Professional Information (PI)

SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

TREMFYA® 100 mg solution for injection in pre-filled syringe.

TREMFYA® 100 mg solution for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TREMFYA 100 mg solution for injection in pre-filled syringe.

Each pre-filled syringe contains 100 mg of guselkumab in 1 mL solution.

TREMFYA 100 mg solution for injection in pre-filled pen

Each pre-filled pen contains 100 mg of guselkumab in 1 mL solution.

For the full list of excipients, see section 6.1.

Contains sugar (sucrose).

Each 1 mL of TREMFYA 100 mg dose contains 79 mg sucrose.

Guselkumab is a fully human immunoglobulin G1 lamda (IgG1λ) monoclonal antibody (mAb) to the interleukin (IL)-23 protein, produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

3. PHARMACEUTICAL FORM

TREMFYA is a clear, colourless to light yellow solution for subcutaneous injection.

TREMFYA is essentially free of visible particulate matter with a pH of approximately 5,8.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Plaque psoriasis

TREMFYA is indicated for the treatment of adults with moderate-to-severe plaque psoriasis.

Safety and efficacy of TREMFYA beyond 5 years has not been established.

Psoriatic arthritis

TREMFYA, alone or in combination with methotrexate (MTX), is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy.

4.2 Posology and method of administration

Posology

Dosage - Adults (18 years and older)

Plaque psoriasis

The recommended dose of TREMFYA is 100 mg to be given as subcutaneous injection at week 0, week 4 and every 8 weeks thereafter.

Psoriatic arthritis

The recommended dose of TREMFYA is 100 mg by subcutaneous injection at weeks 0 and 4, followed by a maintenance dose every 8 weeks. For patients at high risk for joint damage according to clinical judgement, a dose of 100 mg every 4 weeks may be considered.

Consideration should be given to discontinuing treatment in patients who have shown no response after 24 weeks of treatment.

General considerations for administration

TREMFYA is intended for use under the guidance and supervision of a medical practitioner. TREMFYA may be administered by a health care professional, or a patient may self-inject after proper training in subcutaneous injection technique.

Comprehensive instructions for the administration of TREMFYA are given in the Patient Information Leaflet. Full amount of TREMFYA should be injected according to the directions provided.

Switching from other biologics to TREMFYA

TREMFYA has been shown to be safe and effective in patients with plaque psoriasis with an inadequate response to ustekinumab or adalimumab therapy. When switching to treatment with TREMFYA patients with plaque psoriasis, administer TREMFYA at week 0, week 4 and every 8 weeks thereafter.

Special populations

Paediatrics (below 18 years of age)

The safety and efficacy of TREMFYA in paediatric patients have not been evaluated; therefore, no recommendations on dosing can be made *(see section 5.2, Pharmacokinetic properties)*.

Elderly (65 years of age and older)

Of the 3 940 plaque psoriasis and psoriatic arthritis patients exposed to TREMFYA in Phase 2 and Phase 3 clinical trials, a total of 239 patients were 65 years or older, and 19 patients were 75 years or older. No overall differences in safety or effectiveness were observed between older and younger patients who received TREMFYA in clinical studies. However, the number of patients aged 65 years and older was not sufficient to determine whether they respond differently from younger patients *(see section 5.2, Pharmacokinetic Properties)*.

Renal and hepatic impairment

Specific studies of TREMFYA have not been conducted in patients with renal and hepatic insufficiency.

Method of administration

TREMFYA is administered by subcutaneous (SC) injection.

4.3 Contraindications

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

Live vaccines must not be administered to patients receiving TREMFYA.

Clinically important active infections irrespective of pathogen.

Active tuberculosis.

Pregnancy and lactation (*see section 4.6, Fertility, pregnancy and lactation)*.

4.4 Special warnings and precautions for use

Infections

Safety and efficacy of TREMFYA in patients with HIV has not been established.

TREMFYA may increase the risk of infection. Treatment with TREMFYA should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated (*see section 4.3, Contraindications)*.

Infections have been observed in clinical trials in plaque psoriasis (23 % versus 21 % for placebo; ≤ 0,2 % serious infections in both groups) and psoriatic arthritis (21 % in both TREMFYA and placebo groups; ≤ 0,8 % serious infections in both groups).

Instruct patients treated with TREMFYA to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a clinically important or serious infection or is not responding to standard therapy, monitor the patient closely and discontinue TREMFYA until the infection resolves.

Pre-treatment evaluation for tuberculosis

In clinical studies, subjects with latent non-active tuberculosis (TB) who were concurrently treated with TREMFYA and appropriate TB prophylaxis did not develop TB. Evaluate patients for TB infection prior to initiating treatment with TREMFYA. Initiate treatment of latent non-active TB prior to administering TREMFYA. Patients receiving TREMFYA should be monitored for signs and symptoms of active TB during and after treatment. Do not administer TREMFYA to patients with active TB infection. Consider anti-TB therapy prior to initiating TREMFYA in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed *(see section 4.3, Contraindications).*

Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported in the post-marketing setting. Some serious hypersensitivity reactions occurred several days after treatment with guselkumab, including cases with urticaria and dyspnoea. If a serious hypersensitivity reaction occurs, administration of TREMFYA should be discontinued immediately and appropriate therapy initiated.

Hepatic Transaminase Elevations

In psoriatic arthritis clinical studies, an increased incidence of liver enzyme elevations was observed in patients treated with TREMFYA q4w compared to patients treated with TREMFYA q8w or placebo (see section 4.8, Table 3).

When prescribing TREMFYA q4w in psoriatic arthritis, it is recommended to evaluate the liver enzymes at baseline and thereafter according to routine patient management. If increases in alanine aminotransferase [ALT] or aspartate aminotransferase [AST] are observed and drug-induced liver injury is suspected, TREMFYA should be temporarily interrupted until the diagnosis is excluded.

Immunisations

Prior to initiating therapy with TREMFYA, consider completion of all age appropriate immunisations according to current immunisation guidelines. Do not use live vaccines in patients treated with TREMFYA (*see section 4.3, Contraindications*). No data are available on the response to live or inactive vaccines.

Sucrose intolerance

Contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take TREMFYA.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with CYP450 substrates

Although the activity of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, interferon) during chronic inflammation, an *in vitro*

study using human hepatocytes showed that IL-23 did not alter the expression or activity of multiple CYP450 enzymes (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4).

In a Phase 1 study in subjects with moderate to severe plaque psoriasis, changes in systemic exposures (C_{max} and AUC_{inf}) of midazolam, S-warfarin, omeprazole, dextromethorphan, and caffeine after a single dose of guselkumab were not clinically relevant, indicating that medicine interactions between guselkumab and substrates of various CYP enzymes (CYP3A4, CYP2C9, CYP2C19, CYP2D6, and CYP1A2) are unlikely. There is no need for dose adjustment when co-administering guselkumab and CYP450 substrates.

Live vaccines/therapeutic infectious medicines

Live vaccines should not be given while a patient is undergoing therapy with TREMFYA (*see section 4.3: Contraindications).*

4.6 Fertility, pregnancy and lactation

Pregnancy

TREMFYA is contraindicated in pregnant women (*see section 4.3, Contraindications*). Women should use effective contraception during, and up to 12 weeks after, the last treatment with TREMFYA.

Breastfeeding

Women should not breastfeed their infants while receiving TREMFYA.

Fertility

The effect of TREMFYA on human fertility has not been evaluated. No guselkumab-related effects on fertility parameters were identified in female and male fertility studies conducted in guinea pigs.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Clinical studies experience in adult patients with psoriasis and psoriatic arthritis

The safety profile of TREMFYA is based on pooled Phase 2 and Phase 3 studies in 3 940 subjects, including 2 711 with plaque psoriasis and 1 229 subjects with psoriatic arthritis.

Adverse reactions

Adverse reactions to TREMFYA are presented in Table 1. Within each frequency grouping, the adverse reactions are presented within the designated system organ classes in order of decreasing frequency, using the following convention:

Very common	(≥1/10)
Common	(≥1/100, <1/10)
Uncommon	(≥1/1 000, <1/100)

Rare (≥1/10 000, <1/1 000)

Table 1: Summary of Adverse Reactions in Clinical Studies

Infections and infestations	*Very common*: respiratory tract infections *Uncommon*: gastroenteritis, tinea infections, herpes simplex infections
Investigations	*Common*: increased transaminase *Uncommon*: decreased neutrophil count
Nervous system disorders	*Common:* headache
Gastrointestinal disorders	*Common:* diarrhoea
Musculoskeletal and connective tissue disorders	*Common*: arthralgia
General disorders and administration site conditions	*Common*: injection site erythema *Uncommon*: injection site pain

Table 2: Postmarketing data

System Organ class	**Adverse reaction**
Immune system disorders	*Uncommon:* hypersensitivity *Uncommon:* anaphylaxis

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Skin and subcutaneous tissue disorders	*Uncommon:* rash and urticaria
General disorders and administration site conditions	*Common:* injection site reactions

Description of selected adverse reaction

Increased transaminases

In two Phase 3 psoriatic arthritis clinical studies, through the placebo-controlled period, adverse events of increased transaminases (includes increased ALT, increased AST, increased Hepatic Enzyme, increased Transaminases, abnormal Liver Function Test, Hypertransaminasaemia) were reported more frequently in the TREMFYA-treated groups (8.6% in the q4w group and 8.3% in the q8w group) than in the placebo group (4.6%). Through 1 year, adverse events of increased transaminases (as above) were reported in 12,9 % of patients in the q4w group and 11,7 % of patients in the q8w group.

Based on laboratory assessments, most transaminase increases (ALT and AST) were ≤ 3 x upper limit of normal (ULN). Transaminase increases from > 3 to ≤ 5 x ULN and > 5 x ULN were low in frequency, occurring more often in the TREMFYA q4w group compared with the TREMFYA q8w group
(Table 3). A similar pattern of frequency by severity and by treatment group was observed through the end of the 2-year Phase III psoriatic arthritis clinical study.

Table 3: Frequency of patients with transaminase increases post-baseline in two Phase III psoriatic arthritis clinical studies

	Through Week 24[a]			Through 1 Year[b]	
	Placebo N=370[c]	TREMFYA 100 mg q8w N=373[c]	TREMFYA 100 mg q4w N=371[c]	TREMFYA 100 mg q8w N=373[c]	TREMFYA 100 mg q4w N=371[c]
ALT					
>1 to ≤3 x ULN	30.0%	28.2%	35.0%	33.5%	41.2%
>3 to ≤ 5 x ULN	1.4%	1.1%	2.7%	1.6%	4.6%
>5 x ULN	0.8%	0.8%	1.1%	1.1%	1.1%
AST					
>1 to ≤3 x ULN	20.0%	18.8%	21.6%	22.8%	27.8%
>3 to ≤ 5 x ULN	0.5%	1.6%	1.6%	2.9%	3.8%
>5 x ULN	1.1%	0.5%	1.6%	0.5%	1.6%

[a] placebo-controlled period
[b] patients randomised to placebo at baseline and crossed over to TREMFYA are not included
[c] number of patients with at least one post-baseline assessment for the specific laboratory test within the time period

In the psoriasis clinical studies, through 1 year, the frequency of transaminase increases (ALT and AST) for the TREMFYA q8w dose was similar to that observed for the TREMFYA q8w dose in the psoriatic arthritis clinical studies. Through 5 years, the incidence of transaminase elevation did not increase by year of guselkumab treatment. Most transaminase increases were ≤ 3 x ULN.

In most cases, the increase in transaminases was transient and did not lead to discontinuation of treatment.

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 medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the :**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC16.

Mechanism of action

Guselkumab is a human IgG1λ monoclonal antibody (mAb) that binds selectively to the interleukin 23 (IL-23) protein with high specificity and affinity. IL-23, a regulatory cytokine, affects the differentiation, expansion, and survival of T cell subsets, (e.g., Th17 cells and Tc17 cells) and innate immune cell subsets, which represent sources of effector cytokines, including IL-17A, IL-17F and IL-22 that drive inflammatory disease. In humans, selective blockade of IL-23 was shown to normalise production of these cytokines.

Levels of IL-23 are elevated in the skin of patients with plaque psoriasis. In *in-vitro* models, guselkumab was shown to inhibit the bioactivity of IL-23 by blocking its interaction with cell surface IL-23 receptor, disrupting IL-23 mediated signaling, activation and cytokine cascades. Guselkumab exerts clinical effects in plaque psoriasis through blockade of the IL-23 cytokine pathway.

Pharmacodynamic effects

In psoriatic arthritis patients in Phase 3 studies, serum levels of acute phase proteins C-reactive protein, serum amyloid A, and IL-6, and Th17 effector cytokines IL-17A, IL-17F and IL-22 were elevated at baseline. Guselkumab decreased the levels of these proteins within 4 weeks of initiation of treatment. Guselkumab further reduced the levels of these proteins by Week 24 compared to baseline and also to placebo.

Immunogenicity

Plaque psoriasis

There is the potential for immunogenicity. In pooled Phase 2 and Phase 3 analyses, fewer than 6 % of subjects treated with guselkumab developed antidrug antibodies in up to 52 weeks of treatment. Of the subjects who developed antidrug antibodies, approximately 7 % had antibodies that were classified as neutralising which equates to 0,4 % of all subjects treated with guselkumab. Antidrug antibodies were not associated with lower efficacy or development of injection-site reactions.

Psoriatic arthritis

In pooled Phase 3 (DISCOVER 1 and DISCOVER 2) analyses up to Week 52, 4,5 % (n=49) of subjects treated with TREMFYA developed antidrug antibodies. Of these subjects, 5 had antibodies that were classified as neutralising antibodies, and 3 developed injection site reactions through Week 52. Overall, the small number of subjects who were positive for antibodies to guselkumab limits definitive conclusion of the effect of immunogenicity on the pharmacokinetics and efficacy of guselkumab. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralising antibody) positivity 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 TREMFYA with the incidences of antibodies to other products may be misleading.

5.2 Pharmacokinetic properties

Absorption

Following a single 100 mg subcutaneous injection in healthy subjects, guselkumab reached a mean (± SD) maximum serum concentration (C_{max}) of 8,09 ± 3,68 mcg/mL by approximately 5,5 days post dose.

Steady state serum guselkumab concentrations were achieved by Week 20 following subcutaneous administrations of 100 mg guselkumab at Weeks 0 and 4, and every 8 weeks thereafter. The mean (± SD) steady state trough serum guselkumab concentrations in two Phase 3 studies were 1,15 ± 0,73 mcg/mL and 1,23 ± 0,84 mcg/mL.

Serum guselkumab concentrations did not appear to accumulate over time when given subcutaneously every 8 weeks.

The pharmacokinetics of guselkumab in subjects with psoriatic arthritis was similar to that in subjects with psoriasis. Following subcutaneous administration of 100 mg of TREMFYA at Weeks 0, 4, and every 8 weeks thereafter, mean steady-state trough serum guselkumab concentration was also approximately 1,2 mcg/mL. Following subcutaneous administration of 100 mg of TREMFYA every 4 weeks, mean steady-state trough serum guselkumab concentration was approximately 3,8 mcg/mL.

The absolute bioavailability of guselkumab following a single 100 mg subcutaneous injection was estimated to be approximately 49 % in healthy subjects.

Distribution

Mean volume of distribution during the terminal phase (Vz) following a single intravenous administration to healthy subjects ranged from approximately 7 to 10 L (98 to 123 mL/kg) across studies.

Metabolism

The exact pathway through which guselkumab is metabolised has not been characterised. As a human IgG monoclonal antibody, guselkumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Elimination

Mean systemic clearance (CL) following a single intravenous administration to healthy subjects ranged from 0,288 to 0,479 L/day (3,6 to 6,0 mL/day/kg) across studies.
Mean half-life ($T_{1/2}$) of guselkumab was approximately 17 days in healthy subjects and approximately 15 to 18 days in subjects with plaque psoriasis across studies.

Dose linearity

The systemic exposure of guselkumab (C_{max} and AUC) increased in an approximately dose-proportional manner following a single subcutaneous injection at doses ranging from 10 mg to 300 mg in healthy subjects or subjects with plaque psoriasis.

Special populations

Paediatrics (17 years of age and younger)

The safety and efficacy of guselkumab have not been established in paediatric patients.

Elderly (65 years of age and older)

Of the 1 384 plaque psoriasis subjects exposed to guselkumab and included in the population pharmacokinetic analysis, 70 subjects were 65 years of age or older, including 4 subjects who were 75 years of age or older. Of the 746 psoriatic arthritis patients exposed to guselkumab in Phase III clinical studies, a total of 38 patients were 65 years of age or older, and no patients were 75 years of age or older.

Population pharmacokinetic analyses indicated there were no apparent changes in CL/F estimate in subjects ≥ 65 years of age compared to subjects < 65 years of age, suggesting no dose adjustment is needed for elderly patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine

L-histidine monohydrochloride monohydrate

Polysorbate 80

Sucrose

Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in a refrigerator (2 ºC – 8 ºC).

Store in original carton until time of use.

Protect form light.

Do not freeze.

Do not shake.

Keep out of reach of children.

6.5 Nature and contents of container

TREMFYA 100 mg solution for injection in pre-filled syringe

TREMFYA is supplied as a single-use sterile solution in a 1 mL Type I borosilicate glass syringe with a fixed 27G, half inch needle assembled in a clear, plastic passive needle guard delivery system - UltraSafe Plus™ Passive Delivery System (PFS-U). The PFS-U is placed in a light blue polyethylene terephthalate (PET) tray insert packed in an outer carton. The outer carton is made of paper board with white base colour. The components of the UltraSafe™ are presented in tabular format in Table 2. TREMFYA is available as a one pack only.

Table 4: Components of UltraSafe Plus™

Component Part	Material
Body	Medical grade polycarbonate (clear)
Needle guard	Medical grade polycarbonate (clear)
Spring	Type 302 Stainless steel spring wire
Plunger rod	Medical grade polypropylene (aqua/teal)

TREMFYA 100 mg solution for injection in pre-filled pen

1 mL solution in a pre-filled glass syringe assembled in a pre-filled pen with an automatic needle guard, packed in an outer carton. TREMFYA is available as a one pack only.

6.6 Special precautions for disposal and other handling

Following administration of TREMFYA, discard any unused portion. The pre-filled syringe and/or pre-filled pen should be disposed of with accepted medical practices for used syringes and pens. The pre-filled syringe and needle and/or prefilled pen must never be re-used.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

52/30.1/0400

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 5 May 2020

10. DATE OF REVISION OF THE TEXT

6 March 2025