▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PI – SKYRIZI®
(RISANKIZUMAB) – SOLUTION FOR SUBCUTANEOUS INJECTION

1 NAME OF THE MEDICINE

Risankizumab

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.

Each 360 mg/ 2.4 mL pre-filled cartridge contains 360 mg risankizumab in 2.4 mL solution.

Each 600 mg/ 10 mL single-dose vial contains 600 mg risankizumab in 10 mL solution.

SKYRIZI (risankizumab), an interleukin-23 blocker, is a humanised immunoglobin G1 (IgG1) monoclonal antibody. Risankizumab is produced in a mammalian cell line using recombinant DNA technology.

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 contain less than 1 mmol sodium (23 mg) per 150 mg dose and are essentially sodium free.

SKYRIZI 360 mg/2.4 mL contains less than 1 mmol sodium (23mg) per 360 mg dose and is essentially sodium-free.

SKYRIZI 600 mg/ 10 mL contains less than 1 mmol sodium (23 mg) per 600 mg dose and is essentially sodium free.

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

3 PHARMACEUTICAL FORM

Solution for injection in a pre-filled syringe (75 mg/0.83 mL). The solution is colourless to slightly yellow and clear to slightly opalescent. The solution may contain tiny white or clear particles.

Solution for injection in a pre-filled syringe or pre-filled pen (150 mg/ mL). The solution is colourless to yellow and clear to slightly opalescent. The solution may contain tiny white or clear particles.

Solution for subcutaneous (S.C.) injection in a pre-filled cartridge (360 mg/ 2.4 mL) with an on-body injector. The solution is colourless to yellow and clear to slightly opalescent. The solution may contain tiny white or clear particles.

Concentrate solution for Intravenous (I.V.) Infusion single dose vial (600 mg/ 10 mL). The solution is colourless to slightly yellow and clear to slightly opalescent. The solution may contain tiny white or clear particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Psoriasis

SKYRIZI is indicated for the treatment of moderate to severe plaque psoriasis in adults (18 years or older) who are candidates for phototherapy or systemic therapy.

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 anti-rheumatic drugs (DMARDs).

SKYRIZI may be used with or without conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs).

Crohn's Disease

SKYRIZI is indicated for the treatment of moderate to severe Crohn's disease in adult patients, who have an inadequate response, a lost response, an intolerance or a contra-indication to either conventional or biologic therapy.

4.2 Dose and method of administration

Visually inspect SKYRIZI for particulate matter and discolouration prior to administration.

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

Psoriasis & Psoriatic Arthritis

SKYRIZI is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of the indicated conditions.

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.

The injection should be administered in the thigh or abdomen. 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.

If using SKYRIZI 75 mg/0.83 mL, patients should be instructed to inject 2 pre-filled syringes for the full 150 mg dose. For each dose, the injections should be administered at different anatomic locations (such as thighs or abdomen).

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, for 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.

SKYRIZI pre-filled syringe and pre-filled pen are for single use in one patient only. Discard any residue.

Crohn's Disease

For the treatment of Crohn's disease, obtain liver enzymes and bilirubin levels prior to initiating treatment with SKYRIZI (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

SKYRIZI induction dose is intended for use under the guidance and supervision of a healthcare professional.

The recommended dose is 600 mg administered by I.V infusion at Week 0, Week 4 and Week 8 (induction), followed by 360 mg administered by subcutaneous (S.C) injection at Week 12 and every 8 weeks thereafter (maintenance).

SKYRIZI must be kept protected from light in the original packaging, in a refrigerator between 2°C to 8°C. SKYRIZI must not be frozen at any time.

Discard after use. Do not reuse.

Preparation and Administration Instructions

Intravenous Induction -Method of Administration

1. SKYRIZI should be prepared by a healthcare professional using aseptic technique.

2. Prior to administration, SKYRIZI for intravenous administration must be diluted into an intravenous infusion bag or glass bottle containing 5% dextrose in water (D5W) or 0.9% saline (600 mg/ 10 mL in 100 mL, or 250 mL or 500 mL) to a final drug concentration of approximately 1.2 mg/mL to 6 mg/mL.

3. Prior to the start of the intravenous infusion, the content of the infusion bag or glass bottle should be at room temperature. The utilisation of a 0.2 micrometre infusion in-line filter is not mandatory.

4. Infuse the diluted solution over a period of at least one hour; but not more than 4 hours.

5. SKYRIZI vial solution should not be administered concomitantly in the same intravenous line with other medicinal products..

Handling and storage of the vial and diluted solution

- The solution in the vial and dilutions should not be shaken.
- The prepared infusion should be used immediately. If not used immediately, the diluted SKYRIZI solution can be stored (protected from light) for up to 20 hours between 2°C to 8°C.
- Immediately after preparation or removal from refrigeration, the diluted SKYRIZI solution can be stored at room temperature (protected from sunlight) for 4 hours (cumulative time from start of dilution to start of infusion). Do not freeze.
- Infusion time should be limited to 4 hours at room temperature (15^{o}C to 30^{o}C).
- Exposure to indoor light is acceptable during room temperature storage and administration.
- Each vial is for single use only and any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Subcutaneous Maintenance-Method of Administration

Patients should read the Instructions for Use before administration. The SKYRIZI Instructions for Use contains more detailed instructions on the preparation and administration of SKYRIZI.

Administer SKYRIZI pre-filled cartridge with on-body injector subcutaneously.

Do not inject into areas where the skin is tender, bruised, erythematous, indurated or affected by any lesions.

Patients may self-inject SKYRIZI using the pre-filled cartridge with on-body injector after training in subcutaneous injection technique. Provide proper training to patients and/or caregivers on the subcutaneous injection technique of SKYRIZI.

Before using the prefilled cartridge with on-body injector, remove the carton from the refrigerator and allow to reach room temperature out of direct sunlight (45 to 90 minutes) without removing the on-body injector or pre-filled cartridge 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.

Clinically important active infections.

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 (TB)

Prior to initiating treatment with SKYRIZI, patients should be evaluated for TB infection. SKYRIZI must not be given to patients with active TB. Patients receiving SKYRIZI should be monitored for signs and symptoms of active TB. Anti-TB therapy should be considered prior

to initiating SKYRIZI in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed.

Across the Phase 3 psoriasis clinical studies, of the 72 subjects with latent 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 SKYRIZI.

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, administration of risankizumab should be discontinued immediately and appropriate therapy initiated.

Hepatotoxicity in Treatment of Crohn's Disease

A serious adverse reaction of drug-induced liver injury was reported in a patient with Crohn's disease (ALT 54x ULN, AST 30x ULN, and total bilirubin 2.2x ULN) following two intravenous doses of SKYRIZI 600 mg in conjunction with a rash that required hospitalisation. The liver test abnormalities resolved following administration of steroids. SKYRIZI was subsequently discontinued.

For the treatment of Crohn's disease, evaluate liver enzymes and bilirubin at baseline, and during induction at least up to 12 weeks of treatment. Monitor thereafter according to routine patient management.

Consider other treatment options in patients with evidence of liver cirrhosis. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. Interrupt treatment if drug-induced liver injury is suspected, until this diagnosis is excluded. Instruct patients to seek immediate medical attention if they experience symptoms suggestive of hepatic dysfunction.

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**). There is limited information in subjects aged ≥ 65 years.

Paediatric use

The safety and efficacy of SKYRIZI in patients younger than 18 years 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, psoriatic arthritis and Crohn's disease, risankizumab is not expected to 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

Effects on fertility

Studies in male cynomolgus monkeys at doses of up to 50 mg/kg/week (about 70 times the clinical exposures at the maximum recommended human dose (MRHD) for psoriasis (150mg S.C.) and about 7 times the clinical exposure during induction (600 mg I.V. every 4 weeks) and about 28 times the clinical exposure during maintenance, (360 mg S.C. every 8 weeks), in Crohn's disease) with risankizumab did not indicate direct or indirect harmful effects on male fertility. The effects of risankizumab were not directly assessed in a dedicated fertility study in female animals. In the 26-week repeat dose toxicology study, histopathology evaluation of reproductive organs from both male and female cynomolgus monkeys did not show any adverse findings.

Use in 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 or 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 99 times the clinical exposure at the MRHD for psoriasis (150 mg S.C.). For Crohn's disease, these doses produced exposures 10 times the clinical exposures during induction at a dose of 600 mg I.V. every 4 weeks and 39 times the clinical exposures for maintenance when given 360 mg S.C. every 8 weeks. No drug-related fetal/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 17-86% 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.

Use in lactation

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 SKYRIZI therapy, taking into account, the benefit of breast-feeding to the child and the benefit of SKYRIZI therapy to the woman.

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 summarises the adverse reactions that occurred at ≥ 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

Psoriasis

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

A total of 1091 patients had received at least 1 year of risankizumab treatment at the proposed dose of 150 mg up to the time of submission. The frequency of adverse reactions was similar over the long term as that observed during the first 16 weeks of treatment. In ULTIMMA-1 and ULTIMMA-2, 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.

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.

Crohn's Disease

Infections

The majority of infections were non-serious and mild to moderate in severity and did not lead to discontinuation of SKYRIZI.

Induction studies

The rate of infections in the pooled data from the 12-week induction studies was 83.3 events per 100 subject-years in subjects treated with SKYRIZI 600 mg I.V compared to 117.7 events per 100 subject-years in placebo. The rate of serious infections was 3.4 events per 100 subject-years in subjects treated with SKYRIZI 600 mg I.V compared to 16.7 events per 100 subject-years in placebo.

Maintenance study – Long term safety

The rate of infections in the 52-week maintenance study was 57.7 events per 100 subject-years in subjects treated with SKYRIZI 360 mg S.C after SKYRIZI induction compared to 76.0 events per 100 subject-years in subjects who received placebo after SKYRIZI induction. The rate of serious infections was 6.0 events per 100 subject-years in subjects treated with SKYRIZI 360 mg S.C after SKYRIZI induction compared to 5.0 events per 100 subject-years in subjects who received placebo after SKYRIZI induction.

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.

Among the few subjects (approximately 1%; 7/1 000 at Week 16 and 6/598 at Week 52) with high antibody titres (>128), clinical response appeared to be reduced.

Psoriatic Arthritis

For subjects treated with SKYRIZI at the recommended clinical dose for up to 28 weeks in Phase 3 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.

Crohn's Disease

For subjects treated with SKYRIZI at the recommended I.V induction and S.C maintenance doses for up to 64 weeks in CD clinical trials, treatment-emergent anti-drug antibodies and neutralising antibodies were detected in 3.4% (2/58) and 0% (0/58) of evaluated subjects, respectively.

Across all approved indications, available data suggest there are no clear associations between development of antibodies to risankizumab, including neutralising antibodies, on 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 Australia, healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems. In New Zealand, healthcare professionals are asked to report any suspected adverse reactions at 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 information on the management of overdose in Australia contact the Poisons Information Centre on 131126.

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, reductions from baseline were 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. These results are based on exploratory analysis of limited pharmacodynamic data. The relationship between these pharmacodynamic activities and the mechanism(s) by which risankizumab exerts its clinical effects is unknown.

In a Phase 2 study of subjects with Crohn's disease, expression of genes associated with the IL-23/Th17 axis was decreased in gut tissue after multiple doses of risankizumab. Reductions in faecal calprotectin (FCP), serum C reactive protein (CRP) and IL-22 were also observed after multiple doses in Phase 3 induction studies in Crohn's patients. Decreases in FCP, CRP and serum IL-22 were maintained out to week 52 of the maintenance study.

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 and Crohn's disease. IL-23 is up-regulated in lesional skin in comparison to non-lesional skin of patients with plaque psoriasis. IL-23 is elevated in inflamed colonic mucosa from Crohn's patients compared to colonic mucosa from healthy individuals. 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

Psoriasis

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 and were candidates for systemic therapy or phototherapy.

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, 31.3% of subjects had received prior phototherapy, 9.9% of subjects had received prior 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 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.

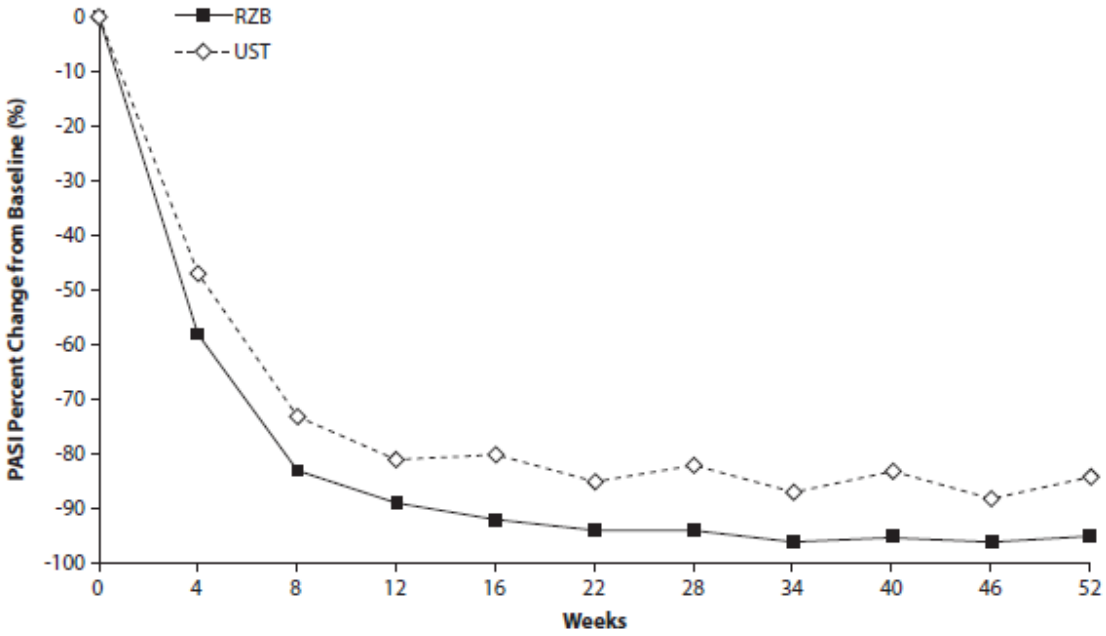
Table 2. Efficacy Results in Adults with Plaque Psoriasis in ULTIMMA-1 and ULTIMMA-2

	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 in ULTIMMA-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 randomised 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) who did not receive prophylaxis during the study, none developed active TB during the mean follow-up of 55 weeks on SKYRIZI.

IMMVENT

IMMVENT enrolled 605 subjects (301 randomised 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 fortnightly 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).

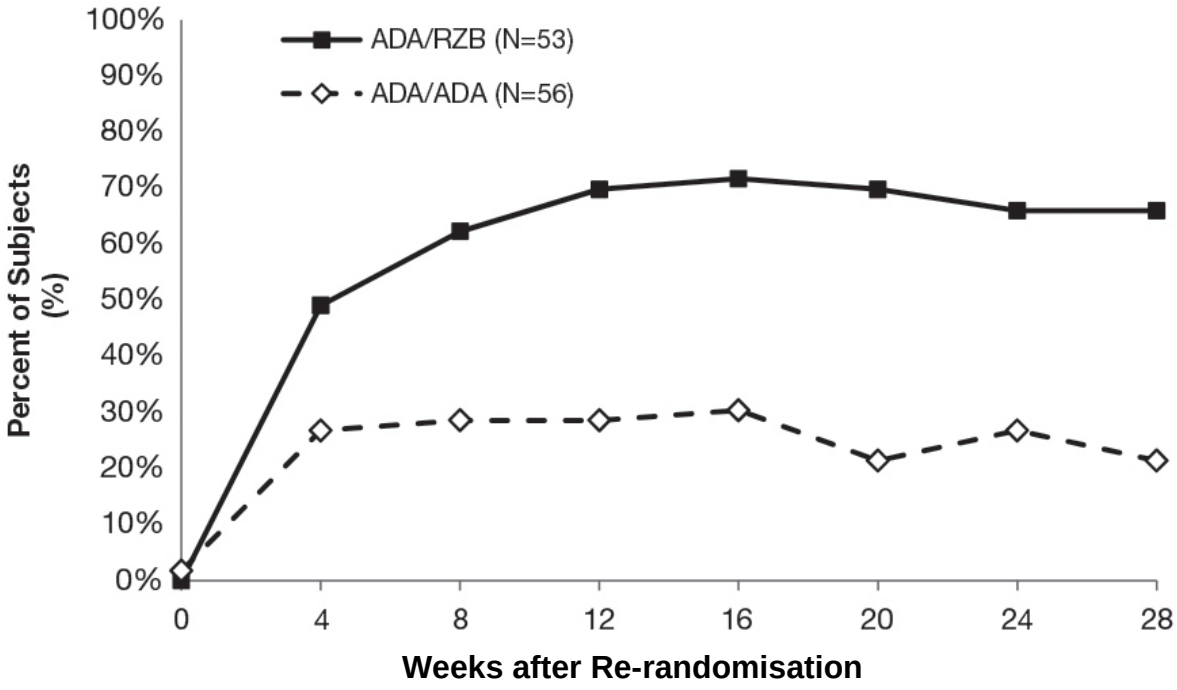
Table 3. Efficacy Results at Week 16 in Adults with Plaque Psoriasis in IMMVENT

	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 wash out 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 to 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 to 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

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 csDMARD therapy and were biologic disease-modifying anti-rheumatic drug (bDMARD) naïve. In KEEPsAKE2, 53.5% of subjects had a previous inadequate response or intolerance to csDMARD therapy and 46.5% of subjects had a previous inadequate response or intolerance to one or two bDMARDs (anti-TNFs, abatacept, rituximab).

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. At baseline 59.6% of subjects from both studies were receiving concomitant methotrexate (MTX), 11.6% were receiving concomitant csDMARDs other than MTX including 5.3% on leflunomide and 1.9% on apremilast, and 28.9% were receiving no concomitant csDMARD.

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 at Week 24 (see Table 5).

In both studies, efficacy was observed regardless of concomitant csDMARD use, number of prior csDMARDs, age, gender, race, and BMI. In KEEPsAKE2, responses were seen regardless of prior bDMARD 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*	-	63/91 (69.2)	-	68/104 (65.4)
ACR50 Response				
Week 24	54 (11.3)	162 (33.4) [b]	20 (9.3)	59 (26.3) [b]
Week 52*	-	37/92 (40.2)	-	37/104 (35.6)
ACR70 Response				
Week 24	23 (4.7)	74 (15.3) [b]	13 (5.9)	27 (12.0) [c]
Week 52*	-	23/92 (25.0)	-	19/104 (18.3)
Resolution of Enthesitis (LEI=0)				
Week 24*	156/448 (34.8)[d]	215/444 (48.4) [a, d]	-	-
Week 52*	-	73/127 (57.5) [d]	-	-
Resolution of Dactylitis (LDI=0)				
Week 24*	104/204 (51.0)[e]	128/188 (68.1) [a, e]	-	-
Week 52*	-	41/53 (77.4) [e]	-	-
Minimal Disease Activity (MDA) Response				
Week 24	49 (10.2)	121 (25.0) [a]	25 (11.4)	57 (25.6) [a]
Week 52*	-	32/95 (33.7)	-	33/105 (31.4)

* 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

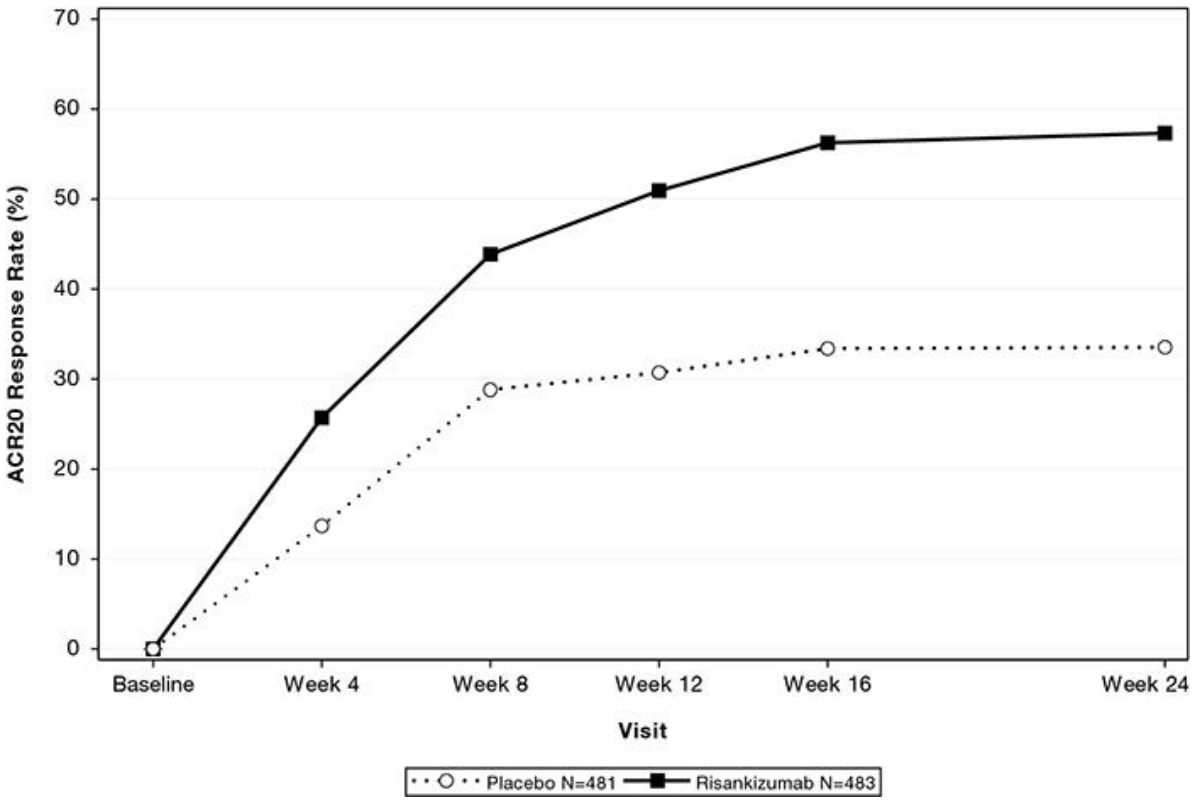
c. nominal p≤0.05 SKYRIZI vs placebo comparison

d. Summarised from pooled data from KEEPsAKE1 and KEEPsAKE2 for subjects with baseline LEI >0.

e. Summarised 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, improvements were shown in all components of the ACR scores including subject's assessment of pain. (see Table 6). These responses were maintained through week 52.

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 [a]	-6.2	-8.4	-5.5	-8.6
Number of Tender Joints (0-68)				
Baseline	20.5	20.8	22.3	22.8
Mean change at Week 24 [a]	-7.1	-11.2	-6.3	-11.6
Patient's Assessment of Pain [c]				
Baseline	57.1	57.1	57.0	55.0
Mean change at Week 24 [a]	-10.2	-21.0	-6.5	-14.7
Patient's Global Assessment [c]				
Baseline	57.4	57.9	56.2	56.2
Mean change at Week 24 [a]	-10.5	-21.6	-7.7	-16.5

Physician Global Assessment [c]				
Baseline	62.4	61.3	60.7	63.0
Mean change at Week 24 [a]	-21.1	-33.9	-19.3	-32.4
Health Assessment Questionnaire - Disability Index (HAQ-DI) [d]				
Baseline	1.17	1.15	1.13	1.10
Mean change at Week 24 [a]	-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 [a]	-0.20	-4.32	0.25	-1.14

[a] Data shown are least squares means.
[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 (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	-	-11.65
PGA-F change from baseline [c]		
Week 24	-0.4	-0.8 [b]
Week 52	-	-1.2

[a.] Summarised for subjects with baseline nail psoriasis (Placebo N=338; SKYRIZI N=309; at week 52, observed SKYRIZI N = 65).
[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).

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).

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 KEEPsAKE1, 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 KEEPsAKE2, 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). Improvements in physical function were maintained through Week 52 in both studies.

In both studies at Week 24, subjects treated with SKYRIZI demonstrated 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.

Crohn's Disease

SKYRIZI has been shown to improve signs and symptoms, as well as decrease mucosal inflammation as measured by endoscopy.

The efficacy and safety of SKYRIZI was assessed in 1419 subjects with moderate to severe active Crohn's disease in three multicentre, randomised, double-blind, placebo-controlled clinical studies. Enrolled subjects were 16 years of age or older with a Crohn's Disease Activity Index (CDAI) of 220 to 450, an average daily stool frequency (SF) ≥ 4 and/or average daily abdominal pain score (APS) ≥ 2, and a Simple Endoscopic Score for CD (SES-CD) of ≥ 6, or ≥4 for isolated ileal disease, excluding the narrowing component and confirmed by a central reviewer.

There were two 12-week intravenous induction studies (ADVANCE and MOTIVATE), which included a 12-week extension period for subjects who did not achieve SF/APS clinical response (≥ 30% decrease in SF and/or ≥ 30% decrease in APS and both not worse than baseline) at Week 12. ADVANCE and MOTIVATE were followed by a 52-week subcutaneous randomised withdrawal maintenance study (FORTIFY) that enrolled subjects with SF/APS clinical response to I.V induction treatment, representing at least 64 weeks of therapy.

ADVANCE and MOTIVATE

In studies ADVANCE and MOTIVATE, subjects were randomised to receive either SKYRIZI 600 mg I.V (recommended dose), SKYRIZI 1200 mg I.V, or placebo, at Week 0, Week 4, and Week 8.

In ADVANCE, 58% (491/850) subjects had failed or were intolerant to treatment with one or more biologic therapies (prior biologic failure), and 42% (359/850) had failed or were intolerant to treatment with conventional therapy but not to biologic therapy (without prior biologic failure). In ADVANCE, among the subjects without prior biologic failure, (87%) 314/359 were naïve to biologic therapy and the remaining 13% had received biologic therapy but never failed nor demonstrated intolerance. All subjects in MOTIVATE had prior biologic failure.

The co-primary endpoints were clinical remission based on SF and APS (average daily SF ≤ 2.8 and not worse than baseline and average daily AP score ≤ 1 and not worse than baseline) at Week 12, and endoscopic response (greater than 50% decrease in SES-CD from baseline, or a decrease of at least 2 points for subjects with a baseline score of 4 and isolated ileal disease) at Week 12. In both studies, a greater proportion of subjects treated with SKYRIZI achieved clinical remission at Week 12 and endoscopic response at Week 12 compared to placebo (Table 8). Enhanced SF/APS clinical response and clinical remission were significant as early as Week 4 in subjects treated with SKYRIZI and continued to improve through Week 12.

Additional secondary endpoints measured at Week 12 included the proportion of subjects with enhanced SF/APS clinical response (with ≥ 60% decrease in average daily SF and/or ≥ 35% decrease in average daily AP score and both not worse than Baseline, and/or clinical remission), endoscopic remission (SES-CD≤ 4 at least a 2 point reduction versus Baseline and no subscore greater than 1 in any individual variable), mucosal healing (SES-CD ulcerated surface subscore of 0 in subjects with a subscore of $\geqslant$ 1 at Baseline), a decrease of least 100 points in baseline CDAI, and a CDAI < 150 at Week 12.

Table 8. Efficacy results in ADVANCE and MOTIVATE

	ADVANCE		MOTIVATE	
	Placebo I.V (N=175) %	**SKYRIZI 600 mg I.V (N=336) %**	**Placebo I.V (N=187) %**	**SKYRIZI 600 mg I.V (N=191) %**
Co-primary Endpoints				
Clinical Remission at Week 12	22%	43%[a]	19%	35%[b]
Endoscopic Response at Week 12	12%	40%[a]	11%	29%[a]
Additional Endpoints				
Enhanced SF/APS Clinical Response at Week 4	31%	46%[b]	32%	45%[c]
Enhanced SF/APS Clinical Response at Week 12	42%	63%[a]	39%	62%[a]
Endoscopic Remission at Week 12	9%	24%[a]	4%	19%[a]

a. Statistically significant under multiplicity control for SKYRIZI vs placebo comparison (p<0.001)
b. Statistically significant under multiplicity control for SKYRIZI vs placebo comparison (p≤0.01)
c. Nominal p≤ 0.01 SKYRIZI vs placebo comparison.

At Week 4, a higher proportion of subjects treated with SKYRIZI achieved a CDAI < 150 compared to placebo (ADVANCE, SKYRIZI = 18%, placebo = 10%, p ≤ 0.05; MOTIVATE, SKYRIZI = 21%, placebo = 11%, p ≤ 0.01).

At Week 12, a higher proportion of subjects treated with SKYRIZI achieved a CDAI < 150 compared to placebo (ADVANCE, SKYRIZI = 45%, placebo = 25%, p < 0.001; MOTIVATE, SKYRIZI = 42%, placebo = 20%, p < 0.001).

At Week 12, a higher proportion of subjects treated with SKYRIZI achieved a decrease of at least 100 points in baseline CDAI compared to placebo (ADVANCE, SKYRIZI = 60%, placebo = 37%, p < 0.001; MOTIVATE, SKYRIZI = 60%, placebo = 30%, p < 0.001).

At Week 12, a higher proportion of subjects treated with SKYRIZI achieved mucosal healing compared to placebo (ADVANCE, SKYRIZI = 21% (N=336), placebo = 8% (N=173), p < 0.001; MOTIVATE, SKYRIZI = 14% (N=190), placebo = 4% (N=186), p = 0.001).

At Week 12, a higher proportion of subjects treated with SKYRIZI achieved both enhanced SF/APS clinical response and endoscopic response at Week 12 compared to placebo (ADVANCE, SKYRIZI = 31%, placebo = 8%, $p < 0.001$; MOTIVATE, SKYRIZI = 21%, placebo = 7%, $p < 0.001$).

CD-related hospitalisations

Rates of CD-related hospitalisations through Week 12 were lower in subjects treated with SKYRIZI compared to placebo (ADVANCE, SKYRIZI = 3%, placebo = 12%, $p<0.001$, MOTIVATE, SKYRIZI = 3%, placebo = 11%, $p\leq0.01$).

In ADVANCE, subjects treated with SKYRIZI who had prior biologic failure and subjects without prior biologic failure achieved clinical remission and endoscopic response at higher rates than subjects who received placebo (Table 9).

Table 9. Efficacy Results at Week 12 in subjects with prior biologic failure and subjects without prior biologic failure in ADVANCE

	ADVANCE	
	Placebo I.V.	**SKYRIZI 600 mg I.V.**
Clinical Remission		
Prior biologic failure	23% (N=97)	41% (N=195)
Without prior biologic failure	21% (N=78)	48% (N=141)
Endoscopic Response		
Prior biologic failure	11% (N=97)	33% (N=195)
Without prior biologic failure	13% (N=78)	50% (N=141)

In ADVANCE, a higher proportion of subjects treated with SKYRIZI with and without prior biologic failure achieved CDAI < 150 compared to placebo (With prior biologic failure, SKYRIZI = 42%, placebo = 26%; Without prior biologic failure, SKYRIZI = 49%, placebo = 23%).

Health-related and quality of life outcomes

Health-related quality of life was assessed by the Inflammatory Bowel Disease Questionnaire (IBDQ), 36-Item Short Form Health Survey (SF-36), and the European Quality of Life 5 Dimensions (EQ-5D). Improvement in fatigue was evaluated by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale.

At Week 12 of ADVANCE and MOTIVATE, subjects treated with SKYRIZI achieved clinically meaningful improvements from baseline in IBDQ total score, all IBDQ domain scores (bowel symptoms, systemic function, emotional function, and social function), SF-36 Physical and Mental Component Summary Score, EQ-5D VAS, and FACIT-Fatigue compared to placebo.

Subjects treated with SKYRIZI experienced more improvements in work productivity compared to placebo, as assessed by the WPAI-CD questionnaire at Week 12. Specifically, greater reductions in impairment while working, overall work impairment, and activity impairment was demonstrated in ADVANCE; and greater reduction in activity impairment was demonstrated in MOTIVATE.

Compared to placebo, subjects treated with SKYRIZI achieved clinically meaningful improvements from baseline in Crohn's-related symptoms and sleep impact as assessed by Crohn's Symptom Severity (CSS) questionnaire at Week 12. These improvements were maintained in subjects treated with SKYRIZI I.V/SKYRIZI S.C in FORTIFY through Week 52.

FORTIFY

The maintenance study FORTIFY evaluated 462 subjects with SF/APS clinical response to 12 weeks of SKYRIZI I.V induction treatment in studies ADVANCE and MOTIVIATE. Subjects were randomised to continue to receive a maintenance regimen of SKYRIZI 360 mg S.C (recommended dose), or SKYRIZI 180 mg S.C every 8 weeks, or to withdraw from SKYRIZI induction and receive placebo S.C every 8 weeks for up to 52 weeks.

The co-primary endpoints were clinical remission at Week 52 and, endoscopic response at Week 52. Co-primary endpoints were also measured in subjects with and without prior biologic failure (Table 10).

Secondary endpoints measured at Week 52 included enhanced SF/APS clinical response, maintenance of clinical remission (clinical remission at Week 52 in subjects with clinical remission at Week 0), mucosal healing, endoscopic remission, deep remission (clinical remission and endoscopic remission), and CDAI < 150.

Table 10. Efficacy Results in FORTIFY at Week 52 (64 weeks from initiation of SKYRIZI induction dose

	FORTIFY	
	SKYRIZI I.V Induction/ Placebo S.C[f] (N=164) %	**SKYRIZI I.V Induction/ SKYRIZI 360 mg S.C (N=141) %**
Co-primary Endpoints		
Clinical Remission	40%	52%[a]
Prior biologic failure	34% (N=123)	48% (N=102)
Without prior biologic failure	56% (N=41)	62% (N=39)
Endoscopic Response	22%	47%[b]
Prior biologic failure	20% (N=123)	44% (N=102)
Without biologic failure	27% (N=41)	54% (N=39)
Additional Endpoints		

Enhanced SF/APS Clinical Response	49%	59%[e]
Maintenance of Clinical Remission	51% (N = 91)	69% (N = 72)[d]
Endoscopic Remission	13%	39%[c]
Mucosal Healing	10% (N=162)	31% (N=141)[c]

a. Statistically significant under multiplicity control for SKYRIZI vs placebo comparison (p≤ 0.01).
b. Statistically significant under multiplicity control for SKYRIZI vs placebo comparison (p< 0.001).
c. Nominal p < 0.001 SKYRIZI vs placebo comparison.
d. Nominal p ≤ 0.01 SKYRIZI vs placebo comparison.
e. Nominal p ≤ 0.05 SKYRIZI vs placebo comparison.
f. The induction-only group consisted of subjects who achieved clinical response to SKYRIZI induction therapy and were randomised to receive placebo in the maintenance study (FORTIFY).

Deep remission at Week 52 was observed at higher rates in subjects treated with SKYRIZI I.V/SKYRIZI S.C compared to subjects who received SKYRIZI I.V/placebo S.C (28% vs. 10%, respectively, p < 0.001).

At Week 52, a higher proportion of subjects treated with SKYRIZI I.V/SKYRIZI S.C achieved CDAI < 150 compared to SKYRIZI IV/placebo S.C (52% vs. 41%, respectively, p ≤ 0.01). A higher proportion of subjects treated with SKYRIZI I.V/SKYRIZI S.C achieved a decrease of at least 100 points in baseline CDAI score compared to subjects treated with SKYRIZI I.V/placebo S.C (62% vs. 48%, respectively, p ≤ 0.01).

91 subjects who did not demonstrate SF/APS clinical response 12 weeks after SKYRIZI induction in studies ADVANCE and MOTIVATE received subcutaneous 360 mg dose of SKYRIZI at Week 12 and Week 20. Of these subjects, 64% (58/91) achieved SF/APS clinical response at Week 24.

During FORTIFY, 30 subjects had loss of response to SKYRIZI 360 mg S.C treatment and received rescue treatment with SKYRIZI (1200 mg I.V single dose, followed by 360 mg S.C every 8 weeks). Of these subjects, 57% (17/30) achieved SF/APS clinical response at Week 52. In addition, 20% (6/30) and 34% (10/29) of subjects achieved clinical remission and endoscopic response at Week 52, respectively.

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 360 mg and 0.25 to 1 mg/kg administered subcutaneously, and 200 to 1800 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 74-89%. 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.

In subjects with Crohn's disease treated with 600 mg I.V induction dose at Weeks 0, 4, and 8 followed by 360 mg S.C maintenance dose at Week 12 and every 8 weeks thereafter, maximum median peak and trough concentrations are estimated to be 156 and 38.8 micrograms/mL respectively during the induction period (Weeks 8-12) and steady state median peak and trough concentrations are estimated to be 28.0 and 8.13 micrograms/mL respectively during the maintenance period (Weeks 40-48).

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 (V_{ss}) was 11.2L, indicating that the distribution of risankizumab is primarily confined to the vascular and interstitial spaces. In a typical 70 kg subject with Crohn's disease, V_{ss} was 7.68 L.

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. For a typical 70 kg subject with Crohn's disease, CL was 0.30 L/day and terminal elimination half-life was 21 days.

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 (such as metformin, atorvastatin, lisinopril, amlodipine, ibuprofen, acetylsalicylate and levothyroxine) used by some subjects with plaque psoriasis during the clinical studies. Similar lack of impact was observed for concomitant use of methotrexate in psoriatic arthritis and Crohn's disease based on population pharmacokinetic analyses (see **4.5 Interactions with other medicines and other forms of interactions**).

Paediatrics

The pharmacokinetics of risankizumab in paediatric subjects under 16 years of age has not been established. Risankizumab exposures in 16- to 17- year-old subjects with Crohn's disease were similar to those in adults. Age was not found to have any significant impact on risankizumab exposure based on the population pharmacokinetic analyses.

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. Of the 1574 subjects with Crohn's disease exposed to SKYRIZI, 72 were 65 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, and/or creatinine clearance, or hepatic function markers (ALT/AST/bilirubin) did not have a meaningful impact on risankizumab clearance in subjects with psoriasis, Crohn's disease 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 (Asian subjects compared to non-Asian subjects including Caucasians) in adult subjects with plaque psoriasis, Crohn's disease or psoriatic arthritis based on population pharmacokinetic analyses. No clinically meaningful differences in risankizumab exposure were observed after accounting for body weight differences in Chinese or Japanese subjects compared to Caucasian subjects in clinical pharmacokinetic studies in healthy volunteers.

5.3 Preclinical safety data

Genotoxicity

Genotoxicity studies have not been conducted with risankizumab.

Carcinogenicity

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 for psoriasis), there were no pre-neoplastic or neoplastic lesions observed. For Crohn's disease, these doses cynomolgus monkeys produced exposures about 7 times the clinical exposures during induction (600 mg I.V. every 4 weeks) and about 28 times the clinical exposures for maintenance (360 mg S.C. every 8 weeks).

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.

Each SKYRIZI 360 mg/ 2.4 mL pre-filled cartridge contains sodium acetate trihydrate, glacial acetic acid, trehalose dihydrate, polysorbate 20 and water for injections.

Each SKYRIZI 600 mg/ 10 mL single-dose vial 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

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

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

SKYRIZI 150 mg/mL pre-filled pen or pre-filled syringe and SKYRIZI 360 mg/2.4 mL pre-filled cartridge with on-body injector may be stored one time out of the refrigerator (up to a maximum of 25°C) for up to 24 hours in the original carton to protect from light.

If unopened and stored below 25°C for less than 24 hours, the SKYRIZI 150 mg/mL pen or 150 mg/mL pre-filled syringe or SKYRIZI prefilled cartridge with on-body injector may be returned to the refrigerator.

6.5 Nature and contents of container

SKYRIZI 75 mg/0.83 mL and 150 mg/mL 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 pre-filled pen contains 150 mg of risankizumab in 1.0 mL in the following packaging configuration:

- Each carton contains 1 pre-filled pen.

SKYRIZI 360 mg/2.4 mL is supplied as a solution for subcutaneous injection in a pre-filled cartridge with an on-body injector.

SKYRIZI 360 mg/2.4 mL pre-filled cartridge:

Each pre-filled cartridge contains 360 mg of risankizumab in 2.4 mL in the following packaging configuration:

- Each carton contains 1 pre-filled cartridge with 1 on-body injector.

SKYRIZI 600 mg/ 10 mL is supplied as a concentrate solution for infusion in a single-dose vial.

SKYRIZI 600 mg/ 10 mL vial:

Each vial contains 600 mg of risankizumab in 10 mL in the following packaging configuration:

- Each carton contains 1 vial.

Not all presentations may be marketed.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

CAS number

CAS Registry Number: 1612838-76-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

16 July 2019

10 DATE OF REVISION

25 August 2023

Summary table of changes

Section Changed	Summary of new information
4.2	Alternative diluent; update to the preparation and administration instructions for the Intravenous induction dose for Crohn's disease.
6.4	Addition of room temperature information for the SKYRIZI 360 mg/2.4 mL prefilled cartridge with on-body injector