-1.25 boundaries. In the case of omeprazole (CYP2C19 substrate), the upper limits of the 90% CI for the GMR of C_{max} and AUC (0-tlast) were 1.26. These results indicate a lack of an interaction effect of mirikizumab on CYP3A, CYP2C9, CYP2D6, CYP1A2, and CYP2C19 under steady-state conditions in patients with moderate to severe psoriasis. However, due to differences in the inflammatory status of UC and psoriasis patients, the lack of a DDI effect in patients with psoriasis cannot be simply extrapolated to UC patients.

Pharmacodynamics

Mechanism of action and primary pharmacology

Mirikizumab binds to the p19 subunit of interleukin-23 (IL-23), a proinflammatory cytokine, and thereby inhibits its interaction with the IL-23 receptor and downstream inflammatory signalling pathways.

Secondary pharmacology (safety)

No dedicated studies have been submitted. Considering the biologic nature of the molecule, effects on the QT interval are considered unlikely and the lack of respective studies is acceptable.

6.2 Dose finding and dose recommendation

Dose finding was mainly based on the results of the AMAC double-blind, placebo-controlled, Phase 2 study, where patients were randomly assigned to a 12-week IV Q4W (every 4 weeks) induction period with either placebo, or 1 of 3 dose regimens of mirikizumab (50 mg mirikizumab IV with an exposure-based dosing, 200 mg mirikizumab IV with an exposure-based dosing, or 600 mg mirikizumab IV fixed dose). Patients in the 200 mg mirikizumab IV arm achieved the best results but almost half of the patients required dose up-titration to an effective dose of 300 mg mirikizumab IV. The latter dose was then further investigated for induction therapy in the pivotal UC studies.
Patients who responded to the IV induction were subsequently treated either with 200 mg mirikizumab SC Q4W (every 4 weeks) or Q12W (every 12 weeks) for up to 52 weeks. Patients being treated every 4 weeks showed slightly favourable response rates at 52 weeks compared to patients being treated every 12 weeks. Therefore, the 200 mg mirikizumab SC Q4W was further investigated for maintenance therapy in the pivotal UC studies.

6.3 Efficacy

Two double-blind pivotal Phase 3 studies (AMAN for the induction phase and AMBG for the maintenance phase) were conducted in order to investigate mirikizumab in patients with moderate to severe UC who previously failed conventional UC therapy, other biologics, or JAK inhibitors.

AMAN study (“induction study”)

Methods: The AMAN study (“induction study”) included 1,281 patients aged 18 to 80 years who had an established diagnosis of UC and a modified Mayo Score of at least 4 (moderate) at baseline with an inadequate response, loss of response, or intolerance to either conventional, biologic, or tofacitinib therapy. Patients were randomised in a 3:1 ratio to 300 mg mirikizumab IV Q4W or placebo IV Q4W for up to 12 weeks. Overall, the investigated population was representative of the intended-to-treat patient population.

Efficacy results: At Week 12, more patients achieved the primary endpoint “clinical remission”[1] in the 300 mg mirikizumab IV Q4W arm compared to placebo (24.2% vs. 13.3%, p = 0.00006); similar results were found for most secondary endpoints, including “clinical response”[2] (63.5% vs 42.2%, p = <0.00001) and “endoscopic remission” (36.3% vs. 21.1%, p < 0.00001).

AMBG study (“maintenance study”)

Methods: The AMBG study (“maintenance study”) included 1,073 patients from the AMAN study, regardless of their response (i.e. mirikizumab responders, placebo responders, but also mirikizumab non-responders, and placebo non-responders). Depending on the induction treatment (mirikizumab or

[1] Clinical remission is based on the modified Mayo score (MMS) and was defined as
- stool frequency (SF) subscore = 0 or 1 with a ≥1-point decrease from baseline, and
- rectal bleeding (RB) subscore = 0, and
- endoscopic score (ES) = 0 or 1 (excluding friability)

[2] Clinical response is based on the modified Mayo Score (MMS) and was defined as:
- a decrease in the MMS of ≥2 points and ≥30% decrease from baseline, and
- a decrease of ≥1 point in the RB subscore from baseline or an RB score of 0 or 1

placebo) and the individual response (response, or non-response), patients were re-randomised to be treated with 200 mg mirikizumab SC Q4W or placebo SC Q4W (mirikizumab responders), and to placebo SC Q4W (placebo responders). All non-responders were treated open-label with 300 mg mirikizumab IV Q4W for 12 weeks ("re-induction"), followed by either 200 mg mirikizumab SC Q4W in case of response or discontinuation of the study in case of non-response after 12 weeks. Patients who responded to the induction therapy were eligible for a rescue therapy in case of loss-of-response during the maintenance phase.

Efficacy results: Overall, the results support maintenance treatment with 200 mg mirikizumab SC Q4W in patients who had responded to the induction treatment. Significantly more patients in the 200 mg mirikizumab SC Q4W treatment group achieved the primary endpoint "clinical remission at week 52" as compared to placebo (49.9% vs. 25.1% ($p < 0.001$)).
Furthermore, the study showed a clinically relevant benefit of a "re-induction" of 3 x 300 mg mirikizumab IV Q4W in case of non-response to a 300 mg mirikizumab IV induction treatment for 12 weeks.
The study also demonstrated a clinically relevant benefit for the rescue treatment with 3 x 300 mg mirikizumab IV Q4W in patients with loss-of-response under mirikizumab treatment during the maintenance phase.

Regarding the subgroup of patients with a history of failed tofacitinib treatment, the sample size in both studies was too small to draw any reliable conclusion. Therefore, this subgroup is not addressed in the indication wording approved for marketing authorisation (MA).

For further details, see the information for healthcare professionals.

6.4 Safety

Methods: Safety data refer to the AMAC dose-finding study, both pivotal studies AMAN (induction study) and AMBG (maintenance study), and partially (due to its ongoing character at MA) the AMAP long-term extension study. Most patients were treated for up to 52 consecutive weeks. In total, the exposure of patients with UC to mirikizumab is roughly 2,250 patient years.

Results: Overall, compliance was high, and only very few patients being treated with mirikizumab discontinued the study due to adverse events (induction phase 1.6%, maintenance phase 1.5%).
Induction phase: Within the first 12 weeks of treatment (induction phase), adverse events reported more often in mirikizumab- as compared to placebo-treated patients refer to Preferred Terms (PTs) within the SOC "infections and infestations" (15.1% vs. 14.0%), but also include headache (3.3% vs. 3.8%), arthralgia (2.1% vs. 1.2%), and pyrexia (1.5% vs. 0.9%).

Maintenance phase: Within the maintenance phase (weeks 13 to 52), the most prevalent adverse events reported at a higher rate in mirikizumab- as compared to placebo-treated patients refer to COVID-19 (2.1% vs. 2.1%), abdominal pain (2.8% vs. 2.1%), diarrhoea (2.6% vs. 0.5%), depression (0.5% vs. 0%), and injection site reactions (2.6% vs. 0.5%).
Several single-case neoplasms (malignant and benign) were reported exclusively in mirikizumab-treated patients. Even though this might give raise to some concern, no clear link to mirikizumab treatment could be established. Several of the reported neoplasms refer to presumably preexisting lower gastrointestinal neoplasms that had not been diagnosed in the baseline endoscopy due to difficult detection in the acutely inflamed mucosa.
During the UC clinical development programme, 5 deaths were reported, with 3 of them being related to COVID-19, so far. Interim data from the AMAP study did not reveal any prohibitive safety signal. Overall, the available safety data are limited, but this is acceptable in light of the ongoing long-term extension study (AMAP) that will contribute to a more precise safety profile.

For further details, see information for healthcare professionals.

6.5 Final clinical benefit-risk assessment

The general ADME characteristics of mirikizumab have been sufficiently described in healthy subjects and patients with UC. Consistent with theoretical expectations for a monoclonal antibody, body weight had a significant effect on mirikizumab exposure, but from the PK perspective, no dose adjustments are required based on demographic factors.

The data submitted demonstrate a statistically significant benefit compared to placebo of mirikizumab treatment in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or intolerance to either conventional therapy or a biologic treatment, or have medical contraindications for these therapies by achieving clinical remission after 12 weeks of induction and 52 weeks of maintenance treatment. Key primary findings are corroborated by the results for most of secondary endpoints.
The safety profile up to 52 weeks of treatment is similar to the already-approved agents in the UC indication in general and are therefore acceptable.
Overall, the benefit-risk assessment of mirikizumab is positive.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Omvoh was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

OMVOH ®

Composition

Active substances

Mirikizumab (monoclonal antibody produced in Chinese Hamster Ovary [CHO] cells)

Excipients

Sodium citrate dihydrate, citric acid, sodium chloride, polysorbate 80, water for injection q.s. ad solutionem pro 1 ml.

Total sodium content: 4 mg/mL.

Pharmaceutical form and active substance quantity per unit

Omvoh 300 mg concentrate for solution for infusion

Each vial contains 300 mg of mirikizumab in 15 ml (20 mg/ml)

Omvoh 100 mg solution for injection in prefilled syringe

Each prefilled syringe contains 100 mg of mirikizumab in 1 ml (100 mg/ml)

Omvoh 100 mg solution for injection in prefilled pen

Each prefilled pen contains 100 mg of mirikizumab in 1 ml (100 mg/ml)

Indications/Uses

Omvoh 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, or have medical contraindications to such therapies (see “Properties/Effects”).

Dosage/Administration

Omvoh is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of ulcerative colitis.

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

The recommended mirikizumab dose regimen has 2 parts:

Initiation of treatment

Induction dose with Omvoh 300mg concentrate for solution for infusion: 300 mg by intravenous infusion for at least 30 minutes at weeks 0, 4 and 8.

Maintenance therapy

Maintenance dose with Omvoh 100mg solution for injection in prefilled syringe or prefilled pen: 200 mg by subcutaneous injection every 4 weeks, starting at Week 12, after completion of induction dosing.

A full maintenance dose is **two** 100 mg pre-filled syringes or **two** 100 mg pre-filled pens.

After training in subcutaneous injection technique, a patient may self-inject with Omvoh.

Duration of treatment

Patients should be evaluated after the 12-week induction dosing and if there is adequate therapeutic response, transitioned to maintenance dosing. If patients do not have adequate therapeutic response at week 12 of induction dosing, consider continuing to dose with 300 mg mirikizumab by intravenous infusion 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 (200 mg) every 4 weeks, starting at week 24. Discontinue mirikizumab in patients who do not show evidence of therapeutic benefit to extended induction therapy by week 24.

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. If clinical benefit is achieved from this additional intravenous therapy, patients may resume mirikizumab subcutaneous dosing every 4 weeks, if not, therapy with mirikizumab should be discontinued.

Special dosage instructions

Patients with hepatic disorders

Omvoh has not been studied in this patient population. No dose recommendations can be made.

Patients with renal disorders

Omvoh has not been studied in this patient population. No dose recommendations can be made.

Elderly patients

No dose adjustment is required.

There is limited information in subjects aged ≥ 75 years.

Children and adolescents

The safety and efficacy of Omvoh in children and adolescents aged 2 to less than 18 years have not been studied.

There is no relevant use of Omvoh in children below 2 years for the indication of ulcerative colitis.

Mode of administration

Omvoh 300 mg concentrate for solution for infusion should only be used for the intravenous doses. It should be administered over at least 30 minutes. For instructions on dilution of the medicinal product before administration, see “Other information / Instructions for handling”.

Omvoh 100 mg solution for injection in pre-filled syringe or prefilled pen should only be used for the subcutaneous maintenance doses. Sites for injection include the abdomen, thigh, and back of the upper

arm. Instruct patients to inject in a different location every time. For example, if the first injection was in the abdomen, the second injection—to complete a full dose—could be in another area of the abdomen. In case of a missed dose, instruct patients to inject as soon as possible. Thereafter, resume dosing every 4 weeks.

Contraindications

Serious hypersensitivity to the active substance or to any of the excipients according to composition.
Clinically relevant, active infection (e.g. active tuberculosis, see «Warnings and Precautions")

Warnings and precautions

Hypersensitivity reactions

Serious hypersensitivity reactions including anaphylaxis may occur with mirikizumab administration. If a serious hypersensitivity reaction occurs, discontinue mirikizumab immediately and initiate appropriate therapy.

Infections

Mirikizumab increases the risk of infection. Mirikizumab must not be administered to patients with a clinically significant, active infection. Consider the risks and benefits of treatment prior to initiating use of mirikizumab in patients with a chronic infection or a history of recurrent infection. Instruct patients to seek medical advice if signs or symptoms of infection occur. If a serious infection develops, patients should be monitored closely and mirikizumab is to be discontinued until the infection resolves. Four deaths occurred in mirikizumab-treated participants in ulcerative colitis trials due to COVID-19 infection. Opportunistic infections were reported in clinical trials with mirikizumab.

Before starting therapy, patients should be evaluated for tuberculosis infection. Mirikizumab must not be given to patients with active tuberculosis (TB). An anti-TB therapy is to be initiated before starting mirikizumab in patients with latent TB. Anti-TB therapy prior to mirikizumab administration should also be considered in patients with a history of latent or active tuberculosis in whom adequate treatment has not been confirmed. Patients receiving mirikizumab should be closely monitored for symptoms of active tuberculosis during and after treatment.

Hepatic Enzyme Elevations

Elevations of aminotransferases have been reported in patients receiving mirikizumab. Evaluate liver enzymes as clinically indicated. If increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) are observed and drug-associated liver injury is suspected, discontinue mirikizumab until this diagnosis is excluded.

Immunizations

Prior to initiating therapy with mirikizumab, all appropriate immunizations should be completed according to current immunization guidelines. Avoid use of live vaccines (e.g. yellow fever vaccine) in

patients treated with mirikizumab. No data are available on the response to live or non-live vaccines including COVID-19 vaccines.

Malignancy

The risk of malignancy is increased in patients with ulcerative colitis. Immunomodulatory medicinal products may increase the risk of malignancy.

In the placebo-controlled induction phase of the ulcerative colitis clinical trials, no patients receiving placebo had a malignancy (without basal cell carcinomas and squamous cell carcinomas), and the incidence rate was 0.9 per 100 years of observation in patients treated with mirikizumab. No events of non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) were reported in patients treated with placebo or mirikizumab.

In the randomized withdrawal placebo-controlled maintenance phase of the ulcerative colitis clinical trials, no patients receiving placebo had a malignancy (without basal cell carcinomas and squamous cell carcinomas), and the incidence rate of malignancy (without basal cell carcinomas and squamous cell carcinomas) was 0.3 per 100 years of observation in patients treated with mirikizumab. The incidence rate of non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) was 0.8 per 100 years of observation in patients receiving placebo after mirikizumab induction and no events were reported in patients treated with mirikizumab in both the induction and maintenance phases.

Among all patients treated with mirikizumab in the UC Phase 3 clinical trials, the incidence rate of malignancies (without basal cell carcinomas and squamous cell carcinomas) was 0.5 per 100 years of observation, and the incidence rate of non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) was 0.2 per 100 years of observation.

Further information

Omvoh 300 mg concentrate for solution for infusion

This medicinal product contains 60 mg sodium per 300 mg dose, equivalent to 3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Omvoh 100 mg solution for injection in prefilled syringe / prefilled pen:

This medicinal product contains less than 1 mmol sodium (23 mg) per 200 mg dose, i.e., essentially “sodium-free”.

Interactions

In ulcerative colitis studies, concomitant use of corticosteroids or oral immunomodulators did not influence the safety of mirikizumab.

Population pharmacokinetic data analyses indicated that the clearance of mirikizumab was not impacted by concomitant administration of 5-ASAs (5-aminosalicylic acid), corticosteroids or oral immunomodulators (azathioprine, mercaptopurine, tioguanine, and methotrexate) in patients with ulcerative colitis.

No drug interaction study was conducted in subjects with ulcerative colitis at the recommended dosage. Based on a clinical drug interaction study, multiple SC doses of 250 mg every 4 weeks of mirikizumab did not result in changes in the exposure of CYP3A, CYP2C9, CYP2D6, CYP2C19, or CYP1A2 substrates in patients with moderate to severe plaque psoriasis.

Pregnancy, lactation

Women of childbearing potential

Women of childbearing potential should use an effective method of contraception during treatment and for at least 10 weeks after treatment.

Pregnancy

There is only a limited amount of data for the use of mirikizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see “Preclinical data”). As a precautionary measure, the use of Omvoh should be avoided during pregnancy.

Lactation

It is unknown whether mirikizumab is excreted in human milk. A risk to the newborn/child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to cease treatment with Omvoh. Both the benefit of breastfeeding for the child and the benefit of therapy for the woman must be taken into account.

Fertility

The effect of mirikizumab on human fertility has not been evaluated. No dedicated animal fertility studies have been conducted. In a repeat-dose toxicity study, no organ weight or histopathology effects were observed in the male or female reproductive tract in sexually mature cynomolgous monkeys.

Effects on ability to drive and use machines

No corresponding studies have been performed.

Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions over the 52-week treatment period were upper respiratory tract infections (most frequently nasopharyngitis), arthralgia, injection site reactions with subcutaneous administration, headache and rash.

List of adverse reactions

Adverse reactions from clinical studies are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each reaction is based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare

(≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000), unknown (cannot be estimated from the available data)

Infections and infestations

Common: upper respiratory tract infections, nasopharyngitis, sinusitis, urinary tract infection, vulvovaginal fungal infection, herpes zoster infection, rhinitis.

Uncommon: herpes simplex infection.

Immune system disorders

Uncommon: infusion-related allergic reaction, hypersensitivity.

Frequency unknown: anaphylaxis.

Psychiatric disorders

Uncommon: depression.

Nervous system disorders

Common: headache, migraine, hypoesthesia.

Uncommon: dizziness.

Eyes disorders

Uncommon: dry eyes.

Respiratory, thoracic and mediastinal disorders

Common: cough, oropharyngeal pain.

Uncommon: nasal congestion.

Gastrointestinal disorders

Common: gastroesophageal reflux.

Skin and subcutaneous tissue disorders

Common: rash.

Uncommon: contact dermatitis.

Musculoskeletal and connective tissue disorders

Common: arthralgia.

General disorders and administration site conditions

Common: injection site reactions[a].

Vascular disorders

Common: hypertension.

Investigations

Uncommon: Alanine aminotransferase increased, aspartate aminotransferase increased.

[a] *Reported in the mirikizumab maintenance study.*

Description of specific adverse reactions and additional information

Infusion-related hypersensitivity reactions

In the first 12 weeks (LUCENT-1), all infusion-related hypersensitivity reactions were reported as non-serious in 4 (0.4 %) mirikizumab-treated patients compared to 1 (0.3 %) patient in the placebo group.

Injection site reactions (LUCENT-2, weeks 12-52)

Injection site reactions were reported in 8.7 % mirikizumab-treated patients compared to 4.2 % patients in the placebo group. The most frequent events were injection site pain (4.4 % mirikizumab; 3.1 % placebo), injection site reaction (2.6 % mirikizumab; 0.5 % placebo) and injection site erythema (2.1 % mirikizumab; 1.0 % placebo). These symptoms were usually reported as non-serious, mild and transient in nature.

Hepatic enzyme elevations

In the first 12 weeks (LUCENT-1), ALT increased was reported in 4 (0.4 %) mirikizumab-treated patients compared to 1 (0.3 %) in the placebo group. AST increased was reported by 5 (0.5 %) mirikizumab-treated patients compared to 1 (0.3 %) in the placebo group. All events were reported as mild to moderate in severity and non-serious.

Over all mirikizumab treatment periods in the ulcerative colitis clinical development program (including the placebo-controlled and open label induction and maintenance periods), there have been elevations of ALT to ≥ 3 x upper limit of normal (ULN) (2.0 %), ≥ 5 x ULN (0.7 %) and ≥ 10 x ULN (0.2 %) and AST to ≥ 3 x ULN (2.1 %), ≥ 5 x ULN (1.1 %) and ≥ 10 x ULN (0.1 %) in patients receiving mirikizumab (see “Warnings and Precautions”). These elevations have been noted with and without concomitant elevations in total bilirubin.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. With 12 months of treatment, up to 23 % of mirikizumab-treated patients developed anti-drug antibodies, most of which tested positive for neutralising activity and with low titer. Higher antibody titers in approximately 2 % of subjects treated with mirikizumab were associated with lower serum mirikizumab concentrations and reduced clinical response. No association was found between anti-mirikizumab antibodies and hypersensitivity or injection-related events.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Mirikizumab doses up to 2400 mg intravenously and up to 500 mg subcutaneously have been administered in clinical trials without dose-limiting toxicity. In the event of overdose, monitor the patient for signs or symptoms of adverse reactions and start appropriate symptomatic treatment immediately.

Properties/Effects

ATC code

L04AC24

Mechanism of action

Mirikizumab is a humanized IgG4 monoclonal, anti-interleukin-23 (anti-IL-23) antibody that binds with high affinity and specificity to the p19 subunit of human IL-23 cytokine and inhibits its interaction with the IL-23 receptor. It has no observed cross-reactivity to other members of the IL-12 cytokine family (that is, IL-12, IL-27, and IL-35).

IL-23 is an important driver of mucosal inflammation in ulcerative colitis and affects the differentiation, expansion, and survival of T cell subsets, and innate immune cell subsets, which represent sources of pro-inflammatory cytokines. Research in animal models has shown that genetic deletion or pharmacologic inhibition of IL-23p19 can ameliorate or prevent intestinal inflammation.

Pharmacodynamics

Inflammatory biomarkers were measured in the phase 3 ulcerative colitis studies. Mirikizumab administered intravenously every 4 weeks during induction dosing significantly reduced levels of fecal calprotectin and C-reactive protein from baseline to week 12. Also, mirikizumab administered subcutaneously every 4 weeks during maintenance dosing sustained significantly reduced levels of fecal calprotectin and C-reactive protein through 40 weeks.

Clinical efficacy

The efficacy and safety of mirikizumab was evaluated in adult patients with moderately to severely active ulcerative colitis in two randomized, double-blind, placebo-controlled, multicentre studies (LUCENT-1 and LUCENT-2). Enrolled patients had a confirmed diagnosis of ulcerative colitis for at least 3 months and moderately to severely active disease, defined as a modified Mayo score of 4 to 9, including a Mayo endoscopy subscore ≥ 2. Patients had to have failed (defined as loss of response, inadequate response or intolerance) corticosteroids or immunomodulators (6-mercaptopurine, azathioprine) or at least one biologic (a TNFα antagonist and/or vedolizumab) or tofacitinib. Patients

who had failed 3 or more biologics were excluded from the studies, as were patients who have previously been treated with ustekinumab or risankizumab.

LUCENT-1 was an intravenous induction study with treatment of up to 12 weeks, followed by a 40 weeks subcutaneous randomized withdrawal maintenance study (LUCENT-2), representing up to 52 weeks of therapy. Mean age at inclusion was 42.5 years. 53.2 % had severely active disease with a modified Mayo score 7 to 9.

Efficacy results presented for LUCENT-1 and LUCENT-2 were based on central reading of endoscopies and histology.

LUCENT-1 included 1 162 patients in the primary efficacy population. Patients were randomised to receive a dose of 300 mg mirikizumab via intravenous infusion or placebo, respectively at week 0, week 4 and week 8 with a 3:1 treatment allocation ratio. The primary endpoint for the induction study was the proportion of subjects in clinical remission [modified Mayo score (MMS) defined as: Stool frequency (SF) subscore = 0 or 1 with a ≥ 1-point decrease from baseline, and rectal bleeding (RB) subscore = 0, and Endoscopic subscore (ES) = 0 or 1 (excluding friability)] at week 12.

Patients in these studies may have received other concomitant therapies including aminosalicylates, immunomodulatory agents (azathioprine, 6-mercaptopurine or methotrexate), and oral corticosteroids (prednisone daily dose up to 20 mg or equivalent). At induction baseline, 39.9 % of patients were receiving oral corticosteroids, 24.1 % were receiving immunomodulators and 74.3 % were receiving aminosalicylates.

57.9 % of patients had failed conventional therapy, but not a biologic or tofacitinib (57.1 % were biologic-naive and tofacitinib-naive). 41.2 % of patients had failed a biologic or tofacitinib. 36.3 % of the patients had failed at least 1 prior anti-TNF therapy. 3.4 % of patients had failed tofacitinib. 23.5 % of patients had an inadequate response to a biologic or tofacitinib.

In LUCENT-1 a significantly greater proportion of patients were in clinical remission in the mirikizumab treated group compared to placebo at week 12 (Table 1).

Table 1: Summary of key efficacy outcomes in LUCENT-1 (week 12)

	Placebo N=294		**Mirikizumab IV N=868**		**Treatment difference and 99.875 % CI**
	N	**%**	**N**	**%**	
Clinical remission*[1]	39	13.3 %	210	24.2 %	11.1 % (3.2 %, 19.1 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	27/171	15.8 %	152/492	30.9 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	10/118	8.5 %	55/361	15.2 %	- - -
Clinical response*[2]	124	42.2 %	551	63.5 %	21.4 % (10.8 %, 32.0 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	86/171	50.3 %	345/492	70.1 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	35/118	29.7 %	197/361	54.6 %	- - -

Endoscopic improvement*[3]	62	21.1 %	315	36.3 %	15.4 % (6.3 %, 24.5 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	48/171	28.1 %	226/492	45.9 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	12/118	10.2 %	85/361	23.5 %	- - -
Symptomatic remission*[4]	82	27.9 %	395	45.5 %	17.5 % (7.5 %, 27.6 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	57/171	33.3 %	248/492	50.4 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	22/118	18.6 %	139/361	38.5 %	- - -
Histo-endoscopic mucosal improvement*[5]	41	13.9 %	235	27.1 %	13.4 % (5.5 %, 21.4 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	32/171	18.7 %	176/492	35.8 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	8/118	6.8 %	56/361	15.5 %	- - -

Abbreviations: CI = confidence interval

*[1] *Clinical remission is based on the modified Mayo score (MMS) and is defined as: Stool frequency (SF) subscore = 0 or 1 with a ≥ 1-point decrease from baseline, and Rectal bleeding (RB) subscore = 0, and Endoscopic subscore (ES) = 0 or 1 (excluding friability)*

*[2] *Clinical response based on the MMS and is defined as: A decrease in the MMS of ≥ 2 points and ≥ 30 % decrease from baseline, and a decrease of ≥ 1 point in the RB subscore from baseline or a RB score of 0 or 1*

*[3] *Endoscopic improvement defined as: ES = 0 or 1 (excluding friability)*

*[4] *Symptomatic remission defined as: SF = 0, or SF = 1 with a ≥ 1-point decrease from baseline, and RB = 0*

*[5] *Histo-endoscopic mucosal improvement defined as achieving both: 1. Histologic improvement, defined using Geboes scoring system with neutrophil infiltration in < 5 % of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue. 2. Endoscopic improvement, defined as ES = 0 or 1 (excluding friability).*

a) An additional 5 patients on placebo and 15 patients on mirikizumab where previously exposed to but did not fail a biologic or JAK-inhibitor.

b) Loss of response, inadequate response or intolerance.

c) p < 0.001

d) Mirikizumab results in the subgroup of patients who failed more than one biologic or JAK-inhibitor were consistent with results in the overall population.

LUCENT-2 evaluated 544 patients who achieved clinical response in LUCENT-1 at week 12. Patients were re-randomized in a 2:1 treatment allocation ratio to receive a subcutaneous maintenance regimen of 200 mg mirikizumab or placebo every 4 weeks for 40 weeks (which is 52 weeks from initiation of the induction dose). Corticosteroid tapering was required upon entrance into LUCENT-2 for patients who were receiving corticosteroids during LUCENT-1. Significantly greater proportions of patients were in clinical remission in the mirikizumab-treated group compared to the placebo group at week 40 (see Table 2).

Table 2: Summary of key efficacy measures in LUCENT-2 (week 40; 52 weeks from initiation of the induction dose)

	Placebo N=179		**Mirikizumab 200mg SC N=365**		**Treatment difference and 95 % CI**
	N	**%**	**N**	**%**	

Clinical remission*[1]	45	25.1 %	182	49.9 %	23.2 % (15.2 %, 31.2 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	35/114	30.7 %	118/229	51.5 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	10/64	15.6 %	59/128	46.1 %	- - -
Maintenance of clinical remission through week 40*[2]	24/65	36.9 %	91/143	63.6 %	24.8 % (10.4 %, 39.2 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	22/47	46.8 %	65/104	62.5 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	2/18	11.1 %	24/36	66.7 %	- - -
Corticosteroid-free remission*[3]	39	21.8 %	164	44.9 %	21.3 % (13.5 %, 29.1 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	30/114	26.3 %	107/229	46.7 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	9/64	14.1 %	52/128	40.6 %	- - -
Endoscopic improvement*[4]	52	29.1 %	214	58.6 %	28.5 % (20.2 %, 36.8 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	39/114	34.2 %	143/229	62.4 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	13/64	20.3 %	65/128	50.8 %	- - -
Histo-endoscopic mucosal remission*[5]	39	21.8 %	158	43.3 %	19.9 % (12.1 %, 27.6 %)[c]
Patients who were biologic and JAK-inhibitor naïve [a]	30/114	26.3 %	108/229	47.2 %	- - -
Patients who failed [b] at least one biologic or JAK-inhibitor [d]	9/64	14.1 %	46/128	35.9 %	- - -

Abbreviations: CI = confidence interval; SC = subcutaneous

**1 See footnotes on Table 1*

**2 The proportion of patients who were in clinical remission at week 40 among patients in clinical remission at week 12, with clinical remission defined as: Stool frequency (SF) subscore = 0 or SF = 1 with a ≥ 1-point decrease from induction baseline, and Rectal bleeding (RB) subscore = 0, and Endoscopic subscore (ES) = 0 or 1 (excluding friability)*

**3 Corticosteroid-free remission without surgery, defined as: Clinical remission at week 40, and Symptomatic remission at Week 28, and no corticosteroid use for ≥ 12 weeks prior to week 40*

**4 Endoscopic improvement defined as: ES = 0 or 1 (excluding friability)*

5 Histo-endoscopic mucosal remission, defined as achieving both: 1. Histologic remission, defined as Geboes subscores of 0 for grades: 2b (lamina propria neutrophils), and 3 (neutrophils in epithelium), and 4 (crypt destruction), and 5 (erosion or ulceration) and 2. Mayo endoscopic score 0 or 1 (excluding friability)

a) An additional 1 patient on placebo and 8 patients on mirikizumab where previously exposed to but did not fail a biologic or JAK-inhibitor.

b) Loss of response, inadequate response or intolerance.

c) $p < 0.001$

d) Mirikizumab results in the subgroup of patients who failed more than one biologic or JAK-inhibitor were consistent with results in the overall population.

The effect of mirikizumab on symptomatic, endoscopic and histologic outcomes was observed in induction and in maintenance both in patients who failed conventional therapy but not a biologic or JAK-inhibitor therapy, as well as in those who had failed at least one or more biologic or JAK-inhibitor. At week 12, 50.2 % of patients who were inadequate responders to a biologic or JAK-inhibitor therapy achieved clinical response with mirikizumab and of those who were rerandomized to mirikizumab for maintenance treatment 45.9 % were in clinical remission at week 40.

The efficacy and safety profile of mirikizumab was consistent across subgroups, i.e. age, gender, body weight, disease activity severity at baseline and region.

At week 40, a greater proportion of patients were in clinical response (defined as decrease in the MMS of ≥ 2 points and ≥ 30 % decrease from baseline, and a decrease of ≥ 1 point in the RB subscore from baseline or a RB score of 0 or 1) in the mirikizumab responder group re-randomized to mirikizumab (80 %) compared to the mirikizumab responder group re-randomized to placebo (49 %).

Week 24 Responders to mirikizumab extended induction (LUCENT-2)

Mirikizumab-treated patients who were not in response at week 12 of LUCENT-1 were eligible to receive extended open label induction therapy in LUCENT-2 (300 mg mirikizumab IV at weeks 0, 4 and 8). Of those 272 patients, 146 (53.7 %) achieved clinical response at week 12 (24 weeks after the first induction dose) or 31 (11.4%) a clinical remission, respectively. Afterwards, 144 patients received the maintenance dose of 200 mg mirikizumab Q4W SC; among these patients, a majority (72.2 %) maintained clinical response and 36.1 % achieved clinical remission at week 40.

Recapture of efficacy after loss of response to mirikizumab maintenance (LUCENT-2)

Patients who developed symptomatic and confirmatory endoscopic loss of response (5.2 %, n=19) between week 12 and 28 of LUCENT-2 while on maintenance therapy with mirikizumab, received open label mirikizumab re-induction therapy with 300 mg mirikizumab Q4W IV for 3 doses (referred to as rescue dosing). Of these, 63.2 % (n=12) patients achieved symptomatic response and 36.8 % (n=7) achieved symptomatic remission after 12 weeks rescue dosing.

Endoscopic normalization at week 40

Normalization of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0. At week 40 of LUCENT-2, endoscopic normalization was achieved in 81/365 (22.2 %) of patients treated with mirikizumab and in 24/179 (13.4 %) of patients in placebo group (p= 0.026, not multiplicity controlled).

Health-related quality of life

Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ). At week 12 of LUCENT-1, patients receiving mirikizumab showed significantly greater clinically relevant improvements on IBDQ total score (p≤0.001), when compared to placebo. IBDQ response was defined as at least a 16 points improvement from baseline in IBDQ score and IBDQ remission was defined as a score of at least 170. At week 12 of LUCENT 1, 57.5 % of mirikizumab-treated patients achieved IBDQ remission versus 39.8 % with placebo (p < 0.001) and 72.7 % of mirikizumab treated patients achieved IBDQ response versus 55.8 % in placebo. In LUCENT 2 at week 40, 72.3 % of mirikizumab treated patients achieved maintenance of IBDQ remission versus 43.0 % placebo-treated patients and 79.2 % mirikizumab treated patients achieved IBDQ response versus 49.2 % of placebo treated patients.

Pharmacokinetics

Mirikizumab has pharmacokinetic characteristics typical of an IgG4 monoclonal antibody. There was no apparent accumulation in serum mirikizumab concentration over time when given subcutaneously every 4 weeks.

Mean (coefficient variation [CV %]) C_{max} and area under the curve (AUC) after induction dosing (300 mg every 4 weeks administered by intravenous infusion) in patients with ulcerative colitis were 99.7 (22.7) µg/mL and 538 (34.4) µg*day/mL, respectively. The mean (CV %) C_{max} and AUC after maintenance dosing (200 mg every 4 weeks by subcutaneous injection) were 10.1 (52.1) µg/mL and 160 (57.6) µg*day/mL, respectively.

Absorption

Following subcutaneous dosing of mirikizumab, peak serum concentrations were achieved 2-3 days post dose with an estimated absolute bioavailability of 44 %.

Injection site location (abdomen, arm, thigh) did not significantly influence absorption of mirikizumab.

Distribution

The mean total volume of distribution was 4.83 L.

Metabolism

Mirikizumab is a humanized IgG4 monoclonal antibody and is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgGs.

Elimination

In the population PK analysis, mean apparent clearance was 0.0229 L/hr and the mean elimination half-life is approximately 9.3 days in patients with ulcerative colitis.

Linearity/non-linearity

Mirikizumab exhibited linear pharmacokinetics with dose-proportional increase in exposure over a dose range of 5 to 2400 mg given as an intravenous infusion or over a dose range of 120 to 400 mg given as a subcutaneous injection in patients with ulcerative colitis or in healthy volunteers.

Kinetics in specific patient groups

Population pharmacokinetic analysis showed that age (18-79 years), sex (male 60.9%), weight (34-152 kg), or race/ethnicity (white or Asian) did not have a clinically meaningful effect on the pharmacokinetics of mirikizumab.

Hepatic and renal impairment

Specific clinical pharmacology studies to evaluate the effects of renal impairment and hepatic impairment on the pharmacokinetics of mirikizumab have not been conducted. Population pharmacokinetic analysis showed that creatinine clearance (range of 36.2 to 291 mL/min) or total bilirubin (range of 1.5 to 29 µmol/L) did not affect mirikizumab pharmacokinetics.

Preclinical data

Nonclinical data from cynomolgus monkeys revealed no special hazards for humans based on repeat-dose toxicity studies, safety pharmacology evaluations, and reproductive and developmental toxicity studies performed with mirikizumab.

Nonclinical studies have not been conducted to evaluate the genotoxic or carcinogenic potential of mirikizumab.

Other information

Incompatibilities

Vial: In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Omvoh should only be diluted with sodium chloride 9 mg/mL (0.9 %) solution or 5% glucose solution for injection. Omvoh should not be administered concomitantly in the same intravenous line with other medicinal products.

Prefilled syringe and prefilled pen: In the absence of compatibility studies, the medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Store in the refrigerator (2-8°C).

Do not freeze. Omvoh that has been frozen must not be used.

Store in the original packaging in order to protect the content from light.

Temporary storage of the reconstituted infusion solution:

From a microbiological point of view, the diluted solution has to be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Chemical and physical in-use stability has been demonstrated for diluted solution prepared with sodium chloride 9 mg/mL (0.9%) solution for 96 hours at 2°C to 8°C and 10 hours up to a temperature of 25°C.

Chemical and physical in-use stability has been demonstrated for diluted solution prepared with 5 % glucose for 48 hours at 2°C to 8°C and 5 hours up to a temperature of 25°C.

Do not freeze the diluted solution in the prepared infusion bag.

Temporary storage of the prefilled syringe and prefilled pen:

Omvoh prefilled syringe and prefilled pen may be stored unrefrigerated for at maximum up to 2 weeks at a temperature not above 30 ºC. Once the medicine has been taken out of the fridge and stored up to 30°C, it must be discarded after 14 days or the expiry date printed on the carton, whichever comes first, even if it is placed back in the refrigerator.

Keep out of the reach of children.

Instructions for handling

Do not shake.

Omvoh is a sterile, preservative free, clear and colorless to slightly yellow solution. Do not use if particles appear or if the solution is cloudy and/or distinctly brown.

The vial, prefilled syringe and prefilled pen are for single use only.

The instructions for use accompanying the patient information leaflet of the prefilled syringe resp. the prefilled pen must be followed carefully.

Omvoh 300 mg concentrate for solution for perfusion: dilution to prepare intravenous infusion and administration

1. Each vial is for single use only.
2. Prepare the infusion solution using aseptic technique to ensure the sterility of the prepared solution.
3. Inspect the content of the vial. The solution should be clear, colourless to slightly yellow and free of visible particles.
4. Withdraw 15 mL of the mirikizumab vial (300 mg) using an appropriately sized needle (18 to 21 gauge is recommended) and transfer to the infusion bag. Mirikizumab should be diluted only in infusion bags (bag size ranging from 50-250 mL) containing EITHER 0.9 % sodium chloride solution for injection OR 5% glucose solution for injection. Do not dilute the infusion solution with other solutions or co-infuse with other electrolytes or medications.
5. Gently invert the infusion bag to mix. Do not shake the prepared bag.
6. Connect the intravenous administration set (infusion line) to the prepared intravenous bag and prime the line. Administer the infusion for at least 30 minutes.
7. At the end of the infusion, to ensure a full dose is administered, the infusion line should be flushed with 0.9 % sodium chloride solution or 5 % glucose solution for injection. The flush should be administered at the same rate as used for Omvoh administration. The time required to flush Omvoh solution from the infusion line is in addition to the minimum 30 minutes infusion time.

Authorisation number

68950, 68951, 68952 (Swissmedic)

Packs

Omvoh 300 mg concentrate for solution for perfusion: 1 (B)

Omvoh 100 mg solution for injection in prefilled syringe: 2 (B)

Omvoh 100 mg solution for injection in prefilled pen: 2 (B)

Marketing authorisation holder

Eli Lilly (Suisse) SA, 1214 Vernier/GE

Date of revision of the text

November 2023