Fraizeron®/™ (secukinumab)

150 mg Powder for solution for injection

LEAFLET

Trade name

Fraizeron 150 mg powder for solution for injection

Description and composition

Pharmaceutical forms

Powder for solution for injection

The powder is a white solid lyophilisate in a 6 mL glass vial.

Active substance

Each vial of powder for solution for subcutaneous injection contains 150 mg of secukinumab when reconstituted with 1 mL water for injection.

Secukinumab is a recombinant fully human monoclonal antibody selective for interleukin-17A. Secukinumab is of the IgG1/κ-class produced in Chinese Hamster Ovary (CHO) cells.

Excipients

Powder for solution for subcutaneous injection: Sucrose, L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, water for injection.

Indications

Plaque psoriasis

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

Dosage and administration

Dosage

Plaque psoriasis:

The recommended dose is 300 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at week 4. Each 300 mg dose is given as two subcutaneous injections of 150 mg.

Special populations

Renal impairment / hepatic impairment

Fraizeron has not been studied specifically in these patient populations.

Pediatric patients

Safety and effectiveness in pediatric patients below the age of 18 years have not yet been established.

Geriatric patients

No dose adjustment is required.

Method of administration

Powder for solution for injection

Fraizeron is administered by subcutaneous injection. Fraizeron powder for solution must be reconstituted before use. Full instructions for use are provided in section Pharmaceutical information.

Contraindications

Severe hypersensitivity reactions to the active substance or to any of the excipients (see section Description and composition, section Warnings and precautions and section Adverse drug reactions).

Warnings and precautions

Infections

Fraizeron has the potential to increase the risk of infections. In clinical studies, infections have been observed in patients receiving Fraizeron (see section Adverse drug reactions). Most of these were mild or moderate.

Caution should be exercised when considering the use of Fraizeron in patients with a chronic infection or a history of recurrent infection.

Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and Fraizeron should not be administered until the infection resolves.

No increased susceptibility to tuberculosis was reported from clinical studies. However, Fraizeron should not be given to patients with active tuberculosis. Anti-tuberculosis therapy should be considered prior to initiation of Fraizeron in patients with latent tuberculosis.

Crohn's disease

Caution should be exercised, when prescribing Fraizeron to patients with active Crohn's disease as exacerbations of Crohn's disease, in some cases serious, were observed in clinical studies in both Fraizeron and placebo groups. Patients who are treated with Fraizeron and have active Crohn's disease should be followed closely.

Hypersensitivity reactions

If an anaphylactic or other serious allergic reaction occurs, administration of Fraizeron should be discontinued immediately and appropriate therapy initiated.

Vaccinations

Live vaccines should not be given concurrently with Fraizeron (see also section Interactions).

Patients receiving Fraizeron may receive concurrent inactivated or non-live vaccinations. In a study, after *meningococcal* and inactivated *influenza* vaccinations, a similar proportion of patients treated with Fraizeron and patients treated with placebo were able to mount an adequate immune response of at least a 4-fold increase in antibody titers to *meningococcal* and *influenza* vaccines. The data suggest that Fraizeron does not suppress the humoral immune response to the *meningococcal* or *influenza* vaccines.

Adverse drug reactions

Summary of the safety profile

A total of 4,498 patients have been treated with Fraizeron in blinded and open-label clinical studies in various indications (plaque psoriasis and other autoimmune conditions). Of these, 1,900 patients were exposed to Fraizeron for at least one year, representing 3,588 patient years of exposure.

Four placebo-controlled phase III studies in plaque psoriasis were pooled to evaluate the safety of Fraizeron in comparison to placebo up to 12 weeks after treatment initiation. In total, 2,076 patients were evaluated (692 patients on 150 mg, 690 patients on 300 mg and 694 patients on placebo).

The most frequently reported adverse drug reactions (ADRs) were upper respiratory tract infections (most frequently nasopharyngitis, rhinitis). Most of the events were mild or moderate in severity.

In the placebo-controlled period of plaque psoriasis phase III studies the proportion of patients who discontinued treatment due to adverse events was approximately 1.2% in the Fraizeron arm and 1.2% in the placebo arm.

ADRs from clinical studies (Table 1) are listed by MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

Table 1 Percentage of patients with adverse drug reactions in clinical studies[1)]

Adverse drug reactions	Secukinumab		Placebo (N=694) n (%)	Frequency category2
	300 mg (N=690) n (%)	150 mg (N=692) n (%)		
Infections and infestations				
Upper respiratory tract infections	117 (17.0)	129 (18.6)	72 (10.4)	Very common
• Nasopharyngitis	79 (11.4)	85 (12.3)	60 (8.6)	Very common
• Upper respiratory tract infection	17 (2.5)	22 (3.2)	5 (0.7)	Common
• Rhinitis	10 (1.4)	10 (1.4)	5 (0.7)	Common
• Pharyngitis	8 (1.2)	7 (1.0)	0 (0)	Common
• Sinusitis	3 (0.4)	6 (0.9)	1(0.1)	Uncommon
• Tonsillitis	4 (0.6)	4 (0.6)	3(0.4)	Uncommon
Oral herpes	9 (1.3)	1 (0.1)	2 (0.3)	Common
Oral candidiasis	4 (0.6)	1 (0.1)	1 (0.1)	Uncommon
Tinea pedis	5 (0.7)	5 (0.7)	0 (0)	Uncommon
Blood and lymphatic system disorders				
Neutropenia	2 (0.3)	1 (0.1)	0 (0)	Uncommon
Eye disorders				
Conjunctivitis	5 (0.7)	2 (0.3)	1 (0.1)	Uncommon
Respiratory, thoracic and mediastinal disorders				
Rhinorrhoea	8 (1.2)	2 (0.3)	1 (0.1)	Common
Gastrointestinal disorders				
Diarrhea	28 (4.1)	18 (2.6)	10 (1.4)	Common
Skin and subcutaneous tissue disorders				
Urticaria	4 (0.6)	8 (1.2)	1 (0.1)	Common

1) *placebo-controlled clinical studies (phase III) in plaque psoriasis patients exposed to 300 mg, 150 mg or placebo up to12-weeks treatment duration*
2) *ADR frequencies are based upon the highest percentage rate seen in any of the secukinumab groups*

Infections

In the placebo-controlled period of clinical studies in plaque psoriasis (a total of 1,382 patients treated with Fraizeron and 694 patients treated with placebo for up to 12 weeks), infections were reported in 28.7% of patients treated with Fraizeron compared with 18.9% of patients treated with placebo. Most of these were mild or moderate. Serious infections occurred in 0.14% of patients treated with Fraizeron and in 0.3% of patients treated with placebo (see section Warnings and precautions).

Over the entire treatment period (a total of 3,430 patients treated with Fraizeron for up to 52 weeks for the majority of patients), infections were reported in 47.5% of patients treated with Fraizeron (0.9 per patient-year of follow-up). Serious infections were reported in 1.2% of patients treated with Fraizeron (0.015 per patient-year of follow-up).

Hypersensitivity reactions

In clinical studies, urticaria and one case of anaphylactic reaction to Fraizeron were observed.

Immunogenicity

Less than 1% of patients treated with Fraizeron developed antibodies to secukinumab up to 52 weeks of treatment. About half of the treatment emergent anti-drug antibodies were neutralizing, but this was not associated with loss of efficacy or PK abnormalities.

Interactions

Live vaccines should not be given concurrently with Fraizeron (see also section Warnings and precautions).

No interaction studies have been performed in humans. Fraizeron has been concomitantly administered with methotrexate in arthritis studies where no interaction was seen. There is no direct evidence for the role of IL-17A 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 inhibitor secukinumab, 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, where the dose is individually adjusted (e.g. warfarin) cannot be excluded. On initiation of secukinumab therapy in patients being treated with these types of medicinal products, therapeutic monitoring should be considered.

Women of child-bearing potential, pregnancy, breast-feeding and fertility

Women of child-bearing potential

There are no special recommendations for women of child-bearing potential.

Pregnancy

There are no adequate data from the use of Fraizeron in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development (see section Non-clinical safety data). Because animal reproduction studies are not always predictive of human response, Fraizeron should be used during pregnancy only if the benefits clearly outweigh the potential risks.

Breast-feeding

It is not known whether secukinumab is excreted in human milk. Because immunoglobulins are excreted in human milk, caution should be exercised when Fraizeron is administered to a woman who is breast-feeding.

Fertility

The effect of Fraizeron on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section Non-clinical safety data).

Overdosage

No cases of overdose have been reported in clinical studies.

Doses up to 30 mg/kg (i.e. approximately 2,000 to 3,000 mg) have been administered intravenously in clinical studies without dose-limiting toxicity. In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

Clinical pharmacology

Pharmacotherapeutic group, ATC

Interleukin inhibitors; ATC code L04AC10.

Mechanism of action (MOA)

Secukinumab is a fully human IgG1 antibody that selectively binds to and neutralizes the proinflammatory cytokine interleukin-17A (IL-17A). Secukinumab works by targeting IL-17A and inhibiting its interaction with the IL-17 receptor, which is expressed on various cell types including keratinocytes. As a result, secukinumab inhibits the release of proinflammatory cytokines, chemokines and mediators of tissue damage and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases. Clinically relevant levels of secukinumab reach the skin and reduce local inflammatory markers. As a direct consequence treatment with secukinumab reduces erythema, induration, and desquamation present in plaque psoriasis lesions.

IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. IL-17A plays a key role in the pathogenesis of plaque psoriasis. Increased numbers of IL-17A producing lymphocytes and innate immune cells and increased levels of IL-17A have been found in the blood and affected skin of patients with plaque psoriasis. IL-17A is highly up-regulated in lesional skin in contrast to non-lesional skin of plaque psoriasis patients.

IL-17A also promotes tissue inflammation, neutrophil infiltration, bone and tissue destruction, and tissue remodeling including angiogenesis and fibrosis.

Pharmacodynamics (PD)

Serum levels of total IL-17A (free and secukinumab-bound IL-17A) are increased due to reduced clearance of secukinumab-bound IL-17A within 2 to 7 days in patients receiving secukinumab, indicating that secukinumab selectively captures free IL-17A which plays a key role in the pathogenesis of plaque psoriasis.

In a study with secukinumab, infiltrating epidermal neutrophils and various neutrophil associated markers that are increased in lesional skin of plaque psoriasis patients were significantly reduced after one to two weeks of treatment.

Pharmacokinetics (PK)

Absorption

Following a single subcutaneous dose of either 150 mg or 300 mg in plaque psoriasis patients, secukinumab reached peak serum concentrations of 13.7 ± 4.8 µg/mL or 27.3 ± 9.5 µg/mL, respectively, between 5 and 6 days post dose.

After the initial weekly dosing during the first month, the time to reach the maximum concentration was between 31 and 34 days.

Peak concentrations at steady-state (Cmax,ss) following subcutaneous administration of 150 mg or 300 mg were 27.6 µg/mL and 55.2 µg/mL, respectively. Steady-state is reached after 20 weeks with monthly dosing regimens.

Compared with exposure after a single dose, patients exhibited a 2-fold increase in peak serum concentrations and AUC following repeated monthly dosing during maintenance.

Secukinumab is absorbed with an average absolute bioavailability of 73%.

Distribution

The mean volume of distribution during the terminal phase (V_z) following a single intravenous administration ranged from 7.10 to 8.60 L in plaque psoriasis patients suggesting that secukinumab undergoes limited distribution to peripheral compartments.

Secukinumab concentrations in interstitial fluid in the skin of plaque psoriasis patients ranged from 28% to 39% of those in serum at 1 and 2 weeks after a single subcutaneous dose of 300 mg secukinumab.

Elimination

Mean systemic clearance (CL) was 0.19 L/d in plaque psoriasis patients. Clearance was dose- and time-independent, as expected for a therapeutic IgG1 monoclonal antibody interacting with a soluble cytokine target, such as IL-17A.

The mean elimination half-life was estimated to be 27 days in plaque psoriasis patients. Estimated half-lives in individual plaque psoriasis patients range from 17 to 41 days.

Dose linearity

The single and multiple dose pharmacokinetics of secukinumab in plaque psoriasis patients were determined in several studies with intravenous doses ranging from 1 x 0.3 mg/kg to 3 x 10 mg/kg and with subcutaneous doses ranging from 1 x 25 mg to multiple doses of 300 mg. Exposure was dose proportional across all dosing regimens.

Special populations

Elderly patients

Of the 3,430 plaque psoriasis patients exposed to Fraizeron in clinical studies, a total of 230 were 65 years of age or older and 32 patients were 75 years of age or older.

Based on population PK analysis, clearance in elderly patients and patients less than 65 years of age was similar.

Patients with renal and hepatic impairment

No pharmacokinetic data are available in patients with hepatic or renal impairment.

Clinical studies

Psoriasis

The safety and efficacy of Fraizeron were assessed in four randomized, double-blind, placebo-controlled phase 3 studies in patients with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy [ERASURE, FIXTURE, FEATURE, JUNCTURE]. The efficacy and safety of Fraizeron 150 mg and 300 mg were evaluated versus either placebo or etanercept. In addition, one study assessed a chronic treatment regimen versus a 'retreatment as needed' regimen [SCULPTURE].

Of the 2,403 patients who were included in the placebo-controlled studies, 79% were biologic-naïve, 45% were non-biologic failures, 8% were biologic failures, 6% were anti-TNF failures, and 2% were anti-p40 failures. Baseline disease characteristics were generally consistent across all treatment groups with a median baseline Psoriasis Area Severity Index (PASI) score from 19 to 20, IGA mod 2011 baseline score ranged from "moderate" (62%) to "severe" (38%), median baseline Body Surface Area (BSA) ≥27 and median Dermatology Life Quality Index (DLQI) score from 10 to 12. Approximately 15 to 25% of patients in phase III studies had psoriatic arthritis (PsA) at baseline.

Psoriasis Study 1 (ERASURE) evaluated 738 patients. Patients randomized to Fraizeron received 150 mg or 300 mg doses at weeks 0, 1, 2, and 3, followed by the same dose every month starting at week 4. Patients randomized to receive placebo who were non-responders at week 12 were then crossed over to receive Fraizeron (either 150 mg or 300 mg) at weeks 12, 13, 14, and 15, followed by the same dose every month starting at week 16. All patients were followed for up to 52 weeks following first administration of study treatment.

Psoriasis Study 2 (FIXTURE) evaluated 1,306 patients. Patients randomized to Fraizeron received 150 mg or 300 mg doses at weeks 0, 1, 2, and 3, followed by the same dose every month starting at week 4. Patients randomized to etanercept received 50 mg doses twice per week for 12 weeks followed by 50 mg every week. Patients randomized to receive placebo who were non-responders at week 12 then crossed over to receive Fraizeron (either 150 mg or 300 mg) at weeks 12, 13, 14, and 15, followed by the same dose every month starting at week 16. All patients were followed for up to 52 weeks following first administration of study treatment.

Psoriasis Study 3 (FEATURE) evaluated 177 patients using a pre-filled syringe compared with placebo after 12 weeks of treatment to assess the safety, tolerability, and usability of Fraizeron self-administration via the pre-filled syringe. Patients randomized to Fraizeron received 150 mg or 300 mg doses at weeks 0, 1, 2, and 3, followed by the same dose every month starting at week 4. Patients were also randomized to receive placebo at weeks 0, 1, 2, and 3, followed by the same dose every month starting at week 4.

Psoriasis Study 4 (JUNCTURE) evaluated 182 patients using a pre-filled pen compared with placebo after 12 weeks of treatment to assess the safety, tolerability, and usability of Fraizeron self-administration via the pre-filled pen. Patients randomized to Fraizeron received 150 mg or 300 mg doses at weeks 0, 1, 2, and 3, followed by the same dose every month starting at week 4. Patients were also randomized to receive placebo at weeks 0, 1, 2, and 3, followed by the same dose every month starting at week 4.

Psoriasis Study 5 (SCULPTURE) evaluated 966 patients. All patients received Fraizeron 150 mg or 300 mg doses at weeks 0, 1, 2, 3, 4, 8 and 12 and then were randomized to receive either a maintenance regimen of the same dose every month starting at Week 12 or a "retreatment as needed" regimen of the same dose. Patients randomized to "retreatment as needed" did not achieve adequate maintenance of response and therefore a fixed monthly maintenance regimen is recommended.

The co-primary endpoints in the placebo and active controlled studies were the proportion of patients who achieved a PASI 75 response and IGA mod 2011 'clear' or 'almost clear' response versus placebo at Week 12 (see Tables 2 and 3). The 300 mg dose provided improved skin clearance across efficacy endpoints of PASI 75/90/100, and IGA mod 2011 'clear' or 'almost clear' responses across all studies with peak effects seen at week 16, therefore this dose is recommended.

Table 2 **Summary of PASI 50/75/90/100 & IGA* mod 2011 'clear' or 'almost clear' clinical response in Psoriasis Studies 1, 3 and 4 (ERASURE, FEATURE and JUNCTURE)**

		Week 12		Week 16		Week 52	
	Placebo	150 mg	300 mg	150 mg	300 mg	150 mg	300 mg
Study 1							
Number of patients	246	244	245	244	245	244	245
PASI 50 response n (%)	22 (8.9%)	203 (83.5%)	222 (90.6%)	212 (87.2%)	224 (91.4%)	187 (77%)	207 (84.5%)
PASI 75 response n (%)	11 (4.5%)	174 (71.6%)**	200 (81.6%)**	188 (77.4%)	211 (86.1%)	146 (60.1%)	182 (74.3%)
PASI 90 response n (%)	3 (1.2%)	95 (39.1%)**	145 (59.2%)**	130 (53.5%)	171 (69.8%)	88 (36.2%)	147 (60.0%)
PASI 100 response n (%)	2 (0.8%)	31 (12.8%)	70 (28.6%)	51 (21.0%)	102 (41.6%)	49 (20.2%)	96 (39.2%)
IGA mod 2011 "clear" or "almost clear" response n (%)	6 (2.40%)	125 (51.2%)**	160 (65.3%)**	142 (58.2%)	180 (73.5%)	101 (41.4%)	148 (60.4%)
Study 3							
Number of patients	59	59	58	-	-	-	-
PASI 50 response n (%)	3 (5.1%)	51 (86.4%)	51 (87.9%)	-	-	-	-
PASI 75 response n (%)	0 (0.0%)	41 (69.5%)**	44 (75.9%)**	-	-	-	-
PASI 90 response n (%)	0 (0.0%)	27 (45.8%)	35 (60.3%)	-	-	-	-
PASI 100 response n (%)	0 (0.0%)	5 (8.5%)	25 (43.1%)	-	-	-	-
IGA mod 2011 "clear" or "almost clear" response n (%)	0 (0.0%)	31 (52.5%)**	40 (69.0%)**	-	-	-	-

	Week 12			Week 16		Week 52	
	Placebo	**150 mg**	**300 mg**	**150 mg**	**300 mg**	**150 mg**	**300 mg**
Study 4							
Number of patients	61	60	60	-	-	-	-
PASI 50 response n (%)	5 (8.2%)	48 (80.0%)	58 (96.7%)	-	-	-	-
PASI 75 response n (%)	2 (3.3%)	43 (71.7%)**	52 (86.7%)**	-	-	-	-
PASI 90 response n (%)	0 (0.0%)	24 (40.0%)	33 (55.0%)	-	-	-	-
PASI 100 response n (%)	0 (0.0%)	10 (16.7%)	16 (26.7%)	-	-	-	-
IGA mod 2011 "clear" or "almost clear" response n (%)	0 (0.0%)	32 (53.3%)**	44 (73.3%)**	-	-	-	-

**The IGA mod 2011 is a 5-category scale including "0 = clear", "1 = almost clear", "2 = mild", "3 = moderate" or "4 = severe", indicating the physician's overall assessment of the psoriasis severity focusing on induration, erythema and scaling. Treatment success of "clear" or "almost clear" consisted of no signs of psoriasis or normal to pink coloration of lesions, no thickening of the plaque and none to minimal focal scaling.*

*** p values versus placebo and adjusted for multiplicity: p<0.0001*

Table 3 Summary of clinical response on Psoriasis Study 2 (FIXTURE)

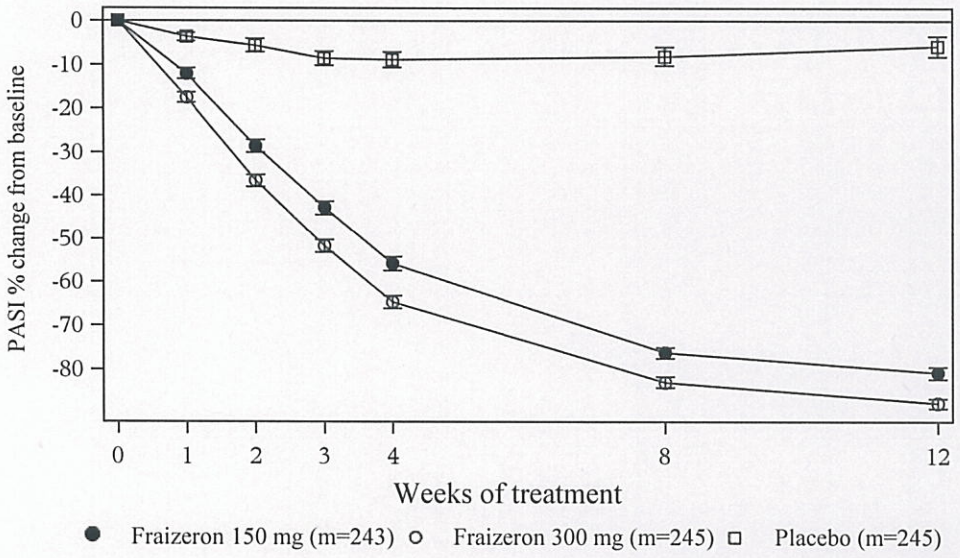
	Week 12				Week 16			Week 52		
	Placebo	150 mg	300 mg	Etanercept	150 mg	300 mg	Etanercept	150 mg	300 mg	Etanercept
Number of patients	324	327	323	323	327	323	323	327	323	323
PASI 50 response n (%)	49 (15.1%)	266 (81.3%)	296 (91.6%)	226 (70.0%)	290 (88.7%)	302 (93.5%)	257 (79.6%)	249 (76.1%)	274 (84.8%)	234 (72.4%)
PASI 75 response n (%)	16 (4.9%)	219 (67.0%) **	249 (77.1%) **	142 (44.0%)	247 (75.5%)	280 (86.7%)	189 (58.5%)	215 (65.7%)	254 (78.6%)	179 (55.4%)
PASI 90 response n (%)	5 (1.5%)	137 (41.9%)	175 (54.2%)	67 (20.7%)	176 (53.8%)	234 (72.4%)	101 (31.3%)	147 (45.0%)	210 (65.0%)	108 (33.4%)
PASI 100 response n (%)	0 (0%)	47 (14.4%)	78 (24.1%)	14 (4.3%)	84 (25.7%)	119 (36.8%)	24 (7.4%)	65 (19.9%)	117 (36.2%)	32 (9.9%)
IGA mod 2011 "clear" or "almost clear" response n (%)	9 (2.8%)	167 (51.1%) **	202 (62.5%) **	88 (27.2%)	200 (61.2%)	244 (75.5%)	127 (39.3%)	168 (51.4%)	219 (67.8%)	120 (37.2%)

*** p values versus etanercept: p=0.0250*

Fraizeron was efficacious in biologic-naive, biologic/anti-TNF-exposed and biologic/anti-TNF-failure patients.

Fraizeron was associated with a fast onset of efficacy as shown in the figure below with a 50% reduction in mean PASI by week 3 for 300 mg.

Figure 1 **Time course of percentage change from baseline of mean PASI score in Study 1 (ERASURE)**



m = number of patients evaluable

All plaque psoriasis phase III studies included approximately 15 to 25% of patients with concurrent psoriatic arthritis at baseline. Improvements in PASI 75 in this patient population were similar to those in the overall plaque psoriasis population.

In the placebo controlled studies 1 and 2 in the subset of psoriatic arthritis patients, physical function was assessed using the HAQ Disability Index (HAQ-DI). In these studies, patients treated with 150 mg or 300 mg Fraizeron showed greater improvement from baseline in the HAQ-DI score (mean decreases of -27.5% and -50.2% at week 12) compared to placebo (-8.9%). This improvement was maintained up to week 52.

Quality of Life / Patient reported outcomes

Statistically significant improvements at week 12 (Studies 1-4) from baseline compared to placebo were demonstrated in the DLQI (Dermatology Life Quality Index), these improvements were maintained for 52 weeks (Studies 1 and 2).

Statistically significant improvements at week 12 from baseline compared to placebo (Studies 1 and 2) in patient reported signs and symptoms of itching, pain and scaling were demonstrated in the validated Psoriasis Symptom Diary©.

Non-clinical safety data [NCO]

Non-clinical data revealed no special hazard for humans based on tissue cross-reactivity testing, safety pharmacology, repeated dose and reproductive toxicity studies performed with secukinumab or a murine anti-murine IL-17A antibody.

Since secukinumab binds to cynomolgus monkey and human IL-17A, its safety was studied in the cynomolgus monkey. No undesirable effects of secukinumab were seen following

subcutaneous administration to cynomolgus monkeys for up to 13 weeks and intraveneous administration up to 26 weeks (including pharmacokinetic, pharmacodynamic, immunogenicity and immunotoxicity (e.g. T cell dependent antibody response and NK cell activity) evaluations). The average serum concentrations observed in monkeys after 13 weekly subcutaneous doses of 150 mg/kg are 48-fold higher than the predicted average serum concentration expected in psoriatic patients at the highest clinical dose. The exposure multiples are even higher when the average serum concentration from the 26 weeks intravenous toxicology study in cynomolgus monkeys are taken into consideration. Antibodies to secukinumab were detected in only one out of 101 animals. No non-specific tissue cross-reactivity was demonstrated when secukinumab was applied to normal human tissues.

Animal studies have not been conducted to evaluate the carcinogenic potential of secukinumab.

In an embryofetal development study in cynomolgus monkeys, secukinumab showed no maternal toxicity, embryotoxicity or teratogenicity when administered throughout organogenesis and late gestation.

No undesirable effects of a murine anti-murine IL-17A antibody were seen in fertility and early embryonic development and pre-and postnatal development studies in mice. The high dose used in these studies was in excess of the maximally effective dose in terms of IL-17A suppression and activity (see section Women of child-bearing potential, pregnancy, breast-feeding and fertility).

Pharmaceutical information

Incompatibilities

Powder for solution for injection: Fraizeron should not be mixed with any medication or diluents other than sterile water for injection.

Special precautions for storage

Store in a refrigerator at 2°C to 8°C.

Store in the original carton to protect from light.

Fraizeron must be kept out of the reach and sight of children.

Do not use beyond the expiry date stated.

Shelf-life: 36 months for vial

Instructions for use and handling

Instruction for Use of Fraizeron 150 mg powder for solution for injection

The following information is intended for medical or healthcare professionals only.

Store the vial of 150 mg powder for solution for injection of Fraizeron in the refrigerator between 2°C to 8°C.

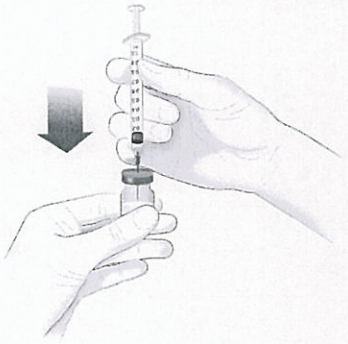
The single-use vial contains 150 mg of Fraizeron for reconstitution with sterile water for injection (SWFI). Do not use the vial after the expiry date shown on the outer box or vial. If it has expired, return the entire pack to the pharmacy.

The preparation of the solution for subcutaneous injection shall be done without interruption ensuring that aseptic technique is used. The preparation time from piercing the stopper until end of reconstitution on average takes 20 minutes and should not exceed 90 minutes.

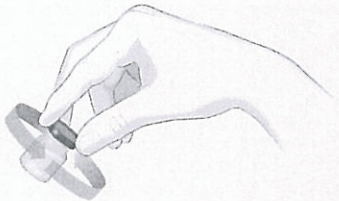
To prepare Fraizeron 150 mg powder for solution for injection please adhere to the following instructions:

Instructions for reconstitution of Fraizeron 150 mg powder for solution for injection:

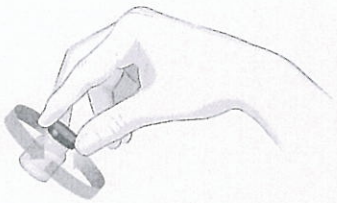
1. Bring the vial of Fraizeron 150 mg powder for solution for injection to room temperature and ensure sterile water for injection (SWFI) is at room temperature.
2. Withdraw slightly more than 1.0 mL sterile water for injection (SWFI) into a 1 mL graduated disposable syringe and adjust to 1.0 mL.
3. Remove the plastic cap from the vial.
4. Insert the syringe needle into the vial containing the lyophilized cake of Fraizeron through the center of the rubber stopper and reconstitute the cake by slowly injecting 1.0 mL of SWFI into the vial. The stream of SWFI should be directed onto the lyophilized cake.



5. Tilt the vial to an angle of approx. 45° and gently rotate between the fingertips for approx. 1 minute. Do not shake or invert the vial.



6. Keep the vial standing at room temperature for a minimum of 10 minutes to allow for dissolution. Note that foaming of the solution may occur.
7. Tilt the vial to an angle of approx. 45° and gently rotate between the fingertips for approx. 1 minute. Do not shake or invert the vial.

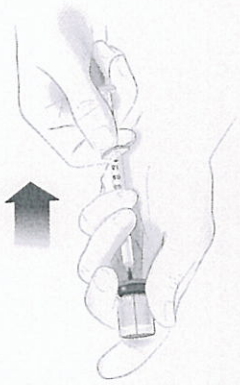


8. Allow the vial to stand undisturbed at room temperature for approximately 5 minutes. The resulting solution should be clear. Its color may vary from colorless to slightly yellow. Do not use if the lyophilized powder has not fully dissolved or if the liquid contains easily visible particles, is cloudy or is distinctly brown.
9. Prepare the required number of vials (1 vial for the 150 mg dose, 2 vials for the 300 mg dose).

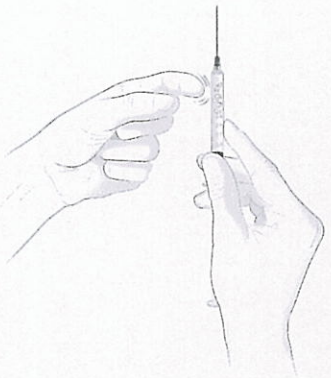
After preparation, the solution for subcutaneous injection can be used immediately or can be stored at 2°C to 8 °C for up to 24 hours. Do not freeze. After storage at 2°C to 8 °C, the solution should be allowed to come to room temperature for approximately 20 minutes before administration. The solution should be administered within 1 hour after removal from the 2°C to 8°C storage.

Instructions for administration of Fraizeron solution

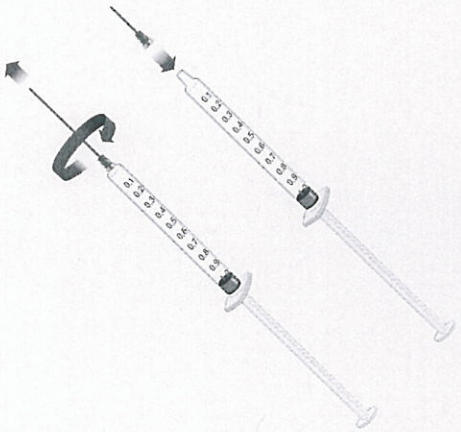
1. Tilt the vial to an angle of approximately 45 degrees and position the needle tip at the very bottom of the solution in the vial when drawing the solution into the syringe. DO NOT invert the vial.



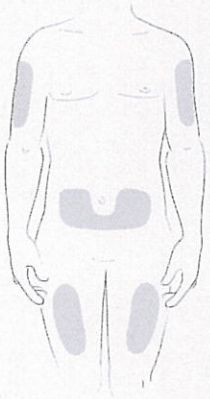
2. Carefully withdraw slightly more than 1.0 mL of the solution for subcutaneous injection from the vial into a 1 mL graduated disposable syringe using a suitable needle (e.g. 21G x 2"). This needle will only be used for withdrawing Fraizeron into the disposable syringe. Prepare the required number of syringes (1 syringe for the 150 mg dose, 2 syringes for the 300 mg dose).
3. With the needle pointing upward, gently tap the syringe to move any air bubbles to the top.



4. Replace the attached needle with a 27G x ½ " needle.



5. Expel the air bubbles and advance the plunger to the 1.0 mL mark.
6. Clean the injection site with an alcohol swab.
7. Inject the Fraizeron solution subcutaneously into the front of thighs, lower abdomen (but **not** the area 2 inches around the navel (belly button) or outer upper arms. Choose a different site each time an injection is administered. Do not inject into areas where the skin is tender, bruised, red, scaly or hard. Avoid areas with scars or stretch marks.



8. Any remaining solution in the vial must not be used and should be discarded in accordance with local requirements. Vials are for single use only. Dispose of the used syringe in a sharps container

(closable, puncture resistant container). For the safety and health of you and others, needles and used syringes **must never** be re-used.

Packaging size

Powder for solution for injection

Box, 1 vial @ 150 mg powder for solution for injection No. Reg.: DKI1667509344A1

HARUS DENGAN RESEP DOKTER

To be dispensed only on the prescription of a physician

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi

Manufactured by Novartis Pharma Stein AG, Stein, Switzerland for Novartis Pharma AG, Basel, Switzerland.

Imported by PT Novartis Indonesia, Jakarta, Indonesia.