SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BIMZELX

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 160 mg of bimekizumab in 1 mL.

Bimekizumab is a humanised IgG1monoclonal antibody produced in a genetically engineered Chinese hamster ovary (CHO) cell line by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (subcutaneous injection).
The solution is clear to slightly opalescent and colourless to pale brownish-yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of plaque psoriasis.

Posology

The recommended dose 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 populations

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 section 5.1).

Elderly (≥65 years)

No dose adjustment is required (see section 5.2).

Renal or hepatic impairment

Bimekizumab has not been studied in these patient populations. Dose adjustments are not considered necessary based on pharmacokinetics (see section 5.2).

Paediatric population

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

Method of administration

This medicinal product 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.
The pre-filled pen must not be shaken.
After proper training in subcutaneous injection technique, patients may self-inject Bimzelx with the pre-filled pen 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 use provided in the package leaflet.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Clinically important active infections (e.g. active tuberculosis, see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infections

Bimekizumab may increase the risk of infections such as upper respiratory tract infections and oral candidiasis (see section 4.8).

Caution should be exercised when considering the use of bimekizumab in patients with a chronic infection or a history of recurrent infection. Treatment with bimekizumab must not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated (see section 4.3).

Patients treated with bimekizumab should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a clinically important infection or is not responding to standard therapy, the patient should be monitored carefully and bimekizumab should not be administered until the infection resolves.

Pre-treatment evaluation for tuberculosis (TB)

Prior to initiating treatment with bimekizumab, patients should be evaluated for TB infection. Bimekizumab should not be given in patients with active TB (see section 4.3). Patients receiving bimekizumab should be monitored for signs and symptoms of active TB. Anti-TB therapy should be considered prior to initiating bimekizumab in patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed.

Inflammatory bowel disease

Cases of new or exacerbations of inflammatory bowel disease have been reported with bimekizumab (see section 4.8). Bimekizumab 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, bimekizumab should be discontinued and appropriate medical management should be initiated.

Hypersensitivity

Serious hypersensitivity reactions including anaphylactic reactions have been observed with IL-17 inhibitors. If a serious hypersensitivity reaction occurs, administration of bimekizumab should be discontinued immediately and appropriate therapy initiated.

Vaccinations

Prior to initiating therapy with bimekizumab, completion of all age appropriate immunizations according to current immunization guidelines should be considered.

Live vaccines should not be given in patients treated with bimekizumab.

Patients treated with bimekizumab may receive inactivated or non-live vaccinations. Healthy individuals who received a single 320 mg dose of bimekizumab two weeks prior to vaccination with an inactivated seasonal influenza vaccine had similar antibody responses compared to individuals who did not receive bimekizumab prior to vaccination.

Important information about some of the ingredients:
This medicinal product contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially "sodium free".

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
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 bimekizumab, may result in normalisation of CYP450 levels with accompanying lower exposure of CYP450-metabolised medicinal products. 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 bimekizumab therapy in patients being treated with these types of medicinal products, therapeutic monitoring should be considered.

Live vaccines should not be given concurrently with bimekizumab (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use an effective method of contraception during treatment and for at least 17 weeks after treatment.

Pregnancy

There is a limited amount of data on the use of bimekizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Bimzelx during pregnancy.

Breast-feeding

It is unknown whether bimekizumab is excreted in human milk. A risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Bimzelx therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of bimekizumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Bimzelx has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were upper respiratory tract infections (14.5%) (most frequently nasopharyngitis) and oral candidiasis (7.3%).

Tabulated list of adverse reactions

Adverse reactions from clinical studies (Table 1) are classified by MedDRA System Organ Class and frequency, using 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), not known (cannot be estimated from the available data).

Table 1: List of adverse reactions

System Organ Class	**Frequency**	**Adverse reaction**
Infections and infestations	Very common	Upper respiratory tract infections
	Common	Oral candidiasis, Tinea infections, Ear infections, Herpes simplex infections, Oropharyngeal candidiasis, Gastroenteritis, Folliculitis
	Uncommon	Mucosal and cutaneous candidiasis (including oesophageal candidiasis), Conjunctivitis
Blood and lymphatic system disorders	Uncommon	Neutropenia
Nervous System disorders	Common	Headache
Gastrointestinal disorders	Uncommon	Inflammatory bowel disease
Skin and subcutaneous tissue disorders	Common	Rash, 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 selected adverse reactions

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. Serious infections occurred in 0.3% of patients treated with bimekizumab and 0% treated with placebo.

The majority of infections consisted of non-serious mild to moderate upper respiratory tract infections such as nasopharyngitis. 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). More than 98% of cases were non-serious, mild or moderate in severity, and did not require treatment discontinuation. A slightly higher incidence of oral candidiasis was reported in patients <70 kg (8.5% *versus* 7.0% in patients ≥70 kg).

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 section 4.4).

Neutropenia

Neutropenia was observed with bimekizumab in phase III clinical studies in plaque psoriasis. 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.

Hypersensitivity

Serious hypersensitivity reactions including anaphylactic reactions have been observed with IL-17 inhibitors.

Immunogenicity

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 neutralising. No evidence of altered clinical response, or significantly altered safety profile was associated with anti-bimekizumab antibodies development.

Elderly patients (≥65 years)

Elderly patients may be more likely to experience certain adverse reactions such as oral candidiasis, dermatitis and eczema when using bimekizumab. In the placebo-controlled period of Phase III clinical studies in plaque psoriasis, oral candidiasis was observed in 18.2% of patients ≥65 years *versus* 6.3 % in <65 years, dermatitis and eczema in 7.3% of patients ≥65 years *versus* 2.8% in <65 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/ and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC21

Mechanism of action

Bimekizumab is a humanised 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.

Clinical efficacy and safety

The safety and efficacy of bimekizumab was evaluated in 1,480 patients with moderate to severe plaque psoriasis in three Phase 3 multicenter, randomised, 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 psoriasis (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 randomised 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 randomised to receive bimekizumab 320 mg every 4 weeks or placebo. At week 16, patients who achieved a PASI 90 response entered the 40-week randomised withdrawal period. Patients initially randomised to bimekizumab 320 mg every 4 weeks were re-randomised to either bimekizumab 320 mg every 4 weeks or bimekizumab 320 mg every 8 weeks or placebo (i.e. withdrawal of bimekizumab). Patients initially randomised 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 randomised withdrawal period also entered the 12-week escape arm.

The BE SURE study evaluated 478 patients for 56 weeks. Patients were randomised 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: patients were predominantly male (70.7%) and white (84.1%), with a mean age of 45.2 years (18 to 83 years), and 8.9% were ≥65 years of age. 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 (primary anti-IL17 failures were excluded) 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, palms and soles), patient reported symptoms and impact on quality of life. The two co-primary endpoints 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 0/1with 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 secondary endpoints in all 3 studies.

Skin disease overall

Treatment with bimekizumab resulted in significant improvement across efficacy endpoints compared to placebo, ustekinumab or adalimumab at week 16. The main efficacy results are shown in Table 2.

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

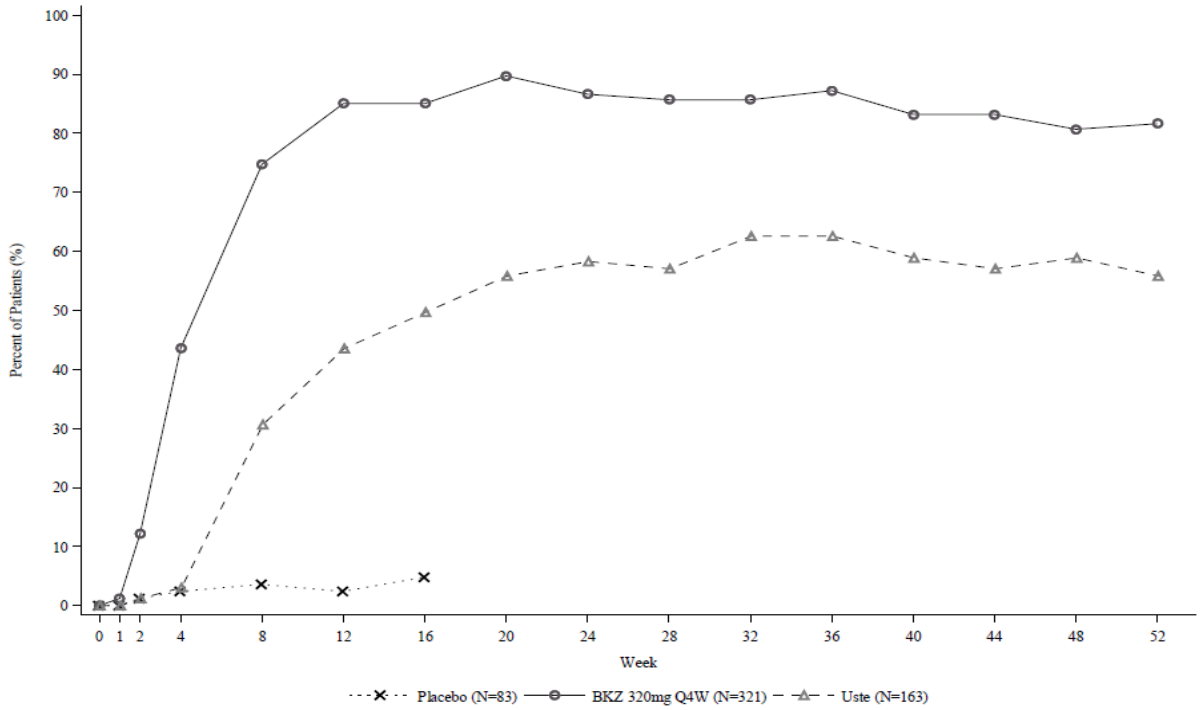
	BE VIVID			**BE READY**		**BE SURE**	
	Placebo (N= 83) n (%)	**Bimekizumab 320 mg Q4W (N= 321) n (%)**	**Ustekinumab (N=163) n (%)**	**Placebo (N= 86) n (%)**	**Bimekizumab 320 mg Q4W (N= 349) n (%)**	**Bimekizumab 320 mg Q4W (N= 319) n (%)**	**Adalimumab (N= 159) n (%)**
PASI 100							
Week 16	0 (0.0)	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	2 (2.4)	247 (76.9)[a, b]	25 (15.3)	1 (1.2)	265 (75.9)[a]	244 (76.5)[a]	50 (31.4)
Week 16	6 (7.2)	296 (92.2)	119 (73.0)	2 (2.3)	333 (95.4)	295 (92.5)	110 (69.2)
IGA 0							
Week 16	0 (0.0)	188 (58.6)[a]	36 (22.1)	1 (1.2)	243 (69.6)[a]	197 (61.8)	39 (24.5)
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 improvement ≥4 (N)	**(N=48)**	**(N=190)**	**(N=90)**	**(N=49)**	**(N=209)**	**(N=222)**	**(N=92)**
Week 16	5 (10.4)	140 (73.7)	54 (60.0)	0 (0.0)	148 (70.8)	143 (64.4)	43 (46.7)
PSD Itch improvement ≥4 (N)	**(N=53)**	**(N=222)**	**(N=104)**	**(N=60)**	**(N=244)**	**(N=248)**	**(N=107)**
Week 16	6 (11.3)	151 (68.0)	57 (54.8)	0 (0.0)	161 (66.0)	153 (61.7)	42 (39.3)
PSD Scaling improvement ≥4 (N)	**(N=56)**	**(N=225)**	**(N=104)**	**(N=65)**	**(N=262)**	**(N=251)**	**(N= 109)**
Week 16	6 (10.7)	171 (76.0)	59 (56.7)	1 (1.5)	198 (75.6)	170 (67.7)	42 (38.5)

Bimekizumab 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 a Patient Symptoms Diary, also referred to as Psoriasis Symptoms and Impacts Measure (P-SIM), measuring psoriasis symptom severity on a scale from 0 (no symptoms) to 10 (very severe symptoms). Response is defined as a decrease ≥4 from baseline to week 16 for pain, itch and scaling on a scale from 0 to 10.
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 significantly 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).

In the BE VIVID study, at week 52, bimekizumab-treated patients (every 4 weeks) achieved significantly higher response rates than the ustekinumab-treated patients on the endpoints of PASI 90 (81.9% bimekizumab vs 55.8% ustekinumab, p<0.001), IGA 0/1 (78.2% bimekizumab vs 60.7% ustekinumab, p<0.001) and PASI 100 (64.5% bimekizumab vs 38.0% ustekinumab).

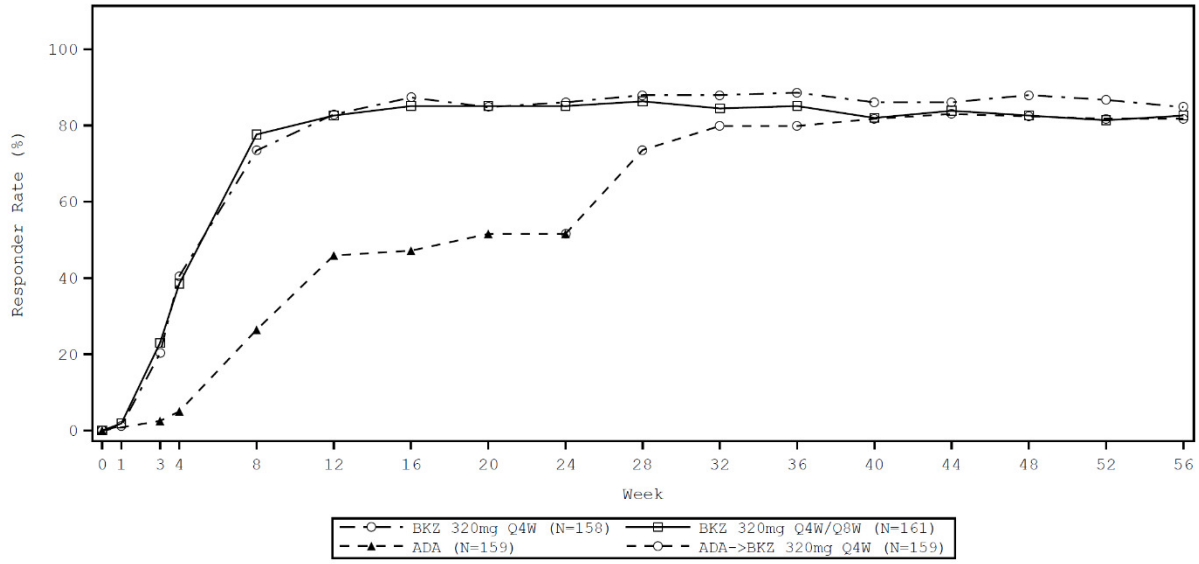
Figure 1: PASI 90 responder rates over time in BE VIVID



BKZ 320 mg Q4W=bimekizumab every 4 weeks; Uste=ustekinumab. NRI is used.

In the BE SURE study at week 24, a significantly higher percentage of patients treated with bimekizumab (Q4W/Q4W and Q4W/Q8W combined dosing arms) achieved PASI 90 and IGA 0/1 responses as compared with adalimumab (85.6% and 86.5% respectively vs 51.6% and 57.9% respectively, p<0.001). At week 56, 70.2% of patients treated with bimekizumab Q8W achieved a PASI 100 response. 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. The safety profile observed in patients who switched from adalimumab to bimekizumab without a wash-out period was similar to patients who initiated bimekizumab after wash out of prior systemic therapies.

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. 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. Efficacy in patients with primary failure to anti-IL17 has not been investigated.

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%).

Improvements were observed in psoriasis involving the scalp, nails, palms and soles in patients treated with bimekizumab at week 16 (see Table 3).

Table 3: Scalp, palmoplantar and nail responses in BE VIVID, BE READY and BE SURE at week 16

	BE VIVID			BE READY		BE SURE	
	Placebo	**Bimekizumab 320 mg Q4W**	**Ustekinumab**	**Placebo**	**Bimekizumab 320 mg Q4W**	**Bimekizumab 320 mg Q4W**	**Adalimumab**
Scalp IGA (N)[a]	(72)	(285)	(146)	(74)	(310)	(296)	(138)
Scalp IGA 0/1, n (%)	11 (15.3)	240 (84.2)[b]	103 (70.5)	5 (6.8)	286 (92.3)[b]	256 (86.5)	93 (67.4)
pp-IGA (N)[a]	(29)	(105)	(47)	(31)	(97)	(90)	(34)
pp-IGA 0/1, n (%)	7 (24.1)	85 (81.0)	39 (83.0)	10 (32.3)	91 (93.8)	75 (83.3)	24 (70.6)
mNAPSI 100 (N)[a]	(51)	(194)	(109)	(50)	(210)	(181)	(95)
mNAPSI 100, n (%)	4 (7.8)	57 (29.4)	15 (13.8)	3 (6.0)	73 (34.8)	54 (29.8)	21 (22.1)

Bimekizumab 320 mg Q4W= bimekizumab every 4 weeks. Non responder imputation (NRI) is used.
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.
[a)] Include 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.
[b)] p<0.001 *versus* placebo, adjusted for multiplicity

Scalp IGA and palmoplantar IGA responses in bimekizumab-treated patients were maintained through week 52 / 56. Nail psoriasis continued to improve beyond week 16. In BE VIVID, at week 52, 60.3% of patients treated with bimekizumab 320 mg every 4 weeks achieved complete nail clearance (mNAPSI 100). 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.

Maintenance of response

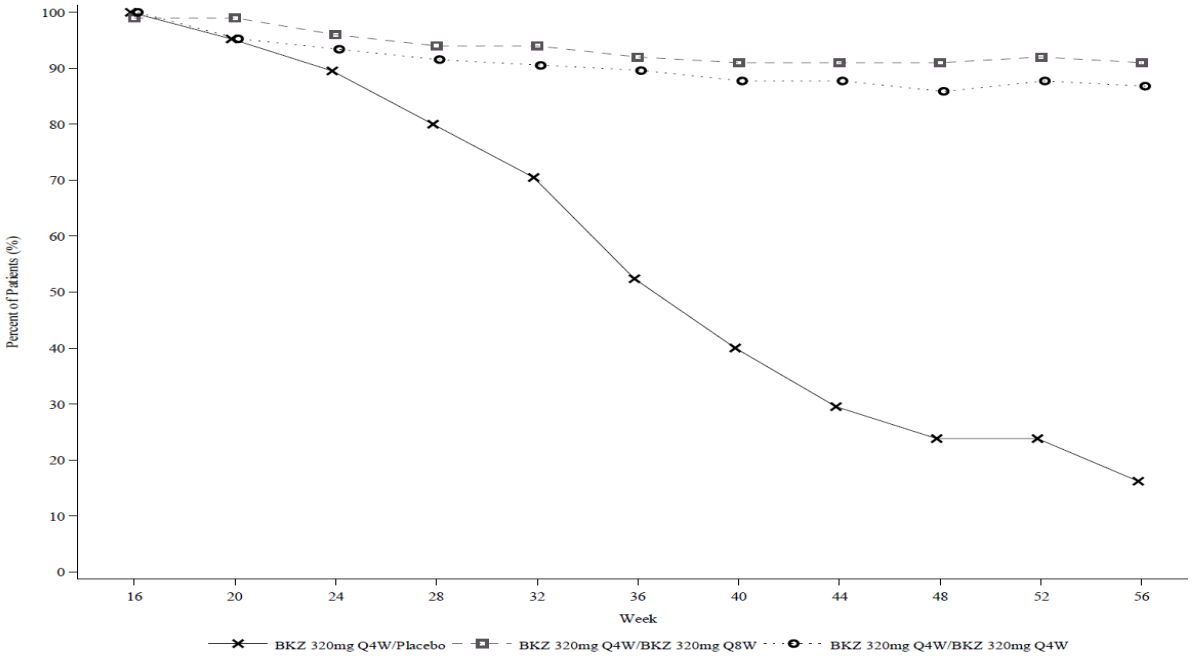
Table 4: Maintenance of responses with bimekizumab at week 52 in PASI100, PASI90, IGA 0/1 and Absolute PASI ≤ 2 responders at week 16*

PASI 100		**PASI 90**		**IGA 0/1**		**Absolute PASI ≤ 2**	
320mg Q4W (N=355) n (%)	**320mg Q8W (N=182) n (%)**	**320mg Q4W (N=516) n (%)**	**320mg Q8W (N=237) n (%)**	**320mg Q4W (N=511) n (%)**	**320mg Q8W (N=234) n (%)**	**320mg Q4W (N=511) n (%)**	**320mg 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.
320 mg Q4W: bimekizumab 320 mg every 4 weeks followed by bimekizumab 320 mg every 4 weeks from week 16.
320 mg Q8W: bimekizumab 320 mg every 4 weeks followed by bimekizumab 320 mg every 8 weeks from week 16.

Durability of response (after bimekizumab discontinuation)

Figure 3: PASI 90 responder rates over time for PASI 90 responders at week 16 – Randomized withdrawal period in BE READY



NRI is used.
At week 16, 105 study participants started the Randomized-Withdrawal Period in the bimekizumab 320 mg Q4W/placebo group, 100 in the bimekizumab 320 mg Q4W/Q8W group, and 106 in the bimekizumab 320 mg Q4W/Q4W group.

In BE READY, for PASI 90 responders at week 16 who were re-randomised 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.

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 (Table 5).

Table 5: Quality of life in study BE VIVID, BE READY and BE SURE

	BE VIVID			**BE READY**		**BE SURE**	
	Placebo (N= 83) n (%)	**Bimekizumab 320 mg Q4W (N= 321) n (%)**	**Ustekinumab (N= 163) n (%)**	**Placebo (N= 86) n (%)**	**Bimekizumab 320 mg Q4W (N= 349) n (%)**	**Bimekizumab 320 mg Q4W (N= 319) n (%)**	**Adalimumab (N= 159) n (%)**
DLQI 0/1[a] Baseline	3 (3.6)	16 (5.0)	5 (3.1)	4 (4.7)	11 (3.2)	10 (3.1)	13 (8.2)
DLQI 0/1[a] Week 16	10 (12.0)	216 (67.3)	69 (42.3)	5 (5.8)	264 (75.6)	201 (63.0)	74 (46.5)

[a)] DLQI absolute score of 0 or 1 indicates no impact of the disease on health-related quality of life. NRI is used.

DLQI 0/1 responses continued to increase beyond week 16 and then were maintained through week 52 / 56. In BE VIVID, DLQI 0/1 response rate at week 52 was 74.8% in patients treated with bimekizumab 320 mg every 4 weeks. In BE SURE 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.

Phase 3b direct comparative study versus secukinumab

The efficacy and safety of bimekizumab were also evaluated in a double-blind study compared with secukinumab, an IL-17A inhibitor, (BE RADIANT - PS0015). Patients were randomized to receive bimekizumab (N=373, 320mg at Week 0, 4, 8, 12 and 16 (Q4W) followed by 320mg every 4 weeks (Q4W/Q4W) or 320 mg every 8 weeks (Q4W/Q8W)) or secukinumab (N=370, 300 mg at Weeks 0,1, 2, 3, 4 followed by 300 mg every 4 weeks). Baseline characteristics were consistent with a population of moderate to severe plaque psoriasis patients with a median BSA of 19% and a median PASI score of 18.

Bimekizumab-treated patients achieved significantly higher response rates compared to secukinumab for the primary endpoint of PASI100 (complete skin clearance) at Week 16. Significantly higher response rates were also achieved with bimekizumab for the secondary endpoint of PASI 100 at Week 48 (for both Q4W/Q4W and Q4W/Q8W regimens). Comparative PASI response rates are presented in Table 6.
Differences in response rates between bimekizumab and secukinumab-treated patients were noted as early as week 1 for PASI 75 (7.2% and 1.4% respectively) and as early as Week 2 for PASI 90 (7.5% and 2.4% respectively).

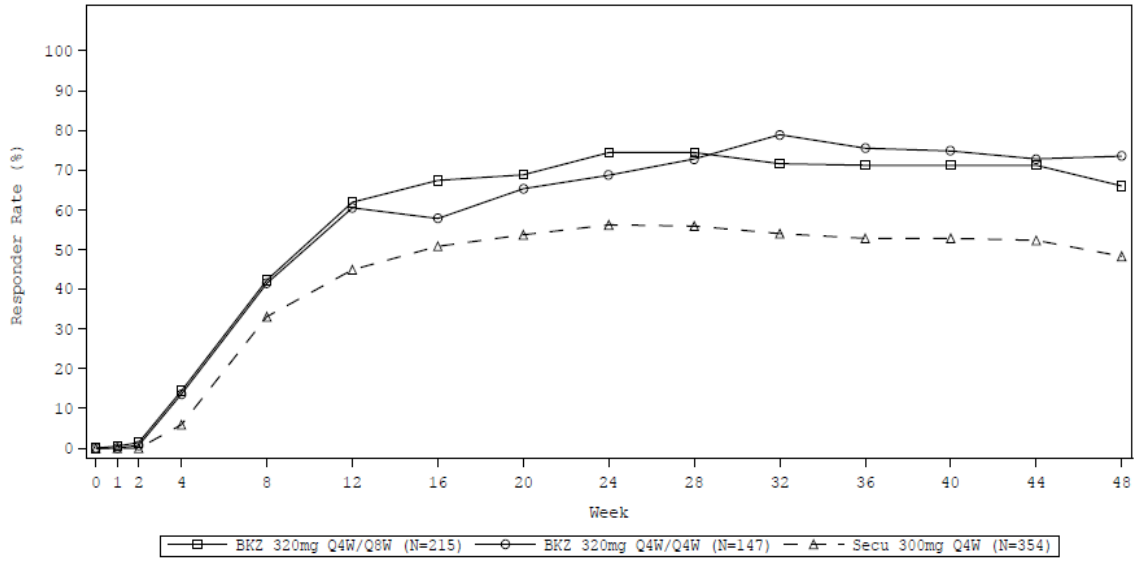
Table 6: PASI response rates from BE RADIANT - bimekizumab versus secukinumab

	Week 4		**Week 16**		**Week 48[a)]**		
	Bimekizumab 320 mg Q4W (N=373) n (%)	**Secukinumab** (N=370) n (%)	**Bimekizumab 320 mg Q4W** (N=373) n (%)	**Secukinumab** (N=370) n (%)	**Bimekizumab 320 mg Q4W/Q4W** (N=147) n (%)	**Bimekizumab 320 mg Q4W/Q8W** (N=215) n (%)	**Secukinumab** (N=354) n (%)
PASI 100	52 (13.9)	23 (6.2)	230 (61.7)*	181 (48.9)	108 (73.5)*	142 (66.0)*	171 (48.3)
PASI 90	134 (35.9)	65 (17.6)	319 (85.5)	275 (74.3)	126 (85.7)	186 (86.5)	261 (73.7)
PASI 75	265 (71.0)*	175 (47.3)	348 (93.3)	337 (91.1)	134 (91.2)	196 (91.2)	301 (85.0)
Absolute PASI<2	151 (40.5)	75 (20.3)	318 (85.3)	283 (76.5)	127 (86.4)	186 (86.5)	269 (76.0)

[a)] Data are from the Maintenance Set consisting of patients who received at least one dose of study treatment at Week 16 or later
*p<0.001 versus secukinumab, adjusted for multiplicity. NRI is used.

Bimekizumab and secukinumab PASI 100 response rates through Week 48 are presented in Figure 4.

Figure 4: PASI 100 response rate over time in BE RADIANT



NRI is used. Maintenance Set consisting of patients who received at least one dose of study treatment at Week 16 or later

The efficacy of bimekizumab in BE RADIANT was consistent with BE VIVID, BE READY and BE SURE.

5.2 Pharmacokinetic properties

Absorption

Based on population pharmacokinetic analysis, following a single subcutaneous dose of 320 mg in plaque psoriasis patients, bimekizumab reached a median (2.5th and 97.5th 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.

Based on simulated data, the median (2.5th and 97.5th 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 (2.5th and 97.5th percentile) peak and trough plasma concentrations are 30 (14 -60) µg/mL and 5 (1-16) µg/mL respectively.

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.

Biotransformation

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.

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 (CL/F) being independent of dose.

Pharmacokinetic/Pharmacodynamic 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. A dose of 320 mg every 4 weeks was shown to be an appropriate dose for the initial treatment period and 320 mg every 8 weeks thereafter is appropriate for the maintenance period for the majority of moderate to severe plaque psoriasis patients (see Special Populations, Body weight).

Special populations

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 section 4.2).

Elderly
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 (see section 4.2).

Renal impairment or hepatic 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.

Race
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.

Gender
Population pharmacokinetic modelling indicated females may have 10% faster apparent clearance (CL/F) compared to males and it is not clinically meaningful. No dose adjustment is required.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard 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 in the cynomolgus monkey.

In cynomolgus monkeys, bimekizumab-related effects were limited to mucocutaneous changes consistent with pharmacologic modulation of commensal microflora.

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.

In a peri- and postnatal development study in the cynomolgus monkey, bimekizumab showed no effects on gestation, parturition, infant survival, foetal 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Sodium acetate trihydrate
Glacial acetic acid
Polysorbate 80
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

The pre-filled pen 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 under these conditions, 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.

6.5 Nature and contents of container

One mL pre-filled pen containing a pre-filled syringe (type I glass) with a fluoropolymer-laminated bromobutyl rubber stopper, staked 27G, ½" thin wall needle, and a polypropylene rigid needle shield.

Pack size of 2 pre-filled pens.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

UCB Pharma S.A., Braine l'Alleud, Belgium.

8. MARKETING AUTHORISATION HOLDER

Neopharm Ltd., Hashiloach 6 St., POB 7063, Petach-Tikva 4917001.

9. MARKETING AUTHORISATION NUMBER

172-46-37409-00

Revised in November 2023 according to MOHs guidelines.