

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr TREMFYA™

guselkumab

Solution for injection

100 mg/1 mL

Interleukin-23 (IL-23) inhibitor

TREMFYA™ (guselkumab) should be prescribed by physicians who have sufficient knowledge of plaque psoriasis and who have fully familiarized themselves with the efficacy/safety profile of the drug.

Janssen Inc.
19 Green Belt Drive
Toronto, Ontario
M3C 1L9

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www.janssen.com/canada

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....3
SUMMARY PRODUCT INFORMATION3
DESCRIPTION.....3
INDICATIONS AND CLINICAL USE.....3
CONTRAINDICATIONS3
WARNINGS AND PRECAUTIONS.....4
ADVERSE REACTIONS.....5
DRUG INTERACTIONS7
DOSAGE AND ADMINISTRATION8
OVERDOSAGE9
ACTION AND CLINICAL PHARMACOLOGY10
STORAGE AND STABILITY11
SPECIAL HANDLING INSTRUCTIONS11
DOSAGE FORMS, COMPOSITION AND PACKAGING12

PART II: SCIENTIFIC INFORMATION13
PHARMACEUTICAL INFORMATION.....13
CLINICAL TRIALS.....13
TOXICOLOGY17

PATIENT MEDICATION INFORMATION19

INSTRUCTIONS FOR USE.....24

TREMFYA™

guselkumab

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|-----------------------------|---|--|
| Subcutaneous Injection (SC) | Sterile solution for injection in pre-filled syringe, (100 mg/1 mL) | None <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i> |

DESCRIPTION

TREMFYA™ (guselkumab) is a fully human immunoglobulin G1 lambda (IgG1 λ) monoclonal antibody (mAb) that binds selectively to the extracellular human interleukin 23 (IL-23) protein with high specificity and affinity. Guselkumab is produced in a mammalian cell line using recombinant DNA technology.

TREMFYA™ is supplied as sterile solution in a single-use 1 mL pre-filled glass syringe with a 27G, half inch fixed needle assembled in a passive needle guard delivery system.

TREMFYA™ does not contain preservatives.

INDICATIONS AND CLINICAL USE

- TREMFYA™ (guselkumab) is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

CONTRAINDICATIONS

TREMFYA™ is contraindicated in patients with known serious hypersensitivity to guselkumab or any of the components. For a complete listing of components, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

WARNINGS AND PRECAUTIONS

Infections

TREMFYA™ is a selective immunomodulatory agent which has the potential to increase the risk of infection. In clinical trials, infections were reported in 23% of subjects in the TREMFYA™ group versus 21% of subjects in the placebo group through 16 weeks of treatment. The most common type of infection reported was upper respiratory infection. The rates of serious infections for the TREMFYA™ group and the placebo group during this period were $\leq 0.2\%$. (See **ADVERSE REACTION, Infections**)

Treatment with TREMFYA™ should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

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.

In clinical studies, subjects with latent 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 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.

Immune Vaccinations

Prior to initiating therapy with TREMFYA™, consider completion of all age appropriate immunizations according to current immunization guidelines. Avoid use of live vaccines in patients treated with TREMFYA™ (see **DRUG INTERACTIONS**). No data are available on the response to live or inactive vaccines.

Special Populations

Pregnant Women:

The use of TREMFYA™ in pregnant women has not been studied. The effect of TREMFYA™ on human pregnancy is unknown. Studies in cynomolgus monkeys showed that guselkumab crosses the placental barrier. Fetal losses and neonatal deaths occurred in the offspring of pregnant monkeys administered weekly subcutaneous injections of guselkumab from the beginning of organogenesis until parturition at C_{max} and AUC_{last} values that were 31- and 8-fold greater, respectively, than the human levels. A drug-related effect could not be ruled out. No adverse developmental effects were observed in surviving infants. Animal studies are not always

predictive of human response, and therefore, the clinical significance of these findings is unknown (see **TOXICOLOGY**).

Women of childbearing potential should use adequate contraception while using TREMFYA™ and for at least 12 weeks after the last TREMFYA™ dose. TREMFYA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women:

There are no data on the presence of guselkumab in human milk, the effects on the breastfed infant, or the effects on milk production. Guselkumab was not detected in the milk of lactating cynomolgus monkeys (see **TOXICOLOGY**). The developmental and health benefits of breastfeeding should be considered, as well as any potential adverse effects on the breastfed infant.

Fertility

The effect of TREMFYA™ on human fertility has not been evaluated. No guselkumab-related effects on fertility parameters were identified in a female fertility study conducted in guinea pigs. In a male guinea pig fertility study, total litter loss was observed in a limited subset of untreated females following administration of males with guselkumab at a subcutaneous dose of 100 mg/kg twice weekly (24-fold the human exposure). This observation was not repeated in a second male fertility study. No effects were observed at 25 mg/kg (C_{max} and AUC_{last} values were 51- and 6-fold greater, respectively, than the human exposure) (see **TOXICOLOGY**).

Pediatrics (<18 years of age):

The safety and efficacy of TREMFYA™ in pediatric patients have not been evaluated.

Geriatrics (≥65 years of age):

Of the 1748 plaque psoriasis patients exposed to TREMFYA™ in Phase 2 and Phase 3 clinical trials, a limited number of patients were 65 years or older (n = 93, 5%) or 75 years and older (n = 4, 0.2%). Thus data in these age groups are limited (see **ACTION AND CLINICAL PHARMACOLOGY**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most frequently reported adverse drug reaction (>10%) through the 16-week, placebo-controlled period of the pooled VOYAGE 1 and VOYAGE 2 clinical trials in TREMFYA™-treated patients was upper respiratory infections.

The proportion of TREMFYA™-treated patients who discontinued treatment due to adverse events was 1.3% (11/823) compared to 0.9% (8/422) in placebo-treated patients. Serious adverse events were reported in 1.9% (16/823) of TREMFYA™-treated patients and 1.4% (6/422) of placebo-treated patients through 16 weeks.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety profile of TREMFYA™ in patients with moderate to severe plaque psoriasis is based on data from the Phase 2 (PSO2001) and Phase 3 (VOYAGE 1, VOYAGE 2, NAVIGATE) studies. Of the 1748 TREMFYA™-treated patients, 1393 patients were exposed for at least 6 months (24 weeks) and 728 patients were exposed for at least 1 year (i.e., treated through Week 48). Most patients (n=1583) received a dosage regimen of 100 mg TREMFYA™ as subcutaneous injection every 8 weeks.

Table 1 provides a summary of adverse reactions that occurred at a rate of at least 1% and at a higher rate in the TREMFYA™ group than in the placebo group during the 16-week, placebo-controlled period of the pooled clinical trials, VOYAGE 1 and VOYAGE 2.

| Table 1: Adverse reactions reported by ≥1% of patients through Week 16 in VOYAGE 1 and VOYAGE 2 | | | |
|--|-----------------------------|---|---|
| | Placebo N = 422 n (%) | TREMFYA™ ^a N = 823 n (%) | Adalimumab ^b N = 581 n (%) |
| Gastrointestinal disorders | | | |
| Diarrhea | 4 (0.9%) | 13 (1.6%) | 7 (1.2%) |
| General disorders and administration site conditions | | | |
| Injection site reactions ^c | 12 (2.8%) | 37 (4.5%) | 42 (7.2%) |
| Infections and Infestations | | | |
| Upper respiratory infections ^d | 54 (12.8%) | 118 (14.3%) | 80 (13.8%) |
| Gastroenteritis ^e | 4 (0.9%) | 11 (1.3%) | 8 (1.4%) |
| Herpes simplex infections ^f | 2 (0.5%) | 9 (1.1%) | 8 (1.4%) |
| Tinea infections ^g | 0 | 9 (1.1%) | 3 (0.5%) |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | 9 (2.1%) | 22 (2.7%) | 11 (1.9%) |
| Nervous system disorders | | | |
| Headache ^h | 14 (3.3%) | 38 (4.6%) | 18 (3.1%) |

^a Subjects received 100 mg of TREMFYA™ at Week 0, Week 4, and every 8 weeks thereafter;

^b Subjects received adalimumab at 80 mg Week 0, 40 mg week 1 then 40 mg q2w thereafter

^c Injection site reactions include injection site erythema, bruising, hematoma, hemorrhage, swelling, edema, pruritus, pain, discoloration, induration, inflammation, and urticaria.

^d Upper respiratory infections include nasopharyngitis, upper respiratory tract infection (URTI), pharyngitis, and viral URTI.

^e Gastroenteritis includes gastroenteritis and viral gastroenteritis

^f Herpes simplex infections include oral herpes, herpes simplex, genital herpes, genital herpes simplex, and nasal herpes simplex.

^g Tinea infections include tinea pedis, tinea cruris, tinea infection, and tinea manuum infections.

^h Headache includes headache and tension headache.

Infections

Infections occurred in 23% (191/823) of TREMFYA™ -treated patients compared to 21% (90/422) of the placebo-treated patients through week 16.

Adverse events of infection reported in $\geq 1\%$ of subjects were upper respiratory infections, gastroenteritis, tinea infections, and herpes simplex infections; all cases were mild to moderate in severity and did not lead to discontinuation of TREMFYA™. The rates of serious infections reported the TREMFYA™ group and the placebo group were $\leq 0.2\%$.

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity with TREMFYA™. The immunogenicity of TREMFYA™ was evaluated using a sensitive and drug-tolerant immunoassay. In subjects with psoriasis in clinical trials, approximately 6% of patients treated with TREMFYA™ developed antidrug antibodies in up to 52 weeks of treatment. Of the patients who developed antidrug antibodies, approximately 7% had antibodies that were classified as neutralizing which equates to 0.4% of all patients treated with TREMFYA™. Among the 46 subjects who developed antibodies to guselkumab and had evaluable data, 21 subjects exhibited lower trough levels of guselkumab, including one subject who experienced loss of efficacy after developing high antibody titers. However, antibodies to guselkumab were generally not associated with changes in clinical response or development of injection-site reactions.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing 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.

Adverse Reactions through Week 48

Through week 48, the types and the frequency of the adverse reactions in the TREMFYA™-treated patients were similar to those observed during the first 16 weeks of treatment.

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

Adverse reactions that occurred at rates $< 1\%$ in the TREMFYA™ group and at a higher rate than in the placebo group through Week 16 in VOYAGE 1 and VOYAGE 2 were:

Infections and Infestations: candida infections

Nervous system disorders: migraine

Skin and subcutaneous tissue disorders: urticaria

DRUG INTERACTIONS

Drug-Drug Interactions

Live vaccines

Live vaccines should not be given while a patient is undergoing therapy with TREMFYA (see **WARNINGS and PRECAUTIONS, Immune**)

Immunosuppression Therapy

The safety and efficacy of TREMFYA™ in combination with immunosuppressant drugs, including biologics, or with phototherapy, have not been evaluated.

Interactions with CYP450 Substrates

The formation of cytochrome P450 (CYP) enzymes can be altered by increased levels of certain cytokines (e.g., interleukin [IL]-β, IL-6, tumor necrosis factor, and interferon) during chronic inflammation. Although 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), the interaction potential cannot be ruled out.

Upon initiation of TREMFYA™ in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for therapeutic effect or drug concentration and consider dosage adjustment as needed.

DOSAGE AND ADMINISTRATION

TREMFYA™ is administered by subcutaneous injection.

Dosing Considerations

TREMFYA™ is intended for use under the guidance and supervision of a physician.

TREMFYA™ may be administered by a healthcare professional, or a patient or caregiver may administer the injection after proper training in subcutaneous injection technique.

Recommended Dose and Dosage Adjustment

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

Special populations

Pediatrics (< 18 years of age)

The safety and efficacy of TREMFYA™ in pediatric patients have not been evaluated; therefore, no recommendations on dosing can be made.

Elderly (≥ 65 years of age)

Of the 1748 plaque psoriasis patients exposed to TREMFYA™ in Phase 2 and Phase 3 clinical trials, a limited number of patients were 65 years or older (n = 93, 5%) or 75 years and older (n = 4, 0.2%). Thus, data in these age groups are limited. (see **ACTION AND CLINICAL PHARMACOLOGY**)

Renal impairment

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

Hepatic impairment

Specific studies of TREMFYA™ have not been conducted in patients with hepatic insufficiency. During the placebo controlled period of clinical trials, increases in liver enzymes were reported in 2.6% of TREMFYA™ treated patients and 1.9% of placebo-treated patients. None of the events led to discontinuation of TREMFYA™ treatment.

Missed Dose

Patients who miss a dose of TREMFYA™ should be advised to inject this missed dose as soon as they become aware of it, and then follow with their next scheduled dose.

Administration

TREMFYA™ is administered by subcutaneous injection. TREMFYA™ is intended for use under the guidance and supervision of a physician. TREMFYA™ may be administered by a healthcare professional or a patient or caregiver may administer the injection after proper training in subcutaneous injection technique.

The full amount of TREMFYA™ should be injected according to the directions provided in the “Instructions for Use” document.

Before injection, remove TREMFYA™ pre-filled syringe from the refrigerator and allow TREMFYA™ to reach room temperature (30 minutes) without removing the needle cap.

Inspect TREMFYA™ visually for particulate matter and discoloration prior to administration. TREMFYA™ is a clear and colourless to light yellow solution. Do not use if the liquid contains large particles, is discoloured or cloudy. Discard any unused product remaining in the pre-filled syringe after injection.

OVERDOSAGE

Single intravenous doses of TREMFYA™ up to 987 mg (10 mg/kg) have been administered in healthy volunteers and single subcutaneous doses of TREMFYA™ up to 300 mg have been administered in patients with plaque psoriasis in clinical trials without dose-limiting toxicity. In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment immediately.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Guselkumab is a human IgG1 λ monoclonal antibody (mAb) that binds selectively to the p19 subunit of interleukin 23 (IL-23) and inhibits its interaction with cell surface IL-23 receptor. IL-23 is a naturally-occurring cytokine that is involved in normal inflammatory and immune responses. Levels of IL-23 are elevated in the skin of patients with plaque psoriasis. Guselkumab inhibits the release of proinflammatory cytokines and chemokines (e.g. IL-17A, IL-17F and IL-22).

Pharmacodynamics

In clinical trials, guselkumab reduced serum levels of IL-17A, IL-17F and IL-22 relative to pre-treatment levels in subjects with psoriasis. The relationship between these pharmacodynamic markers and the mechanism(s) by which guselkumab exerts its clinical effects is not fully understood.

Pharmacokinetics

Guselkumab exhibited linear pharmacokinetics in healthy subjects or patients with psoriasis over a dose range from 10 mg to 300 mg following subcutaneous injections.

Absorption:

Following a single 100 mg subcutaneous injection in healthy subjects, guselkumab reached a mean (\pm SD) maximum serum concentration (C_{max}) of 8.09 ± 3.68 mcg/mL by approximately 5.5 days post dose.

In subjects with psoriasis, 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 (\pm 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.

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

Distribution:

In subjects with plaque psoriasis, apparent volume of distribution was 13.5 L.

Metabolism:

The exact pathway through which guselkumab is metabolized has not been characterized. 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:

Apparent clearance in subjects with plaque psoriasis was 0.516 L/day. 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.

Special Populations

Clearance and volume of distribution of guselkumab increase as body weight increases, based on population pharmacokinetic analyses. However, observed clinical trial data indicate that dose adjustment for body weight is not warranted.

Population pharmacokinetic analyses indicated that concomitant use of ibuprofen, acetylsalicylic acid, or acetaminophen did not affect the clearance of guselkumab.

Pediatrics: The safety and efficacy of guselkumab have not been established in pediatric patients.

Geriatrics:

Of the 1384 plaque psoriasis patients exposed to TREMFYA™ 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. Population pharmacokinetic analyses indicated there were no apparent changes in clearance estimate in subjects ≥ 65 years of age compared to subjects < 65 years of age, suggesting no dose adjustment is needed for elderly patients.

Gender, Race, Age: The clearance of guselkumab was not impacted by sex, age, or race.

Hepatic Insufficiency: No specific study has been conducted to determine the effect of hepatic impairment on the pharmacokinetics of guselkumab.

Renal Insufficiency: No specific study has been conducted to determine the effect of renal impairment on the pharmacokinetics of guselkumab.

STORAGE AND STABILITY

TREMFYA™ is sterile and preservative-free. Discard any unused portion after injection.

Store in a refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze.

Store in original carton until time of use. Protect from light. Do not shake.

Keep out of sight and reach of children.

SPECIAL HANDLING INSTRUCTIONS.

Following administration of TREMFYA™, discard any unused portion. The syringe should be disposed of in a puncture resistant container. Patients or caregivers should be instructed on how to properly dispose of the syringe and needle, and told not to reuse these items.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TREMFYA™ is supplied as a sterile solution in a single-use 1mL glass syringe with a 27G, half inch fixed needle assembled in a passive needle guard delivery system.

Each mL of TREMFYA™ contains 100 mg of guselkumab and the inactive ingredients: L-histidine, L-histidine monohydrochloride monohydrate, sucrose, polysorbate 80 and water for injection.

TREMFYA™ does not contain preservatives.

TREMFYA™ is supplied as a sterile solution for injection in a pre-filled syringe containing 100 mg guselkumab, (100 mg/ 1 mL in a 1 mL syringe volume) packaged in a carton.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

| | |
|---------------------------------------|--|
| Proper name: | TREMFYA™ |
| Chemical name: | Guselkumab |
| Molecular formula and molecular mass: | Guselkumab is a fully human immunoglobulin IgG1 λ mAb with an average molecular weight of 146,613 Daltons |
| Physicochemical properties: | TREMFYA™ is a clear and colorless to light yellow solution and essentially free of visible particulate material with a pH of approximately 5.8 |

Product Characteristics

TREMFYA™ is supplied as a 100 mg/mL sterile solution in a single-use 1 mL glass syringe with a fixed 27G, half inch needle assembled in a passive needle guard delivery system.

TREMFYA™ does not contain preservatives.

CLINICAL TRIALS

The efficacy and safety of TREMFYA™ was assessed in two Phase 3, multicenter, randomized, double-blind studies (VOYAGE 1 and VOYAGE 2) in patients 18 years or older with moderate to severe plaque psoriasis (with or without PsA) defined by Investigator's Global Assessment (IGA) ≥ 3 , a Body Surface Area (BSA) involvement $\geq 10\%$, and Psoriasis Area and Severity Index (PASI) score ≥ 12 , and were candidates for systemic therapy or phototherapy for psoriasis. Patients with guttate, erythrodermic, or pustular psoriasis were excluded from the studies. No concomitant antipsoriatic therapies were allowed during the studies.

The two pivotal studies (VOYAGE 1 and 2) evaluated the efficacy and safety of guselkumab for the treatment of subjects with moderate to severe plaque-type psoriasis and enrolled a total of 1829 patients who were randomized to placebo, TREMFYA™, or adalimumab.

A summary of the study design and demographics is presented in the following Table 2.

Study demographics and trial design

| Study # | Trial design | Dosage, route of administration and duration | Total number of subjects | Mean age (Range) | Gender |
|----------------|--|---|---------------------------------|-------------------------|----------------|
| VOYAGE 1 | A phase 3, multicenter, randomized, double-blind, placebo and active comparator controlled study | Guselkumab (n=329) 100 mg SC Weeks 0, 4 then q8w Placebo (n=174) SC Weeks 0, 4, 12 → guselkumab 100 mg SC Week 16, 20 then q8w ^a Adalimumab (n=334) SC 80 mg Week 0, 40 mg week 1 then 40 mg q2w. | 837 | 43.7 (18-87) | M=608 F=229 |
| VOYAGE 2 | A phase 3, multicenter, randomized, double-blind, placebo and active comparator controlled study | Guselkumab (n=496) 100 mg SC Weeks 0, 4, 12 and 20 Placebo (n=248) SC Weeks 0, 4, 12 → guselkumab 100 mg SC Week 16, 20 ^a Adalimumab (n=248) 80 mg Week 0, 40 mg week 1 then 40 mg q2w. ^b | 992 | 43.0 (18-74) | M=692 F=300 |

^a The placebo group crossed over to receive guselkumab at Weeks 16 and 20 then q8w

^b PASI 90 non-responders at week 28 started to receive TREMFYA™ at week 28 and then week 32 and every 8 weeks thereafter.

The co-primary endpoints in VOYAGE 1 and VOYAGE 2 were the proportions of patients who achieved an IGA score of cleared (0) or minimal (1) and the proportions of patients who achieved a PASI 90 response at Week 16, comparing the TREMFYA™ group and the placebo group.

The IGA is a 5-category scale: 0 = cleared, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe, that indicates the physician's overall assessment of psoriasis focusing on plaque thickness/induration, erythema and scaling.

Other endpoints included the proportions of patients who achieved an IGA score of cleared (0), a PASI 100, PASI 75 response and regional disease as measured by scalp-specific IGA (ss-IGA). Patient-reported outcomes were assessed based on the Psoriasis Symptoms and Signs Diary (PSSD) and Dermatology Life Quality Index (DLQI).

Baseline disease characteristics were generally consistent across all treatment groups for the study populations in VOYAGE 1 and 2 with a median BSA of 22% and 24%, a median baseline PASI score of 19 for both studies, a baseline IGA score of severe for 25% and 23% of patients, and a history of psoriatic arthritis for 19% and 18% patient, respectively.

Of all patients who were included in the VOYAGE 1 and VOYAGE 2 studies, 32% and 29% were naïve to conventional systemic and biologic systemic therapy; 54% and 57% had received prior phototherapy, and 62% and 64% had received prior conventional systemic therapy,

respectively. In both studies, 21% had received prior biologic systemic therapy, including 11% who had received at least one anti-tumour necrosis factor alpha (TNF α) agent, and approximately 10% who had received an anti-IL-12/IL-23 agent.

Study results

The results of VOYAGE 1 and VOYAGE 2 studies are presented in Table 3 and Table 4 below.

| Table 3 Summary of Clinical Responses at Week 16 (NRI^a) in Psoriasis Studies (Co- Primary Endpoints) | | | | | | |
|--|---------------------------------------|--------------------------------------|--|---------------------------------------|--------------------------------------|--|
| | VOYAGE 1 | | | VOYAGE 2 | | |
| | TREMFYA™ (N=329) n (%) | Placebo (N=174) n (%) | Treatment difference^b (95% CI) | TREMFYA™ (N=496) n (%) | Placebo (N=248) n (%) | Treatment difference^b (95% CI) |
| IGA response of 0/1 | 280 (85%) ^c | 12 (7%) | 78% (73%,83%) | 417 (84%) ^c | 21 (8%) | 76% (71%,80%) |
| PASI 90 response | 241 (73%) ^c | 5 (3%) | 70% (65%,76%) | 347 (70%) ^c | 6 (2%) | 68% (64%,72%) |

^a Non-responder imputation.
^b Treatment difference versus placebo adjusted by investigator site with Mantel-Haenszel weights.
^c p-value < 0.001; p-value is based on the Cochran-Mantel-Haenszel chi-square test stratified by investigator site.

| Table 4 Summary of Clinical Responses (NRI^a) in Psoriasis Studies (Secondary Endpoints) | | | | | | |
|---|---------------------------------------|---|--|---------------------------------------|---|--|
| | VOYAGE 1 | | | VOYAGE 2 | | |
| | TREMFYA™ (N=329) n (%) | Adalimumab (N=334) n (%) | Treatment difference^b (95% CI) | TREMFYA™ (N=496) n (%) | Adalimumab (N=248) n (%) | Treatment difference^b (95% CI) |
| IGA response of 0/1 | | | | | | |
| Week 16 | 280 (85%) ^c | 220 (66%) | 19% (13%,25%) | 417 (84%) ^c | 168 (68%) | 16% (11%,22%) |
| Week 24 | 277 (84%) ^c | 206 (62%) | 23% (17%,29%) | 414 (83%) ^c | 161 (65%) | 18% (12%,25%) |
| IGA response of 0 | | | | | | |
| Week 24 | 173 (53%) ^c | 98 (29%) | 25% (18%,31%) | 257 (52%) ^c | 78 (31%) | 20% (13%,27%) |
| PASI 75 response | | | | | | |
| Week 16 | 300 (91%) ^c | 244 (73%) | 18% (13%,23%) | 428 (86%) ^c | 170 (69%) | 18% (12%,24%) |
| PASI 90 response | | | | | | |
| Week 16 | 241 (73%) ^c | 166 (50%) | 24% (17%,31%) | 347 (70%) ^c | 116 (47%) | 23% (17%,30%) |
| Week 24 | 264 (80%) ^c | 177 (53%) | 28% (22%,34%) | 373 (75%) ^c | 136 (55%) | 20% (14%,27%) |

^a Non-Responder Imputation.
^b Treatment difference versus adalimumab adjusted by investigator site with Mantel-Haenszel weights.
^c p-value < 0.001; p-value is based on the Cochran-Mantel-Haenszel chi-square test stratified by investigator site. Type 1 error rate is controlled based on a pre-defined hierarchical testing procedure.

TREMFYA™ demonstrated superiority to placebo for the co-primary endpoints of IGA cleared (0) or minimal (1), and PASI 90 at week 16 (Table 3).

In addition, TREMFYA™ demonstrated statistical superiority to adalimumab for IGA cleared or minimal (0 or 1), PASI 90 and PASI 75 at week 16 and IGA cleared (0), IGA cleared or minimal (0 or 1) and PASI 90 at week 24 (see Table 4). In VOYAGE 1, with continued treatment over 48 weeks, IGA cleared (0), IGA cleared or minimal (0 or 1) and PASI 90 responses in guselkumab treated patients were maintained and remained significantly greater than those achieved with adalimumab (IGA cleared (0), 50% vs 26%, IGA cleared or minimal (0 or 1), 81% vs 55%, PASI 90, 76% vs. 48%).

In the VOYAGE 1 study, at week 16, 37% of patients receiving TREMFYA™ achieved PASI 100 compared to 17% of adalimumab treated patients, and 1% of placebo treated patients. In VOYAGE 2, at Week 16, 34% of patients receiving TREMFYA™ achieved PASI 100 compared to 21% of adalimumab treated patients, and 1% of placebo-treated patients.

In TREMFYA™ treated-patients, improvement was seen in psoriasis involving the scalp (as measured by the Scalp-specific Investigator Global Assessment [ss-IGA]). Specifically, in the subset of patients with a baseline ss-IGA score ≥ 2 , 83.4% and 80.6% in the TREMFYA™ group in VOYAGE 1 and VOYAGE 2, respectively, achieved an ss-IGA score of 0 or 1 and at least a 2-grade improvement from baseline compared to 14.5% and 10.9% in the placebo group, respectively at week 16.

Maintenance and Durability of Response

To evaluate the maintenance and durability of response, patients originally randomized to TREMFYA™ and who were PASI 90 responders at Week 28 in the VOYAGE 2 study were re-randomized to continue maintenance treatment with TREMFYA™ or be withdrawn from therapy (i.e., placebo). At week 48, 88.6% of patients in the continuous maintenance treatment group were PASI 90 responders compared with 36.8% in the withdrawal group.

Patient-reported outcomes

Significantly greater improvements in psoriasis symptoms (itch, pain, stinging, burning and skin tightness) at Week 16 were seen in TREMFYA™ compared to placebo in both studies based on the Psoriasis Symptoms and Signs Diary (PSSD). Significantly greater proportions of patients on TREMFYA™ compared to adalimumab achieved a PSSD symptom score of 0 (symptom-free) at Week 24 in both studies.

Improvements in the Dermatology Life Quality Index (DLQI) from baseline were observed in patients treated with TREMFYA™ compared to placebo at Week 16.

Active-Controlled Study in Ustekinumab Inadequate Responders–NAVIGATE

The NAVIGATE study evaluated the efficacy of 24 weeks of treatment with TREMFYA™ in patients (N=268) who had an inadequate response (defined as IGA ≥ 2) at Week 16 after initial treatment with ustekinumab (dosed at Week 0 and Week 4). These patients were randomized to either continue ustekinumab treatment every 12 weeks or to switch to TREMFYA™ 100 mg given at Weeks 16, 20, and every 8 weeks thereafter. Baseline characteristics for randomized subjects were similar to those observed in VOYAGE 1 and VOYAGE 2.

In patients with an inadequate response to ustekinumab, a greater proportion of patients who

switched to TREMFYA™ treatment achieved an IGA score of 0 or 1 and had a ≥ 2 -grade improvement at Week 28 compared to patients who continued ustekinumab treatment (31% vs 14%, respectively).

TOXICOLOGY

General Toxicity Studies

In repeat-dose toxicity studies in cynomolgus monkeys, guselkumab was well-tolerated at weekly doses up to 50 mg/kg intravenously for 5 weeks or 50 mg/kg subcutaneously for up to 24 weeks. Additionally, there were no effects on cardiovascular, respiratory, and nervous system function, clinical pathology, or anatomical pathology parameters. At the NOAEL (50 mg/kg once weekly), C_{\max} and AUC_{last} values were approximately 206-fold and 50-fold higher, respectively, than those following a single administration of a 100 mg SC dose to psoriasis patients (4.81 $\mu\text{g/mL}$ and 108.48 $\mu\text{g}\cdot\text{h/mL}$, respectively).

Carcinogenicity and Genotoxicity

Studies have not been conducted to evaluate the carcinogenic or genotoxic potential of guselkumab.

Reproductive and Developmental Toxicology

In a combined embryo-fetal developmental and pre- and post-natal development toxicity study, pregnant cynomolgus monkeys (19, 20, and 20 in the 0, 10 and 50 mg/kg groups, respectively) were administered weekly subcutaneous doses of guselkumab from the beginning of organogenesis to parturition. Neonatal deaths occurred in the offspring of 1 of 16 control monkeys and of 3 of 14 monkeys in each of the guselkumab-administered groups (C_{\max} and AUC_{last} values were 31- and 8-fold greater, respectively, than the human levels). These neonatal deaths were attributed to maternal neglect, trauma, and early or late delivery, although a drug-related effect could not be ruled out. Fetal losses (spontaneous abortions, including stillbirths) were also observed at all dose levels, all of which were within the historical control range for the testing facility, but for which a drug-related effect could also not be ruled out. The clinical significance of these findings is unknown. No guselkumab-related effects on functional or immunological development were observed in the infants from birth through 6 months of age.

No effects on fertility or early embryonic development were observed following administration of female guinea pigs with guselkumab at subcutaneous doses up to 100 mg/kg twice-weekly before mating, through mating, and during early gestation to implantation (C_{\max} and AUC_{last} values were 106- and 12-fold greater, respectively, than the human levels).

In a male fertility and early embryonic development toxicity study conducted in guinea pigs, the incidence of total litter loss (5 of 22 untreated females) was increased following administration of males with guselkumab at a subcutaneous dose of 100 mg/kg twice weekly prior to mating

and through mating for a total of 21 doses. In a second male fertility and early embryonic developmental toxicity study, there were no total litter losses in untreated females mated with treated males (100 mg/kg twice weekly). No effects on male fertility or early embryonic development were observed at a dose of 25 mg/kg (C_{\max} and AUC_{last} values were 51- and 6-fold greater, respectively, than the human levels).

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION**

**TREMFYA™
(guselkumab)
Solution for injection
100 mg/mL**

Read this carefully before you start taking **TREMFYA™** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TREMFYA™**.

What is TREMFYA™ used for?

TREMFYA™ is a prescription medicine used to treat adults with moderate to severe “plaque psoriasis”, an inflammatory condition affecting the skin and nails. Plaque psoriasis can cause raised, thick, red and scaly patches (“psoriatic lesions”) that can appear anywhere on your body. **TREMFYA™** reduces the inflammation and other symptoms of the disease.

How does TREMFYA™ work?

TREMFYA™ contains the active substance guselkumab. Guselkumab is a monoclonal antibody. Monoclonal antibodies are proteins that recognize and bind specifically to certain proteins in the body. This medicine works by neutralizing the activity of a protein called IL-23, which is present at increased levels in diseases such as plaque psoriasis.

Using **TREMFYA™** should improve your skin clearance and reduce your symptoms of psoriasis such as itching, pain, stinging, burning and skin tightness.

What are the ingredients in TREMFYA™?

Medicinal ingredients: guselkumab

Non-medicinal ingredients: L-histidine, L-histidine monohydrochloride monohydrate, sucrose, polysorbate 80 and water for injection.

TREMFYA™ comes in the following dosage forms:

100mg/mL solution for injection in a pre-filled syringe

Do not use TREMFYA™ if:

- You are allergic to guselkumab or any of the ingredients in **TREMFYA™**. See **What are the ingredients in TREMFYA™**.

If you think you are allergic, ask your healthcare professional for advice before using **TREMFYA™**.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TREMFYA™. Talk about any health conditions or problems you may have, including if you:

- are being treated for an infection or if you have an infection that does not go away or keeps coming back. TREMFYA™ may lower your ability to fight infections and may increase your risk of infections.
- have tuberculosis (TB) or have been in close contact with someone with TB.
- think you have an infection or have symptoms of an infection such as
 - fever or flu-like symptoms
 - muscle aches
 - cough
 - shortness of breath
 - burning when you urinate or urinating more often than normal
 - blood in your phlegm (mucus)
 - weight loss
 - warm, red or painful skin or sores on your body different from your psoriasis
 - diarrhea or stomach pain
- have recently had a vaccination or if you are due to have a vaccination during treatment with TREMFYA™. You should not be given certain types of vaccines (live vaccines) while using TREMFYA™.
- are pregnant, think that you may be pregnant or are planning to have baby. If you are a woman of childbearing potential, use adequate contraception while using TREMFYA™ and for at least 12 weeks after the last TREMFYA™ dose. Talk to your doctor about your contraception options.
- are breast-feeding or plan to breast-feed. You and your doctor should decide if you will breast-feed while using TREMFYA™.

After starting TREMFYA™, call your healthcare provider right away if you have any of the symptoms of infection listed above.

- Do not use TREMFYA™ if you have any symptoms of infection unless you are instructed to by your healthcare provider.

Children and adolescents (below the age of 18 years)

TREMFYA™ is not recommended for children and adolescents (under 18 years of age) because it has not been studied in this age group.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take TREMFYA™:

Always use this medicine exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.

TREMFYA™ is given by injection under your skin (subcutaneous injection).

You and your healthcare professional should decide if you should inject TREMFYA™ yourself. It is important not to try to inject yourself until you have been trained by your healthcare professional. A caregiver may also give you your TREMFYA™ injection after proper training.

Before use, remove the carton from the refrigerator. Keep the pre-filled syringe inside the carton and allow it to reach room temperature by waiting for 30 minutes before injection.

Read the “Instructions for Use” document carefully before using TREMFYA™.

Usual dose:

Your doctor will decide how much TREMFYA™ you need and for how long.

- The dose is 100 mg (the content of 1 pre-filled syringe) by subcutaneous injection.
- The first dose may be given by your healthcare provider.
- After the first dose, you will have the next dose 4 weeks later, and then every 8 weeks.

TREMFYA™ is for long-term treatment. Your healthcare professional will regularly monitor your condition to check that the treatment is having the desired effect.

You should not stop using TREMFYA™ unless you think it is causing a severe side effect. Speak to your doctor as soon as possible if this happens.

Overdose:

If you accidentally inject more TREMFYA™ than you should or the dose has been given sooner than prescribed, inform your healthcare professional.

If you think you have taken too much TREMFYA™, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take your TREMFYA™ dose, inject a dose as soon as you remember. Then, take your next dose at your regular scheduled time. If you are not sure what to do, contact your healthcare professional.

What are possible side effects from using TREMFYA™?

As with all medicines, this medicine can cause side effects, although not everybody gets them.

Most of the following side effects are mild to moderate. If any of these side effects becomes severe, tell your healthcare professional.

Some side effects are very common (may affect more than 1 in 10 people)

- Infections of the nose, sinuses, or throat (e.g. common cold)

Some side effects are common (may affect up to 1 in 10 people):

- Redness, pain, swelling, bruising and/or itching at the injection site

- stomach flu (gastroenteritis)
- diarrhea
- headache
- joint pain
- fungal infections of the skin (e.g. athlete's foot)
- herpes simplex infections (e.g. cold sores, genital herpes)

Some side effects are uncommon (may affect up to 1 in 100 people):

- migraine
- yeast infections
- rash

These are not all the possible side effects you may feel when taking TREMFYA™. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect® (www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 1908C
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect® (www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store TREMFYA™ in the refrigerator between 2°C to 8°C (36°F to 46°F)

Do not freeze. Do not use if TREMFYA™ has been frozen.

Do not shake TREMFYA™.

Store in original packaging to protect from light until use.

Keep out of reach and sight of children.

Do not use TREMFYA™:

- if you notice that it is damaged or the seal is broken.
- if the liquid is discoloured, cloudy or you can see other particles floating in it.
- after the expiry date which is stated on the label and on the outer carton after “EXP.”.

This medicine is for single use only. Ask your healthcare professional how to throw away medicines no longer required.

If you want more information about TREMFYA™:

- Talk to your healthcare professional
- For questions or concerns, contact the manufacturer, Janssen Inc. (www.janssen.com/canada)
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website <http://hc-sc.gc.ca/index-eng.php>; the manufacturer’s website www.janssen.com/canada, or by contacting the manufacturer at: 1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by Janssen Inc., Toronto, Ontario, M3C 1L9.

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INSTRUCTIONS FOR USE

TREMFYA™ (guselkumab) Pre-filled syringe



SINGLE-DOSE

PLEASE READ THESE INSTRUCTIONS BEFORE USE **Important**

TREMFYA™ comes as a single-use pre-filled syringe containing one 100 mg dose. Each pre-filled syringe can be used only one time. Throw the used pre-filled syringe away (see Step 3) after each dose, even if there is medicine left in it. Do not reuse your pre-filled syringe.

If your doctor decides that you or a caregiver may be able to give your injections of TREMFYA™ at home, you should receive training on the right way to prepare and inject TREMFYA™ using the pre-filled syringe before attempting to inject.

Read this Instructions for Use document before using the TREMFYA™ pre-filled syringe and each time you get a refill. There may be new information. This instruction guide does not take the place of talking with your doctor about your medical condition or your treatment. Please also read the Package Insert carefully and discuss any questions you may have with your doctor or nurse.

The TREMFYA™ pre-filled syringe is intended for injection under the skin, not into the muscle or vein. After injection, the needle will retract into the body of the device and lock into place.



Storage information

Store in refrigerator at 2° to 8°C. Do not freeze.

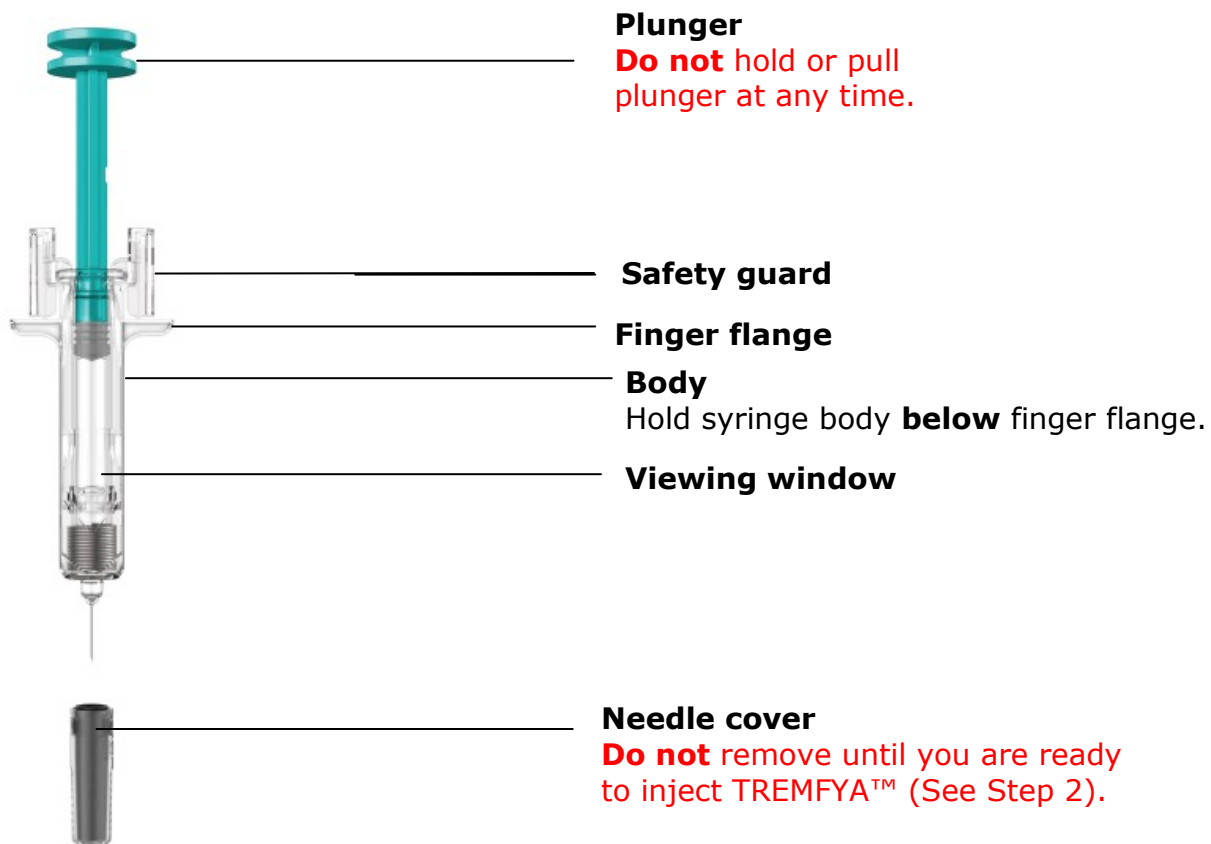
Keep TREMFYA™ and all medicines out of reach and sight of children.

Do not shake the pre-filled syringe.

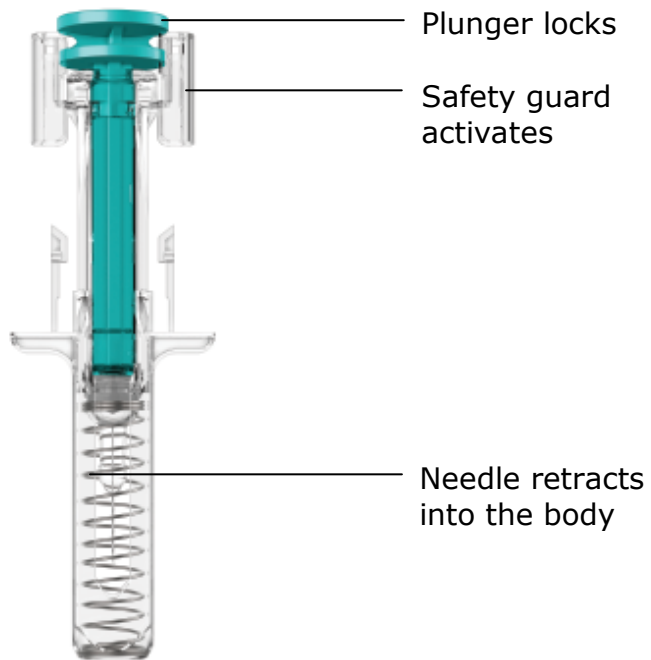
Keep TREMFYA™ pre-filled syringe in the original carton to protect from light and physical damage.

Pre-filled syringe parts

Before injection

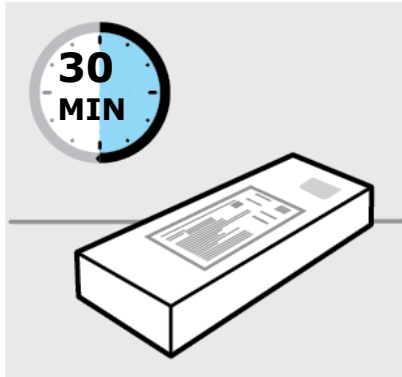


After injection



- **1 Alcohol swab**
- **1 Cotton ball or gauze pad**
- **1 Adhesive bandage**
- **1 Sharps container (See Step 3)**

1. Prepare for your injection



Inspect carton

Remove carton with the pre-filled syringe from the refrigerator. Keep the pre-filled syringe in the carton and let it sit on a flat surface at room temperature for **at least 30 minutes** before use.

Do not warm any other way.

Check the expiration date ('EXP') on the back panel of the carton.

Do not use if the expiration date has passed.

Do not inject TREMFYA™ if the perforations on the carton are broken. Call your doctor or pharmacist for a refill.



Choose injection site

Select from the following areas for your injection:

- **Front of thighs** (recommended)

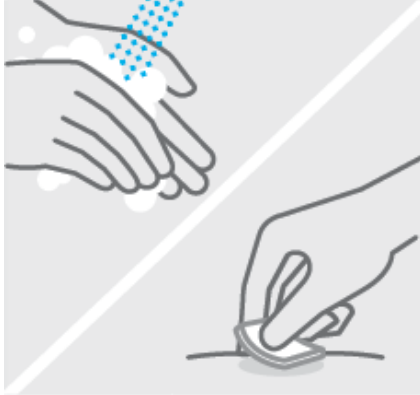
- Lower abdomen

Do not use the 2-inch (5-centimetre) area around belly-button.

- Back of upper arms (if a caregiver is giving you the injection)

Do not inject into skin that is tender, bruised, red, scaly or hard.

Do not inject into areas with scars or stretch marks.

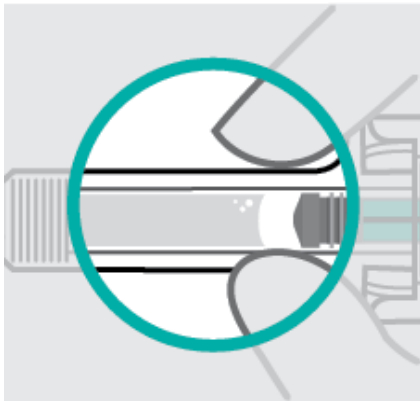


Clean injection site

Wash your hands well with soap and warm water.

Wipe your chosen injection site with an alcohol swab and allow it to dry.

Do not touch, fan or blow on the injection site after you have cleaned it.



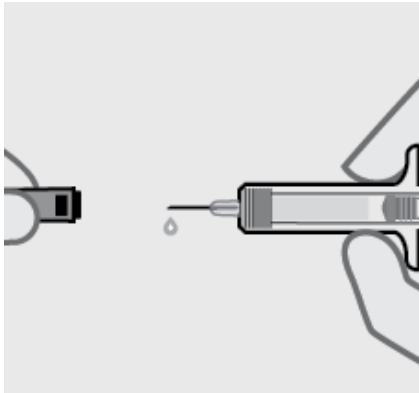
Inspect liquid

Take the pre-filled syringe out of the carton.

Check the liquid in the viewing window. It should be clear to slightly yellow and may contain tiny white or clear particles. You may also see one or more air bubbles. This is normal.

Do not inject if the liquid is cloudy or discolored, or has large particles. Call your doctor or pharmacist for a refill.

2. Inject TREMFYA™ using the pre-filled syringe



Remove needle cover

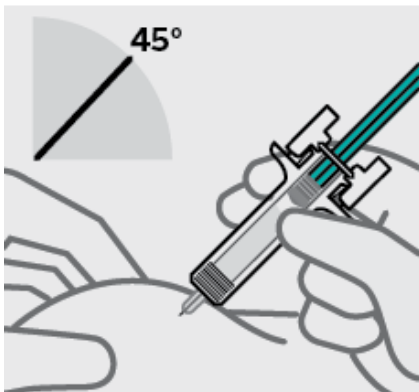
Hold syringe by the body and pull needle cover straight off. It is normal to see a drop of liquid.

Inject within 5 minutes of removing the needle cover.

Do not put needle cover back on, as this may damage the needle or cause a needle stick injury.

Do not touch needle or let it touch any surface.

Do not use the TREMFYA™ pre-filled syringe if it is dropped. Call your doctor or pharmacist for a refill.



Position fingers and insert needle

Place your thumb, index and middle fingers **directly under the finger flange**, as shown.

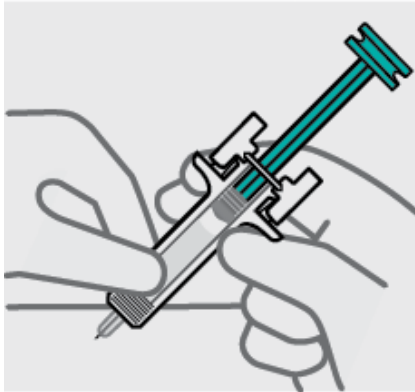
Do not touch plunger or area above finger flange as this may cause the needle safety device to activate.

Use your other hand to pinch skin at the injection site. Position syringe at about a 45 degree angle to the skin.

It is important to pinch enough skin to **inject under**

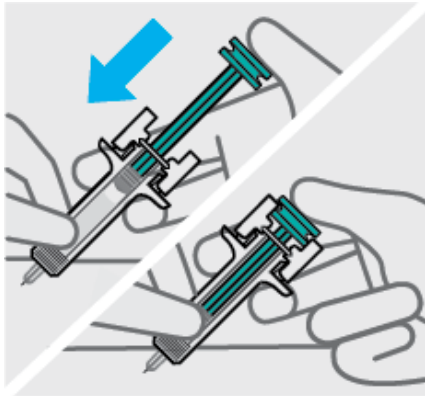
the skin and not into the muscle.

Insert needle with a quick, dart-like motion.



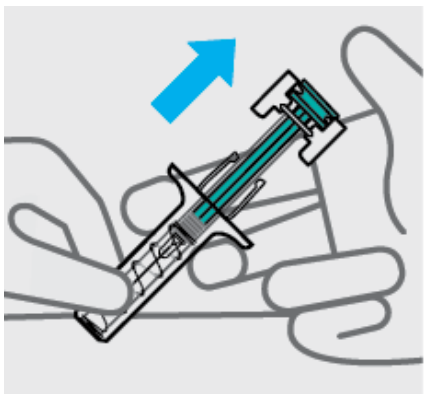
Release pinch and reposition hand

Use your free hand to grasp the body of the syringe.



Press plunger

Place thumb from the opposite hand on the plunger and press the plunger **all the way down until it stops**.



Release pressure from plunger

The safety guard will cover the needle and lock into place, removing the needle from your skin.

3. After your injection

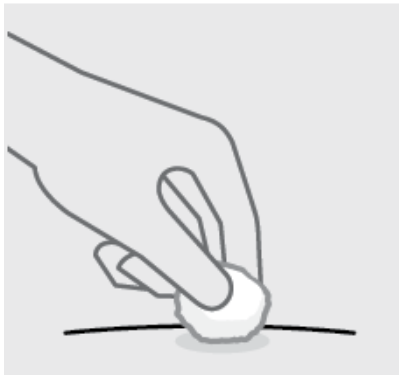


Throw the used pre-filled syringe away

Put your used syringe in a sharps disposal container right away after use.

Do not dispose in your household trash.

Make sure you dispose of the bin as instructed by your doctor or nurse when the container is full.



Check injection site

There may be a small amount of blood or liquid at the injection site. Hold pressure over your skin with a cotton ball or gauze pad until any bleeding stops.

Do not rub the injection site.

If needed, cover injection site with a bandage.



Need Help?

Call your doctor to talk about any questions you may have. For questions or concerns visit the manufacturer's website www.janssen.com/canada, or call 1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by Janssen Inc., Toronto, Ontario, M3C 1L9.

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