1 NAME OF THE MEDICINAL PRODUCT

Skyrizi® 600 mg concentrate for solution for infusion

Skyrizi® 360 mg solution for injection in Pre-filled cartridge

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Skyrizi 600 mg concentrate for solution for infusion

Each vial contains 600 mg of risankizumab in 10.0 mL of solution (60mg/mL).

Skyrizi 360 mg solution for injection in Pre-filled cartridge

Each Pre-filed cartridge contains 360 mg of risankizumab in 2.4 mL solution (150 mg/mL).

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Skyrizi 600 mg concentrate for solution for infusion (infusion)

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

Skyrizi 360 mg solution for injection (injection)

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Risankizumab is indicated for the treatment of patients 16 years and older 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, or if such therapies are not advisable.

4.2 Posology and method of administration

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

Posology

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

Missed dose

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

Special populations

Elderly (aged 65 years and over)

No dose adjustment is required (see section 5.2).

There is limited information in subjects aged ≥65 years.

Renal or hepatic impairment

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

Paediatric population

The safety and efficacy of Skyrizi for the treatment of Crohn's disease in children and adolescents younger than 16 years of age have not yet been established. No data are available.

Overweight patients

No dose adjustment is required (see section 5.2).

Method of administration

Skyrizi 600mg is administered by intravenous infusion.

Skyrizi 600 mg concentrate for solution for infusion is for intravenous use only. It should be administered over at least one hour. For instructions on dilution of the medicinal product before administration, see section 6.6.

Skyrizi 360mg is administered by subcutaneous injection.

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 damaged.

Patients may self-inject Skyrizi after training in subcutaneous injection technique with the on-body injector. Patients should be instructed to read the 'Instructions for use' provided in the package leaflet before administration.

4.3 Contraindications

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

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

4.4 Special warnings and precautions for use

Traceability

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

Infections

Risankizumab may increase the risk of infection.

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

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

Tuberculosis

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

Immunisations

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

Hypersensitivity

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

Excipients with known effect

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Concomitant immunosuppressive therapy

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use an effective method of contraception during treatment and for at least 21 weeks after treatment.

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of risankizumab in pregnant women. Animal studies do not indicate direct or

indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of risankizumab during pregnancy.

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were upper respiratory infections.

Tabulated list of adverse reactions

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

Table 1: List of adverse reactions

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

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

Description of selected adverse reactions

Infections

Psoriasis

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

Crohn's disease

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

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

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 risankizumab 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 risankizumab 600 mg IV compared to 16.7 events per 100 subject-years in placebo (see section 4.4).

The rate of infections in the 52-week maintenance study was 57.7 events per 100 subject-years in subjects treated with risankizumab 360 mg SC after risankizumab induction compared to 76.0 events per 100 subject-years in subjects who received placebo after risankizumab induction. The rate of serious infections was 6.0 events per 100 subject-years in subjects treated with risankizumab 360 mg SC after risankizumab induction compared to 5.0 events per 100 subject-years in subjects who received placebo after risankizumab induction (see section 4.4).

Immunogenicity

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

For subjects with Crohn's disease treated with risankizumab 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.

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

Elderly

There is limited safety information in subjects aged ≥65 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

https://sideeffects.health.gov.il

4.9 Overdose

In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment be instituted immediately.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC18

Mechanism of action

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

Pharmacodynamic effects

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

In a Phase 2 study of subjects with Crohn's disease, expression of genes associated with the IL-23/Th17 axis were 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.

Clinical efficacy

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 risankizumab were assessed in 1 419 subjects with moderately to severely 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 at Week 12 (≥ 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 risankizumab at either 600 mg (recommended dose), 1 200 mg, 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 therapy with conventional therapies but not biologic therapies (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 a biologic but never failed or demonstrated intolerance. All patients 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) %**	**Treatment difference[e] (95% CI)**	**Placebo IV (N=187) %**	**Skyrizi 600 mg IV (N=191) %**	**Treatment difference[e] (95% CI)**
Clinical remission at Week 12[a]	22%	43%	22% [14%, 30%][b]	19%	35%	15% [6%, 24%][c]
Endoscopic response at Week 12[a]	12%	40%	28% [21%, 35%][b]	11%	29%	18% [10%, 25%][b]
Enhanced SF/APS clinical response at Week 4	31%	46%	15% [6%, 23%][c]	32%	45%	14% [4%, 23%][d]
Enhanced SF/APS clinical response at Week 12	42%	63%	21% [12%, 30%][b]	39%	62%	23% [13%, 33%][b]
Mucosal healing at Week 12	8%	21%	14% [8%, 19%][b]	4%	14%	9% [4%, 15%][c]
Endoscopic remission at Week 12	9%	24%	15% [9%, 21%][b]	4%	19%	15% [9%, 21%][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 ($p\leq0.01$).

[d] Nominal $p \leq 0.01$ SKYRIZI vs placebo comparison.

[e] Adjusted treatment difference.

At Week 4, a higher proportion of subjects treated with Skyrizi achieved a CDAI <150 compared to placebo (ADVANCE, Skyrizi=18%, placebo=10%, $p\leq0.05$; MOTIVATE, Skyrizi=21%, placebo=11%, $p\leq0.01$).

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 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).

The results for the co-primary endpoints for subjects with and without prior biologic failure are presented in Table 3.

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

	ADVANCE	
	Placebo IV	**Skyrizi 600 mg**
Clinical remission per SF/AP Score		
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%).

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≤0.01).

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 MOTIVIATE. 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 (see 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 induction dose)

	FORTIFY

	Skyrizi IV induction/ Placebo SC[g] (N=164) %	Skyrizi IV induction/ Skyrizi 360 mg SC (N=141) %	Treatment difference (95% CI)
Clinical remission[a]	40%	52%	15% [5%, 25%][b,h]
Prior biologic failure	34% (N=123)	48% (N=102)	14% [1%,27%]
Without prior biologic failure	56% (N=41)	62% (N=39)	5% [-16%,27%]
Endoscopic response[a]	22%	47%	28% [19%, 37%][c,h]
Prior biologic failure	20% (N=123)	44% (N=102)	23% [11%, 35%]
Without biologic failure	27% (N=41)	54% (N=39)	27% [6%, 48%]
Enhanced SF/APS clinical response	49%	59%	13% [2%, 23%][f,h]
Maintenance of clinical remission	(N = 91) 51%	(N = 72) 69%	21% [6%, 35%][e,h]
Endoscopic remission	13%	39%	28% [20%, 37%][d,h]
Mucosal healing	(N = 162) 10%	(N = 141) 31%	22% [14%, 30%][d,h]

[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 ($p \leq 0.001$).

[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).

[h] Adjusted treatment difference.

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 (1 200 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.

Paediatric population

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

5.2 Pharmacokinetic properties

Absorption

Risankizumab exhibited linear pharmacokinetics with dose-proportional increase in exposure across dose ranges of 18 to 360 mg and 0.25 to 1 mg/kg administered subcutaneously, and 200 to 1 800 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

The mean (±standard deviation) steady-state volume of distribution (V_{ss}) of risankizumab was 11.4 (±2.7) L in Phase 3 studies in subjects with psoriasis, indicating that the distribution of risankizumab is primarily confined to the vascular and interstitial spaces. In a typical 70 kg subject with Crohn's disease, V_{ss} was 7.68 L.

Biotransformation

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

Elimination

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

Linearity/non-linearity

Risankizumab exhibited linear pharmacokinetics with approximately dose-proportional increases in systemic exposure (C_{max} and AUC) in the evaluated dose ranges of 18 to 360 mg or 0.25 to 1 mg/kg subcutaneous administration and 200 to 1 800 mg and 0.01 to 5 mg/kg administered intravenously in healthy subjects or subjects with psoriasis or Crohn's disease.

Interactions

An 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 interactions through these enzymes.

Population pharmacokinetic analyses indicated that risankizumab exposure was not impacted by concomitant medicinal products used by some subjects with plaque psoriasis during the clinical studies. Similar lack of impact by concomitant medications was observed based on population pharmacokinetic analyses in Crohn's disease.

Special populations

Paediatric population

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 exposures based on the population pharmacokinetic analyses.

Elderly

Of the 2 234 subjects with plaque psoriasis exposed to risankizumab, 243 were 65 years or older and 24 subjects were 75 years or older. Of the 1 574 subjects with Crohn's disease exposed to risankizumab, 72 were 65 years or older. No overall differences in risankizumab exposure were observed between older and younger subjects who received risankizumab.

Patients with renal or hepatic impairment

No specific studies have been conducted to determine the effect of renal or hepatic impairment on the pharmacokinetics of risankizumab. Based on population pharmacokinetic analyses, serum creatinine levels, creatinine clearance, or hepatic function markers (ALT/AST/bilirubin) did not have a meaningful impact on risankizumab clearance in subjects with psoriasis, 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.

Body weight

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

Gender or race

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

5.3 Preclinical safety data

Nonclinical 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, producing 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.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trehalose dihydrate
Sodium acetate trihydrate
Polysorbate 20

Acetic acid glacial
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Skyrizi 600mg should only be diluted in a 5% dextrose in water (D5W) IV infusion bag or glass bottle. Skyrizi 600mg should not be administered concomitantly in the same intravenous line with other medicinal products.

6.3 Shelf life

Skyrizi 600mg

Unopened vial: the expiry date of the product is indicated on the packaging materials.

Diluted solution for intravenous infusion:

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. 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.

Skyrizi 360 mg

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

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

Keep the Pre-filled cartridge or the vial in the outer carton in order to protect from light.

For Skyrizi 600 mg storage conditions after dilution, see section 6.3

6.5 Nature and contents of container

Skyrizi 600mg

10.0 mL concentrate solution for infusion in a glass vial closed with a coated rubber stopper.

Skyrizi 600 mg is available in packs containing 1 vial pack.

Skyrizi 360mg

A 360 mg solution in a single-use cartridge made with cyclic olefin resin with rubber septum and rubber piston as product-contact materials, and a resin cap. The cartridge is assembled with a telescopic screw assembly. The cartridge assembly is co-packed with an on-body injector (administration device). The fluid path within the on-body injector contains polyvinyl chloride tubing and a stainless steel 29-gauge needle. The on-body injector contains silver oxide-zinc batteries and an adhesive skin patch made from polyester with an acrylic adhesive. The administration device is designed for use with the provided 360 mg cartridge.

Skyrizi 360 mg is available in packs containing 1 pre-filled cartridge and 1 on-body injector.

6.6 Special precautions for disposal

Skyrizi 600mg

The solution in the vial and dilutions should not be shaken. The solutions should be visually inspected for particulate matter or discoloration prior to administration. The solution should be colourless to slightly yellow and clear to slightly opalescent. The medicinal product and its dilutions should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present.

Instructions for dilution

Skyrizi should be prepared by a healthcare professional using aseptic technique.

Skyrizi medicinal product must be diluted before administration.

Solutions of Skyrizi for intravenous administration are prepared by dilution of the drug product into an intravenous infusion bag or glass bottle containing 5% dextrose in water (D5W) (600 mg/10 mL in 100 mL, 250 mL or 500 mL) to a final drug concentration of approximately 1.2 mg/mL to 6 mg/mL.

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

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

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

Skyrizi 360mg

Skyrizi is intended for use under the guidance and supervision of a healthcare professional.

Prior to use, a visual inspection of the cartridge is recommended. The solution is free from foreign particles and practically free from product-related particles. Skyrizi should not be used if the solution is cloudy or discoloured, or contains large particles.

The solution should be colourless to yellow and clear to slightly opalescent.

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 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 injecting, patients should remove the carton from the refrigerator and allow to reach room temperature (up to 25°C), out of direct sunlight, for 45 to 90 minutes without removing the cartridge from the carton.

Comprehensive instructions for use are provided in the package leaflet.

Each on-body injector with cartridge is for single use only.

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

7 MANUFACTURER

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8 LICENSE HOLDER

AbbVie biopharmaceuticals LTD., 4 Haharash., Hod Hasharon, Israel.

9 REGISTRATION NUMBER

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