Date: 6 December 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Bimzelx

International non-proprietary name: bimekizumab
Pharmaceutical form: solution for injection in a pre-filled syringe
Dosage strength(s): 160 mg
Route(s) of administration: subcutaneous
Marketing Authorisation Holder: UCB-Pharma SA
Marketing Authorisation No.: 68548
Decision and Decision date: approved on 27 October 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Table of contents

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AI	Auto-injector
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
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	U.S. Food and Drug Administration
GLP	Good Laboratory Practice
HPLC	High performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IL	Interleukin
INN	International nonproprietary 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
PFS	Pre-filled syringe
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetic
PSO	Psoriasis
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SAE	Serious adverse event
SE	Size exclusion
SS	Safety syringe
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)

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance bimekizumab of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Bimzelx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

2.2.2 Approved Indication

Bimzelx is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy.

2.2.3 Requested Dosage

Summary of the applied standard dosage:
The recommended dose of Bimzelx is 320 mg administered as two subcutaneous injections of 160 mg at week 0, 4, 8, 12 and 16, and every eight weeks thereafter.
A dose of 320 mg every four weeks may be considered for patients with a body weight above ≥120 kg beyond 16 weeks of treatment.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	16 June 2021
Formal control completed	12 August 2021
List of Questions (LoQ)	8 December 2021
Answers to LoQ	7 March 2022
Predecision	2 June 2022
Answers to Predecision	27 July 2022
Final Decision	27 October 2022
Decision	approval

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

3 Medical Context

Psoriasis (PSO) is a common, chronic inflammatory disease characterised by a series of linked cellular changes in the skin: hyperplasia of epidermal keratinocytes, vascular hyperplasia and ectasia, and infiltration of T lymphocytes, neutrophils and other types of leucocytes into affected skin. Prevalence varies in Europe, due in part to different study populations and variability in ascertainment methods, with rates ranging between 2% and 6%. Individuals with PSO are at an increased risk of developing other chronic and serious health diseases. These comorbid diseases include psoriatic arthritis, metabolic syndrome or components of the syndrome, cardiovascular disorders and several other diseases such as anxiety and depression, non-alcoholic fatty liver disease, Crohn's disease and lymphoma. Risk factors for the development of psoriasis include genetic, environmental and behavioural factors, with genetic factors being the largest contributor. The hallmark of psoriasis is sustained inflammation that leads to uncontrolled keratinocyte proliferation and dysfunctional differentiation.
There are a variety of forms of PSO including plaque, guttate, inverse, pustular and erythrodermic. Plaque PSO (PSO vulgaris) is the most common, comprising approximately 80% to 90% of all cases. It is estimated that approximately 80% of patients with plaque PSO have mild to moderate disease while 20% of patients have more severe disease, which affects either greater than 5% of body surface area or is located on high impact areas including the scalp, genitals, hands and nails . The disease usually manifests as raised, well-demarcated, erythematous oval plaques with adherent silvery scales, commonly presents on the elbows, knees and scalp, and may remain localised or become generalised. The scalp is the most frequently and earliest affected area of the body in both paediatric and adult patients with PSO.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

4 Quality Aspects

4.1 Drug Substance

Bimekizumab is a humanised monoclonal antibody of the IgG1 subclass. It selectively binds and neutralises IL-17A, IL-17F and IL-17AF cytokines, blocking their interaction with the IL-17RA/IL-17RC receptor complex. The inhibition of IL-17A and IL-17F by bimekizumab results in normalisation of inflammatory responses.

The bimekizumab drug substance is produced from a mammalian cell line (Chinese hamster ovary, CHO) using a fed-batch production process in a production bioreactor. The cell culture broth is harvested and subsequently purified using a series of chromatography and ultrafiltration steps, including specific steps for virus inactivation and reduction, with a final 0.2 µm filtration. The drug substance is finally stored frozen.

The fermentation and purification processes of bimekizumab drug substance were validated using three consecutive batches. The validation data show that the manufacturing process is consistent while effectively reducing process-related impurities.

Several changes were implemented during the development of the bimekizumab drug substance process, including changes to production scale and site, cell-line, drug substance concentration and drug substance formulation. However, the analytical comparability studies, which considered clinical and commercial drug substance batches, demonstrated comparability between the products of different processes. For this assessment release, characterisation and stability data were evaluated.

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 appearance, identity, pH, several purity tests (e.g. SE-HPLC, imaged capillary isoelectric focusing), protein concentration and a cell-based bioassay. Specifications are based on clinical data and batch analysis (release and stability data), and are in conformance with current compendial or regulatory guidelines.

Batch analysis data of clinical and process performance qualification batches were provided. All batch release data comply with the drug product specifications valid at the time of batch release. All specific analytical methods are described and were fully validated.

The drug substance is stored frozen. During storage, no changes were observed under the proposed storage conditions.

4.2 Drug Product

Bimekizumab drug product is supplied as a sterile, preservative-free solution, suitable for administration by subcutaneous injection. The drug product is supplied in a 1 mL type I glass pre-filled syringe (PFS). Each single-use syringe contains bimekizumab drug substance at a nominal formulation of 160 mg/mL in sodium acetate trihydrate, glycine, glacial acetic acid, polysorbate 80 and water for injection. All excipients used comply with the European Pharmacopoeia.

The finished product is presented as a combination of the syringe containing bimekizumab and the device presentation. The device presentations are single-use, needle-safe, subcutaneous self-administration systems. The dose delivered is not less than 1.0 mL. The finished product may be presented with one of two device presentations: the safety syringe (bimekizumab-SS-1mL) or the auto-injector/pre-filled pen (bimekizumab-AI-1mL).

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

During development a few changes were implemented for the drug product, e.g. between the Phase 2 and Phase 3 clinical studies for psoriasis a site change took place, and the primary container was changed from a vial to a pre-filled syringe. A comparability assessment considering batch release data and stability data under accelerated stability conditions was performed, and all predefined comparability acceptance criteria were met.

As the drug substance and drug product formulation are identical, the finished product manufacturing process for the syringes consists only of thawing/homogenisation, bioburden reduction filtration and pooling, in-line sterile filtration and aseptic filling, stoppering, visual inspection and storage.

The validation for the drug product manufacturing process was performed with four consecutive process performance qualification (PPQ) batches.
The validation of the assembly process for the safety syringe (bimekizumab-SS-1mL) and the auto-injector/pre-filled pen (bimekizumab-AI-1mL) was also demonstrated.

The release and stability specifications include relevant tests and limits, e.g. for identity, purity, protein concentration, potency, and other general tests, including tests for the safety syringe and auto-injector. All specific methods are described and validated.
Release and stability specifications are also defined for the safety syringe (bimekizumab-SS-1mL) and the auto-injector/pre-filled pen (bimekizumab-AI-1mL), e.g. extractable volume, injection time for the AI-1 mL.

Batch analysis data (PFS, AI-1 mL, SS-1 mL) of development, clinical and process performance qualification batches were provided. All batch release data comply with the drug product specifications valid at the time of batch release.

The primary packaging for the bimekizumab drug product consists of a 1 mL glass syringe fitted with a staked 27G, ½" special thin wall needle. The syringe is closed using a grey fluoropolymer-laminated bromobutyl rubber stopper and a rigid needle shield (RNS) consisting of a thermoplastic elastomer needle cover and a polypropylene rigid shield. All components are USP and Ph. Eur.-compliant.
A positive Notified Body Opinion for the safety syringe (bimekizumab-SS-1mL) and the auto-injector/pre-filled pen (bimekizumab-AI-1mL) was provided.

The drug product shelf-life acceptance criteria are fulfilled when the product is stored at the proposed long-term storage conditions at 2 – 8°C. A shelf-life of 36 months 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.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

5 Nonclinical Aspects

Regarding the marketing authorisation application for Bimzelx, the Nonclinical Assessment Division conducted an abridged evaluation, which was based on the EMA assessment report (24 June 2021). Overall, the submitted non-clinical documentation is considered appropriate to support the approval of Bimzelx in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. There were no safety issues identified in the non-clinical studies that would be of concern for human use. The safety margins are considered adequate. All non-clinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

6 Clinical and Clinical Pharmacology Aspects

The evaluation of the clinical and clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the EMA. The publicly available assessment report (EMA/346926/2021) and respective product information from the EMA were used as a basis for the clinical and clinical pharmacology evaluation.

7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken in order 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. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. 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 occurring in populations or indications not included in the Swiss authorisations.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Bimzelx 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 reference document, which is valid and relevant 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. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

▼ 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.

BIMZELX

Composition

Active substances

Bimekizumab, manufactured from genetically modified CHO (Chinese Hamster Ovary) cells.

Excipients

Glycine, Sodium acetate trihydrate (E262), Glacial acetic acid, Polysorbate 80, Water for injection q.s. in a solution of 1 ml.
Each pre-filled pen (1ml) contains 0.45 mg sodium.
Each pre-filled syringe (1ml) contains 0.45 mg sodium.

Pharmaceutical form and active substance quantity per unit

Solution for injection, in a pre-filled pen or in a pre-filled syringe for subcutaneous use.
Each pre-filled pen contains 160 mg bimekizumab in 1 ml.
Each pre-filled syringe contains 160 mg bimekizumab in 1 ml.

Appearance
The solution is clear to slightly opalescent and pale brownish-yellow.

Indications/Uses

Bimzelx is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy.

Dosage/Administration

Bimzelx is intended for use under the guidance and supervision of a doctor experienced in diagnosing and treating plaque psoriasis.
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 dose of Bimzelx for adult patients with plaque psoriasis is 320 mg (given as 2 subcutaneous injections of 160 mg each) at Week 0, 4, 8, 12, 16 and every 8 weeks thereafter.

Consideration should be given to discontinuing treatment in patients who have shown no improvement by 16 weeks of treatment.

Special dosage instructions

Overweight patients
For some patients with a body weight ≥ 120 kg who did not achieve complete skin clearance at Week 16, 320 mg every 4 weeks after Week 16 may further improve treatment response (see *Clinical efficacy)****Erreur ! Signet non défini.****.*

Patients with hepatic disorders

Bimzelx has not been studied in these patient populations. Dose adjustments are not considered necessary based on pharmacokinetics (see *Pharmacokinetics*).

Patients with renal disorders

Bimzelx has not been studied in these patient populations. Dose adjustments are not considered necessary based on pharmacokinetics (see *Pharmacokinetics*).

Elderly patients

No dose adjustment is required (see *Pharmacokinetics*).

Children and adolescents

The safety and efficacy of Bimzelx in children and adolescents below the age of 18 years has not been established. No data are available.

Mode of administration

Bimzelx is administered by subcutaneous injection.
Suitable areas for injection include thigh, abdomen and upper arm. Injection sites should be rotated, and injections should not be given into psoriasis plaques or areas where the skin is tender, bruised, erythematous, or indurated.
After proper training in subcutaneous injection technique, patients may self-inject if their physician determines that it is appropriate and with medical follow-up as necessary. Patients should be instructed to inject the full amount of Bimzelx according to the instructions for handling (see *Patient information*).

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section “Composition”.
Clinically important active infections (e.g., active tuberculosis).

Warnings and precautions

Infections

Bimzelx may increase the risk of infections such as upper respiratory tract infections and oral candidiasis (see *Undesirable Effects*).

Caution should be exercised when considering the use of Bimzelx in patients with a chronic infection or a history of recurrent infection. Treatment with Bimzelx should not be initiated in patients with any clinically important active infection (particularly HIV, HBV, or HCV infections) until the infection resolves or is adequately treated. Patients treated with Bimzelx should be instructed to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a clinically important infection or is not responding to standard therapy, the patient should be closely monitored and Bimzelx should not be administered until the infection resolves.

Pre-treatment evaluation for tuberculosis (TB)

In clinical studies, patients with latent TB receiving Bimzelx and an anti-TB therapy did not develop active TB. Prior to initiating treatment with Bimzelx, patients should be evaluated for TB infection. Bimzelx should not be given in patients with active TB. Patients receiving Bimzelx should be monitored for signs and symptoms of active TB. Anti-TB therapy should be considered prior to initiating Bimzelx in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed.

Malignancies

No increased risk of malignancy was observed with Bimzelx treatment in clinical studies up to one year. Results of long-term safety studies are not yet available.

As psoriasis patients are an at-risk population, patients should be evaluated for skin tumours before and during treatment with Bimzelx.

Inflammatory bowel disease

Cases of new or exacerbations of inflammatory bowel disease have been reported with Bimzelx. Bimzelx is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease, or experiences an exacerbation of pre-existing inflammatory bowel disease, Bimzelx should be discontinued and appropriate medical management should be initiated.

Hypersensitivity reactions

If a serious hypersensitivity reaction occurs, administration of Bimzelx should be discontinued immediately and appropriate therapy initiated.

Vaccinations

Prior to initiating therapy with Bimzelx, completion of all age-appropriate immunizations according to current immunization guidelines is recommended. Live vaccines should not be given in patients treated with Bimzelx. Patients treated with Bimzelx may receive inactivated or non-live vaccinations. Healthy individuals who received a single 320 mg dose of Bimzelx two weeks prior to vaccination with an inactivated seasonal influenza vaccine had similar antibody responses compared to individuals who did not receive Bimzelx prior to vaccination.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per pre-filled pen, that is to say essentially 'sodium-free'.

This medicinal product contains less than 1 mmol sodium (23 mg) per pre-filled syringe, that is to say essentially 'sodium-free'.

Interactions

No CYP450 interaction studies have been performed in humans. There is no direct evidence for the role of IL-17A or IL-17F in the expression of CYP450 enzymes. The formation of some CYP450 enzymes is suppressed by increased levels of cytokines during chronic inflammation. Thus, anti-inflammatory treatments, such as with the IL-17A and IL-17F inhibitor Bimzelx, may result in normalisation of CYP450 levels with accompanying lower exposure of CYP450-metabolised co-medications. Therefore, a clinically relevant effect on CYP450 substrates with a narrow therapeutic index, in which the dose is individually adjusted (e.g. warfarin) cannot be excluded. On initiation of Bimzelx therapy in patients being treated with these types of medicinal products, therapeutic monitoring should be considered.

Pregnancy, lactation

Pregnancy

There is a limited amount of data on the use of Bimzelx in pregnant women. Women of childbearing potential should use an effective method of contraception during treatment and for at least 17 weeks after treatment. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see *Preclinical Data*). Bimzelx should only be used during pregnancy if the benefit to the mother clearly outweighs the potential risk to the foetus.

Lactation

It is not known whether Bimzelx is excreted in human milk or absorbed systemically by the infant. The developmental and health benefits of breastfeeding should be considered along with the mother's

clinical need for Bimzelx and any potential adverse effects on the breastfed infant from Bimzelx or from the underlying maternal condition.

Fertility

The effect of Bimzelx on human fertility has not been evaluated. Animal trials do not indicate direct or indirect harmful effects on fertility (see *Preclinical Data*).

Effects on ability to drive and use machines

The influence of Bimzelx on the ability to drive and use machines has not been specifically studied.

Undesirable effects

Summary of the safety profile

Clinical studies

Overview

A total of 1789 patients have been treated with bimekizumab in blinded and open-label clinical studies in plaque psoriasis representing 1830.4 patient-years of exposure. Of these, over 1000 patients were exposed to bimekizumab for at least one year.

The most frequently reported adverse drug reactions (ADRs) were upper respiratory tract infections (most frequently nasopharyngitis) and oral candidiasis.

List of adverse reactions

The adverse reactions for bimekizumab are classified by MedDRA System Organ Class and frequency, using the following convention: very common (≥ 1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), not known (frequency cannot be estimated from the available data).

Table 1: List of adverse reactions in clinical studies

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Very common (14.5%)	Upper respiratory tract infections
	Common	Oral candidiasis, Tinea infections, Ear infections, Herpes simplex infections, Oropharyngeal candidiasis, Gastroenteritis, Folliculitis
	Uncommon	Conjunctivitis
Blood and lymphatic system	Uncommon	Neutropenia

disorders		
Nervous System disorders	Common	Headache
Skin and subcutaneous tissue disorders	Common	Dermatitis and eczema, Acne
General disorders and administration site conditions	Common	Injection site reactions[a], Fatigue
[a)] Includes: injection site erythema, reaction, oedema, pain, swelling.		

Description of specific adverse reactions and additional information

Infections

In the placebo-controlled period of Phase III clinical studies in plaque psoriasis, infections were reported in 36.0% of patients treated with bimekizumab for up to 16 weeks compared with 22.5% of patients treated with placebo. The majority of infections consisted of non-serious mild to moderate upper respiratory tract infections such as nasopharyngitis. Serious infections occurred in 0.3% of patients treated with bimekizumab and 0% treated with placebo.

There were higher rates of oral and oropharyngeal candidiasis in patients treated with bimekizumab consistent with the mechanism of action (7.3% and 1.2% respectively compared to 0% for placebo-treated patients). The vast majority of cases were non-serious, mild or moderate in severity, and did not require treatment discontinuation.

Over the entire treatment period of Phase III studies in plaque psoriasis, infections were reported in 63.2% of patients treated with bimekizumab (120.4 per 100 patient-years). Serious infections were reported in 1.5% of patients treated with bimekizumab (1.6 per 100 patient-years) (see *Warnings and Precautions*).

Neutropenia

Neutropenia was observed with bimekizumab in phase III clinical studies in plaque psoriasis. In the 16 weeks placebo-controlled period neutropenia grade 3/4 were observed at the same frequency of 0.6% in patients receiving bimekizumab or placebo. Over the entire treatment period of Phase III studies, neutropenia grade 3/4 were observed in 1% of patients treated with bimekizumab. Most cases were transient and did not require treatment discontinuation. No serious infections were associated with neutropenia.

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity with bimekizumab. The detection of anti-drug antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of anti-drug antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to bimekizumab with the incidence of antibodies to other products may be misleading.
Approximately 45% of plaque psoriasis patients treated with bimekizumab up to 56 weeks at the recommended dosing regimen (320 mg every 4 weeks up to Week 16 and 320 mg every 8 weeks thereafter) developed anti-drug antibodies. Of the patients who developed anti-drug antibodies, approximately 34% (16% of all patients treated with bimekizumab) had antibodies that were classified as neutralizing. No conclusive changes in clinical response or safety profile associated with the development of anti-bimekizumab antibodies have been described.

Hypersensitivity reactions:
Serious hypersensitivity reactions, including anaphylactic reactions, have been observed during treatment with IL-17 inhibitors.

Elderly (≥ 65 years of age)
Limited data are available regarding this age group. In the placebo-controlled period of the Phase III clinical trials in patients with plaque psoriasis, oral candidiasis was observed in 18.2% of patients ≥ 65 years of age versus 6.3% in patients <65 years of age. Dermatitis and eczema affected 7.3% of patients ≥ 65 years of age compared to 2.8% of patients < 65 years of age.

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

Single doses of 640 mg intravenously or 640 mg subcutaneously, followed by 320 mg subcutaneously every two weeks for five doses have been administered in clinical studies without dose-limiting toxicity. In the event of overdose, it is recommended that the patient be monitored for any signs and symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

Properties/Effects

ATC code

L04AC21

Mechanism of action

Bimekizumab is a humanized IgG1/κ monoclonal antibody that selectively binds with high affinity to IL-17A, IL-17F and IL-17AF cytokines, blocking their interaction with the IL-17RA/IL-17RC receptor complex. Elevated concentrations of IL-17A and IL-17F have been implicated in the pathogenesis of several immune-mediated inflammatory diseases including plaque psoriasis. Bimekizumab inhibits these proinflammatory cytokines, resulting in the normalization of skin inflammation and as a consequence improvement in clinical symptoms associated with psoriasis. From in vitro models, bimekizumab was shown to inhibit psoriasis-related gene expression and cytokine production to a greater extent than inhibition of IL-17A alone.

Pharmacodynamics

No formal pharmacodynamic studies have been conducted with bimekizumab.

Clinical efficacy

The safety and efficacy of bimekizumab was evaluated in 1480 patients with moderate to severe plaque psoriasis in three Phase III multicenter, randomized, placebo and/or active comparator-controlled studies. Patients were at least 18 years of age, had a Psoriasis Area and Severity Index (PASI) score ≥12 and Body Surface Area (BSA) affected by PSO ≥10%, an Investigators Global Assessment (IGA) score ≥3 on a 5-point scale and were candidates for systemic psoriasis therapy and/or phototherapy. The efficacy and safety of bimekizumab were evaluated versus placebo and ustekinumab (BE VIVID – PS0009), versus placebo (BE READY – PS0013) and versus adalimumab (BE SURE - PS0008).

The BE VIVID study evaluated 567 patients for 52 weeks where patients were randomized to receive either bimekizumab 320 mg every 4 weeks, ustekinumab (45 mg or 90 mg, depending on patient weight, at baseline and Week 4 and then every 12 weeks), or placebo for an initial 16 weeks followed by bimekizumab 320 mg every 4 weeks.

The BE READY study evaluated 435 patients for 56 weeks. Patients were randomized to receive bimekizumab 320 mg every 4 weeks or placebo. At Week 16, patients who achieved a PASI 90 response entered the 40-week randomized withdrawal period. Patients initially randomized to bimekizumab 320 mg every 4 weeks were re-randomized to either bimekizumab 320 mg every 4 weeks or bimekizumab 320 mg every 8 weeks or placebo (i.e. withdrawal of bimekizumab). Patients initially randomized to placebo continued to receive placebo provided they were PASI 90 responders. Patients who did not achieve a PASI 90 response at Week 16 entered an open-label escape arm and received bimekizumab 320 mg every 4 weeks for 12 weeks. Patients who relapsed (did not achieve PASI 75 response) during the randomized withdrawal period also entered the 12-week escape arm.

The BE SURE study evaluated 478 patients for 56 weeks. Patients were randomized to receive either bimekizumab 320 mg every 4 weeks through Week 56, bimekizumab 320 mg every 4 weeks through Week 16 followed by bimekizumab 320 mg every 8 weeks through Week 56 or adalimumab as per

labeling recommendation through Week 24 followed by bimekizumab 320 mg every 4 weeks through Week 56.

Baseline characteristics were consistent across all 3 studies. Among those, the median baseline BSA was 20%, the median baseline PASI score was 18 and the baseline IGA score was severe in 33% of patients. The median baseline scores for Patient Symptoms Diary (PSD) pain, itch and scaling items ranged between 6 and 7 on a 0-10 points scale and the median baseline Dermatology Life Quality Index (DLQI) total score was 9.

Across all 3 studies, 38% of patients had received a prior biologic therapy; 23% had received at least one anti-IL17 agent and 13% had received at least one TNF-antagonist. Twenty-two percent were naïve to any systemic therapy (including non-biologic and biologic) and 39% of patients had received prior phototherapy or photochemotherapy.

The efficacy of bimekizumab was evaluated with respect to impact on skin disease overall, specific body locations (scalp, nails and hand and foot), patient reported symptoms and impact on quality of life. The two co-primary end-points in all 3 studies were the proportion of patients who achieved 1) a PASI 90 response and 2) an IGA “clear or almost clear” (IGA 0/1 with at least two points improvement from baseline) response at Week 16. PASI 100, IGA 0 response at Week 16 and PASI 75 response at Week 4 were key secondary endpoints in all 3 studies.

Skin disease overall

Treatment with bimekizumab resulted in significant improvement in the measures of disease activity compared to placebo, ustekinumab or adalimumab at Week 16. The key efficacy results are shown in Table 2.

Table 2: Summary of clinical responses in BE VIVID, BE READY and BE SURE

	BE VIVID			**BE READY**		**BE SURE**	
	Placebo (N= 83) n (%)	**BKZ 320 mg Q4W (N= 321) n (%)**	**Ustekinumab (N=163) n (%)**	**Placebo (N= 86) n (%)**	**BKZ 320 mg Q4W (N= 349) n (%)**	**BKZ 320 mg Q4W (N= 319) n (%)**	**Adalimumab (N= 159) n (%)**
PASI 100 Week 16	0 (0.0)	188 (58.6) [a]	34 (20.9)	1 (1.2)	238 (68.2) [a]	194 (60.8) [a]	38 (23.9)
PASI 90 Week 16	4 (4.8)	273 (85.0) [a, b]	81 (49.7)	1 (1.2)	317 (90.8) [a]	275 (86.2) [a]	75 (47.2)
PASI 75 Week 4 Week 16	2 (2.4) 6 (7.2)	247 (76.9) [a, b] 296 (92.2)	25 (15.3) 119 (73.0)	1 (1.2) 2 (2.3)	265 (75.9) [a] 333 (95.4)	244 (76.5) [a] 295 (92.5)	50 (31.4) 110 (69.2)
IGA 0 Week 16	0 (0.0)	188 (58.6) [a]	36 (22.1)	1 (1.2)	243 (69.6) [a]	-	-

IGA 0/1 Week 16	4 (4.8)	270 (84.1) [a, b]	87 (53.4)	1 (1.2)	323 (92.6) [a]	272 (85.3) [a]	91 (57.2)
Absolute PASI ≤ 2 Week 16	3 (3.6)	273 (85.0)	84 (51.5)	1 (1.2)	315 (90.3)	280 (87.8)	86 (54.1)
PSD Pain (N) Week 16	(N=54) 9 (16.7)	(N=229) 177 (77.3) [a]	(N=107) 73 (68.2)	(N=67) 6 (9.0)	(N=255) 201 (78.8) [a]	-	-
PSD Itch (N) Week 16	(N=61) 8 (13.1)	(N=244) 187 (76.6) [a]	(N=117) 77 (65.8)	(N=72) 4 (5.6)	(N=278) 210 (75.5) [a]	-	-
PSD Scaling (N) Week 16	(N=63) 8 (12.7)	(N=246) 193 (78.5) [a]	(N=116) 69 (59.5)	(N=70) 4 (5.7)	(N=286) 223 (78.0) [a]	-	-

BKZ 320 mg Q4W= bimekizumab every 4 weeks. Non-Responder Imputation (NRI) is used.

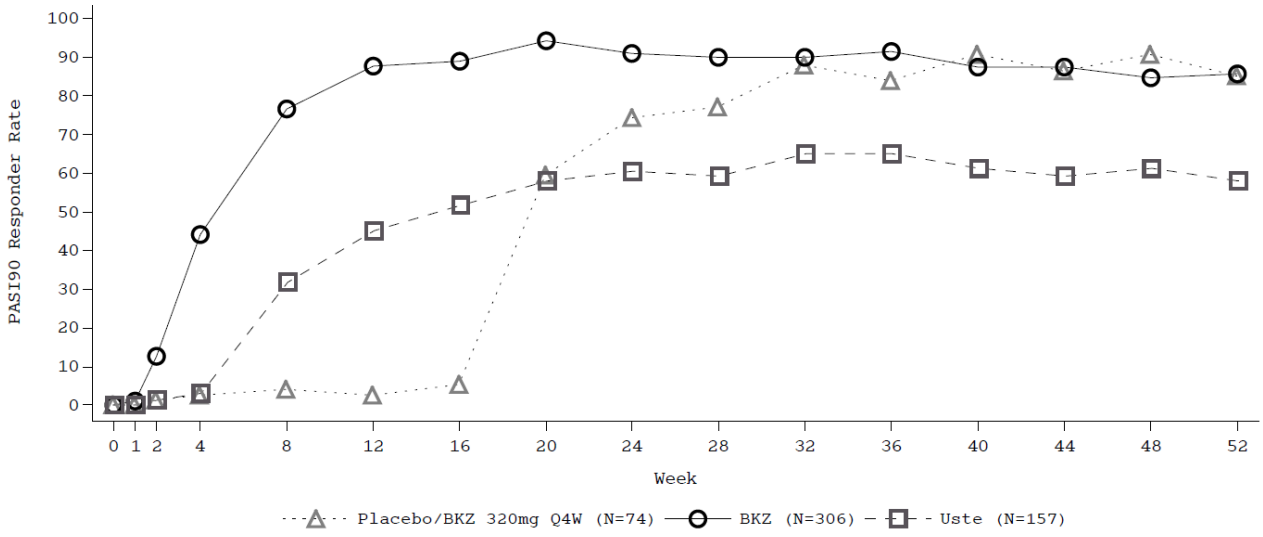
IGA 0/1 response was defined as Clear (0) or Almost Clear (1) with at least a 2-category improvement from Baseline at Week 16. IGA 0 response was defined as Clear (0) with at least a 2-category improvement from Baseline at Week 16. PSD is Patient Symptoms Diary. PSD response is defined as a change from baseline to Week 16 ≥ to a pre-specified threshold (1.98, 2.39, and 2.86 respectively for pain itch and scaling).

a) p<0.001 versus placebo (BE VIVID and BE READY), versus adalimumab (BE SURE), adjusted for multiplicity.

b) p<0.001 versus ustekinumab (BE VIVID), adjusted for multiplicity.

Bimekizumab was associated with a rapid onset of efficacy. In BE VIVID, at week 2 and week 4, PASI 90 response rates were higher for bimekizumab-treated patients (12.1% and 43.6% respectively) compared to placebo (1.2% and 2.4% respectively) and ustekinumab (1.2% and 3.1% respectively).

Figure 1: PASI 90 responder rates over time in BE VIVID

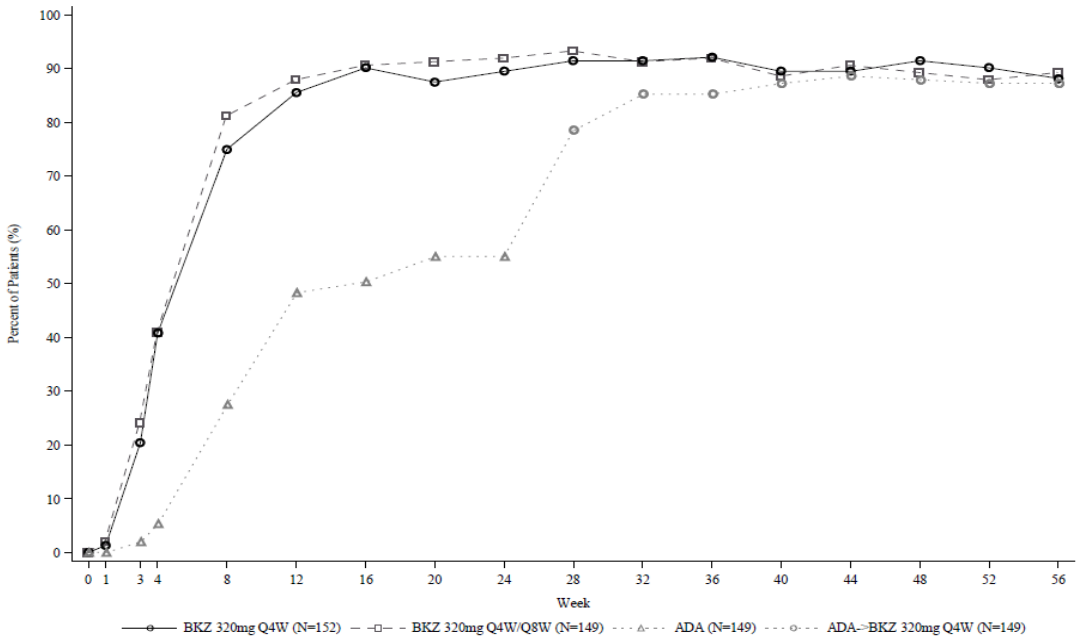


BKZ=bimekizumab; Uste=ustekinumab. NRI is used. Note: Patients in the Placebo/BKZ group switched from Placebo to BKZ in the Maintenance Treatment Period starting at Week 16.

In the BE VIVID study, at Week 52, bimekizumab-treated patients achieved higher response rates than the ustekinumab-treated patients on the endpoints of PASI 90 (81.6% bimekizumab vs 55.8% ustekinumab, p<0.001), IGA 0/1 (77.9% bimekizumab vs 60.7% ustekinumab, p<0.001) and PASI 100 (64.2% bimekizumab vs 38.0% ustekinumab).

In the BE SURE study at Week 24, a higher percentage of patients treated with bimekizumab achieved a PASI 90 and an IGA 0/1 responses as compared with adalimumab (85.6% and 86.5% respectively vs 51.6% and 57.9% respectively, p<0.001). Among the 65 adalimumab non-responders at Week 24 (< PASI 90), 78.5% achieved a PASI 90 response after 16 weeks of treatment with bimekizumab. No new safety findings were observed in patients who switched from adalimumab to bimekizumab. At Week 56, 70.2% of bimekizumab-treated patients achieved a PASI 100 response.

Figure 2: PASI 90 responder rates over time in BE SURE



BKZ 320 mg Q4W = bimekizumab every 4 weeks; BKZ 320 mg Q8W = bimekizumab every 8 weeks; ADA = adalimumab.
Note: Only patients who received bimekizumab at Week 24 or later are included. Patients in the BKZ Q4W/Q8W group switched from Q4W to Q8W dosing at Week 16. Patients in the ADA/BKZ 320 mg Q4W group switched from ADA to BKZ Q4W at Week 24. NRI is used.

The efficacy of bimekizumab was demonstrated regardless of age, gender, race, disease duration, body weight, PASI baseline severity and previous treatment with a biologic. Bimekizumab was efficacious in prior biologic exposed patients, including anti-TNF / anti IL-17 and in systemic treatment-naïve patients. Based on population PK / PD analysis and supported by clinical data, patients with higher body weight (≥120 kg) who did not achieve complete skin clearance at week 16 benefited from continued bimekizumab 320 mg every four weeks (Q4W) after the initial 16 weeks of treatment. In the BE SURE study, patients received bimekizumab 320 mg Q4W through week 16, followed by either Q4W or every

eight weeks (Q8W) dosing through week 56, regardless of responder status at week 16. Patients in the ≥120 kg group (N=37) on the Q4W maintenance regimen showed greater improvement in PASI100 between week 16 (23.5%) and week 56 (70.6%) compared to those on the Q8W maintenance regimen (week 16: 45.0% vs week 56: 60.0%).

Maintenance of response

Table 3: Maintenance of responses at Week 52 in responders at Week 16*

PASI 100		PASI 90		IGA 0/1		Absolute PASI ≤ 2	
BKZ 320mg Q4W/Q4W (N=355) n (%)	BKZ 320mg Q4W/Q8W (N=182) n (%)	BKZ 320mg Q4W/Q4W (N=516) n (%)	BKZ 320mg Q4W/Q8W (N=237) n (%)	BKZ 320mg Q4W/Q4W (N=511) n (%)	BKZ 320mg Q4W/Q8W (N=234) n (%)	BKZ 320mg Q4W/Q4W (N=511) n (%)	BKZ 320mg Q4W/Q8W (N= 238) n (%)
295 (83.1)	161 (88.5)	464 (89.9)	214 (90.3)	447 (87.5)	214 (91.5)	460 (90.0)	215 (90.3)

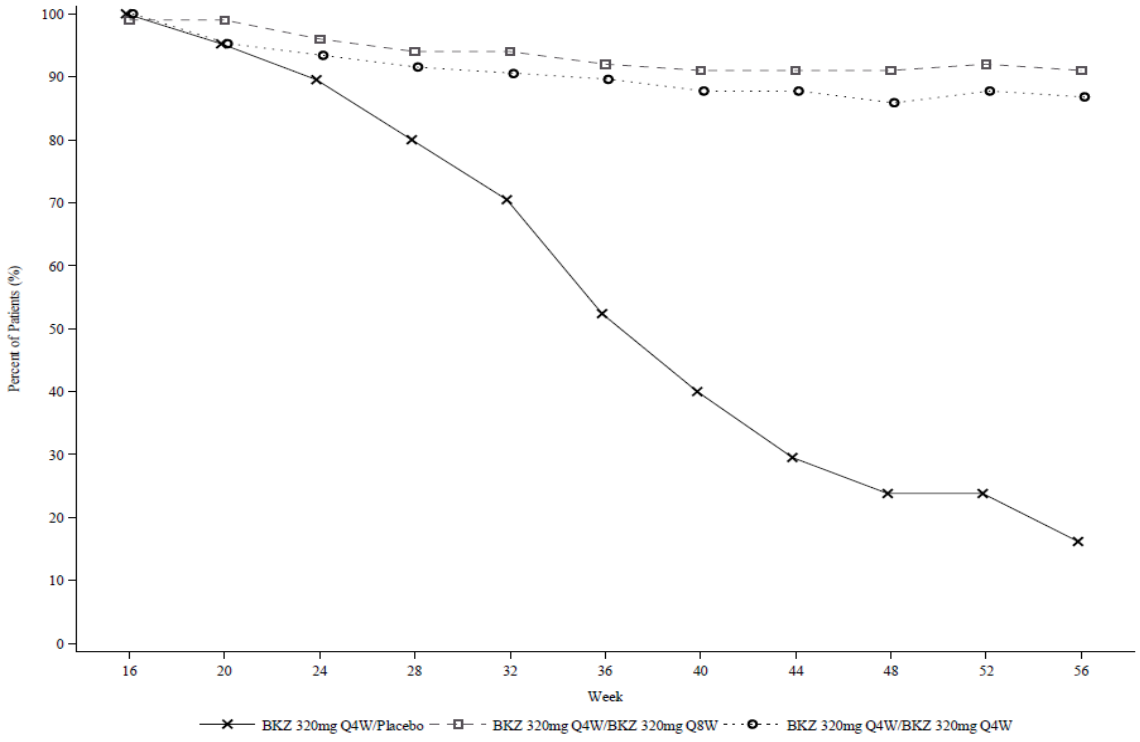
* Integrated analysis of BE VIVID, BE READY and BE SURE. NRI is used.

BKZ 320 mg Q4W/Q4W: bimekizumab 320 mg every 4 weeks followed by bimekizumab 320mg every 4 weeks from Week 16.

BKZ 320 mg Q4W/Q8W: bimekizumab 320 mg every 4 weeks followed by bimekizumab 320mg every 8 weeks from Week 16.

Durability of PASI 90 response (after bimekizumab discontinuation)

Figure 3: PASI 90 responder rates over time – Randomized withdrawal period in BE READY



NRI is used.

In BE READY, for PASI 90 responders at Week 16 who were re-randomized to placebo and withdrawn from bimekizumab, the median time to relapse, defined as loss of PASI 75, was approximately 28 weeks

(32 weeks after the last bimekizumab dose). Among these patients, 88.1% regained a PASI 90 response within 12 weeks of restarting treatment with bimekizumab 320 mg every 4 weeks.

Specific body locations

Significant improvements were observed in psoriasis involving the scalp, nails and hands and feet in patients treated with bimekizumab at Week 16 in the studies BE VIVID and BE READY versus placebo (see Table 4).

Table 4: Specific body location responses in BE VIVID and BE READY at Week 16

	BE VIVID			BE READY	
	Placebo	**BKZ 320 mg Q4W**	**Ustekinumab**	**Placebo**	**BKZ 320 mg Q4W**
Scalp IGA (N)[a] Scalp IGA 0/1, n (%)	(72) 11 (15.3)	(285) 240 (84.2) [b]	(146) 103 (70.5)	(74) 5 (6.8)	(310) 286 (92.3) [b]
pp-IGA (N)[a] pp-IGA 0/1, n (%)	(29) 7 (24.1)	(105) 85 (81.0)	(47) 39 (83.0)	(31) 10 (32.3)	(97) 91 (93.8)
mNAPSI 100 (N)[a] mNAPSI 100, n (%)	(51) 4 (7.8)	(194) 57 (29.4)	(109) 15 (13.8)	(50) 3 (6.0)	(210) 73 (34.8)

NRI is used

a) Includes only patients with a scalp Investigator Global Assessment (IGA) of 2 or greater, a palmoplantar IGA of 2 or greater and a modified Nail Psoriasis and Severity Index (mNAPSI) score > 0 at baseline. Scalp IGA 0/1 and pp-IGA 0/1 responses were defined as Clear (0) or Almost Clear (1) with ≥2 category improvement relative to Baseline.

b) $p<0.001$ versus placebo, adjusted for multiplicity.

Scalp IGA and palmoplantar IGA responses were maintained through Week 52/56. Nail psoriasis continued to improve beyond Week 16. In BE VIVID, at Week 52, a higher proportion of patients treated with bimekizumab achieved a complete nail clearance (mNAPSI 100) compared to patients treated with ustekinumab (60.3% vs 40.4% respectively). In BE READY, at Week 56, 67.7% and 69.8% of Week 16 PASI 90 responders achieved complete nail clearance with bimekizumab 320 mg every 8 weeks and bimekizumab 320 mg every 4 weeks respectively.

Health-related Quality of Life / Patient reported outcomes

Across all 3 studies, a greater proportion of patients treated with bimekizumab experienced no impact of psoriasis on their quality of life as measured by the Dermatology Life Quality Index (DLQI) compared to placebo and active comparator-treated patients at Week 16.

In BE READY, the percentage of patients with Dermatology Life Quality Index (DLQI) of 0/1 (no impact of psoriasis on health-related quality of life) at Week 16 were 75.6% and 5.8%, in the bimekizumab and placebo groups, respectively.

In BE VIVID, DLQI 0/1 response rates at Week 16 were 67.3%, 42.3% and 12.0%, in the bimekizumab, ustekinumab and placebo groups, respectively. DLQI 0/1 response rates continued to increase beyond week 16 and then were maintained through week 52 (74.8% in patients treated with bimekizumab 320 mg every 4 weeks).
In BE SURE, DLQI 0/1 response rates at Week 16 were 63.0% and 46.5%, in the bimekizumab and adalimumab groups, respectively. At week 56, 78.9% and 74.1% of patients had a DLQI 0/1 with bimekizumab 320 mg every 8 weeks and bimekizumab 320 mg every 4 weeks, respectively.

Pharmacokinetics

Absorption

Based on population pharmacokinetic analysis, following a single subcutaneous dose of 320 mg in plaque psoriasis patients, bimekizumab reached a median (2.5^{th} and 97.5^{th} percentile) peak plasma concentration of 25 (12-50) µg/ml, between 3 and 4 days post dose.
Population pharmacokinetic analysis showed that bimekizumab was absorbed with an average absolute bioavailability of 70.1% in healthy volunteers.

Distribution

Based on population pharmacokinetic analyses, the median (coefficient of variation %) volume of distribution (V/F) at steady state was 11.2 (30.5%) L in plaque psoriasis patients.

Metabolism

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

Elimination

Based on population pharmacokinetic analyses, the median (coefficient of variation %) apparent clearance (CL/F) of bimekizumab was 0.337 L/day (32.7%) and the mean terminal elimination half-life of bimekizumab was 23 days in clinical studies in patients with plaque psoriasis.

Based on simulated data, the median (2.5^{th} and 97.5^{th} percentile) peak and trough concentration at steady-state following subcutaneous administration of 320 mg every 4 weeks are 43 (20-91) µg/ml and 20 (7-50) µg/ml respectively and steady-state is reached after approximately 16 weeks with every 4 weeks dosing regimen. Compared with exposure after a single dose, the population pharmacokinetic analysis showed that patients exhibited a 1.74-fold increase in peak plasma concentrations and area under the curve (AUC) following repeated four weekly dosing.
After switching from the 320 mg every 4 weeks dosing regimen to 320 mg every 8 weeks dosing regimen at Week 16, steady-state is achieved approximately 16 weeks after the switch. Median (2.5^{th}

and 97.5th percentile) peak and trough plasma concentrations are 30 (14-60) µg/ml and 5 (1-16) µg/ml respectively.

Linearity/non-linearity

Bimekizumab exhibited dose-proportional pharmacokinetics in patients with plaque psoriasis over a dose range from 64 mg to 480 mg following multiple subcutaneous administrations, with apparent clearance being independent of dose.

Pharmacokinetic (PK) / Pharmacodynamic (PD) relationship

A population pharmacokinetic/pharmacodynamic model was developed using all available data in moderate to severe plaque psoriasis patients. The analysis showed that higher bimekizumab concentrations are related to better Psoriasis Area and Severity Index (PASI) and Investigators Global Assessment (IGA) response and a dose of 320 mg at Week 0, 4, 8, 12, 16 and every 8 weeks thereafter provides maximum benefit to the majority of moderate to severe plaque psoriasis patients (see Kinetics in specific patient groups and *Body Weight*).

Kinetics in specific patient groups

Hepatic and renal impairment

No specific studies have been conducted to determine the effect of renal or hepatic impairment on the pharmacokinetics of bimekizumab. The renal elimination of intact bimekizumab, an IgG monoclonal antibody, is expected to be low and of minor importance. Similarly, IgGs are mainly eliminated via intracellular catabolism and hepatic impairment is not expected to influence clearance of bimekizumab. Based on population pharmacokinetic analyses, hepatic function markers (ALT/ bilirubin) did not have any impact on bimekizumab clearance in patients with plaque psoriasis.

Elderly patients

Based on population pharmacokinetic analysis with a limited number of elderly patients (n = 110 for age ≥ 65 years and n = 14 for age ≥ 75 years), apparent clearance (CL/F) in elderly patients and patients less than 65 years of age was similar. No dose adjustment is required.

Body weight

Population pharmacokinetic modelling indicated that exposure decreased as body weight increased. The average plasma concentration in adult patients weighing ≥120 kg following a 320 mg subcutaneous injection was predicted to be at least 30% lower than in adult patients weighing 90 kg. Dose adjustment may be appropriate in some patients (see "*Dosage/Administration*").

Race / Gender

No clinically meaningful differences in bimekizumab exposure were observed in Japanese subjects compared to Caucasian subjects in a clinical pharmacokinetic study. No dose adjustment is required. A population pharmacokinetic analysis indicated females may have 10% faster apparent clearance (CL/F) compared to males and it is not clinically meaningful. No dose adjustment is required.

Preclinical data

Non-clinical data revealed no special hazards for humans based on tissue cross-reactivity testing, repeat-dose toxicity studies (including safety pharmacology endpoints and assessment of fertility-related endpoints) and evaluation of pre- and postnatal development.

Genotoxicity / Carcinogenicity

No mutagenicity or carcinogenicity studies were conducted with bimekizumab. However monoclonal antibodies are not expected to damage DNA or chromosomes. In a 26-week chronic toxicology study in cynomolgus monkeys there were no pre-neoplastic or neoplastic lesions observed at a dose resulting in 109 times the human exposure at 320 mg every 4 weeks.

Reproductive toxicity

In an enhanced peri- and postnatal development study in the cynomolgus monkey, bimekizumab showed no effects on gestation, parturition, infant survival, fetal and postnatal development when administered throughout organogenesis until parturition at a dose resulting in 27 times the human exposure at 320 mg every 4 weeks based on AUC. At birth, serum bimekizumab concentrations in infant monkeys were comparable to those of mothers.

Other information

Incompatibilities

In the absence of compatibility studies, this 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.
Keep the pre-filled pen in the outer carton in order to protect from light.
Keep the pre-filled syringe in the outer carton in order to protect from light.
The Bimzelx pre-filled pen and pre-filled syringe may be stored at room temperature (up to 25°C) for a single period of maximum 25 days with protection from light. Once removed from the refrigerator and

stored at room temperature, discard after 25 days or by the expiry date printed on the container, whichever occurs first. A field for the date is provided on the carton to record the date removed from the refrigerator.
Keep out of the reach of children.

Authorisation number

68548, 68612 (Swissmedic)

Packs

Bimzelx 160 mg solution for injections in pre-filled pen.
1 pre-filled pen (B).
2 pre-filled pens (B).
Bimzelx 160 mg solution for injections in pre-filled syringe.
1 pre-filled syringe (B).
2 pre-filled syringes (B).

Marketing authorisation holder

UCB-Pharma AG, Bulle

Date of revision of the text

June 2022