

1. NAME OF THE MEDICINAL PRODUCT

Fraizeron 150 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains 150 mg secukinumab*. After reconstitution, 1 mL of solution contains 150 mg secukinumab.

*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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection

The powder is a white solid lyophilisate.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Plaque psoriasis

Fraizeron is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA.

Psoriatic arthritis

Fraizeron is indicated for the treatment of adult patients with active psoriatic arthritis. Fraizeron can be used alone or in combination with methotrexate.

Ankylosing spondylitis

Fraizeron is indicated for the treatment of adult patients with active ankylosing spondylitis.

4.2 Posology and method of administration

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

Posology

Plaque psoriasis:

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

Psoriatic arthritis

The recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4 followed by monthly maintenance dosing. Based on clinical response, the dose can be increased to 300 mg.

For patients who are anti-TNF α inadequate responders (IR) or patients with concomitant moderate to severe plaque psoriasis, the recommended dose is 300 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4 followed by monthly maintenance dosing. Each 300 mg dose is given as two subcutaneous injections of 150 mg.

Ankylosing spondylitis

The recommended dose is 150 mg by subcutaneous injection with initial dosing at Weeks 0, 1, 2, 3 and 4 followed by monthly maintenance dosing. Based on clinical response, the dose can be increased to 300 mg.

Each 300 mg dose is given as two subcutaneous injections of 150 mg.

Consideration should be given to discontinuing treatment in patients who have shown no response up to 16 weeks of treatment. Some patients with initially partial response may subsequently improve with continued treatment beyond 16 weeks.

Special populations

Elderly patients (aged 65 years and over)

No dose adjustment is required (see section 5.2).

Renal impairment / hepatic impairment

Fraizeron has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population

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

Method of administration

Fraizeron is to be administered by subcutaneous injection. If possible, areas of the skin that show psoriasis should be avoided as injection sites. The powder for solution for injection must be reconstituted before use. For instructions on reconstitution of the medicinal product before administration, see section 6.6 and the Instructions for Use in the package leaflet.

4.3 Contraindications

Severe hypersensitivity reactions to the active substance or to any of the excipients listed in section 6.1.

Clinically important, active infection (e.g. active tuberculosis; see section 4.4).

4.4 Special warnings and precautions for use**Infections**

Fraizeron has the potential to increase the risk of infections. In clinical studies, infections have been observed in patients receiving Fraizeron (see section 4.8). Most of these were mild or moderate upper respiratory tract infections such as nasopharyngitis and did not

require treatment discontinuation.

Related to the mechanism of action of Fraizeron, non-serious mucocutaneous candida infections were more frequently reported for secukinumab than placebo in the psoriasis clinical studies (3.55 per 100 patient years for secukinumab 300 mg versus 1.00 per 100 patient years for placebo) (see section 4.8).

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 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 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.

Patients receiving Fraizeron may receive concurrent inactivated or non-live vaccinations. In a study, after *meningococcal* and inactivated *influenza* vaccinations, a similar proportion of healthy volunteers treated with 150 mg of secukinumab and those treated with placebo were able to mount an adequate immune response of at least a 4-fold increase in antibody titres to *meningococcal* and *influenza* vaccines. The data suggest that Fraizeron does not suppress the humoral immune response to the *meningococcal* or *influenza* vaccines.

Concomitant immunosuppressive therapy

In psoriasis studies, the safety and efficacy of Fraizeron in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated (see also section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

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

No interaction studies have been performed in humans. 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.

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 20 weeks after treatment.

Pregnancy

There are no adequate data from the use of secukinumab 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 Fraizeron in pregnancy.

Breast-feeding

It is not known whether secukinumab is excreted in human milk. Immunoglobulins are excreted in human milk and it is not known if secukinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from secukinumab, a decision on whether to discontinue breast-feeding during treatment and up to 20 weeks after treatment or to discontinue therapy with Fraizeron must be made taking into account the benefit of breast-feeding to the child and the benefit of Fraizeron therapy to the woman.

Fertility

The effect of secukinumab 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

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

4.8 Undesirable effects

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 reactions were mild or moderate in severity.

Tabulated list of adverse reactions

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: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

Table 1 List of adverse reactions in clinical studies¹⁾

System Organ Class		Fraizeron		Placebo (N=694) n (%)
		300 mg (N=690) n (%)	150 mg (N=692) n (%)	
Infections and infestations				
Very common	Upper respiratory tract infections	117 (17.0)	129 (18.6)	72 (10.4)
Common	Oral herpes	9 (1.3)	1 (0.1)	2 (0.3)
Uncommon	Oral candidiasis	4 (0.6)	1 (0.1)	1 (0.1)
Uncommon	Tinea pedis	5 (0.7)	5 (0.7)	0 (0)
Uncommon	Otitis externa	5 (0.7)	3 (0.4)	0 (0)
Blood and lymphatic system disorders				
Uncommon	Neutropenia	2 (0.3)	1 (0.1)	0 (0)
Eye disorders				
Uncommon	Conjunctivitis	5 (0.7)	2 (0.3)	1 (0.1)
Respiratory, thoracic and mediastinal disorders				
Common	Rhinorrhoea	8 (1.2)	2 (0.3)	1 (0.1)
Gastrointestinal disorders				
Common	Diarrhoea	28 (4.1)	18 (2.6)	10 (1.4)
Skin and subcutaneous tissue disorders				
Common	Urticaria	4 (0.6)	8 (1.2)	1 (0.1)
1) Placebo-controlled clinical studies (phase III) in plaque psoriasis patients exposed to 300 mg, 150 mg or placebo up to 12 weeks treatment duration Note: A single case of anaphylactic reaction was observed in a non-psoriasis study as outlined below.				

Description of selected adverse reactions

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. The majority of infections consisted of non-serious and mild to moderate upper respiratory tract infections, such as nasopharyngitis, which did not necessitate treatment discontinuation. There was an increase in mucosal or cutaneous candidiasis, consistent with the mechanism of action, but the cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in 0.14% of patients treated with Fraizeron and in 0.3% of patients treated with placebo (see section 4.4).

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).

Neutropenia

Neutropenia was more frequently observed with secukinumab than with placebo, but most cases were mild, transient and reversible. Neutropenia $<1.0-0.5 \times 10^9/l$ (CTCAE Grade 3) was reported in 18 out of 3,430 (0.5%) patients on secukinumab, with no dose dependence and no temporal relationship to infections in 15 out of 18 cases. There were no reported cases of more severe neutropenia. Non-serious infections with usual response to standard care and not requiring discontinuation of Fraizeron were reported in the remaining 3 cases.

Hypersensitivity reactions

In clinical studies, urticaria and one case of anaphylactic reaction to Fraizeron were observed (see also section 4.4).

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 neutralising, but this was not associated with loss of efficacy or pharmacokinetic abnormalities.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

No cases of overdose have been reported in clinical studies.

Doses up to 30 mg/kg (approximately 2000 to 3000 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC10

Mechanism of action

Secukinumab is a fully human IgG1/ κ monoclonal antibody that selectively binds to and neutralises 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 and is up-regulated in lesional skin in contrast to non-lesional skin of plaque psoriasis patients.

Pharmacodynamic effects

Serum levels of total IL-17A (free and secukinumab-bound IL-17A) are initially increased in patients receiving secukinumab. This is followed by a slow decrease due to reduced clearance of secukinumab-bound IL-17A, 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.

Clinical efficacy and safety

The safety and efficacy of Fraizeron were assessed in four randomised, double-blind, placebo-controlled phase III 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 and 8% were biologic failures (6% were anti-TNF failures, and 2% were anti-p40 failures). Approximately 15 to 25% of patients in phase III studies had psoriatic arthritis (PsA) at baseline.

Psoriasis Study 1 (ERASURE) evaluated 738 patients. Patients randomised 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. Psoriasis Study 2 (FIXTURE) evaluated 1,306 patients. Patients randomised 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 randomised to etanercept received 50 mg doses twice per week for 12 weeks followed by 50 mg every week. In both Study 1 and Study 2, patients randomised 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. 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. In both Study 3 and Study 4, patients randomised 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 randomised 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 randomised 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 randomised 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 particularly for “clear” or “almost clear” skin across the efficacy endpoints of PASI 90, PASI 100, and IGA mod 2011 0 or 1 response 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%)**	-	-	-	-

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 colouration 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

An additional psoriasis study (CLEAR) evaluated 676 patients. Secukinumab 300 mg met the primary and secondary endpoints by showing superiority to ustekinumab based on PASI 90 response at Week 16 (primary endpoint), speed of onset of PASI 75 response at Week 4, and longterm PASI 90 response at Week 52. Greater efficacy of secukinumab compared to ustekinumab for the endpoints PASI 75/90/100 and IGA mod 2011 0 or 1 response (“clear” or “almost clear”) was observed early and continued through Week 52.

Table 5 Summary of clinical response on CLEAR Study

	Week 4		Week 16		Week 52	
	Secukinumab 300 mg	Ustekinumab*	Secukinumab 300 mg	Ustekinumab*	Secukinumab 300 mg	Ustekinumab*
Number of patients	334	335	334	335	334	335
PASI 75 response n (%)	166 (49.7%)**	69 (20.6%)	311 (93.1%)	276 (82.4%)	306 (91.6%)	262 (78.2%)
PASI 90 response n (%)	70 (21.0%)	18 (5.4%)	264 (79.0%)**	192 (57.3%)	250 (74.9%***)	203 (60.6%)
PASI 100 response n (%)	14 (4.2%)	3 (0.9%)	148 (44.3%)	95 (28.4%)	150 (44.9%)	123 (36.7%)
IGA mod 2011 "clear" or "almost clear" response n (%)	128 (38.3%)	41 (12.2%)	278 (83.2%)	226 (67.5%)	261 (78.1%)	213 (63.6%)

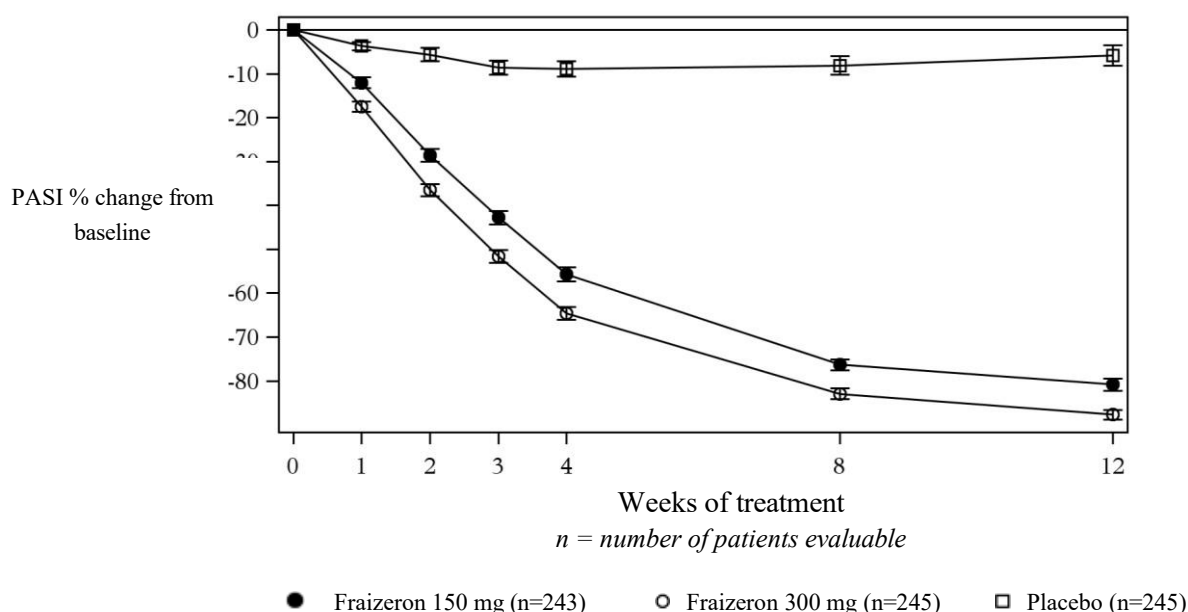
*Patients treated with secukinumab received 300 mg doses at Weeks 0, 1, 2, 3, and 4 followed by the same dose every 4 weeks until Week 52. Patients treated with ustekinumab received 45 mg or 90 mg at Weeks 0 and 4, then every 12 weeks until Week 52 (dosed by weight as per approved posology)

** p values versus ustekinumab: $p < 0.0001$ for primary endpoint of PASI 90 at Week 16 and secondary endpoint of PASI 75 at Week 4

*** p value versus ustekinumab: $p = 0.0001$ for secondary endpoint of PASI 90 at Week 52

Fraizeron was efficacious in systemic treatment-naïve, biologic-naïve, biologic/anti-TNF-exposed and biologic/anti-TNF-failure patients. Improvements in PASI 75 in patients with concurrent psoriatic arthritis at baseline were similar to those in the overall plaque psoriasis population.

Fraizeron was associated with a fast onset of efficacy with a 50% reduction in mean PASI by Week 3 for the 300 mg dose.

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

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). Mean decreases (improvements) in DLQI from baseline ranged from -10.4 to -11.6 with secukinumab 300 mg, from -7.7 to -10.1 with secukinumab 150 mg, versus -1.1 to -1.9 for placebo at Week 12. These improvements were maintained for 52 weeks (Studies 1 and 2).

Forty percent of the participants in Studies 1 and 2 completed the Psoriasis Symptom Diary®. For the participants completing the diary in each of these studies, statistically significant improvements at

Week 12 from baseline compared to placebo in patient-reported signs and symptoms of itching, pain and scaling were demonstrated.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Fraizeron in plaque psoriasis in paediatric patients aged from birth to less than 6 years (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with Fraizeron in plaque psoriasis in paediatric patients aged from 6 years to less than 18 years (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following a single subcutaneous dose of 300 mg as a liquid formulation in healthy volunteers, secukinumab reached peak serum concentrations of 43.2 ± 10.4 µg/ml between 2 and 14 days post dose.

Based on population pharmacokinetic analysis, 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 initial weekly dosing during the first month, time to reach the maximum concentration was between 31 and 34 days based on population pharmacokinetic analysis.

On the basis of simulated data, peak concentrations at steady-state ($C_{max,ss}$) following subcutaneous administration of 150 mg or 300 mg were 27.6 µg/ml and 55.2 µg/ml, respectively. Population pharmacokinetic analysis suggests that steady-state is reached after 20 weeks with monthly dosing regimens.

Compared with exposure after a single dose, the population pharmacokinetic analysis showed that patients exhibited a 2-fold increase in peak serum concentrations and area under the curve (AUC) following repeated monthly dosing during maintenance.

Population pharmacokinetic analysis showed that secukinumab was absorbed with an average absolute bioavailability of 73% in patients with plaque psoriasis. Across studies, absolute bioavailabilities in the range between 60 and 77% were calculated.

Distribution

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

Biotransformation

The majority of IgG elimination occurs via intracellular catabolism, following fluid-phase or receptor mediated endocytosis.

Elimination

Mean systemic clearance (CL) following a single intravenous administration to patients with plaque psoriasis ranged from 0.13 to 0.36 l/day. In a population pharmacokinetic analysis, the mean systemic clearance (CL) was 0.19 l/day in plaque psoriasis patients. The CL was not impacted by gender. Clearance was dose- and time-independent.

The mean elimination half-life, as estimated from population pharmacokinetic analysis, was 27 days in plaque psoriasis patients, ranging from 18 to 46 days across psoriasis studies with intravenous administration.

Linearity/non-linearity

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

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 pharmacokinetic analysis with a limited number of elderly patients (n=71 for age ≥ 65 years and n=7 for age ≥ 75 years), clearance in elderly patients and patients less than 65 years of age was similar.

Patients with renal or hepatic impairment

No pharmacokinetic data are available in patients with renal or hepatic impairment. The renal elimination of intact Fraizeron, an IgG monoclonal antibody, is expected to be low and of minor importance. IgGs are mainly eliminated via catabolism and hepatic impairment is not expected to influence clearance of Fraizeron.

5.3 Preclinical safety data

Non-clinical data revealed no special risks 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 intravenous 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 were considerably higher than the predicted average serum concentration expected in psoriatic patients at the highest clinical dose. Antibodies to secukinumab were detected in only one of the exposed animals. No non-specific tissue cross-reactivity was observed when secukinumab was applied to normal human tissue.

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

In an embryofoetal 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 maximum effective dose in terms of IL-17A suppression and activity (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
L-histidine
L-histidine hydrochloride monohydrate
Polysorbate 80

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

After reconstitution

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C. From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
For storage conditions after reconstitution of the medicinal product, see section 6.3

6.5 Nature and contents of container

Fraizeron is supplied in a colourless glass vial with a grey coated rubber stopper and aluminium cap with a white flip-off component containing 150 mg of secukinumab.

Fraizeron is available in packs containing one vial.

6.6 Special precautions for disposal and other handling

The single-use vial contains 150 mg secukinumab for reconstitution with sterile water for injections. The resulting solution should be clear and colourless to slightly yellow. Do not use if the lyophilised powder has not fully dissolved or if the liquid contains easily visible particles, is cloudy or is distinctly brown. Detailed instructions for use are provided in the package leaflet.

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

7. MARKETING AUTHORISATION HOLDER

Novartis Novartis Overseas Investment AG

8. MARKETING AUTHORISATION NUMBER(S)

Kenya: H2021/CTD8461/16389

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 20 September 2021

10. DATE OF REVISION OF THE TEXT