ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Skyrizi 75 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 75 mg risankizumab in 0.83 ml solution.

Risankizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody selective to the interleukin (IL)-23 protein produced in Chinese Hamster Ovary cells using recombinant DNA technology.

Excipients with known effect

This medicinal product contains 68.0 mg sorbitol per 150 mg dose.

This medicinal product contains less than 1 mmol sodium (23 mg) per 150 mg dose, that is to say essentially 'sodium free'.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

The solution is colourless to slightly yellow and clear to slightly opalescent.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Skyrizi 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

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

Posology

The recommended dose is 150 mg (two 75 mg injections) administered by subcutaneous injection at week 0, week 4, and every 12 weeks thereafter.

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

Missed dose

If a dose is missed, the dose should be administered as soon as possible. Thereafter, dosing should be resumed at the regular scheduled time.

Special populations

Elderly (aged 65 years and over)

No dose adjustment is required (see section 5.2).
There is limited information in subjects aged ≥65 years.

Renal or hepatic impairment

No specific studies were conducted to assess the effect of hepatic or renal impairment on the pharmacokinetics of Skyrizi. These conditions are generally not expected to have any significant impact on the pharmacokinetics of monoclonal antibodies and no dose adjustments are considered necessary (see section 5.2).

Paediatric population

The safety and efficacy of Skyrizi in children and adolescents aged 6 to 18 years have not yet been established. No data are available.

There is no relevant use of Skyrizi in children aged below 6 years for the indication of moderate to severe plaque psoriasis.

Overweight patients

No dose adjustment is required (see section 5.2).

Method of administration

Skyrizi is administered by subcutaneous injection. For each dose, the injections should be administered at different anatomic locations (such as thighs or abdomen), and not into areas where the skin is tender, bruised, erythematous, indurated or affected by psoriasis. Administration of Skyrizi in the upper, outer arm may only be performed by a healthcare professional or caregiver.

Patients may self-inject Skyrizi after training in subcutaneous injection technique. Patients should be instructed to inject 2 pre-filled syringes for the full 150 mg dose and to read the 'Instructions for use' provided in the package leaflet before administration.

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

Risankizumab may increase the risk of infection.

In patients with a chronic infection, a history of recurrent infection, or known risk factors for infection, risankizumab should be used with caution. Treatment with risankizumab should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

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

Tuberculosis

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

Immunisations

Prior to initiating therapy with risankizumab, completion of all appropriate immunisations should be considered according to current immunisation guidelines. If a patient has received live vaccination (viral or bacterial), it is recommended to wait at least 4 weeks prior to starting treatment with risankizumab. Patients treated with risankizumab should not receive live vaccines during treatment and for at least 21 weeks after treatment (see section 5.2).

Hypersensitivity

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

Excipients with known effect

This medicinal product contains 68.0 mg sorbitol per 150 mg dose.
The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

This medicinal product contains less than 1 mmol sodium (23 mg) per 150 mg dose, that is to say essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

Risankizumab is not expected to undergo metabolism by hepatic enzymes or renal elimination. Drug interactions between risankizumab and inhibitors, inducers, or substrates of drug metabolising enzymes are not expected and no dose adjustment is needed (see section 5.2).

Concomitant immunosuppressive therapy or phototherapy

The safety and efficacy of risankizumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated.

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 21 weeks after treatment.

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of risankizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of risankizumab during pregnancy.

Breast-feeding

It is unknown whether risankizumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which decreases to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. A decision should be made whether to discontinue/abstain from risankizumab therapy, taking into account the benefit of breast-feeding to the child and the benefit of risankizumab therapy to the woman.

Fertility

The effect of risankizumab on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

Risankizumab 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 infections, which occurred in 13% of patients.

Tabulated list of adverse reactions

Adverse reactions for risankizumab from clinical studies (Table 1) are listed by MedDRA system organ class and are based on the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); and very rare (< 1/10,000).

Table 1: List of adverse reactions in clinical studies

System Organ Class	Frequency	Adverse Reactions
Infections and infestations	Very common	Upper respiratory infections[a]
	Common	Tinea infections[b]
	Uncommon	Folliculitis
Nervous system disorders	Common	Headache[c]
Skin and subcutaneous tissue disorders	Common	Pruritus
General disorders and administration site conditions	Common	Fatigue[d] Injection site reactions[e]

[a] Includes: respiratory tract infection (viral, bacterial or unspecified), sinusitis (including acute), rhinitis, nasopharyngitis, pharyngitis (including viral), tonsillitis
[b] Includes: tinea pedis, tinea cruris, body tinea, tinea versicolor, tinea manuum, onychomycosis
[c] Includes: headache, tension headache, sinus headache
[d] Includes: fatigue, asthenia
[e] Includes: injection site bruising, erythema, haematoma, haemorrhage, irritation, pain, pruritus, reaction, swelling

Description of selected adverse reactions

Infections

Over the entire psoriasis programme including long-term exposure to risankizumab, the rate of infections was 75.5 events per 100 subject-years. The majority of cases were non-serious and mild to moderate in severity and did not lead to discontinuation of risankizumab. The rate of serious infections was 1.7 events per 100 subject-years (see section 4.4).

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity with risankizumab. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

For subjects treated with risankizumab at the recommended clinical dose for up to 52 weeks in psoriasis clinical trials, treatment-emergent anti-drug antibodies and neutralising antibodies were detected in 24% (263/1,079) and 14% (150/1,079) of evaluated subjects, respectively.

For most subjects, antibodies to risankizumab including neutralising antibodies were not associated with changes in clinical response or safety. Among the few subjects (approximately 1%; 7/1,000 at week 16 and 6/598 at week 52) with high antibody titers (>128), clinical response appeared to be reduced. The incidence of injection site reactions is numerically higher in the anti-drug antibody-positive compared with anti-drug antibody-negative groups over short-term (16 weeks: 2.7% vs 1.3%) and longer term treatment (>52 weeks: 5.0% vs 3.3%). The injection site reactions were all mild to moderate in severity, none were serious, and none led to discontinuation of risankizumab.

Elderly

There is limited safety information in subjects aged ≥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. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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: L04AC18

Mechanism of action

Risankizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds with high affinity to the p19 subunit of human interleukin 23 (IL-23) cytokine without binding to IL-12 and inhibits its interaction with the IL-23 receptor complex. IL-23 is a cytokine that is involved in inflammatory and immune responses. By blocking IL-23 from binding to its receptor, risankizumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines.

Pharmacodynamic effects

In a study of subjects with psoriasis, expression of genes associated with the IL-23/IL-17 axis was decreased in the skin after single doses of risankizumab. Reductions in epidermal thickness, infiltration of inflammatory cells, and expression of psoriatic disease markers were also observed in psoriatic lesions.

Clinical efficacy and safety

The efficacy and safety of risankizumab was assessed in 2,109 subjects with moderate to severe plaque psoriasis in four multicentre, randomised, double-blind studies (ULTIMMA-1, ULTIMMA-2, IMMHANCE, and IMMVENT). Enrolled subjects were 18 years of age and older with plaque psoriasis who had a body surface area (BSA) involvement of ≥10%, a static Physician Global Assessment (sPGA) score of ≥3 in the overall assessment (plaque thickness/induration, erythema, and scaling) of psoriasis on a severity scale of 0 to 4, a Psoriasis Area and Severity Index (PASI) score ≥12, and who were candidates for systemic therapy or phototherapy.

Overall, subjects had a median baseline PASI score of 17.8, a median BSA of 20.0%, and a median baseline DLQI score of 13.0. Baseline sPGA score was severe in 19.3% of subjects and moderate in 80.7% of subjects. A total of 9.8% of study subjects had a history of diagnosed psoriatic arthritis.

Across all studies, 30.9% of subjects were naïve to any systemic therapy (including non-biologic and biologic), 38.1% had received prior phototherapy or photochemotherapy, 48.3% had received prior non-biologic systemic therapy, 42.1% had received prior biologic therapy, and 23.7% had received at least one anti-TNF alpha agent for the treatment of psoriasis.

ULTIMMA-1 and ULTIMMA-2

ULTIMMA-1 and ULTIMMA-2 enrolled 997 subjects (598 randomised to risankizumab 150 mg, 199 to ustekinumab 45 mg or 90 mg [according to baseline weight], and 200 to placebo). Subjects received treatment at week 0, week 4, and every 12 weeks thereafter. The two co-primary endpoints in ULTIMMA-1 and ULTIMMA-2 were the proportion of subjects who achieved 1) PASI 90 response and 2) sPGA score of clear or almost clear (sPGA 0 or 1) at week 16 versus placebo. The results for the co-primary and other endpoints are presented in Table 2 and Figure 1.

Table 2: Efficacy and quality of life results in adults with plaque psoriasis in ULTIMMA-1 and ULTIMMA-2

	ULTIMMA-1			ULTIMMA-2		
	Risankizumab (N=304) n (%)	**Ustekinumab (N=100) n (%)**	**Placebo (N=102) n (%)**	**Risankizumab (N=294) n (%)**	**Ustekinumab (N=99) n (%)**	**Placebo (N=98) n (%)**
sPGA of clear or almost clear (0 or 1)						
Week 16[a]	267 (87.8)	63 (63.0)	8 (7.8)	246 (83.7)	61 (61.6)	5 (5.1)
Week 52	262 (86.2)	54 (54.0)	--	245 (83.3)	54 (54.5)	--
sPGA of clear (0)						
Week 16	112 (36.8)	14 (14.0)	2 (2.0)	150 (51.0)	25 (25.3)	3 (3.1)
Week 52	175 (57.6)	21 (21.0)	--	175 (59.5)	30 (30.3)	--
PASI 75						
Week 12	264 (86.8)	70 (70.0)	10 (9.8)	261 (88.8)	69 (69.7)	8 (8.2)
Week 52	279 (91.8)	70 (70.0)	--	269 (91.5)	76 (76.8)	--
PASI 90						
Week 16[a]	229 (75.3)	42 (42.0)	5 (4.9)	220 (74.8)	47 (47.5)	2 (2.0)
Week 52	249 (81.9)	44 (44.0)	--	237 (80.6)	50 (50.5)	--
PASI 100						
Week 16	109 (35.9)	12 (12.0)	0 (0.0)	149 (50.7)	24 (24.2)	2 (2.0)
Week 52	171 (56.3)	21 (21.0)	--	175 (59.5)	30 (30.3)	--
DLQI 0 or 1[b]						
Week 16	200 (65.8)	43 (43.0)	8 (7.8)	196 (66.7)	46 (46.5)	4 (4.1)
Week 52	229 (75.3)	47 (47.0)	--	208 (70.7)	44 (44.4)	--
PSS 0 (symptom-free)[c]						
Week 16	89 (29.3)	15 (15.0)	2 (2.0)	92 (31.3)	15 (15.2)	0 (0.0)
Week 52	173 (56.9)	30 (30.0)	--	160 (54.4)	30 (30.3)	--

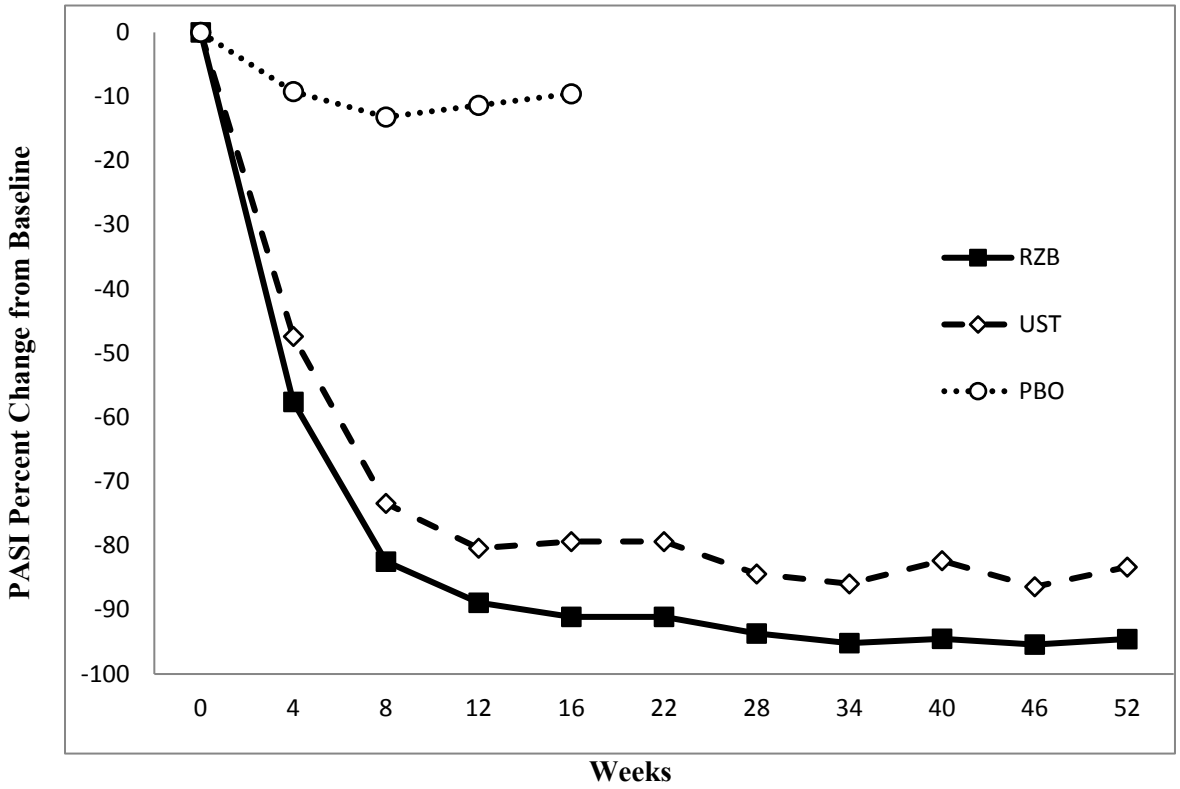
All comparisons of risankizumab versus ustekinumab and placebo achieved $p<0.001$ except for PASI 75 at week 52 in ULTIMMA-2 where $p=0.001$

[a] Co-primary endpoints versus placebo

[b] No impact on health-related quality of life

[c] Psoriasis Symptom Scale (PSS) of 0 means no symptoms of pain, itching, redness, and burning during the last 24 hours

Figure 1: Time course of mean percent change from baseline of PASI in ULTIMMA-1 and ULTIMMA-2



RZB = risankizumab
UST = ustekinumab
PBO = placebo
$p<0.001$ at each time point

Examination of age, gender, race, body weight ≤130 kg, baseline PASI score, concurrent psoriatic arthritis, previous non-biologic systemic treatment, previous biologic treatment, and previous failure of a biologic did not identify differences in response to risankizumab among these subgroups.

Improvements were observed in psoriasis involving the scalp, the nails, and the palms and soles at week 16 and week 52 in subjects treated with risankizumab.

Table 3: Mean changes from baseline in NAPSI, PPASI, and PSSI

	ULTIMMA-1		ULTIMMA-2		IMMHANCE	
	Risankizumab	**Placebo**	**Risankizumab**	**Placebo**	**Risankizumab**	**Placebo**
NAPSI: Change at Week 16 (SE)	N=178; -9.0 (1.17)	N=56; 2.1 (1.86) ***	N=177; -7.5 (1.03)	N=49; 3.0 (1.76) ***	N=235; -7.5 (0.89)	N=58; 2.5 (1.70) ***
PPASI: Change at Week 16 (SE)	N=95; -5.93 (0.324)	N=34; -3.17 (0.445) ***	N=86; -7.24 (0.558)	N=23; -3.74 (1.025) **	N=113; -7.39 (0.654)	N=26; -0.27 (1.339) ***
PSSI: Change at Week 16 (SE)	N=267; -17.6 (0.47)	N=92; -2.9 (0.69) ***	N=252; -18.4 (0.52)	N=83; -4.6 (0.82) ***	N=357; -20.1 (0.40)	N=88; -5.5 (0.77) ***
NAPSI: Change at Week 52 (SE)	N=178; -15.7 (0.94)	-	N=183; -16.7 (0.85)	-	-	-
PPASI: Change at Week 52 (SE)	N=95; -6.16 (0.296)	-	N=89; -8.35 (0.274)	-	-	-
PSSI: Change at Week 52 (SE)	N=269; -17.9 (0.34)	-	N=259; -18.8 (0.24)	-	-	-

Nail Psoriasis Severity Index (NAPSI), Palmoplantar Psoriasis Severity Index (PPASI), Psoriasis Scalp Severity Index (PSSI), and Standard Error (SE)
** $P < 0.01$ comparing to risankizumab
*** $P < 0.001$ comparing to risankizumab

Anxiety and depression, as measured by the Hospital Anxiety and Depression Scale (HADS), improved in the risankizumab group at week 16 compared with the placebo group.

Maintenance of response

In an integrated analysis of subjects receiving risankizumab in ULTIMMA-1 and ULTIMMA-2 for PASI 100 responders at week 16, 79.8% (206/258) of the subjects who continued on risankizumab maintained the response at week 52. For PASI 90 responders at week 16, 88.4% (398/450) of subjects maintained the response at week 52.

The safety profile of risankizumab with up to 77 weeks of exposure was consistent with the profile observed up to 16 weeks.

IMMHANCE

IMMHANCE enrolled 507 subjects (407 randomised to risankizumab 150 mg and 100 to placebo). Subjects received treatment at week 0, week 4 and every 12 weeks thereafter. Subjects who were originally on risankizumab and had a sPGA response of clear or almost clear at week 28 were re-randomised to continue risankizumab every 12 weeks or have treatment withdrawn.

At week 16, risankizumab was superior to placebo on the co-primary endpoints of sPGA of clear or almost clear (83.5% risankizumab vs 7.0% placebo) and PASI 90 (73.2% risankizumab vs 2.0% placebo).

Of the 31 subjects from the IMMHANCE study with latent tuberculosis (TB) who did not receive prophylaxis during the study, none developed active TB during the mean follow-up of 55 weeks on risankizumab.

Among subjects with sPGA of clear or almost clear at week 28 in IMMHANCE, 81.1% (90/111) of subjects re-randomised to continued treatment with risankizumab maintained this response at week 104 compared to 7.1% (16/225) who were re-randomised to withdrawal from risankizumab. Of these subjects, 63.1% (70/111) of subjects re-randomised to continued treatment with risankizumab achieved a sPGA clear response at week 104 compared to 2.2% (5/225) who were re-randomised to withdrawal from risankizumab.

IMMVENT

IMMVENT enrolled 605 subjects (301 randomised to risankizumab and 304 to adalimumab). Subjects randomised to risankizumab received 150 mg of treatment at week 0, week 4 and every 12 weeks thereafter. Subjects randomised to adalimumab received 80 mg at week 0, 40 mg at week 1 and 40 mg every other week through week 15. Starting at week 16, subjects who were receiving adalimumab continued or switched treatment based on response:

- <PASI 50 were switched to risankizumab
- PASI 50 to <PASI 90 were re-randomised to either continue adalimumab or switch to risankizumab
- PASI 90 continued to receive adalimumab

Results are presented in Table 4.

Table 4: Efficacy and quality of life results at week 16 in adults with plaque psoriasis in IMMVENT

	Risankizumab (N=301) n (%)	**Adalimumab (N=304) n (%)**
sPGA of clear or almost clear[a]	252 (83.7)	183 (60.2)
PASI 75	273 (90.7)	218 (71.7)
PASI 90[a]	218 (72.4)	144 (47.4)
PASI 100	120 (39.9)	70 (23.0)
DLQI 0 or 1[b]	198 (65.8)	148 (48.7)
All comparisons achieved p<0.001 [a] Co-primary endpoints [b] No impact on health-related quality of life		

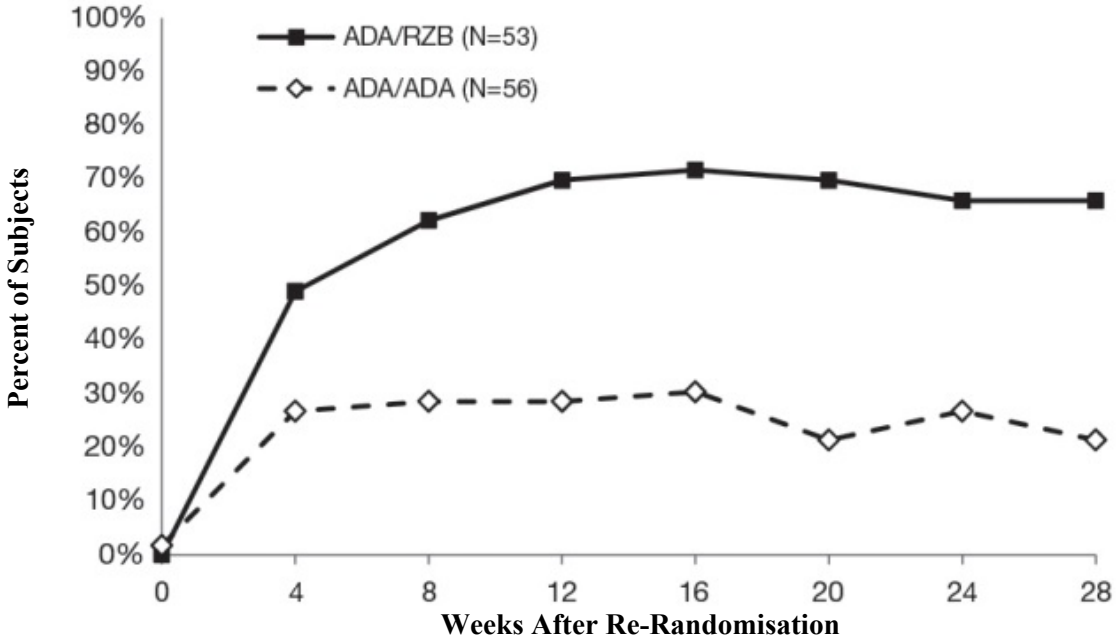
For subjects who had PASI 50 to <PASI 90 with adalimumab at week 16 and were re-randomised, differences in PASI 90 response rates between switching to risankizumab and continuing adalimumab were noted 4 weeks after re-randomisation (49.1% vs 26.8%, respectively).

Results 28 weeks after re-randomisation are presented in Table 5 and Figure 2.

Table 5: Efficacy results 28 weeks after re-randomisation in IMMVENT

	Switched to Risankizumab (N=53) n (%)	Continued on Adalimumab (N=56) n (%)
PASI 90	35 (66.0)	12 (21.4)
PASI 100	21 (39.6)	4 (7.1)
All comparisons achieved p<0.001		

Figure 2: Time course of PASI 90 after re-randomisation in IMMVENT



ADA/ADA: Subjects randomised to adalimumab and continued on adalimumab
ADA/RZB: Subjects randomised to adalimumab and switched to risankizumab
p<0.05 at week 4 and p<0.001 at each time point beginning at week 8

In 270 patients who switched from adalimumab to risankizumab without a washout period, the safety profile of risankizumab was similar to that in patients who initiated risankizumab after wash out of any prior systemic therapies.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with risankizumab in one or more subsets of the paediatric population in the treatment of plaque psoriasis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Risankizumab exhibited linear pharmacokinetics with dose-proportional increase in exposure across dose ranges of 18 to 300 mg and 0.25 to 1 mg/kg administered subcutaneously, and 200 to 1,200 mg and 0.01 to 5 mg/kg administered intravenously.

Following subcutaneous dosing of risankizumab, peak plasma concentrations were achieved between 3-14 days after dosing with an estimated absolute bioavailability of 89%. With dosing of 150 mg at week 0, week 4 and every 12 weeks thereafter, estimated steady-state peak and trough plasma concentrations are 12 and 2 μg/mL, respectively.

Distribution

The mean (±standard deviation) steady-state volume of distribution (V_{ss}) of risankizumab was 11.4 (±2.7) L in Phase 3 studies in subjects with psoriasis, indicating that the distribution of risankizumab is primarily confined to the vascular and interstitial spaces.

Biotransformation

Therapeutic IgG monoclonal antibodies are typically degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgGs. Risankizumab is not expected to be metabolised by cytochrome P450 enzymes.

Elimination

The mean (±standard deviation) systemic clearance (CL) of risankizumab was 0.3 (±0.1) L/day in Phase 3 studies in subjects with psoriasis. The mean terminal elimination half-life of risankizumab ranged from 28 to 29 days in Phase 3 studies in subjects with psoriasis.

As an IgG1 monoclonal antibody, risankizumab is not expected to be filtered by glomerular filtration in the kidneys or to be excreted as an intact molecule in the urine.

Linearity/non-linearity

Risankizumab exhibited linear pharmacokinetics with approximately dose-proportional increases in systemic exposure (C_{max} and AUC) in the evaluated dose ranges of 18 to 300 mg or 0.25 to 1 mg/kg subcutaneous administration in healthy subjects or subjects with psoriasis.

Drug interactions

A drug interaction study was conducted in subjects with plaque psoriasis to assess the effect of repeated administration of risankizumab on the pharmacokinetics of cytochrome P450 (CYP) sensitive probe substrates. The exposure of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), metoprolol (CYP2D6 substrate) and midazolam (CYP3A substrate) following risankizumab treatment were comparable to their exposures prior to risankizumab treatment, indicating no clinically meaningful drug interactions through these enzymes.

Population pharmacokinetic analyses indicated that risankizumab exposure was not impacted by concomitant medications (metformin, atorvastatin, lisinopril, amlodipine, ibuprofen, acetylsalicylate and levothyroxine) used by some subjects with plaque psoriasis during the clinical studies.

Special populations

Paediatric patients

The pharmacokinetics of risankizumab in paediatric subjects has not been established.

Elderly patients

Of the 2,234 subjects with plaque psoriasis exposed to risankizumab, 243 were 65 years or older and 24 subjects were 75 years or older. No overall differences in risankizumab exposure were observed between older and younger subjects who received risankizumab.

Patients with renal or hepatic impairment

No specific studies have been conducted to determine the effect of renal or hepatic impairment on the pharmacokinetics of risankizumab. Based on population pharmacokinetic analyses, serum creatinine

levels, creatinine clearance, or hepatic function markers (ALT/AST/bilirubin) did not have a meaningful impact on risankizumab clearance in subjects with psoriasis.

As an IgG1 monoclonal antibody, risankizumab is mainly eliminated via intracellular catabolism and is not expected to undergo metabolism via hepatic cytochrome P450 enzymes or renal elimination.

Body weight

Risankizumab clearance and volume of distribution increase as body weight increases which may result in reduced efficacy in subjects with high body weight (>130 kg). However, this observation is based on a limited number of subjects. No dose adjustment based on body weight is currently recommended.

Gender or race

The clearance of risankizumab was not significantly influenced by gender or race in adult subjects with plaque psoriasis. No clinically meaningful differences in risankizumab exposure were observed in Chinese or Japanese subjects compared to Caucasian subjects in a clinical pharmacokinetic study.

5.3 Preclinical safety data

Nonclinical data revealed no special hazard for humans based on repeat-dose toxicity studies including safety pharmacology evaluations, and a reproductive and developmental toxicity study in cynomolgus monkeys at doses of up to 50 mg/kg/week (producing exposures of about 70 times the clinical exposure at maximum recommended human dose [MRHD]).

Mutagenicity and carcinogenicity studies have not been conducted with risankizumab. In a 26-week chronic toxicology study in cynomolgus monkeys at doses of up to 50 mg/kg/week (about 70 times the clinical exposure at the MRHD), there were no pre-neoplastic or neoplastic lesions observed and no adverse immunotoxicity or cardiovascular effects were noted .

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium succinate hexahydrate
Succinic acid
Sorbitol
Polysorbate 20
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

2 years

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.
Keep the pre-filled syringes in the outer carton in order to protect from light.

6.5 Nature and contents of container

Pre-filled glass syringe with a fixed needle and needle cover, assembled in an automatic needle guard. Each pre-filled syringe contains 75 mg risankizumab in 0.83 ml.

Skyrizi is available in packs containing 2 pre-filled syringes and 2 alcohol pads.

6.6 Special precautions for disposal and other handling

Before injecting, patients may remove the carton from the refrigerator and allow to reach room temperature out of direct sunlight (15 to 30 minutes) without removing the pre-filled syringes from the carton.

Prior to use, a visual inspection of each pre-filled syringe is recommended. The solution should be colourless to slightly yellow and clear to slightly opalescent. It may contain a few translucent to white product-related particles. Skyrizi should not be used if the solution is cloudy or discoloured, or contains large particles.

Two pre-filled syringes should be injected for the full 150 mg dose. Comprehensive instructions for use are provided in the package leaflet.

Each pre-filled syringe is for single use only.

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

7. MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1361/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 April 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Str. 65
88397 Biberach a.d.R.
GERMANY

Name and address of the manufacturer(s) responsible for batch release

AbbVie S.r.l.
148, Pontina Km 52 snc
04011
Campoverde di Aprilia (LT)
ITALY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.
The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Skyrizi 75 mg solution for injection in pre-filled syringe
risankizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe contains 75 mg risankizumab.

3. LIST OF EXCIPIENTS

Excipients: disodium succinate hexahydrate, succinic acid, sorbitol, polysorbate 20 and water for injections. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
2 pre-filled syringes
2 alcohol pads

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use

For single use only.

Open here

For more information and support on Skyrizi go to www.skyrizi.eu or scan this code.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1361/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

skyrizi

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Skyrizi 75 mg solution for injection in pre-filled syringe
risankizumab

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AbbVie (as logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

For subcutaneous use

PC

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Skyrizi 75 mg injection
risankizumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Skyrizi 75 mg solution for injection in pre-filled syringe
risankizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Skyrizi is and what it is used for

Skyrizi contains the active substance risankizumab.

Skyrizi is used to treat adults with moderate to severe plaque psoriasis.

How Skyrizi works
This medicine works by stopping a protein in the body called ‘IL-23’, which causes inflammation. It reduces the inflammation. It also reduces symptoms of psoriasis such as burning, itching, pain, redness and scaling.

2. What you need to know before you use Skyrizi

Do not use Skyrizi
- if you are allergic to risankizumab or any of the other ingredients of this medicine (listed in section 6).
- if you have an infection, including active tuberculosis, which your doctor thinks is important.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before and during the use of Skyrizi:
- if you currently have an infection or if you have an infection that keeps coming back.
- if you have tuberculosis (TB).
- if you have recently received or plan to receive an immunisation (vaccine). You should not be given certain types of vaccines while using Skyrizi.

Allergic reactions
Tell your doctor or seek medical help immediately if you notice any signs of an allergic reaction while you are taking Skyrizi such as:
- difficulty breathing or swallowing
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps

Children and adolescents
Skyrizi is not recommended for children and adolescents under 18 years of age. This is because Skyrizi has not been studied in this age group.

Other medicines and Skyrizi
Tell your doctor, pharmacist or nurse:
- if you are using, have recently used or might use any other medicines.
- if you have recently had or are going to have a vaccination. You should not be given certain types of vaccines while using Skyrizi.

If you are not sure, talk to your doctor, pharmacist or nurse before and during the use of Skyrizi.

Pregnancy, contraception and breast-feeding
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. This is because it is not known how this medicine will affect the baby.

If you are a woman who can become pregnant, you should use contraception while using this medicine and for at least 21 weeks after your last dose of Skyrizi.

If you are breast-feeding or are planning to breast-feed, talk to your doctor before using this medicine.

Driving and using machines
Skyrizi is not likely to affect your driving and use of machines.

Skyrizi contains sorbitol and sodium
This medicine contains 68 mg sorbitol per 150 mg dose.

This medicine contains less than 1 mmol sodium (23 mg) per 150 mg dose, that is to say essentially ‘sodium-free’.

3. How to use Skyrizi

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

This medicine is given as 2 injections under your skin (called ‘subcutaneous injections’).

How much Skyrizi to use

The dose is 150 mg given as two 75 mg injections.

	How much?	**When?**
1st dose	150 mg (**two** 75 mg injections)	When your doctor tells you
2nd dose	150 mg (**two** 75 mg injections)	4 weeks after 1st dose
Further doses	150 mg (**two** 75 mg injections)	Every 12 weeks starting after 2nd dose

You and your doctor, pharmacist or nurse will decide if you should inject this medicine yourself. Do not inject yourself with this medicine unless you have been trained by your doctor, pharmacist or nurse. A caregiver may also give your injections after they have been trained.

Read section 7 'Instructions for use' at the end of this leaflet before injecting Skyrizi yourself.

If you use more Skyrizi than you should
If you have used more Skyrizi than you should or the dose has been given sooner than prescribed, talk to your doctor.

If you forget to use Skyrizi
If you forget to use Skyrizi, inject a dose as soon as you remember. Talk to your doctor if you are not sure what to do.

If you stop using Skyrizi
Do not stop using Skyrizi without talking to your doctor first. If you stop treatment, your symptoms may come back.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Talk to your doctor or get medical help immediately if you have symptoms of a serious infection such as:
- fever, flu-like symptoms, night sweats
- feeling tired or short of breath, cough which will not go away
- warm, red and painful skin, or a painful skin rash with blisters

Your doctor will decide if you can keep using Skyrizi.

Other side effects
Tell your doctor, pharmacist or nurse if you get any of the following side effects

Very common: may affect more than 1 in 10 people
- upper respiratory infections with symptoms such as sore throat and stuffy nose

Common: may affect up to 1 in 10 people
- feeling tired
- fungal skin infection
- injection site reactions (such as redness or pain)
- itching
- headache

Uncommon: may affect up to 1 in 100 people
- small raised red bumps on the skin

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Skyrizi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the syringe label and outer carton after 'EXP'.

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

Keep the pre-filled syringes in the original carton in order to protect from light.

Do not use this medicine if the liquid is cloudy or contains flakes or large particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Skyrizi contains
- The active substance is risankizumab. Each pre-filled syringe contains 75 mg of risankizumab in 0.83 ml solution.
- The other ingredients are disodium succinate hexahydrate, succinic acid, sorbitol, polysorbate 20 and water for injections.

What Skyrizi looks like and contents of the pack
Skyrizi is a clear and colourless to slightly yellow liquid in a pre-filled syringe with needle guard. The liquid may contain tiny white or clear particles.

Each pack contains 2 pre-filled syringes and 2 alcohol pads.

Marketing Authorisation Holder

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

Manufacturer

AbbVie S.r.l.
04011 Campoverde di Aprilia
(Latina)
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

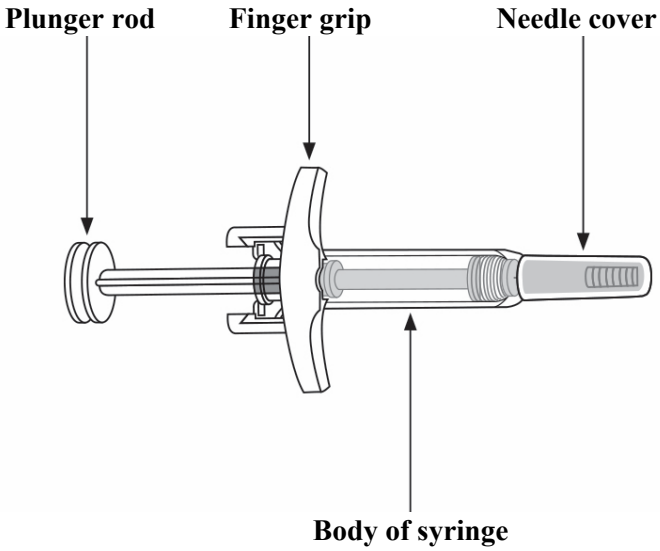
Detailed and updated information on this product is available by scanning the QR code included below or on the outer carton with a smartphone. The same information is also available at the following URL:
www.skyrizi.eu

QR code to be included

To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.

7. Instructions for use

Please read all of section 7 before using Skyrizi



Important information to know before you inject Skyrizi

- You should receive training on how to inject Skyrizi before giving an injection. Talk to your doctor, pharmacist or nurse if you need help
- Mark the dates on your calendar so you know when to inject Skyrizi
- Keep Skyrizi in the original carton to protect the medicine from light until it is time to use it
- **Do not** inject if the liquid is cloudy or contains flakes or large particles. The liquid should look clear to slightly yellow and may contain tiny white or clear particles
- **Do not** shake the syringe
- Wait to remove the needle cover until just before the injection

Return this medicine to the pharmacy

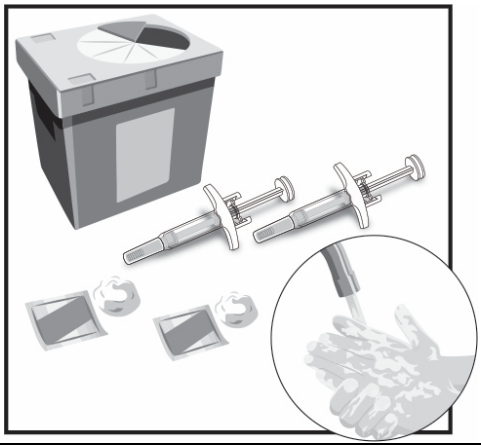
- if the expiry date (EXP) has passed
- if the liquid has ever been frozen (even if thawed)
- if the syringe has been dropped or damaged
- if the syringe paper tray cover is broken or missing

For a more comfortable injection: Take the carton out of the refrigerator and leave it at room temperature, out of direct sunlight, for **15 to 30 minutes** before injecting.

- Skyrizi should not be warmed in any other way (for example, in a microwave or in hot water)
- Keep the syringes in the carton until ready to inject

Follow the steps below each time you use Skyrizi

STEP 1



Place the following items on a clean, flat surface:

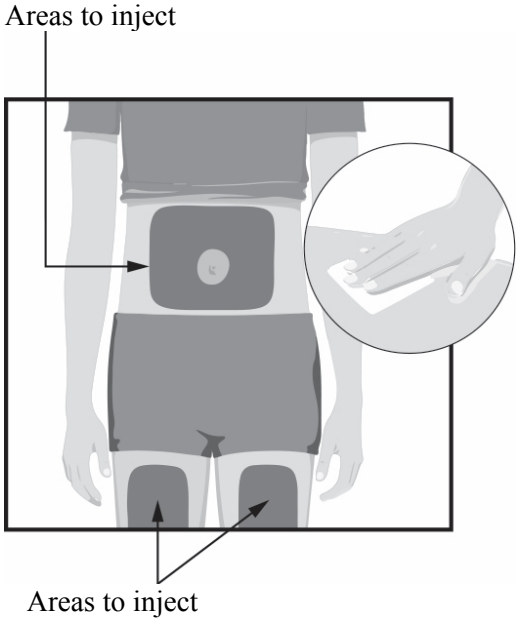
- 2 pre-filled syringes and 2 alcohol pads (included in the carton)
- 2 cotton balls or gauze pads (not included in the carton)
- Special disposal container (not included in the carton)

Wash and dry your hands.

Start with one syringe for the first injection.

For a full dose, 2 injections are required, one after the other.

STEP 2



Choose from these 3 areas to inject:

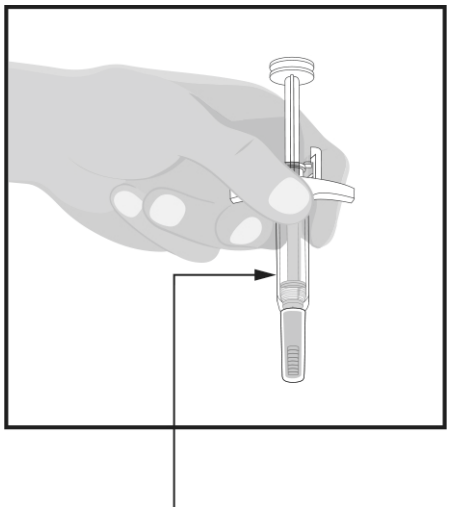
- front of left thigh
- front of right thigh
- your belly (abdomen) at least 5 cm from your belly button (navel)

For the second syringe, inject at least 3 cm away from the first injection. **Do not** inject into the same place.

Before each injection, wipe where you will inject in a circular motion with an alcohol pad.

- **Do not** touch or blow on the injection site after it is cleaned. Allow the skin to dry before injecting
- **Do not** inject through clothes
- **Do not** inject into skin that is sore, bruised, red, hard, scarred, or has stretch marks
- **Do not** inject into areas affected by psoriasis

STEP 3



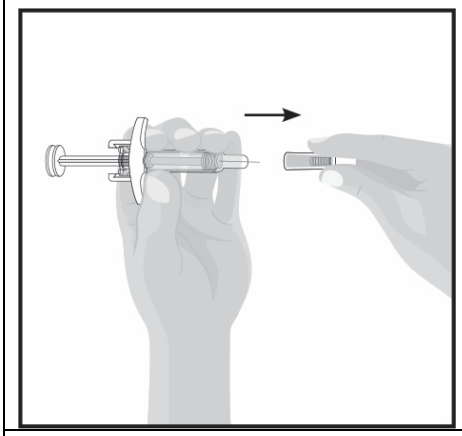
Check liquid

Hold the syringe with the covered needle pointing down, as shown.

Check the liquid in the syringe.

- It is normal to see bubbles in the window
- The liquid should look clear to slightly yellow and may contain tiny white or clear particles
- **Do not** use if the liquid is cloudy or contains flakes or large particles

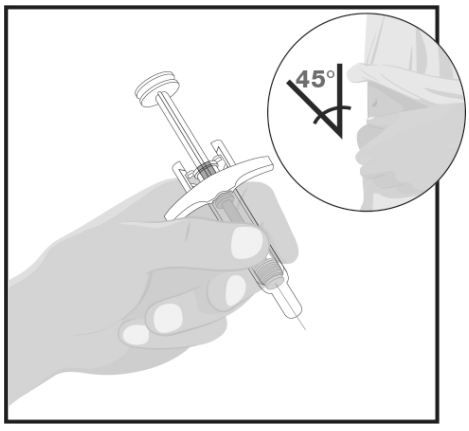
STEP 4



Removing the needle cover:

- Hold the syringe in one hand between the finger grip and needle cover
- With the other hand, gently pull the needle cover straight off
- **Do not** hold or pull the plunger rod when removing the needle cover
- You may see a drop of liquid at the end of the needle. This is normal
- Throw away the needle cover
- **Do not** touch the needle with your fingers or let the needle touch anything

STEP 5

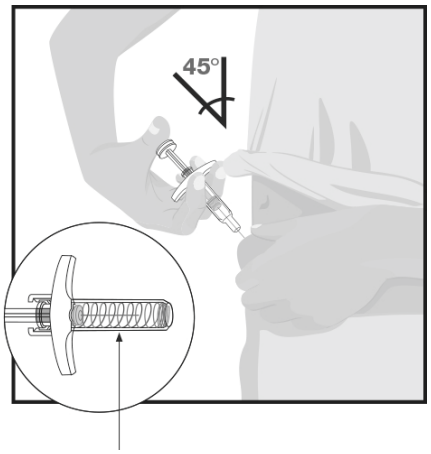


Hold the body of the syringe in one hand between the thumb and index finger, like you would a pencil.

Gently pinch the area of cleaned skin with your other hand and hold it firmly.

Insert the needle all the way into the skin at about a 45-degree angle using a quick, short movement. Keep the syringe steady at the same angle.

STEP 6



Needle guard

Slowly push the plunger rod all the way in until all of the liquid is injected.

Pull the needle out of the skin while keeping the syringe at the same angle.

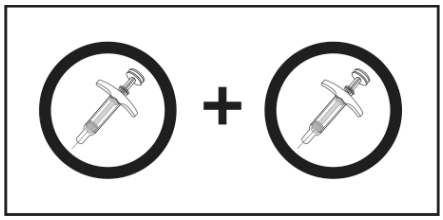
Slowly take your thumb off the plunger rod. The needle will then be covered by the needle guard.

- The needle guard will not activate unless all the liquid is injected
- Speak to your doctor, pharmacist or nurse if you think you have not given a full dose

Press a cotton ball or gauze pad where you have injected and hold for 10 seconds.

Do not rub the skin where you have injected. You may have slight bleeding from where you injected. This is normal

STEP 7

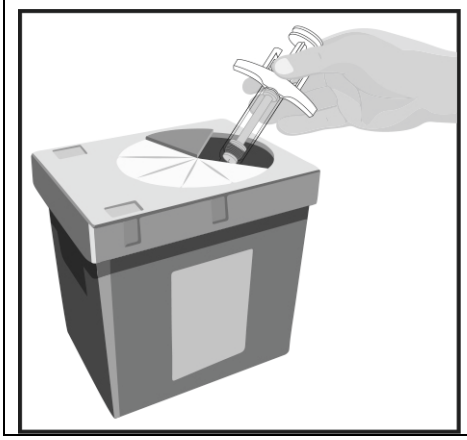


2 Injections Required

For a full dose, two injections are needed, one after the other.

- Repeat Steps 2 through 6 with the second syringe
- Inject the second syringe straight after the first injection but at least 3 cm away from the first injection

STEP 8



Throw away used syringes in a special disposal container straight after use.

- **Do not** throw away used syringes in the household waste
- Your doctor, pharmacist or nurse will tell you how to return the full special disposal container