SKYRIZI CONCENTRATE FOR SOLUTION FOR INFUSION 600mg/10mL

SKYRIZI SOLUTION FOR INJECTION IN PRE-FILLED CARTRIDGE WITH ON-BODY INJECTOR 360mg/2.4mL

(risankizumab)

1. PRODUCT NAME

1.1 Generic Name

risankizumab

1.2 Trade Name

SKYRIZI

2. INDICATIONS

2.1 Crohn's Disease

SKYRIZI is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy.

3. DOSAGE AND ADMINISTRATION

3.1 Recommended Dosage

Crohn's Disease

The recommended dose is 600 mg administered by intravenous (IV) infusion at Week 0, Week 4, and Week 8, followed by 360 mg administered by subcutaneous (SC) injection at Week 12, and every 8 weeks thereafter.

3.2 Missed Dose

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

3.3 Dosing in Special Populations

Pediatrics

The safety and efficacy of SKYRIZI in pediatric patients with Crohn's disease younger than 18 years of age have not yet been established.

Geriatric

No dose adjustment is required *(see* **PHARMACOLOGIC PROPERTIES***)*.

There is limited information in subjects aged ≥ 65 years.

Renal or Hepatic Impairment

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

4. CONTRAINDICATIONS

SKYRIZI is contraindicated in patients with a history of serious hypersensitivity reaction to risankizumab or any of the excipients listed in section 15.2 *(see* **WARNINGS AND PRECAUTIONS***)*.

Clinically important active infections (e.g. active tuberculosis, see section 5.2)

5. WARNINGS AND PRECAUTIONS

Traceability: In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

5.1 Hypersensitivity Reactions

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

5.2 Infections

SKYRIZI may increase the risk of infections.

In patients with a chronic infection, a history of recurrent infection or known risk factors for infection, the risks and benefits should be considered prior to prescribing SKYRIZI. Treatment with SKYRIZI should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. 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.

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. In patients with latent TB, consider anti-TB therapy prior to initiating SKYRIZI.

5.3 Immunizations

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

6. DRUG INTERACTIONS

SKYRIZI is not expected to undergo metabolism by hepatic enzymes or renal elimination. Drug interactions between SKYRIZI and inhibitors/inducers of drug metabolizing 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 would not cause or be impacted by drug-drug interactions *(see* **PHARMACOLOGIC PROPERTIES***)*.

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

7. PREGNANCY AND LACTATION

7.1 Pregnancy

Data available with SKYRIZI use in pregnant women are insufficient to inform any drug-associated risks. As a precautionary measure, it is preferable to avoid the use of SKYRIZI during pregnancy.

Data (Animal and/or Human)

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. For Crohn's disease, these doses produced exposures 10 times the clinical exposures during induction at a dose of 600 mg IV every 4 weeks and 39 times the clinical exposures for maintenance when given 360 mg SC 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 immunotoxicology 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.

Women of Childbearing Potential

Women of childbearing potential should use an effective method of contraception during treatment and for at least 20 weeks after treatment.

7.2 Lactation

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. A decision should be made whether to discontinue breast-feeding or to discontinue SKYRIZI taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

8. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

9. ADVERSE REACTIONS

9.1 Clinical Trials Experience

Plaque 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.

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

Adverse Reactions	SKYRIZI[1,2,4] N = 1306 n (%)	Placebo[1,2] N = 300 n (%)	Ustekinumab[1,3] N = 239 n (%)	Adalimumab[4] N = 304 n (%)
Upper respiratory infections[a]	170 (13.0)	29 (9.7)	28 (11.7)	42 (13.8)
Headache[b]	46 (3.5)	6 (2.0)	9 (3.8)	20 (6.6)
Fatigue[c]	33 (2.5)	3 (1.0)	7 (2.9)	8 (2.6)
Injection site reactions[d]	19 (1.5)	3 (1.0)	9 (3.8)	17 (5.6)
Tinea infections[e]	15 (1.1)	1 (0.3)	1 (0.4)	2 (0.7)
[a] Includes: respiratory tract infection (viral, bacterial or unspecified), sinusitis (including acute), rhinitis, nasopharyngitis, pharyngitis (including viral), tonsillitis				

[b] Includes: headache, tension headache, sinus headache, cervicogenic headache
[c] Includes: fatigue, asthenia
[d] Includes: injection site bruising, erythema, extravasation, hematoma, hemorrhage, infection, inflammation, irritation, pain, pruritus, reaction, swelling, warmth
[e] Includes: tinea pedis, tinea cruris, body tinea, tinea versicolor, tinea manuum, tinea infection, onychomycosis
[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

Adverse reactions that occurred in < 1% but > 0.1% of subjects in the SKYRIZI group and at a higher rate than in the placebo group through Week 16 was 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.

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

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 with up to 52 weeks of exposure was consistent with the profile observed up to 24 weeks.

Crohn’s Disease

The adverse drug reaction profile observed in patients with Crohn’s disease treated with SKYRIZI was consistent with the adverse drug reaction profile observed in patients with plaque psoriasis. No new adverse reactions were identified in SKYRIZI Crohn’s disease studies.

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

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 IV 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 IV compared to 16.7 events per 100 subject-years in placebo.

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 SC 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 SC after SKYRIZI induction compared to 5.0 events per 100 subject-years in subjects who received placebo after SKYRIZI induction.

9.2 Post Marketing Experience

The following adverse reactions have been identified during post-approval use of SKYRIZI. Because 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

9.3 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 neutralizing 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.

Plaque 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 neutralizing antibodies were detected in 24% (263/1079) and 14% (150/1079) of evaluated subjects, respectively.

For most subjects, antibodies to risankizumab including neutralizing antibodies were not associated with changes in clinical response or safety. Higher antibody titers observed in approximately 1% (7/1000 at Week 16 and 6/598 at Week 52) of subjects treated with SKYRIZI appeared to be associated with a reduced clinical response.

Psoriatic Arthritis

For subjects treated with SKYRIZI at the recommended clinical dose for up to 28 weeks in Phase 3 psoriatic arthritis clinical trials (KEEPSAKE1 and KEEPSAKE2), treatment-emergent anti-

drug antibodies and neutralizing antibodies were detected in 12.1% (79/652) and 0% (0/652) of evaluated subjects, respectively.

Crohn's Disease

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

Across all indications, antibodies to risankizumab including neutralizing antibodies were not associated with changes in clinical response or safety.

10. DRUG ABUSE AND DEPENDENCY

None.

11. 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.

12. PHARMACOLOGIC PROPERTIES

12.1 Mechanism of Action

Risankizumab is a humanized 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 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 signaling and release of proinflammatory cytokines.

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

12.2 Pharmacodynamics

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.

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 fecal 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.

12.3 Pharmacokinetics

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 dosing of 150 mg at Week 0, Week 4, and every 12 weeks thereafter, estimated steady-state peak and trough plasma concentrations are 12 and 2 µg/mL, respectively.

In subjects with Crohn's disease treated with 600 mg IV induction dose at Weeks 0, 4, and 8 followed by 360 mg SC maintenance dose at Week 12 and every 8 weeks thereafter, maximum median peak and trough concentrations are estimated to be 156 and 38.8 µg/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 ug/mL respectively during the maintenance period (Weeks 40-48).

Distribution

In a typical 90 kg subject with psoriasis, the steady-state volume of distribution (V_{ss}) was 11.2 L, 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 metabolized 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 (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 based on population pharmacokinetic analyses in Crohn's disease *(see* **DRUG INTERACTIONS***)*.

12.4 Pharmacokinetics in Special Populations

Pediatric

The pharmacokinetics of risankizumab in pediatric 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.

Geriatric

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* **DOSAGE AND ADMINISTRATION***)*.

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, psoriatic arthritis, or Crohn's disease.

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* **DOSAGE AND ADMINISTRATION***)*.

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, psoriatic arthritis, or Crohn's disease. No clinically meaningful

differences in risankizumab exposure were observed in Chinese or Japanese subjects compared to Caucasian subjects in clinical pharmacokinetic studies in healthy volunteers.

13. CLINICAL STUDIES

13.1 Crohn's Disease

SKYRIZI has been shown to improve signs and symptoms and health related quality of life, as well as decrease mucosal inflammation as measured by endoscopy.

The efficacy and safety of SKYRIZI was assessed in 1419 subjects with moderately to severely active Crohn's disease in three multicenter, randomized, 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 randomized withdrawal study of subcutaneous maintenance treatment (FORTIFY) that enrolled subjects with SF/APS clinical response to IV induction treatment, representing at least 64 weeks of therapy.

ADVANCE and MOTIVATE

In studies ADVANCE and MOTIVATE, subjects were randomized to receive either SKYRIZI 600 mg IV (recommended dose), SKYRIZI 1,200 mg IV, 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 2). 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 and 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 ≥ 1 at Baseline), a decrease of least 100 points in baseline CDAI, and a CDAI < 150 at Week 12.

Table 2. Efficacy Results in ADVANCE and MOTIVATE

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

[a] Co-primary endpoints
[b] Statistically significant under multiplicity control for SKYRIZI vs placebo comparison ($p < 0.001$).
[c] Statistically significant under multiplicity control for SKYRIZI vs placebo comparison ($p \leq 0.01$).
[d] Nominal $p \leq 0.01$ 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%, $p \leq 0.05$; MOTIVATE, SKYRIZI = 21%, placebo = 11%, $p \leq 0.01$).

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 hospitalizations

Rates of CD-related hospitalizations 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%, $p \leq 0.01$).

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 3).

Table 3. Efficacy Results at Week 12 in subjects with prior biologic failure and subjects without prior biologic failure in ADVANCE

	ADVANCE	
	Placebo IV	**SKYRIZI 600 mg**
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%).

FORTIFY

The maintenance study FORTIFY evaluated 462 subjects with SF/APS clinical response to 12 weeks of SKYRIZI IV induction treatment in studies ADVANCE and MOTIVATE. Subjects were randomized to continue to receive a maintenance regimen of SKYRIZI 360 mg SC (recommended dose), or SKYRIZI 180 mg SC every 8 weeks, or to withdraw from SKYRIZI induction and receive placebo SC 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 4).

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

	FORTIFY	
	SKYRIZI IV Induction/ Placebo SC[g] (N=164) %	**SKYRIZI IV Induction/ SKYRIZI 360 mg SC (N=141) %**
Clinical Remission[a]	40%	52%[b]
Prior biologic failure	34% (N=123)	48% (N=102)
Without prior biologic failure	56% (N=41)	62% (N=39)
Endoscopic Response[a]	22%	47%[c]
Prior biologic failure	20% (N=123)	44% (N=102)
Without biologic failure	27% (N=41)	54% (N=39)
Enhanced SF/APS Clinical Response	49%	59%[f]
Maintenance of Clinical Remission	51% (N=91)	69% (N=72)[e]
Endoscopic Remission	13%	39%[d]
Mucosal Healing	10% (N=162)	31% (N=141)[d]

[a] Co-primary endpoints
[b] Statistically significant under multiplicity control for SKYRIZI vs placebo comparison ($p \leq 0.01$).
[c] Statistically significant under multiplicity control for SKYRIZI vs placebo comparison ($p < 0.001$).
[d] Nominal $p < 0.001$ SKYRIZI vs placebo comparison.
[e] Nominal $p \leq 0.01$ SKYRIZI vs placebo comparison.
[f] Nominal $p \leq 0.05$ SKYRIZI vs placebo comparison.
[g] The induction-only group consisted of subjects who achieved clinical response to SKYRIZI induction therapy and were randomized to receive placebo in the maintenance study (FORTIFY).

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

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

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; 33 of the subjects achieving SF/APS clinical response enrolled in

FORTIFY and continued receiving SKYRIZI 360 mg SC every 8 weeks for up to 52 weeks. Among these subjects, 55% (18/33) achieved clinical remission and 45% (15/33) achieved endoscopic response at Week 52.

During FORTIFY, 30 subjects had loss of response to SKYRIZI 360 mg SC treatment and received rescue treatment with SKYRIZI (1200 mg IV single dose, followed by 360 mg SC 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.

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 IV/SKYRIZI SC in FORTIFY through Week 52.

14. PRE-CLINICAL SAFETY DATA

Non-clinical data revealed no special hazard for humans based on repeat-dose toxicity studies including safety pharmacology evaluations and an enhanced pre- and post-natal developmental toxicity study in cynomolgus monkeys at doses of up to 50 mg/kg/week. For Crohn's disease, these doses produced exposures 10 times the clinical exposures during induction at a dose of 600 mg IV every 4 weeks and 39 times the clinical exposures for maintenance when given 360 mg SC every 8 weeks.

14.1 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, there were no pre-neoplastic or neoplastic lesions observed. For Crohn's disease, these doses in the 26-week chronic study in cynomolgus monkeys produced exposures 7 times the clinical exposures during

induction at a dose of 600 mg IV every 4 weeks and 28 times the clinical exposures for maintenance when given 360 mg SC every 8 weeks.

14.2 Mutagenicity

Mutagenicity studies have not been conducted with SKYRIZI.

14.3 Impairment of Fertility

Studies in cynomolgus monkeys at doses of up to 50 mg/kg/week (about 7 and 28 times the clinical exposures during induction and maintenance, respectively, in Crohn's disease) with SKYRIZI did not indicate direct or indirect harmful effects on male or female fertility. In the 26-week repeat dose toxicology study, histopathology evaluation of reproductive organs from both male and female cynomolgus monkeys did not show any relevant adverse findings. In a 26-week repeat dose study in sexually mature male cynomolgus monkeys, no effects on male fertility parameters were observed.

14.4 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. For Crohn's disease, these doses in the 26-week chronic study in monkeys produced exposures 7 times the clinical exposures during induction at a dose of 600 mg IV every 4 weeks and 28 times the clinical exposures for maintenance when given 360 mg SC every 8 weeks.

15. PHARMACEUTICAL PROPERTIES

15.1 Description

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

Subcutaneous Injection

Each 360 mg/2.4 mL prefilled cartridge contains 360 mg risankizumab in 2.4 mL solution. The solution is colorless to yellow and clear to slightly opalescent.

The solution may contain a few translucent to white product-related particles. SKYRIZI should not be used if the solution is cloudy or discolored, or contains large particles.

Intravenous Infusion

Each 600 mg/10.0 mL single-dose vial contains 600 mg risankizumab in 10.0 mL solution. The solution is colorless to slightly yellow and clear to slightly opalescent.

15.2 List of Excipients

Each SKYRIZI 360 mg/2.4 mL prefilled cartridge contains acetic acid (0.130 mg), polysorbate 20 (0.48 mg), sodium acetate trihydrate (2.98 mg), trehalose dihydrate (168 mg), and water for injection.

Each SKYRIZI 600 mg/10 mL single-dose vial contains, acetic acid (0.54 mg), polysorbate 20 (2 mg) sodium acetate trihydrate (12.4 mg), trehalose dihydrate (700 mg), and water for injection.

15.3 Information about Certain Excipients

SKYRIZI 360 mg/2.4 mL contains less than 1 mmol sodium (23 mg) per 360 mg dose, i.e., essentially 'sodium-free'.

SKYRIZI 600 mg/10.0 mL contains less than 1 mmol sodium (23 mg) per 600 mg dose, i.e., essentially 'sodium-free'.

15.4 General Considerations for Administration

- SKYRIZI is intended for use under the guidance and supervision of a healthcare professional.
- Visually inspect SKYRIZI for particulate matter and discoloration prior to administration.
- SKYRIZI 360 mg/2.4 mL is a colorless to yellow, and clear to slightly opalescent solution. SKYRIZI 600 mg/10 mL is a colorless to slightly yellow, and clear to slightly opalescent solution.
- The solution may contain a few translucent to white particles. Do not use if the solution contains large particles or is cloudy or discolored.
- SKYRIZI must be kept protected from light in the original packaging, in a refrigerator between 2°C to 8°C (36°F to 46°F). Drug must not be frozen at any time.
- Discard after use. Do not reuse.

15.5 Preparation and Administration Instructions (Crohn's Disease)

<u>Intravenous Induction Dosing Regimen:</u>

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

2. Prior to administration, withdraw 10mL of SKYRIZI solution from the vial and inject into an intravenous infusion bag or glass bottle containing 5% dextrose in water (D5W) (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. The solution in the vial and dilutions should not be shaken.

4. Prior to the start of the intravenous infusion, the content of the infusion bag or glass bottle should be at room temperature.

5. Infuse the diluted solution over a period of at least one hour. The infusion should be completely administered within 8 hours of the dilution in the infusion bag.

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

7. Each vial is for single use only and any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Storage of Diluted Solution:

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 (36°F to 46°F). Subsequently, the diluted SKYRIZI solution can be stored (protected from direct and indirect sunlight) for 8 hours at room temperature after dilution (cumulative time after preparation including the storage and infusion period). Do not freeze.

Subcutaneous Maintenance Dosing Regimen:

- Administer SKYRIZI prefilled 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 prefilled 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 prefilled cartridge from the carton.
- If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.
- The SKYRIZI "Instructions for Use" contains more detailed instructions on the preparation and administration of SKYRIZI. Instruct the patient to read the Instructions for Use before administration.

15.6 Storage

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

15.7 How Supplied

SKYRIZI is supplied as a solution for injection in a prefilled cartridge with on-body injector.

- SKYRIZI 360 mg/2.4 mL prefilled cartridge: Each carton contains 1 prefilled cartridge with 1 on body injector.

SKYRIZI is supplied as a concentrate for solution for infusion in a single-dose vial.

- SKYRIZI 600 mg/10.0 mL vial: Each carton contains 1 vial.

Product Registrant:
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