swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Extension of therapeutic indication

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:	extension of therapeutic indication approved on 20 June 2025

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
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
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
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)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

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

Crohn's disease
Omvoh is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment.

2.2.2 Approved indication

Crohn's disease
Omvoh is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment.

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended mirikizumab dose regimen has 2 parts:

- induction dose: 900 mg (3 vials) by intravenous infusion for at least 90 minutes at weeks 0, 4 and 8.
- maintenance dose: 300 mg (1 x 100 mg + 1 x 200 mg) by subcutaneous injection every 4 weeks, starting at Week 12.

Duration of treatment
Discontinue mirikizumab in patients who do not show evidence of therapeutic benefit by week 24. Patients with loss of therapeutic response during maintenance treatment may receive 900 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, otherwise therapy with mirikizumab should be discontinued. The efficacy and safety of repeated re-induction therapy have not been evaluated.

Special dosage instructions
…
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 or Crohn's disease.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	31 July 2024
Formal control completed	29 August 2024
List of Questions (LoQ)	23 December 2024
Response to LoQ	26 February 2025
Preliminary decision	11 April 2025
Response to preliminary decision	25 April 2025
Final decision	20 June 2025
Decision	approval

3 Quality aspects

3.1 Drug substance

No change to effective text for drug substance (see published SwissPAR dated 12 March 2024).

3.2 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 and 200 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 validation 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 (size exclusion chromatography (SEC), non-reduced capillary electrophoresis-sodium dodecyl sulfate (CE-SDS), imaged capillary isoelectric focusing (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 appropriate Type I glass vials or 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 European Pharmacopoeia (Ph.Eur.)- and United States Pharmacopoeia (USP)-compliant. A shelf-life of 24 months at 2 – 8 °C has been accepted.

3.3 Quality conclusions

No change to effective text (see published SwissPAR dated 12 March 2024).

4 Nonclinical aspects

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

5 Clinical aspects

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

6 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.

7 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

Omvoh 300 mg concentrate for solution for infusion

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.

Omvoh 100 mg solution for injection in prefilled syringe

Omvoh 100 mg solution for injection in prefilled pen

Omvoh 200 mg solution for injection in prefilled syringe

Omvoh 200 mg solution for injection in prefilled pen

Histidine, histidine hydrochloride monohydrate, sodium chloride, mannitol, polysorbate 80, water for injection q.s. ad solutionem pro 1 ml.

Total sodium content: 1.15 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)

Omvoh 200 mg solution for injection in prefilled syringe

Each prefilled syringe contains 200 mg of mirikizumab in 2 ml (100 mg/ml)

Omvoh 200 mg solution for injection in prefilled pen

Each prefilled pen contains 200 mg of mirikizumab in 2 ml (100 mg/ml)

Indications/Uses

Ulcerative colitis

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”).

Crohn’s disease

Omvoh is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment.

Dosage/Administration

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

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

Ulcerative colitis

The recommended mirikizumab dose regimen has 2 parts:

Initiation of treatment

The induction dose with Omvoh 300mg concentrate for solution for infusion is 300 mg (1 vial) by intravenous infusion for at least 30 minutes at weeks 0, 4 and 8.

Maintenance therapy

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

A full 200 mg maintenance dose is **two** 100 mg pre-filled syringes or **two** 100 mg pre-filled pens.

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.

Crohn's disease

The recommended mirikizumab dose regimen has 2 parts.

Initiation of treatment

The induction dose with Omvoh 300mg concentrate for solution for infusion is 900 mg (3 vials) by intravenous infusion for at least 90 minutes at weeks 0, 4 and 8.

Maintenance therapy

The maintenance dose with Omvoh solution for injection in prefilled syringe or prefilled pen is 300 mg by subcutaneous injection every 4 weeks, starting at Week 12, after completion of induction dosing.

A full 300 mg maintenance dose is **one** 100 mg pre-filled syringe rep. prefilled pen **and one** 200 mg pre-filled syringe rep. prefilled pen. The 100 mg injection and 200 mg injection may be administered in any order.

The 200 mg pre-filled syringe and 200 mg pre-filled pen are only for treatment of Crohn's disease.

Duration of treatment

Discontinue mirikizumab in patients who do not show evidence of therapeutic benefit by week 12.

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

In case of a missed dose, instruct patients to inject as soon as possible. Thereafter, resume dosing every 4 weeks.

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 or Crohn's disease.

Mode of administration

Omvoh 300 mg concentrate for solution for infusion should only be used for the intravenous doses. The infusion should be administered over at least 30 minutes for ulcerative colitis and at least 90 minutes for Crohn's disease. 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 resp. 180 mg sodium per 900 mg dose, equivalent to 3 % resp. 9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Omvoh 100 mg and 200 mg solution for injection in prefilled syringe / prefilled pen:

This medicinal product contains less than 1 mmol sodium (23 mg) per 200 mg resp. 300 mg dose, i.e., is essentially “sodium-free”.

Interactions

In ulcerative colitis and Crohn’s disease 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 or Crohn’s disease.

No drug interaction study was conducted in subjects with ulcerative colitis or Crohn’s disease 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.

The integrated database of all mirikizumab exposures for the ulcerative colitis and Crohn's disease indications included 2632 patients and 5605 total patient years of exposure.

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, herpes zoster infection, rhinitis.

Uncommon: vulvovaginal fungal infection, 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.

Uncommon: dizziness hypoesthesia.

Eyes disorders

Uncommon: dry eyes.

Respiratory, thoracic and mediastinal disorders

Common: cough, oropharyngeal pain.

Uncommon: nasal congestion.

Gastrointestinal disorders

Uncommon: gastroesophageal reflux.

Hepatobiliary disorders

Uncommon: Alanine aminotransferase increased, aspartate aminotransferase increased.

Skin and subcutaneous tissue disorders

Common: rash.

Uncommon: contact dermatitis.

Musculoskeletal and connective tissue disorders

Common: arthralgia.

General disorders and administration site conditions

Very common: injection site reactions (10.8%)[a].

Vascular disorders

Common: hypertension.

[a] *Reported during maintenance treatment*

Description of specific adverse reactions and additional information

Infusion-related hypersensitivity reactions

In the first 12 weeks (induction therapy), all infusion-related hypersensitivity reactions were reported as non-serious in 7 (0.4 %) mirikizumab-treated patients compared to 2 (0.4 %) patients in the placebo group.

*Injection site reactions (*maintenance therapy)

Injection site reactions were reported in 10.8 % of mirikizumab-treated patients compared to 6.5 % patients in the placebo group. The most frequent events were injection site pain (3.5 % mirikizumab; 6.5 % placebo), injection site reaction (4.2 % mirikizumab; 0 % placebo) and injection site erythema (1.0 % mirikizumab; 0 % placebo). These symptoms were usually reported as non-serious, mild and transient in nature.

The results described above were obtained with the original formulation of Omvoh. In a double blind, 2-arm, randomized, single-dose, parallel design study in 60 healthy subjects comparing 200 mg mirikizumab (2 injections of 100 mg/mL in a pre-filled syringe) of the original formulation with the

revised citrate-free formulation statistically significantly lower pain was reported 1 minute after the injection.

Hepatic enzyme elevations

In the first 12 weeks, ALT increased was reported in 10 (0.6 %) mirikizumab-treated patients compared to 2 (0.4 %) in the placebo group. AST increased was reported by 7 (0.4 %) mirikizumab-treated patients compared to 1 (0.2 %) 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 and Crohn's disease 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) (2.3 %), ≥ 5 x ULN (0.7 %) and ≥ 10 x ULN (0.1 %) and AST to ≥ 3 x ULN (2.2 %), ≥ 5 x ULN (0.8 %) 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.

In the ulcerative colitis studies, up to 23 % of mirikizumab-treated patients with 12 months of treatment, 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.

In the Crohn's disease study, 12.7% of mirikizumab-treated patients with 12 months of treatment developed anti-drug antibodies, most of which were of low titer and tested positive for neutralizing activity.

No association was found between anti-drug antibodies and hypersensitivity or injection-related events in either the ulcerative colitis or the Crohn's disease studies.

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 Crohn's disease 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 and Crohn's disease 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 up to 52 weeks.

Clinical efficacy

Ulcerative colitis

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 ($p \leq 0.001$), 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.

Crohn's disease

The efficacy and safety of mirikizumab was evaluated in a randomized, double-blind, placebo- and active controlled treat-through designed clinical study VIVID-1 in adult patients with moderately to severely active Crohn's disease who had an inadequate response with, loss of response, or intolerance to corticosteroids, immunomodulators (e.g. azathioprine, 6-mercaptopurine), or a biologic treatment (e.g. TNFα antagonist or integrin receptor antagonist). This study included a mirikizumab 12-week intravenous infusion induction period followed by a 40-week subcutaneous injection maintenance

period. This study also included an ustekinumab comparator arm in the induction and maintenance periods.

VIVID-1

In VIVID-1, efficacy was evaluated in 1065 patients who were randomized 6:3:2 to receive mirikizumab 900 mg by intravenous infusion (IV) at week 0, week 4, and week 8 followed by a maintenance dose of 300 mg by subcutaneous injection (SC) at week 12 and then every 4 weeks (Q4W) for 40 weeks, ustekinumab approximately 6 mg/kg by IV administration at week 0 followed by 90 mg SC administration every 8 weeks (Q8W) starting at week 8, or placebo. Patients randomised to placebo at baseline who achieved clinical response by Patient-Reported Outcome (PRO) at week 12 (defined as at least a 30% decrease in stool frequency (SF) and/or abdominal pain (AP) with neither score worse than baseline) remained on placebo. Patients randomized to placebo at baseline who did not achieve clinical response by PRO at week 12 received mirikizumab 900 mg by IV infusion at week 12, week 16, and week 20 followed by a maintenance dose of 300 mg Q4W SC at week 24 through week 48.

Disease activity at baseline was assessed by (1) the unweighted daily average of SF (2), the unweighted daily average AP (ranging from 0 to 3) and (3) Simple Endoscopic Score for Crohn's disease (SES-CD) (ranging from 0 to 56).

Moderately to severely active CD was defined by SF ≥4 and/or AP ≥2 and SES-CD ≥7 (centrally read) for patients with ileal-colonic and isolated colonic disease or ≥4 for patients with isolated ileal disease. At baseline patients had a median SF of 6, AP of 2 and SES-CD of 12.

Patients had a mean age of 36 years (range 18 to 76 years); 45 % were female; and 72 % identified as White, 25 % as Asian, 2 % as Black, and 1 % as another racial group. Patients were permitted to use stable doses of corticosteroids, immunomodulators (e.g., 6-mercatopurine, azathioprine or methotrexate) and/or aminosalicylates. At baseline, 31 % of patients were receiving oral corticosteroids, 27 % were receiving immunomodulators, and 44 % were receiving aminosalicylates.

At baseline, 49 % had a loss of response, inadequate response, or intolerance to one or more biologic therapy (prior biologic failure).

The co-primary endpoints were (1) clinical response by PRO at week 12 and endoscopic response at week 52 versus placebo and (2) clinical response by PRO at week 12 and clinical remission by Crohn's Disease Activity Index (CDAI) at week 52; the results for the co-primary endpoints and the major secondary endpoints at week 52 versus placebo are provided in table 3.
The major secondary endpoints at week 12 versus placebo are provided in table 4.

Table 3. Proportion of patients with Crohn's disease meeting efficacy endpoints in VIVID-1 at week 52

	Placebo N=199		Mirikizumab 300 mg SC[a] N=579		Treatment Difference from Placebo[b] (99.5% CI)
	n/N	%	n/N	%	
Co-primary endpoints					
Clinical response by PRO[c] at week 12 and endoscopic response[d] at week 52					
Total population	18/199	9 %	220/579	38 %	29%[e] (21 %, 37 %)
Without prior biologic failure	12/102	12 %	117//298	39 %	
Prior biologic failure[f]	6/97	6 %	103/281	37 %	
Clinical response by PRO[c] at week 12 and clinical remission by CDAI[g] at week 52					
Total population	39/199	20 %	263/579	45 %	26 %[e] (16 %, 36 %)
Without prior biologic failure	27/102	27 %	141/298	47 %	
Prior biologic failure[f]	12/97	12 %	122/281	43 %	
Major secondary endpoints					
Endoscopic response[d] at week 52					
Total population	18/199[h]	9 %	280/579	48 %	39 %[e] (31 %, 47 %)
Without prior biologic failure	12/102[h]	12 %	154/298	52 %	
Prior biologic failure[f]	6/97[h]	6 %	126/281	45 %	
Clinical remission by CDAI[h] at week 52					
Total population	39/199[h]	20 %	313/579	54 %	35 %[e] (25 %, 44 %)
Without prior biologic failure	27/102[h]	27 %	169/298	57 %	
Prior biologic failure[f]	12/97[h]	12 %	144/281	51 %	
Clinical response by PRO[c] at week 12 and clinical remission by PRO[i] at week 52					
Total population	39/199	20 %	263/579	45 %	26 %[e](16 %, 36 %)
Clinical response by PRO[c] at week 12 and endoscopic remission[j] at week 52					
Total population	8/199	4 %	136/579	24 %	19 %[e] (13 %, 26 %)
Clinical response by PRO[c] at week 12 and corticosteroid-free clinical remission by CDAI[g, k] at Week 52					
Total population	37/199	19 %	253/579	44 %	25 %[e] (15 %, 35 %)

Abbreviations: AP = abdominal pain; CDAI = Crohn's Disease Activity Index; CI = confidence interval; PRO = 2 of the patient-reported items of the CDAI (SF and AP); SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency.

a *Following mirikizumab 900 mg as an IV infusion at week 0, week 4, and week 8 patients received mirikizumab 300 mg as a SC injection at week 12 and every 4 weeks thereafter for up to an additional 40 weeks.*
b *For binary endpoints adjusted treatment difference was based on Cochran-Mantel-Haenszel method adjusted for baseline covariates.*
c *Clinical response by PRO is defined as at least a 30% decrease in SF and/or AP and neither score worse than baseline.*
d *Endoscopic response is defined as ≥50% reduction from baseline in SES-CD total score, based on central reading.*
e *p <0.000001*
f *Prior biologic failure includes loss of response, inadequate response, or intolerance to one or more biologic therapy (e.g. TNFα antagonist or integrin receptor antagonist).*
g *Clinical remission by CDAI is defined as CDAI total score < 150.*
h *Placebo sample size includes all patients randomized to placebo at baseline. Placebo patients that did not achieve clinical response by PRO at week 12 were considered non-responders at week 52.*
i *Clinical remission by PRO is defined as SF ≤3 and not worse than baseline (according to the Bristol Stool Scale Category 6 or 7) and AP ≤1 and not worse than baseline.*
j *Endoscopic remission is defined as SES-CD Total Score ≤4 and at least a 2-point reduction versus baseline and no subscore >1 in any individual variable, based on central reading.*
k *Corticosteroid-free is defined as patients who were corticosteroid-free from week 40 to week 52.*

Bowel urgency remission

Bowel urgency remission was assessed during VIVID-1 with an urgency numeric rating scale (NRS) of 0 to 10. A greater proportion of patients with a baseline urgency NRS weekly average score ≥3 treated

with mirikizumab compared to placebo achieved clinical response by PRO at week 12 and an urgency NRS weekly average score of ≤ 2 at week 52 (33 % versus 11 %).

Table 4. Proportion of patients with Crohn's disease meeting efficacy endpoints in VIVID -1 at week 12

	Placebo N=199		Mirikizumab 900 mg IV[a] N=579		Treatment Difference from Placebo[b] (99.5% CI)
	n/N	%	n/N	%	
Clinical response by PRO[c]					
Total population	103/199	52 %	409/579	71 %	19 %[e] (8 %, 30 %)
Clinical remission by CDAI[g]					
Total population	50/199	25 %	218/579	38 %	12 %[f] (2 %, 23 %)
Endoscopic response[d]					
Total population	25/199	13 %	188/579	32 %	20 %[e] (11 %, 28 %)
Endoscopic remission[j]					
Total population	14/199	7 %	102/579	18 %	11 %[f](4 %, 17 %)
Change from baseline in FACIT-fatigue[h]					
	LS Mean	**SE**	**LS Mean**	**SE**	
Total population	2.6	0.61	5.9	0.36	3.2[f] (1.2, 5.2)

Abbreviations: FACIT-fatigue = Functional Assessment of Chronic Illness Therapy – fatigue; LS Mean = Least Square Mean; SE = Standard Error; others see above table 3.

a Weeks 0, 4, 8

b see table 3.

c, d, e, g, j see table 3

f p-value <0.005

h For change from baseline in FACIT-fatigue, the LS means and treatment difference were based on ANCOVA model adjusted for baseline FACIT-fatigue and other covariates. At baseline, mean FACIT-fatigue values were similar across treatment groups and ranged from 32.3-31.5.

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

Active comparator arm

VIVID-1 included an active comparator arm. At week 52, mirikizumab demonstrated non-inferiority (pre-specified margin of -10%) to ustekinumab on clinical remission by CDAI (mirikizumab 54 %; ustekinumab 48 %). Superiority over ustekinumab in week 52 endoscopic response was not achieved (mirikizumab 48 %, ustekinumab 46 %).

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.

Ulcerative colitis: 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.

Crohn's Disease: Mean (coefficient of variation [CV%]) C_{max} and area under the curve (AUC) after induction dosing (900 mg every 4 weeks administered by intravenous infusion) in patients with Crohn's disease were 332 (20.6) µg/mL and 1820 (38.1) µg*day/mL, respectively. The mean (CV %) C_{max} and AUC after maintenance dosing (300 mg every 4 weeks by subcutaneous injection) were 13.6 (48.1) µg/mL and 220 (55.9) µg*day/mL, respectively.

Absorption

Following subcutaneous dosing of mirikizumab, peak serum concentrations were achieved 3-7 days post dose with a geometric mean (CV%) absolute bioavailability of 44 % (34%) in ulcerative colitis and 36.3% (31%) in Crohn's disease.

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

Distribution

The geometric mean total volume of distribution was 4.83 L (21%) in patients with ulcerative colitis and 4.40 L (14%) in patients with Crohn's disease.

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, geometric mean (CV%) clearance was 0.0229 L/hr (34%) and the geometric mean (CV%) half-life is approximately 9.3 days (40%) in patients with ulcerative colitis. The geometric mean (CV%) clearance was 0.0202 L/hr (38 %) and the geometric mean (CV %) half-life is also approximately 9.3 days (26 %) in patients with Crohn's disease.

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 Crohn's disease 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 in patients with ulcerative colitis or Crohn's disease.

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.

In patients with ulcerative colitis, 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.

In patients with Crohn's disease, population pharmacokinetic analysis showed that creatinine clearance (range of 26.5 to 269 mL/min) or total bilirubin (range of 1.5 to 36 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. Prepare the infusion bag for treatment of either ulcerative colitis or Crohn's disease as specified below. Note that there are unique instructions and volumes specified for each indication.

   Ulcerative colitis: One 15 mL Vial (300 mg)

   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 administered for ulcerative colitis 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.

   Crohn's disease: Three 15 mL Vials; total dose = 45 mL (900 mg)

   First, withdraw and discard 45 mL of diluent from the infusion bag. Next, withdraw 15 mL from each of the three mirikizumab vials (900 mg) using an appropriately sized syringe and needle (18 to 21 gauge is recommended). Mirikizumab administered for Crohn's disease should be diluted only in infusion bags (bag size ranging from 100-250 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. For ulcerative colitis, administer the infusion for at least 30 minutes. For Crohn's disease, administer the infusion for at least 90 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 (ulcerative colitis) or 90 minutes (Crohn's disease) infusion time.

Authorisation number

68950, 68951, 68952 (Swissmedic)

Packs

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

Packs for treatment of ulcerative colitis (200 mg)

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

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

Packs for treatment of Crohn's disease (300 mg)

Omvoh 100 mg / 200 mg solution for injection in prefilled syringe: 1 prefilled syringe 100 mg + 1 prefilled syringe 200 mg (B)

Omvoh 100 mg / 200 mg solution for injection in prefilled pen: 1 prefilled pen 100 mg + 1 prefilled pen 200 mg 2 (B)

Marketing authorisation holder

Eli Lilly (Suisse) SA, 1214 Vernier/GE

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