NEW ZEALAND DATA SHEET

1 SKYRIZI® 75mg/0.83mL solution for injection
SKYRIZI® 150 mg/mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each 150 mg/mL pre-filled pen or pre-filled syringe contains 150 mg risankizumab in 1 mL solution.

Skyrizi (risankizumab), an interleukin-23 blocker, is a humanised immunoglobin G1 (IgG1) monoclonal antibody.

Risankizumab is a recombinant human monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells using recombinant DNA technology.

Excipients with known effect

Skyrizi 75 mg/0.83 mL contains 68 mg sorbitol per 150 mg dose.

Skyrizi 150 mg/mL and Skyrizi 75 mg/0.83 mL contains less than 1 mmol sodium (23 mg) per 150 mg dose and is essentially sodium free.

For the full list of excipients, see **Section 6.1 List of Excipients.**

3 PHARMACEUTICAL FORM

75 mg/0.83 mL: Solution for injection in a pre-filled syringe.

The solution is colourless to slightly yellow and clear to slightly opalescent. The solution may contain a few translucent to white product-related particles.

150 mg/ mL: Solution for injection in a pre-filled syringe or pre-filled pen.

The solution is colourless to yellow and clear to slightly opalescent. The solution may contain a few translucent to white product-related particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Psoriasis

Skyrizi is indicated for the treatment of moderate to severe plaque psoriasis in adults.

Psoriatic Arthritis

Skyrizi is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to or are intolerant to one or more disease modifying antirheumatic drugs (DMARDs). Skyrizi may be used as monotherapy or in combination with a conventional synthetic disease modifying antirheumatic drug (csDMARD).

4.2 Dose and Method of Administration

Psoriasis & Psoriatic Arthritis

The recommended dose is 150 mg administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter.

Patients may self-inject Skyrizi after training in subcutaneous injection technique.

Patients should read the Instructions for Use before administration.

Skyrizi should not be used if the solution is cloudy or discoloured or contains large particles.

If using Skyrizi 75 mg/0.83 mL, patients should be instructed to inject two pre-filled syringes for the full 150 mg dose Each pre-filled syringe and pre-filled pen are for single use only.

Discard any residue.

Patients should not inject 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.

Before injecting, for a more comfortable injection, patients using the pre-filled syringe 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.

Before injecting the pre-filled pen, patients should remove the carton from the refrigerator and allow to reach room temperature out of direct sunlight (30 to 90 minutes) without removing the pre-filled pen from the carton.

Missed Dose

If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in **Section 6.1.**

4.4 Special warnings and precautions for use

Infections

Skyrizi may increase the risk of infections.

In patients with a chronic infection or a history of recurrent infection, the risks and benefits should be considered prior to prescribing Skyrizi. Patients should be instructed to seek medical advice if signs or symptoms of clinically important 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 Skyrizi should not be administered until the infection resolves.

Tuberculosis

Across the Phase 3 psoriasis clinical studies, of the 72 subjects with latent tuberculosis (TB) who were concurrently treated with Skyrizi and appropriate TB prophylaxis during the studies, none developed active TB during the mean follow-up of 61 weeks on risankizumab. In patients with latent TB, consider anti-TB therapy prior to initiating Skyrizi. Skyrizi must not be given to patients with active TB.

Immunisations

Prior to initiating therapy with Skyrizi, completion of all appropriate immunisations should be considered according to current immunisation guidelines. Skyrizi should not be used with live vaccines. No data are available on the response to live or inactive vaccines.

Hypersensitivity

If a serious hypersensitivity reaction occurs, discontinue Skyrizi and initiate appropriate therapy immediately.

Use in Hepatic Impairment

No specific studies were conducted to assess the effect of hepatic impairment on the pharmacokinetics of Skyrizi. This condition is generally not expected to have any

significant impact on the pharmacokinetics of monoclonal antibodies and no dose adjustments are considered necessary (*see* **5.2 PHARMACOKINETIC PROPERTIES**).

Use in Renal Impairment

No specific studies were conducted to assess the effect of renal impairment on the pharmacokinetics of Skyrizi. This condition is generally not expected to have any significant impact on the pharmacokinetics of monoclonal antibodies and no dose adjustments are considered necessary (*see* **5.2 PHARMACOKINETIC PROPERTIES**).

Use in the Elderly

No dose adjustment is required (*see* **5.2 PHARMACOKINETIC PROPERTIES**).

Paediatric use

The safety and effectiveness of Skyrizi in patients younger than 18 years of age have not yet been established.

Effects on Laboratory Tests

No data available.

4.5 Interactions with Other Medicines and Other Forms of Interactions

Skyrizi is not expected to undergo metabolism by hepatic enzymes or renal elimination. Drug interactions between Skyrizi and inhibitors/inducers of drug metabolising enzymes are not expected.

Based on results from a drug-drug interaction study in subjects with plaque psoriasis and population pharmacokinetic analyses in plaque psoriasis and psoriatic arthritis, risankizumab would not cause or be impacted by drug-drug interactions (*see* **5.2 PHARMACOKINETIC PROPERTIES-Drug Interactions**).

No dose adjustment is needed when co-administering risankizumab and cytochrome P450 substrates.

4.6 Fertility, Pregnancy and Lactation

Pregnancy (Pregnancy Category B1)

Data available with Skyrizi use in pregnant women are insufficient to inform any drug-associated risks.

An enhanced pre- and post-natal developmental toxicity study was conducted in cynomolgus monkeys. Pregnant cynomolgus monkeys were administered weekly

subcutaneous doses of risankizumab at 5 and 50 mg/kg from gestation day 20 to parturition and the cynomolgus monkeys (mother and infants) were followed for 6 months (180 days) after delivery. These doses produced exposures of up to approximately 70 times the clinical exposure at the maximum recommended human dose (MRHD). No drug-related foetal/infant deaths and/or malformations were observed. There were no effects on infant growth and development, which included the assessment of external, visceral, skeletal and neurobehavioral parameters and developmental immuno-toxicology endpoints. In the infants, mean serum concentrations increased in a dose-dependent manner and were approximately 20% - 90% of the respective maternal concentrations. Following delivery, most adult female cynomolgus monkeys and all infants from the risankizumab-treated groups had measurable serum concentrations of risankizumab up to 91 days postpartum. Serum concentrations were below detectable levels at 180 days postpartum.

Skyrizi should be used in pregnancy only if the benefits outweigh the potential risks.

Breastfeeding

There are no data on the presence of risankizumab in human milk, the effects on the breastfed infant, or the effects on milk production. Although human IgG is secreted into human milk, published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Skyrizi.

Fertility

Studies in cynomolgus monkeys at doses of up to 50 mg/kg/week (about 70 times the clinical exposure at the MRHD) with Skyrizi did not indicate direct or indirect harmful effects on male or female fertility. In the 26-week repeat dose toxicology study, histopathology of reproductive organs from both male and female cynomolgus monkeys did not show any relevant adverse finding. In a 26-week repeat dose study in sexually mature male cynomolgus monkeys, no effects on male fertility parameters were observed.

4.7 Effects on Ability to Drive and use Machines

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

4.8 Adverse Effects (Undesirable Effects)

Psoriasis

A total of 2234 subjects were treated with Skyrizi in clinical development studies in plaque psoriasis, representing 2167 subject-years of exposure. Of these, 1208 subjects with psoriasis were exposed to Skyrizi for at least one year.

Data from placebo- and active-controlled studies were pooled to evaluate the safety of Skyrizi for up to 16 weeks. In total, 1306 subjects were evaluated in the Skyrizi 150 mg group. Serious adverse events occurred in 2.4% for the Skyrizi group (9.9 events per 100 subject-years) compared with 4.0% for the placebo group (17.4 events per 100 subject-years), 5.0% for the ustekinumab group (18.4 events per 100 subject-years) and 3.0% for the adalimumab group (14.7 events per 100 subject-years).

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the Skyrizi group than the placebo group during the 16-week controlled period of pooled clinical studies. Adverse reactions are listed by MedDRA system organ class.

Table 1. Adverse Reactions Occurring in ≥ 1% of Subjects on Skyrizi through Week 16

	Skyrizi[1,2,4] N=1306 n (%)	**Placebo[1,2] N = 300 n (%)**	**Ustekinumab[1, 3] N = 239 n (%)**	**Adalimumab[4] N=304 n (%)**
Infections and infestations				
Upper respiratory infections[a]	170 (13.0)	29 (9.7)	28 (11.7)	42 (13.8)
Tinea infections[b]	15 (1.1)	1 (0.3)	1 (0.4)	2 (0.7)
Nervous system disorders				
Headache[c]	46 (3.5)	6 (2.0)	9 (3.8)	20 (6.6)
General disorders and administration site conditions				
Fatigue[d]	33 (2.5)	3 (1.0)	7 (2.9)	8 (2.6)
Injection site reactions[e]	19 (1.5)	3 (1.0)	9 (3.8)	17 (5.6)

[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 versicolour, tinea manuum, tinea infection, onychomycosis
[c] Includes: headache, tension headache, sinus headache, cervicogenic headache
[d] Includes: fatigue, asthenia
[e] Includes: injection site bruising, erythema, extravasation, haematoma, haemorrhage, infection, inflammation, irritation, pain, pruritus, reaction, swelling, warmth
[1] Includes data from ULTIMMA-1 and ULTIMMA-2 studies
[2] Includes data from IMMHANCE study
[3] Includes data from Phase 2 Study 1311.2
[4] Includes data from IMMVENT study

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Infections and Infestations: folliculitis

Specific Adverse Reactions

Infections

In the first 16 weeks, infections occurred in 22.1% of the Skyrizi group (90.8 events per 100 subject-years) compared with 14.7% of the placebo group (56.5 events per 100 subject-years), 20.9% of the ustekinumab group (87.0 events per 100 subject-years) and 24.3% of the adalimumab group (104.2 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 Skyrizi.

Over the entire psoriasis program including long-term exposure to Skyrizi, the rate of infections (75.5 events per 100 subject-years) was similar to that observed during the first 16 weeks of treatment.

Long-Term Safety

Through Week 52, the frequency of the adverse reactions was similar to the safety profile observed during the first 16 weeks of treatment. Through Week 52, the exposure-adjusted rates of serious adverse events per 100 subject-years were 9.4 for subjects treated with Skyrizi and 10.9 for those treated with ustekinumab. For those subjects exposed to a maximum of 77 weeks of Skyrizi, no new adverse reactions were identified compared with the first 16 weeks of treatment.

Psoriatic Arthritis

Overall, the safety profile observed in patients with psoriatic arthritis treated with Skyrizi was consistent with the safety profile observed in patients with plaque psoriasis. The safety profile of Skyrizi was consistent with the profile observed up to 24 weeks.

Post marketing experience

The following adverse reactions have been identified during post-approval use of Skyrizi. As these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Skin and subcutaneous tissue disorders: eczema, rash and urticaria

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity with Skyrizi. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity (including neutralising antibody) in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to risankizumab with the incidence of antibodies to other products may be misleading.

Psoriasis

For subjects treated with Skyrizi 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% (263/1079) and 14% (150/1079) of evaluated subjects, respectively.

Antibodies to risankizumab including neutralising antibodies were not associated with changes in clinical response or safety.

Psoriatic Arthritis

For subjects treated with Skyrizi at the recommended clinical dose for up to 28 weeks in psoriatic arthritis clinical trials, treatment-emergent anti-drug antibodies and neutralising antibodies were detected in 12.1% (79/652) and 0% (0/652) of evaluated subjects, respectively. Antibodies to risankizumab including neutralising antibodies were not associated with changes in clinical response or safety.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. In New Zealand, healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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.

For advice on the management of overdose in New Zealand, please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

ATC code: L04AC18.

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.

In a study of subjects with psoriatic arthritis, clinically meaningful reduction from baseline was observed at Week 24 in IL-23- and IL-17-associated biomarkers, including serum IL-17A, IL-17F, and IL-22 following treatment with risankizumab at 150 mg administered subcutaneously at Week 0, Week 4, and every 12 weeks thereafter.

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 and inhibits its interaction with the IL-23 receptor complex. IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses. IL-23 supports the development, maintenance and activation of Th17 cells, which produces IL-17A, IL-17F, and IL-22, as well as other pro-inflammatory cytokines, and plays a key role in driving inflammatory autoimmune diseases, such as psoriasis. IL-23 is up-regulated in lesional skin in comparison to non-lesional skin of patients with plaque psoriasis. By blocking IL-23 from binding to its receptor, risankizumab inhibits IL-23-dependent cell signalling and release of pro-inflammatory cytokines.

Risankizumab does not bind to human IL-12, which shares the p40 subunit with IL-23.

Clinical Trials

<u>Psoriasis</u>

The efficacy and safety of Skyrizi was assessed in 2109 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, and a Psoriasis Area and Severity Index (PASI) score ≥ 12.

Overall, subjects had a median baseline PASI score of 17.8 and a median BSA of 20.0%. Baseline sPGA score was severe in 19.3% 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 both non-biologic systemic and biologic therapy, 38.1% of subjects had received prior phototherapy, 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 Skyrizi 150 mg, 199 to ustekinumab 45 mg or 90 mg, and 200 to placebo). Subjects received treatment at Week 0, Week 4, and every 12 weeks thereafter. The results are presented in Table 2 and Figure 1.

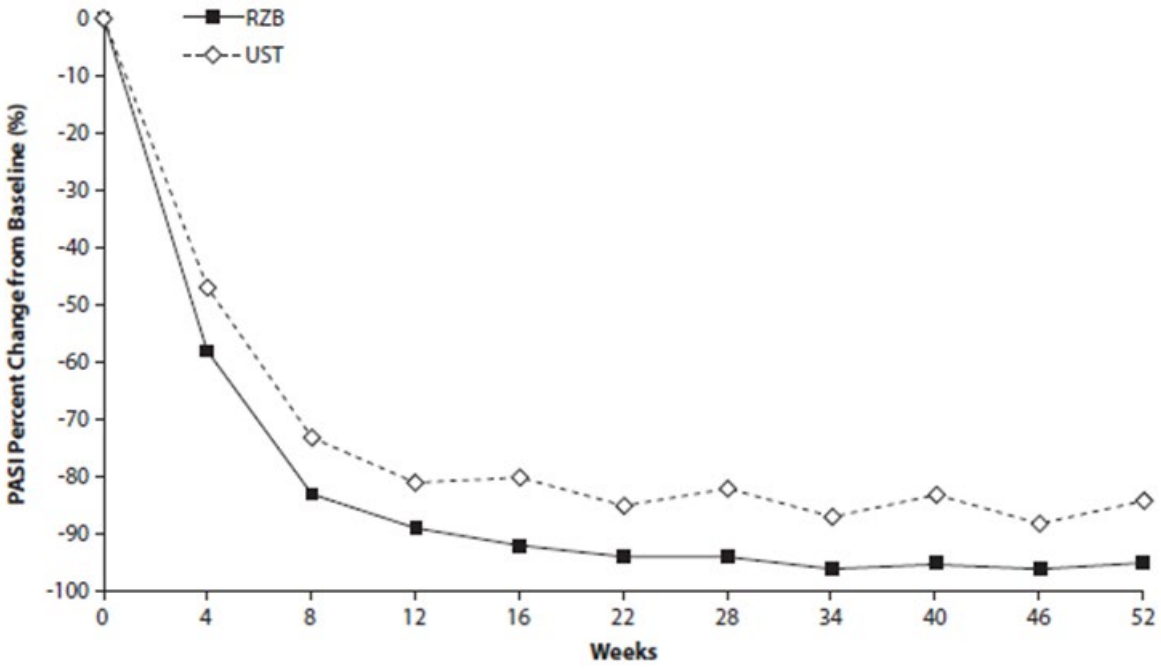
Table 2. Efficacy Results in Adults with Plaque Psoriasis in ULTIMMA-1 and ULTIMMA-2

	ULTIMMA-1			ULTIMMA-2		
	Skyrizi (N=304) n (%)	**Ustekinumab (N=100) n (%)**	**Placebo (N=102) n (%)**	**Skyrizi (N=294) n (%)**	**Ustekinumab (N=99) n (%)**	**Placebo (N=98) n (%)**
sPGA of clear or almost clear (0 or 1)						
Week 12	250 (82.2)	65 (65.0)	9 (8.8)	242 (82.3)	64 (64.6)	9 (9.2)
Week 16	267 (87.8)[a]	63 (63.0)	8 (7.8)	246 (83.7)[a]	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	229 (75.3)[a]	42 (42.0)	5 (4.9)	220 (74.8)[a]	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)	—

All comparisons of Skyrizi 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

Figure 1. Time Course of Mean Percent Change from Baseline of PASI inULTIMMA-1 and ULTIMMA-2



RZB = risankizumab
UST = ustekinumab
P < 0.001 at each time point

Examination of age, gender, race, body weight, 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 Skyrizi 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 Skyrizi.

IMMHANCE

IMMHANCE enrolled 507 subjects (407 randomized to Skyrizi 150 mg and 100 to placebo). Subjects received treatment at Week 0, Week 4 and every 12 weeks thereafter.

At Week 16, Skyrizi was superior to placebo on the co-primary endpoints of sPGA of clear or almost clear (83.5% Skyrizi vs 7.0% placebo) and PASI 90 (73.2% Skyrizi vs 2.0% placebo). More subjects on Skyrizi had clear skin [sPGA 0 (46.4% Skyrizi vs 1.0% placebo) or PASI 100 (47.2% Skyrizi vs 1.0% placebo)] at Week 16. Subjects receiving Skyrizi were also more likely to have a PASI 75 response compared with placebo (88.7% Skyrizi vs 8.0% placebo).

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

IMMVENT

IMMVENT enrolled 605 subjects (301 randomized to Skyrizi and 304 to adalimumab). Subjects randomised to Skyrizi 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 Skyrizi
- PASI 50 to < PASI 90 were re-randomised to either continue adalimumab or switch to Skyrizi
- PASI 90 continued to receive adalimumab

Similar results for Skyrizi at Week 16 were seen in IMMVENT as in other clinical studies (Table 3 and Figure 2).

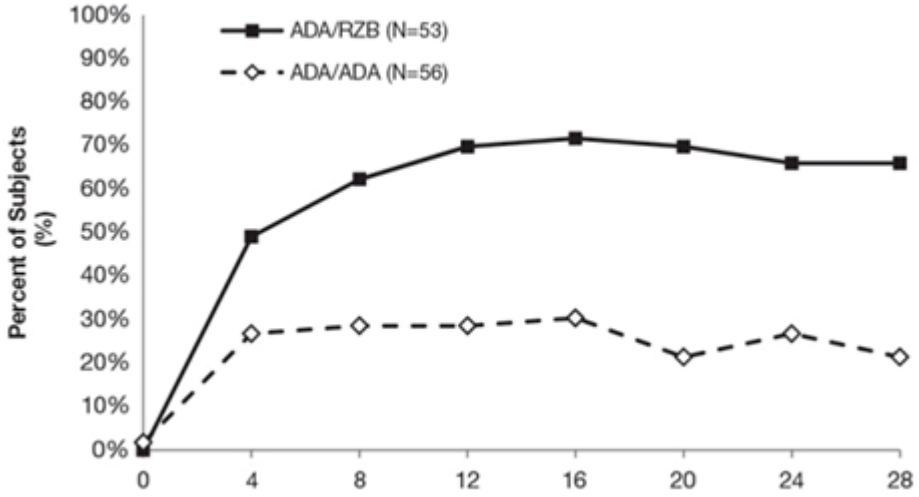
Table 3. Efficacy Results at Week 16 in Adults with Plaque Psoriasis in IMMVENT

	Skyrizi (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)

All comparisons achieved p < 0.001
[a] Co-primary endpoints

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 Skyrizi and continuing adalimumab were noted as early as 4 weeks after re-randomisation (49.1% vs 26.8%, respectively). 66.0% (35/53) of subjects achieved PASI 90 following 28 weeks of Skyrizi, compared with 21.4% (12/56) who continued to receive adalimumab. Other levels of response were also higher following Skyrizi: 39.6% PASI 100, 39.6% sPGA of clear, and 73.6% sPGA of clear or almost clear had response after switching to Skyrizi, compared with 7.1% PASI 100, 7.1% sPGA of clear, and 33.9% sPGA of clear or almost clear who continued to receive adalimumab.

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 Skyrizi
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 Skyrizi without a washout period, the safety profile was similar to that in patients who initiated Skyrizi after washout of any prior systemic therapies.

Maintenance and Durability of Response

In an integrated analysis of subjects receiving Skyrizi in ULTIMMA-1 and ULTIMMA-2 for PASI 100 responders at Week 16, 79.8% (206/258) of the subjects who continued on Skyrizi 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.

IMMHANCE subjects originally on Skyrizi who achieved sPGA of clear or almost clear at Week 28 were re-randomised to continue Skyrizi every 12 weeks through Week 88 (n=111) or were withdrawn from therapy (n=225). At Week 52 and Week 104 (16 weeks after last Skyrizi dose), 87.4% and 81.1% of the subjects continuing Skyrizi achieved sPGA of clear or almost clear compared with 61.3% and 7.1% for those withdrawn from Skyrizi. sPGA clear response rates at Week 52 and Week 104 were: 64.9% and 63.1% for subjects continuing Skyrizi compared with 30.7% and 2.2% for those withdrawn from Skyrizi. Among subjects who achieved sPGA of clear or almost clear at Week 28 and relapsed (sPGA ≥3) following withdrawal from Skyrizi, 83.7% (128/153) regained sPGA of clear or almost clear response after 16 weeks of retreatment.

Quality of Life/Patient-Reported Outcomes

Significantly more subjects treated with Skyrizi achieved a Dermatology Life Quality Index (DLQI) score of 0 or 1 [no impact on health-related quality of life] at Week 16 compared with placebo, adalimumab, or ustekinumab (Table 4). Improvement in health-related quality of life continued through Week 52 (ULTIMMA-1 and ULTIMMA-2).

Table 4. Health-related Quality of Life in ULTIMMA-1, ULTIMMA-2, and IMMVENT

	ULTIMMA - 1			ULTIMMA - 2			IMMVENT	
	Skyrizi (N= 304) n (%)	Ustekinumab (N = 100) n (%)	Placebo (N = 102) n (%)	Skyrizi (N = 294) n (%)	Ustekinumab (N = 99) n (%)	Placebo (N = 98) n (%)	Skyrizi (N= 301) n (%)	Adalimumab (N= 304) n (%)
DLQI 0 or 1								
Week 16	200 (65.8)	43 (43.0)	8 (7.8)	196 (66.7)	46 (46.5)	4 (4.1)	198 (65.8)	148 (48.7)
Week 52	229 (75.3)	47 (47.0)	--	208 (70.7)	44 (44.4)	--	--	--
All comparisons of Skyrizi versus ustekinumab, adalimumab and placebo achieved p < 0.001								

In ULTIMMA-1 and ULTIMMA-2, significantly greater improvements in psoriasis symptoms (itch, pain, redness and burning, as measured by the Psoriasis Symptom Score [PSS]) were demonstrated with Skyrizi compared with placebo at Week 16. A significantly greater proportion of subjects on Skyrizi achieved a PSS of 0 (symptom-

free) at Week 16 compared with ustekinumab and with placebo. By Week 52, 55.7% (333/598) of subjects on Skyrizi reported no itch, pain, redness or burning.

Anxiety and depression, as measured by the Hospital Anxiety and Depression Scale (HADS) improved in the Skyrizi group at Week 16 compared with those receiving placebo in ULTIMMA-1 and ULTIMMA-2.

A greater improvement in the Work Limitations Questionnaire (WLQ) at Week 16 was achieved in subjects receiving Skyrizi compared with those receiving adalimumab in IMMVENT.

Psoriatic Arthritis

Skyrizi has been shown to improve signs and symptoms, physical function, health-related quality of life, and the proportion of subjects with no radiographic progression in adults with active psoriatic arthritis (PsA).

The safety and efficacy of Skyrizi were assessed in 1407 subjects in 2 randomised, double-blind, placebo-controlled studies (964 in KEEPsAKE1 and 443 in KEEPsAKE2) in subjects 18 years and older with active PsA.

Subjects in these studies had a diagnosis of PsA for at least 6 months based on the Classification Criteria for Psoriatic Arthritis (CASPAR), a median duration of PsA of 4.9 years at baseline, ≥ 5 tender joints and ≥ 5 swollen joints, and active plaque psoriasis or nail psoriasis at baseline. 55.9% of subjects had ≥3% BSA with active plaque psoriasis. 63.4% and 27.9% of subjects had enthesitis and dactylitis, respectively. In KEEPsAKE1 where nail psoriasis was further assessed, 67.3% had nail psoriasis.

In KEEPsAKE1, all subjects had a previous inadequate response or intolerance to non-biologic DMARD therapy and were biologic naïve. In KEEPsAKE2, 53.5% of subjects had a previous inadequate response or intolerance to non-biologic DMARD therapy and 46.5% of subjects had a previous inadequate response or intolerance to biologic therapy.

In both studies, subjects were randomised to receive Skyrizi 150 mg or placebo at Weeks 0, 4, and 16. Starting from Week 28, all subjects received Skyrizi every 12 weeks. Both studies include a long-term extension for up to an additional 204 weeks. 59.6% of subjects from both studies were receiving concomitant methotrexate (MTX), 11.6% were receiving concomitant non-biologic DMARDs other than MTX, and 28.9% were receiving Skyrizi monotherapy.

For both studies, the primary endpoint was the proportion of subjects who achieved an American College of Rheumatology (ACR) 20 response at Week 24.

Clinical Response

In both studies, treatment with Skyrizi resulted in significant improvement in measures of disease activity compared to placebo at Week 24. See Table 5 for key efficacy results.

Time to onset of efficacy was rapid across measures with greater responses versus placebo seen as early as Week 4 in 25.7% and 19.6% of subjects for ACR20 for KEEPsAKE1 and KEEPsAKE2, respectively.

Treatment with Skyrizi resulted in statistically significant improvement in dactylitis and enthesitis in patients with pre-existing dactylitis or enthesitis (see Table 5).

In both studies, similar responses were seen regardless of concomitant non-biologic DMARD use, number of prior non biologic DMARDs, age, gender, race, and BMI. In KEEPsAKE2, responses were seen regardless of prior biologic therapy.

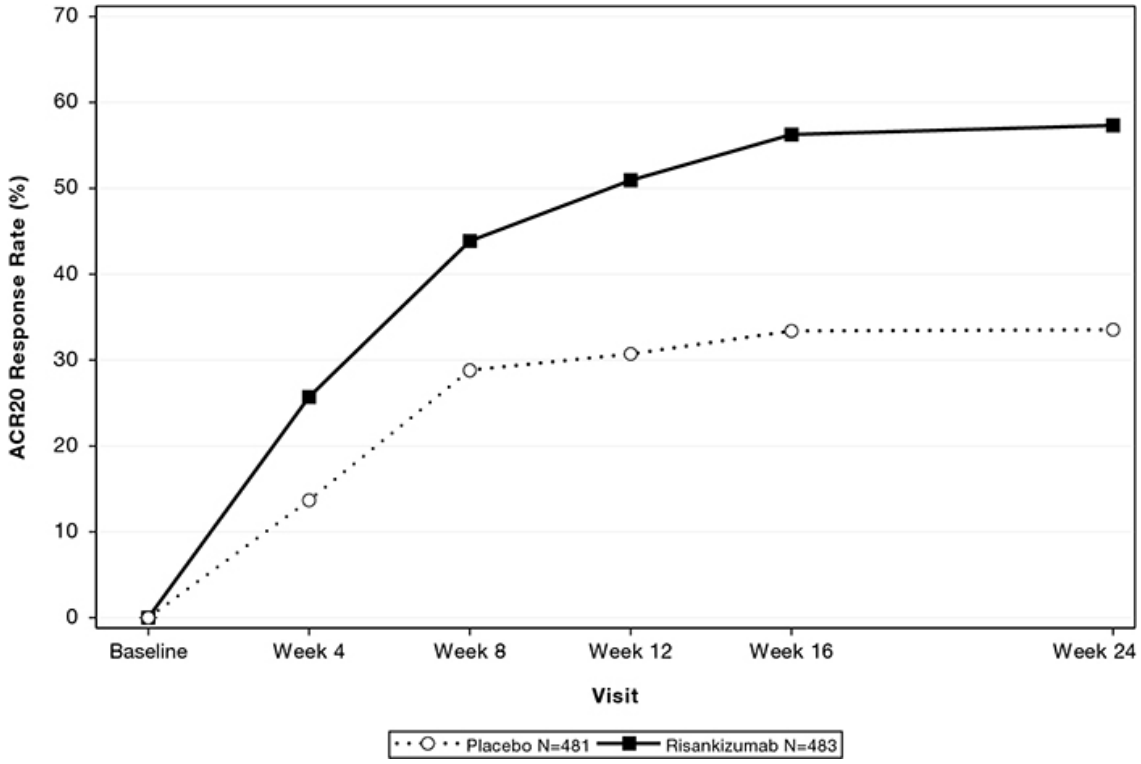
Table 5. Efficacy Results in Studies KEEPsAKE1 and KEEPsAKE2

	KEEPsAKE1		**KEEPsAKE2**	
Endpoint	**Placebo N=481 n(%)**	**Skyrizi N=483 n(%)**	**Placebo N=219 n(%)**	**Skyrizi N=224 n(%)**
ACR20 Response				
Week 16	161 (33.4)	272 (56.3)[a]	55 (25.3)	108 (48.3)[a]
Week 24	161 (33.5)	277 (57.3)[a]	58 (26.5)	115 (51.3)[a]
Week 52*	-	338/433 (78.1)	-	131/191 (68.6)
ACR50 Response				
Week 24	54 (11.3)	162 (33.4)[b]	20 (9.3)	59 (26.3)[b]
Week 52*	-	209/435 (48.0)	-	72/192 (37.5)
ACR70 Response				
Week 24	23 (4.7)	74 (15.3)[b]	13 (5.9)	27 (12.0)[c]
Week 52*	-	125/437 (28.6)	-	37/192 (19.3)
Resolution of Enthesitis (LEI=0)				
Week 24*	156/448 (34.8)[d]	215/444 (48.4)[a, d]	-	-
Week 52*	-	244/393 (62.1)[d]	-	-
Resolution of Dactylitis (LDI=0)				
Week 24*	104/204 (51.0)[e]	128/188 (68.1)[a, e]	-	-
Week 52*	-	143/171 (83.6)[e]	-	-
Minimal Disease Activity (MDA) Response				
Week 24	49 (10.2)	121 (25.0)[a]	25 (11.4)	57 (25.6)[a]
Week 52*	-	183/444 (41.2)	-	61/197 (31.0)
* Data are shown for available subjects in the format of n/N observed (%).				

[a] Multiplicity-controlled p≤0.001 Skyrizi vs placebo comparison.
[b] Nominal p≤0.001 Skyrizi vs placebo comparison.
[c] Nominal p≤0.05 Skyrizi vs placebo comparison.
[d] Summarized from pooled data from KEEPSAKE1 and KEEPSAKE2 for subjects with baseline LEI >0.
[e] Summarized from pooled data from KEEPSAKE1 and KEEPSAKE2 for subjects with baseline LDI >0.

The percent of subjects achieving ACR20 responses in study KEEPsAKE1 through week 24 is shown in Figure 3.

Figure 3. Percent of Subjects Achieving ACR20 Responses in Study KEEPsAKE1 through Week 24



In both studies, the proportion of subjects achieving modified PsA Response Criteria (PsARC) at Week 24 was higher in subjects receiving Skyrizi compared with placebo. In addition, subjects receiving Skyrizi achieved greater improvement in Disease Activity Score (28 joints) using CRP (DAS28-CRP) compared with placebo at Week 24 in both studies. Improvements were maintained through Week 52 for PsARC and DAS28-CRP in both studies.

In both studies, improvements were shown in all components of the ACR scores including subject's assessment of pain (see Table 6).

Table 6. Mean Change from Baseline in ACR Components

	KEEPsAKE1		KEEPsAKE2	
	Placebo (N=481)	**Skyrizi (N=483)**	**Placebo (N=219)**	**Skyrizi (N=224)**
Number of Swollen Joints (0-66)				
Baseline	12.2	12.1	13.6	13.0
Mean change at Week 24	-6.2	-8.4[a]	-5.5	-8.6[a]
Number of Tender Joints (0-68)				
Baseline	20.5	20.8	22.3	22.8
Mean change at Week 24	-7.1	-11.2[a]	-6.3	-11.6[a]
Patient's Assessment of Pain[c]				
Baseline	57.1	57.1	57.0	55.0
Mean change at Week 24	-10.2	-21.0[a]	-6.5	-14.7[a]
Patient's Global Assessment[c]				
Baseline	57.4	57.9	56.2	56.2
Mean change at Week 24	-10.5	-21.6[a]	-7.7	-16.5[a]
Physician Global Assessment[c]				
Baseline	62.4	61.3	60.7	63.0
Mean change at Week 24	-21.1	-33.9[a]	-19.3	-32.4[a]
Health Assessment Questionnaire - Disability Index (HAQ-DI)[d]				
Baseline	1.17	1.15	1.13	1.10
Mean change at Week 24	-0.11	-0.31[b]	-0.05	-0.22[b]
hs-CRP (mg/L)				
Baseline	11.33	11.88	8.16	7.45
Mean change at Week 24	-0.20	-4.32[a]	0.25	-1.14

[a] Nominal p≤0.001 Skyrizi vs placebo comparison
[b] Multiplicity-controlled p≤0.001 Skyrizi vs placebo comparison
[c] Assessment based on Visual Analog Scale (100 mm) with the left end indicating "no pain" (for patient's assessment of pain), "very well" (for patient global assessment), or "no arthritis activity" (for physician global assessment) and the right end indicating "the worst possible pain" (for patient assessment of pain), "poor" (for patient global assessment), or "extremely active arthritis (for physician global assessment).
[d] Disability Index of the Health Assessment Questionnaire; 0 = no difficulty to 3 = inability to perform, measures the patient's ability to perform the following: dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living

Treatment with Skyrizi resulted in statistically significant improvement in the skin manifestations of psoriasis in subjects with psoriatic arthritis.

Treatment with Skyrizi resulted in statistically significant improvement in nail psoriasis as measured by modified Nail Psoriasis Severity Index (mNAPSI) and the 5-point Physician's Global Assessment of Fingernail Psoriasis (PGA-F) in subjects

with nail psoriasis at baseline (67.3%) in KEEPsAKE1. This improvement was maintained through Week 52 (see Table 7).

Table 7. Nail Psoriasis Efficacy Results in KEEPsAKE1

	Placebo N=338	Skyrizi N=309
mNAPSI change from baseline[a]		
Week 24	-5.57	-9.76[b]
Week 52	-	-13.64
PGA-F change from baseline[a]		
Week 24	-0.4	-0.8[b]
Week 52	-	-1.2
PGA-F clear/minimal and ≥2-grade improvement[c]		
Week 24 n (%)	30 (15.9)	71 (37.8)[d]
Week 52 (n) (%)	-	105 (58.0)

[a] Summarised for subjects with baseline nail psoriasis (Placebo N=338; Skyrizi N=309; at Week 52, for mNAPSI, observed Skyrizi N=290, for PGA-F, observed Skyrizi N=291.
[b] Multiplicity-controlled p≤0.001 Skyrizi vs placebo comparison.
[c] Summarised for subjects with nail psoriasis and a PGA-F overall global assessment score of 'Mild', 'Moderate' or 'Severe' at Baseline (Placebo N=190; Skyrizi N=188, at Week 52 observed Skyrizi N=181).
[d] Nominal p≤0.001 Skyrizi vs placebo comparison.

Radiographic Response

In Study KEEPsAKE1, inhibition of progression of structural damage was assessed radiographically and expressed as the change in modified Total Sharp Score (mTSS) at Week 24, compared with baseline. The mTSS score was modified for psoriatic arthritis by addition of hand distal interphalangeal (DIP) joints. Skyrizi numerically reduced the mean progression of structural damage at Week 24 compared with placebo (mean change from baseline in mTSS score was 0.23 in the Skyrizi group compared with 0.32 in the placebo group [not statistically significant]). The proportion of subjects with no radiographic progression (defined as a change from baseline in mTSS ≤ 0) was higher with Skyrizi (92.4%) compared with placebo (87.7%) at Week 24 (nominal p-value = 0.016). This response was maintained through Week 52.

Physical Function and Health Related Quality of Life

In KEEPsAKE1 and KEEPsAKE2, physical function and disability were assessed by the Health Assessment Questionnaire-Disability Index (HAQ-DI), 36-Item Short Form

Health Survey (SF-36) V2. Fatigue was assessed using Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-Fatigue).

In KEEPsAKE 1, subjects treated with Skyrizi showed statistically significant improvement from baseline in physical function as assessed by HAQ-DI at Week 24 (-0.31) compared with placebo (-0.11) (p-value ≤0.001). In KEEPsAKE 2, subjects treated with Skyrizi showed statistically significant improvement from baseline in HAQ-DI at Week 24 (-0.22) compared with placebo (-0.05) (p-value ≤0.001). In both studies, a greater proportion of subjects achieved a clinically meaningful reduction of at least 0.35 in HAQ-DI score from baseline in the Skyrizi group compared with placebo at Week 24. Improvements in physical function were maintained through Week 52 in both studies.

In both studies at Week 24, subjects treated with Skyrizi also demonstrated significant improvements in the SF-36 V2 physical component summary scores and in FACIT-Fatigue scores compared with subjects who received placebo. Improvements in SF-36 physical component as well as FACIT-Fatigue scores were maintained through Week 52 in both studies.

At baseline, psoriatic spondylitis was reported in 19.6% and 19.6% of subjects in KEEPsAKE1 and KEEPsAKE2, respectively. Subjects with psoriatic spondylitis who were treated with Skyrizi showed improvements from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity (ASDAS) scores compared with placebo at Week 24. Improvements were maintained through Week 52.

5.2 Pharmacokinetic Properties

The pharmacokinetics of risankizumab was similar between subjects with plaque psoriasis and psoriatic arthritis.

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 1200 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 the dosing regimen in subjects with psoriasis (150 mg at Week 0, Week 4, and every 12 weeks thereafter), estimated steady-state peak and trough plasma concentrations are 12 and 2 micrograms/mL, respectively.

Bioequivalence was demonstrated between a single risankizumab 150 mg/mL injection and two risankizumab 75 mg/0.83 mL injections in pre-filled syringes. Bioequivalence was also demonstrated between risankizumab 150mg/mL pre-filled syringe and pre-filled pen.

Distribution

In a typical 90 kg subject with psoriasis, the steady-state volume of distribution (Vss) was 11.2L, indicating that the distribution of risankizumab is primarily confined to the vascular and interstitial spaces.

Metabolism

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.

Excretion

The systemic clearance (CL) of risankizumab was 0.31 L/day and terminal elimination half-life was 28 days for a typical 90 kg subject 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.

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 used by some subjects with plaque psoriasis during the clinical studies. Similar lack of impact was observed based on population pharmacokinetic analyses in psoriatic arthritis (*see* **4.4 Interactions with other medicines and other forms of interactions**).

Paediatrics

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

Use in the Elderly

Of the 2234 subjects with plaque psoriasis exposed to Skyrizi, 243 were 65 years or older and 24 subjects were 75 years or older. No overall differences in risankizumab exposure, safety and effectiveness were observed between older and younger subjects who received Skyrizi (*see* **4.4 Special warnings and precautions for use - Use in the Elderly**).

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 or psoriatic arthritis.

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 (*see* **4.4 Special warnings and precautions for use - Use in hepatic impairment, use in renal impairment**).

Body Weight

Risankizumab clearance and volume of distribution increase as body weight increases. However, clinically meaningful changes in efficacy and safety of risankizumab were not observed with increased body weight, therefore no dose adjustment is necessary based on body weight.

Gender or Race

The clearance of risankizumab was not significantly influenced by gender or race in adult subjects with plaque psoriasis or psoriatic arthritis. 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

Non-clinical 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]).

Genotoxicity

No data available.

Mutagenicity

Mutagenicity studies have not been conducted with Skyrizi.

Carcinogenicity

Carcinogenicity studies have not been conducted with Skyrizi. 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.

Animal pharmacology and/ or toxicology

In a 26-week toxicology study with weekly subcutaneous doses of up 50 mg/kg, no adverse effects were observed in male and female cynomolgus monkeys at exposures of about 70 times higher than the clinical exposure at the MRHD.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Each Skyrizi 75 mg/0.83 mL pre-filled syringe contains sodium succinate hexahydrate, succinic acid, sorbitol, polysorbate 20 and water for injections.

Each Skyrizi 150 mg/mL pre-filled syringe or pre-filled pen contains sodium acetate trihydrate, glacial acetic acid, trehalose dihydrate, polysorbate 20 and 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

24 months.

6.4 Special Precautions for Storage

Store at 2°C to 8°C. Refrigerate. Do not freeze. Keep in the outer carton in order to protect from light.

Skyrizi 150 mg/mL pre-filled pen or pre-filled syringe may be stored out of the refrigerator (up to a maximum of 25°C) for up to 24 hours in the original carton to protect from light.

6.5 Nature and Contents of Container

Skyrizi is supplied as a sterile solution for subcutaneous injection.

Skyrizi 75 mg/0.83 mL pre-filled syringe:

Each pre-filled syringe with needle guard contains 75 mg of risankizumab in 0.83 mL in the following packaging configuration:

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

Skyrizi 150 mg/mL pre-filled syringe:

Each pre-filled syringe with needle guard contains 150 mg of risankizumab in 1.0 mL in the following packaging configuration:

- Each carton contains 1 pre-filled syringe.

Skyrizi 150 mg/mL pre-filled pen:

- Each carton contains 1 pre-filled pen

6.6 Special Precautions for Disposal

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

6.7 Physicochemical Properties

CAS number

CAS Registry Number: 1612838-76-2

7 MEDICINE SCHEDULE

Prescription only Medicine

8 SPONSOR

AbbVie Limited

6th Floor, 156-158 Victoria St

Wellington, 6011

NEW ZEALAND

PH: 0800 900 030

9 DATE OF FIRST APPROVAL

24 September 2020

10 DATE OF REVISION

21 June 2022

Summary table of changes

Section changed	Summary of new information
4.4	Addition of Hypersensitivity
4.8	Addition of Post marketing experience