PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr DUPIXENT™

dupilumab

solution for subcutaneous injection

150 mg/mL

Immunomodulator, Interleukin inhibitor

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Control No: 201285 Date of Approval: November 30, 2017

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous injection	Solution in a pre-filled syringe with needle shield (PFS-S) or pre-filled syringe (PFS) 150 mg/mL	L-arginine hydrochloride, L-histidine, polysorbate 80, sodium acetate, sucrose, acetic acid for pH adjustment, water for injection. For a complete listing see *Dosage Forms, Composition and Packaging* section.

DESCRIPTION

DUPIXENT is a recombinant human IgG4 monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. DUPIXENT inhibits IL-4 signaling via the Type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4Rα/IL-13Rα).

INDICATIONS AND CLINICAL USE

DUPIXENT™ (dupilumab) is indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

DUPIXENT can be used with or without topical corticosteroids**.**

Geriatrics (≥65 years of age):

Of the 1472 patients with atopic dermatitis exposed to DUPIXENT in a phase 2 dose-ranging study or phase 3 placebo-controlled studies, a total of 67 were 65 years or older. Although no differences in safety or efficacy were observed between older and younger patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and

Conditions). No dose adjustment is recommended for elderly patients.

Pediatrics (< 18 years of age):

Safety and efficacy in pediatric patients have not been established.

CONTRAINDICATIONS

DUPIXENT is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

WARNINGS AND PRECAUTIONS

General

Driving a vehicle or performing other hazardous tasks
DUPIXENT has no or negligible influence on the ability to drive or operate machinery.

Immune

Hypersensitivity
If a systemic hypersensitivity reaction occurs, including generalized urticaria and serum sickness or serum-sickness-like reactions (occurred in less than 1% of subjects who received DUPIXENT in clinical trials), administration of DUPIXENT should be discontinued immediately and appropriate therapy initiated. One case of serum sickness-like reaction and one case of serum sickness reaction, both considered serious, have been reported in clinical trials following the administration of DUPIXENT (see ADVERSE REACTIONS*)*.

Helminth Infection
Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until infection resolves.

Conjunctivitis and Keratitis
Conjunctivitis and keratitis occurred more frequently in subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis recovered or were recovering during the treatment period (see ADVERSE REACTIONS). Keratitis was reported in <1% of the DUPIXENT group (1 per 100 subject-years) in the 16-week monotherapy trials. In the 52-week DUPIXENT + topical corticosteroids (TCS) trial, keratitis was reported in 4% of the DUPIXENT + TCS group (12 per 100 subject-years). Most subjects with keratitis recovered or were recovering during the

treatment period. Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

Concomitant Atopic Conditions
Safety and efficacy have not been established in allergic or atopic conditions other than atopic dermatitis. Patients with comorbid atopic conditions (such as asthma) should be advised not to adjust their treatment without consultation with their physicians. When discontinuing DUPIXENT consider the potential effects on other atopic conditions.

Special Populations

Pregnant Women:
No studies have been conducted with DUPIXENT in pregnant women and relevant data from clinical use are very limited. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. An enhanced pre- and post-natal study exposing pregnant cynomolgus monkeys to a surrogate antibody against IL-4Rα during organogenesis through parturition did not reveal any developmental effects in offspring (see PART II - Toxicology).

Nursing Women:
There is no information regarding the presence of DUPIXENT in human breast milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

Pediatrics (< 18 years of age):
Safety and efficacy in pediatric patients have not been established.

Geriatrics (> 65 years of age):
Of the 1472 patients with atopic dermatitis exposed to DUPIXENT in a phase 2 dose-ranging study or phase 3 placebo-controlled studies, a total of 67 were 65 years or older. Although no differences in safety or efficacy were observed between older and younger patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

ADVERSE REACTIONS

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*.

In the overall exposure pool, a total of 2526 patients with atopic dermatitis were treated with DUPIXENT in controlled and uncontrolled clinical trials. Of these, 739 patients were exposed for at least 1 year.

The safety of DUPIXENT monotherapy was evaluated through week 16 based on data from three randomized, double-blind, placebo-controlled multicenter studies (SOLO 1, SOLO 2, and a phase 2, dose-ranging study) that included 1564 adult patients with moderate-to-severe atopic dermatitis (AD). The study population had a mean age of 38.2 years, 41.1 % was female, 67.9 % white, 21.9 % Asian, 7.1% black, and reported co-morbid atopic conditions such as asthma (39.6%), allergic rhinitis (49.0%), food allergy (37.3%), and allergic conjunctivitis (23.1%).

The safety of DUPIXENT with concomitant topical corticosteroids (TCS) was evaluated based on data from one randomized, double-blind, placebo-controlled multicenter study (CHRONOS). A total of 740 patients were treated up to 52 weeks. The study population had a mean age of 37.1 years, 39.7% was female, 66.2% white, 27.2% Asian, 4.6% black, and reported co-morbid atopic conditions such as asthma (39.3%), allergic rhinitis (42.8%), food allergy (33.4%), and allergic conjunctivitis (23.2%).

In the monotherapy studies, the proportion of patients who discontinued treatment due to adverse events was 1.9% of the placebo group and 1.9% of the DUPIXENT 300 mg every other week (Q2W) group.

In the concomitant TCS study, the proportion of patients who discontinued treatment due to adverse events was 7.6% of the placebo + TCS group and 1.8% of the DUPIXENT 300 mg Q2W + TCS group.

Table 1 summarizes the adverse reactions that occurred in ≥1% of patients treated with DUPIXENT during the first 16-weeks of treatment in placebo-controlled trials.

Table 1 - Adverse Reactions Occurring in ≥1% of Patients with Atopic Dermatitis Treated with DUPIXENT through Week 16 in Placebo-Controlled Trials

Adverse Reaction	DUPIXENT Monotherapy [a]		DUPIXENT + TCS [b]	
	Placebo N=517 n (%)	DUPIXENT 300 mg Q2W N=529 n (%)	Placebo +TCS N=315 n (%)	DUPIXENT 300 mg Q2W + TCS N=110 n (%)
Injection site reaction	28 (5.4%)	51 (9.6%)	18 (5.7%)	11 (10.0%)
Conjunctivitis[c]	12(2.3%)	51(9.6%)	15 (4.8%)	10(9.1%)
Blepharitis	1 (0.2%)	2 (0.4%)	2 (0.6%)	5 (4.5%)
Oral herpes	8 (1.5%)	20 (3.8%)	5 (1.6%)	3 (2.7%)
Eye pruritus	1 (0.2%)	3 (0.6%)	2 (0.6%)	2 (1.8%)
Dry eye	0	1 (0.2%)	1 (0.3%)	2 (1.8%)
Herpes simplex[c]	4 (0.8%)	9 (1.7%)	1 (0.3%)	1 (0.9%)
Keritits[e]	0	1 (0.2%)	0	4(3.6%)
Eosinophilia	2 (0.4%)	9 (1.7%)	0	1 (0.9%)

[a] Safety data from a phase 2, dose-ranging study and the SOLO 1 and SOLO 2 studies.
[b] Safety data from the CHRONOS study. Patients were on background TCS therapy.
[c] Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.
[d] In clinical trials, herpes simplex cases were mucocutaneous, generally mild to moderate in severity, and did not include eczema herpeticum. Eczema herpeticum cases were reported separately and incidence was lower in patients treated with DUPIXENT compared to placebo.
[e] Keratitis cluster includes keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, and ophthalmic herpes simplex.
Q2W: every other week; TCS: topical corticosteroids

The safety profile of DUPIXENT + TCS through week 52 is consistent with the safety profile observed at week 16.

Hypersensitivity
In the overall exposure pool, there was one case reported as serum sickness reaction and one case reported as serum sickness-like reaction following administration of DUPIXENT (see WARNINGS AND PRECAUTIONS, Immune).

Overall Infections
No increase was observed in the overall incidence of infections or serious infections with DUPIXENT compared to placebo in clinical studies. In the 16-week monotherapy clinical studies, serious infections were reported in 1.0% of patients treated with placebo and 0.5% of patients treated with DUPIXENT. In the 52-week CHRONOS study, serious infections were reported in 0.6% of patients treated with placebo and 0.2% of patients treated with DUPIXENT.

Eczema Herpeticum and Herpes Zoster
The rate of eczema herpeticum was similar in the placebo and DUPIXENT groups in 16 week monotherapy studies. However, in the placebo-controlled 52-week long-term CHRONOS study, the incidence of eczema herpeticum in the DUPIXENT combined group (0.2%) was significantly

lower (p=0.047) than the incidence for the placebo group (1.9%).
Herpes zoster was reported in <0.1% of the DUPIXENT groups (<1%) and in <1% of the placebo group (1 per 100 subject-years) in the 16-week monotherapy trials. In the 52-week DUPIXENT + TCS trial, herpes zoster was reported in 1% of the DUPIXENT + TCS group (1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years).

Conjunctivitis
During the 52-week treatment period of concomitant therapy trial (CHRONOS), conjunctivitis was reported in 16% of the DUPIXENT 300 mg Q2W + TCS group (20 per 100 subject-years) and in 9% of the placebo + TCS group (10 per 100 subject-years).

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity with dupilumab. In the 52 week study, approximately 3% of patients in the placebo group and 2% of patients in the DUPIXENT group had anti-drug antibody (ADA) responses lasting more than 12 weeks. Among these patients, 0.7% on placebo and 0.2% treated with DUPIXENT also had neutralizing antibody responses, which were not generally associated with loss of efficacy.

ADA responses were not generally associated with impact on DUPIXENT exposure, safety, or efficacy. In the overall exposure pool, less than 0.1% of patients exhibited high titer ADA responses associated with reduced exposure and efficacy. In addition, there was one patient with serum sickness and one with serum sickness-like reaction (<0.1%) associated with high ADA titers (see WARNINGS AND PRECAUTIONS, Immune).

The observed incidence of persistent ADA responses and neutralizing activity in the assay are highly dependent on the sensitivity and specificity of the assay used. Additionally, the observed incidence of 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 status of the individual patient. For these reasons, comparison of the incidence of antibodies to DUPIXENT with the incidence of antibodies to other products may be misleading.

Abnormal Hematologic and Clinical Chemistry Findings
In clinical studies, transient elevations in blood eosinophils were observed after initiating DUPIXENT treatment in a minority of patients. Eosinophilia was reported in <2% of patients treated with DUPIXENT (see Table 1). There were no other clinically significant laboratory abnormalities.

DRUG INTERACTIONS

Overview

The impact of dupilumab on cytochrome P450 (CYP) enzyme activity has not been studied. Published in vitro studies suggest that IL-4 and IL-13 may modulate CYP450 enzymes; however, the clinical significance of these data is not fully understood.

Drug-Vaccine Interactions

Live Vaccines
DUPIXENT has not been studied with live vaccines. Live vaccines should not be given concurrently with DUPIXENT.

Non-Live Vaccines
Immune responses to vaccination were assessed in a study in which patients with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab. After 12 weeks of dupilumab administration, patients were vaccinated with a Tdap vaccine (T cell-dependent, Adacel®) and a meningococcal polysaccharide vaccine (T cell-independent, Menomune®) and immune responses were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated patients. No adverse interactions between either of the non-live vaccines and dupilumab were noted in the study.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

DUPIXENT is administered by subcutaneous injection.

The recommended dose of DUPIXENT for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week.

DUPIXENT can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.

Missed Dose

If a dose is missed, instruct the patient to administer the injection within 7 days from the missed dose and then resume the patient's original schedule. If the missed dose is not administered within 7 days, instruct the patient to wait until the next dose on the original schedule.

Administration

For the initial 600 mg dose, administer two 300 mg DUPIXENT injections consecutively in different injection sites.

DUPIXENT is intended for use under the guidance of a healthcare provider. A patient may self-inject DUPIXENT or the patient's caregiver may administer DUPIXENT. Provide proper training to patients and/or caregivers on the preparation and administration of DUPIXENT prior to use according to the Instructions for Use (IFU).

DUPIXENT is self-administered by subcutaneous injection into the thigh or abdomen, except for the 5 cm (2 inches) around the navel, using a single-use pre-filled syringe. If somebody else administers the injection, the upper arm can also be used.

It is recommended to rotate the injection site with each injection.

DUPIXENT should not be injected into skin that is tender, damaged or has bruises or scars.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Special populations

Pediatrics (< 18 years of age):
Safety and efficacy in pediatric patients have not been established (see ACTIONS AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Geriatrics (>65 years of age):
No dose adjustment is recommended for elderly patients (see ACTIONS AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Hepatic impairment
No data are available in patients with hepatic impairment (see ACTIONS AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Renal impairment
No dosage adjustment is needed in patients with mild or moderate renal impairment. No data are available in patients with severe renal impairment (see ACTIONS AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Body weight
No dose adjustment for body weight is recommended (see ACTIONS AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

OVERDOSAGE

In clinical studies, no safety issues were identified with single intravenous doses up to 12 mg/kg.

There is no specific treatment for DUPIXENT overdose. In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

DUPIXENT is a recombinant human IgG4 monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. DUPIXENT inhibits IL-4 signaling via the Type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4Rα/IL-13Rα).

IL-4 and IL-13 are key type 2 (including Th2) cytokines involved in atopic disease.

Pharmacodynamics

In clinical trials, treatment with DUPIXENT was associated with decreases from baseline in concentrations of type 2-associated biomarkers, such as thymus and activation-regulated chemokine (TARC/CCL17), total serum IgE, and allergen-specific IgE in serum. A reduction of lactate dehydrogenase (LDH), a biomarker associated with AD disease activity and severity, was observed with DUPIXENT treatment.

DUPIXENT suppressed TARC relative to placebo as early as week 2, with a trend of continued decline to a maximal and sustained suppression by Week 12. The majority of patients treated with DUPIXENT in the CHRONOS study (87.0% and 84.9% of patients in the DUPIXENT 300 mg Q2W and 300 mg QW, respectively) achieved normalized TARC levels compared to 20.0% in the placebo group at week 52.

Total IgE was reduced -74.8% and -73.9% by Week 52 (median change from baseline) with DUPIXENT 300 mg Q2W and 300 mg QW, respectively compared to a 0% reduction in the placebo group. Similar trends were observed for allergen specific IgEs. After 52 weeks of treatment, total IgE was normalized in 11.7% and 15.9% of patients receiving DUPIXENT 300 mg Q2W and 300 mg QW, respectively compared to 4.4% in the placebo group. Similar trends were observed with antigen-specific IgEs, including S. aureus specific enterotoxin A, grass and tree allergens.

Pharmacokinetics

Absorption:
After a single subcutaneous (SC) dose of 75-600 mg dupilumab, median times to maximum concentration in serum (t_{max}) were 3-7 days. The absolute bioavailability of dupilumab following a SC dose is estimated to be 64%, as determined by a population pharmacokinetic (PK) analysis.

Administration of a single loading dose of 600 mg on Day 1 leads to rapid attainment of clinically effective concentrations within 2 weeks.

For every other week dosing (Q2W) with 300 mg, starting with a loading dose of 600 mg, population PK analysis determined steady state concentrations to be achieved after 10 weeks in a typical patient. Mean steady state trough concentration was 74 mg/L.

For weekly dosing (QW) with 300 mg, starting with a loading dose of 600 mg, population PK analysis determined steady state concentrations to be achieved after 13 weeks in a typical patient. Mean steady state trough concentration was 189 mg/L.

Dose Linearity
Due to nonlinear clearance, dupilumab exposure, as measured by area under the concentration-time curve, increases with dose in a greater than proportional manner following single SC doses from 75 - 600 mg.

Distribution:
A volume of distribution for dupilumab of approximately 4.6 L was estimated by population PK analysis, indicating that dupilumab is distributed primarily in the vascular system.

Metabolism:
Specific metabolism studies were not conducted because dupilumab is a protein. Dupilumab is expected to degrade to small peptides and individual amino acids.

Excretion:
Dupilumab elimination is mediated by parallel linear and nonlinear pathways. At higher concentrations, dupilumab elimination is primarily through a non-saturable proteolytic pathway, while at lower concentrations, the non-linear saturable IL-4Rα target-mediated elimination predominates.

After the last steady state dose, the median time for dupilumab concentrations to decrease below the lower limit of detection, determined by population PK analysis, was 10 weeks for the 300 mg Q2W regimen and 13 weeks for the 300 mg QW regimen.

Special Populations and Conditions

Pediatrics:
The pharmacokinetics of dupilumab in pediatric patients has not been studied.

Geriatrics:
Of the 1472 patients with atopic dermatitis exposed to DUPIXENT in a phase 2 dose-ranging study or phase 3 placebo-controlled studies, a total of 67 were 65 years or older. Although no differences in safety or efficacy were observed between older and younger patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

In subjects who are 65 years and older, the mean steady-state trough concentrations of dupilumab were 69.4 mg/L and 166 mg/L, respectively, for 300 mg administered every 2 weeks and weekly. No dose adjustment in this population is recommended.

Age was not found to be associated with any clinically meaningful impact on the systemic exposure of DUPIXENT determined by population PK analysis.

Gender:
Gender was not found to be associated with any clinically meaningful impact on the systemic exposure of DUPIXENT determined by population PK analysis.

Race:
Race was not found to be associated with any clinically meaningful impact on the systemic exposure of DUPIXENT by population PK analysis.

Hepatic Impairment:
Dupilumab, as a monoclonal antibody, is not expected to undergo significant hepatic elimination. No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of dupilumab.

Renal Impairment:
Dupilumab, as a monoclonal antibody, is not expected to undergo significant renal elimination. No clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of dupilumab. Population PK analysis did not identify mild or moderate renal impairment as having a clinically meaningful influence on the systemic exposure of DUPIXENT. No data are available in patients with severe renal impairment.

Body weight:
No dose adjustment for body weight is recommended.

STORAGE AND STABILITY

Store refrigerated at 2°C to 8°C in the original carton to protect from light.

Do not freeze.

Do not expose to heat.

Do not shake.

Do not use beyond the expiry date stamped on the carton and container label.

SPECIAL HANDLING INSTRUCTIONS

The patient may either self -inject DUPIXENT, or a caregiver may administer DUPIXENT, after guidance has been provided by a healthcare professional on proper subcutaneous injection technique.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If the solution is discolored or contains visible particulate matter, the solution should not be used.

The pre-filled syringe with a needle shield or pre-filled syringe should be allowed to reach room temperature by waiting for 45 min before injecting DUPIXENT.

If necessary, pre-filled syringes may be kept at room temperature up to 25°C for a maximum of 14 days. Do not store above 25°C. After removal from the refrigerator, DUPIXENT must be used within 14 days or discarded.

The pre-filled syringe should not be exposed to heat or direct sunlight.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

DUPIXENT is supplied as a clear to slightly opalescent, colorless to pale yellow sterile, preservative-free, solution, which is free from visible particulates.

DUPIXENT is available in a single-use pre-filled syringe with needle shield (PFS-S) or a single-use pre-filled syringe (PFS), designed to deliver 300 mg dupilumab in 2 mL solution (150 mg/mL) via subcutaneous injection.

Non-medicinal ingredients: L-arginine hydrochloride, L-histidine, polysorbate 80, sodium acetate, sucrose, and water for injection, adjusted to pH 5.9 with acetic acid.

Pre-Filled Syringe with needle shield

- DUPIXENT' is provided as a single dose in a 2.25-mL siliconized clear Type-1 glass pre-filled syringe with a fixed 27 gauge ½ inch, thin wall stainless steel staked needle and passive needle shield.
- The needle cap is not made with natural rubber latex.

Pre-filled Syringe

- DUPIXENT is provided as a single dose in a 2.25-mL siliconized clear Type-1 glass pre-filled syringe with a fixed 27 gauge ½ inch, thin wall stainless steel staked needle.
- The needle cap is not made with natural rubber latex.

DUPIXENT is available in packs containing 1 or 2 pre-filled syringes with needle shield or pre-filled syringes.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

DUPIXENT is a fully human IgG4 monoclonal antibody produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture.
Dupilumab is a covalent heterotetramer consisting of two disulfide-linked human heavy chains, each covalently linked through a disulfide bond to a human kappa light chain. There is a single N-linked glycosylation site in each heavy chain, located within the CH2 domain of the Fc constant region of the molecule. The DUPIXENT heavy chain has an immunoglobulin (Ig) G4P isotype constant region. IgG4P is an IgG4 constant region with a single amino acid substitution in the hinge region that recreates the IgG1 hinge sequence in order to stabilize IgG4 dimer formation. The variable domains of the heavy and light chains combine to form the IL-4Rα binding site within the antibody.

Dupilumab has a molecular weight of approximately 147 kDa.

CLINICAL TRIALS

Study demographics and trial design

Three randomized, double-blind, placebo-controlled trials (SOLO 1, SOLO 2, and CHRONOS) enrolled a total of 2119 subjects 18 years of age and older with moderate-to-severe atopic dermatitis (AD) not adequately controlled by topical medication(s). Disease severity was defined by an Investigator's Global Assessment (IGA) score ≥3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥16 on a scale of 0 to 72, and a minimum body surface area involvement of ≥10%. At baseline, 59% of subjects were male, 67% were white, 52% of subjects had a baseline IGA score of 3 (moderate AD), and 48% of subjects had a baseline IGA of 4 (severe AD). The baseline mean EASI score was 33 and the baseline weekly averaged peak pruritus Numeric Rating Scale (NRS) was 7 on a scale of 0-10.

In all three trials, subjects in the DUPIXENT group received subcutaneous injections of DUPIXENT 600 mg at Week 0, followed by 300 mg every other week (Q2W). In the monotherapy trials (SOLO 1 and SOLO 2), subjects received DUPIXENT or placebo for 16 weeks.

In the concomitant therapy trial (CHRONOS), subjects received DUPIXENT or placebo with concomitant topical corticosteroids (TCS) and as needed topical calcineurin inhibitors for problem areas only, such as the face, neck, intertriginous and genital areas for 52 weeks.

All three trials assessed the primary endpoint, the change from baseline to Week 16 in the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement. Other endpoints included the proportion of subjects with EASI-75 (improvement of at least 75% in EASI score from baseline), and reduction in itch as defined by at least a 4point improvement in the peak pruritus NRS from baseline to Week 16.

Table 2 - Summary of patient demographics for clinical trials in patients with moderate-to-severe atopic dermatitis (AD)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender
SOLO 1	Randomized, double-blind, placebo-controlled, parallel group, in adults with moderate-to-severe AD	Subcutaneous: dupilumab vs. placebo - Dupilumab: 600 mg loading dose, then 300 mg Q2W or 300 mg QW - Placebo 16 weeks	Dupilumab: - 300 mg Q2W: n = 224 - 300 mg QW: n = 223 Placebo: n = 224	39.5 (18-85)	M: 58.1% F: 41.9%

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender
SOLO 2	Randomized, double-blind, placebo-controlled, parallel group, in adults with moderate-to-severe AD	Subcutaneous: dupilumab vs. placebo - Dupilumab: 600 mg loading dose, then 300 mg Q2W or 300 mg QW - Placebo 16 weeks	Dupilumab: - 300 mg Q2W: n = 233 - 300 mg QW: n = 239 Placebo: n = 236	37.1 (18-88)	M: 57.6% F: 42.4%
CHRONOS	Randomized, double-blind, placebo-controlled, parallel group, in adults with moderate-to-severe AD	Dupilumab + topical corticosteroids (TCS) vs. placebo+TCS* Subcutaneous: - Dupilumab: 600 mg loading dose, then 300 mg Q2W or 300 mg QW - Placebo 52 weeks	Dupilumab: - 300 mg Q2W: n = 106 - 300 mg QW: n = 319 Placebo: n = 315	37.1 (18-81)	M: 60.3% F: 39.7%

* Patients received DUPIXENT or placebo with concomitant use of TCS starting at baseline using a standardized regimen. Patients were also permitted to use topical calcineurin inhibitors (TCI)
Q2W: every other week; QW: weekly

Study results

Clinical response at Week 16 (Trials SOLO 1, SOLO 2, and CHRONOS)

In SOLO 1, SOLO 2 and CHRONOS, from baseline to week 16, a clinically and significantly greater proportion of patients randomized to DUPIXENT achieved an IGA 0 or 1 response, EASI-75, and/or an improvement of ≥4 points on the pruritus NRS compared to placebo (see Table 3).

Table 3: Efficacy Results of DUPIXENT Monotherapy and concomitant TCS[f] at Week 16 (FAS)

	SOLO 1 (FAS)[a]		SOLO 2 (FAS)[a]		CHRONOS (FAS)[f]	
	Placebo	**DUPIXENT 300 mg Q2W**	**Placebo**	**DUPIXENT 300 mg Q2W**	**Placebo + TCS**	**DUPIXENT 300 mg Q2W+TCS**
Patients randomized	224	224	236	233	315	106
IGA 0 or 1[b], % responders [c]	10.3 %	37.9 %[e]	8.5 %	36.1 %[e]	12.4 %	38.7 %
EASI-75, % responders [c]	14.7 %	51.3 %[e]	11.9 %	44.2 %[e]	23.2 %	68.9 %[e]
EASI-90, % responders [c]	7.6 %	35.7 %[e]	7.2 %[e]	30.0 %	11.1 %[e]	39.6 %[e]
Number of patients with baseline pruritus NRS score ≥4	212	213	221	225	299	102
Pruritus NRS (≥4-point improvement), % responders [c, d]	12.3 %	40.8 %[e]	9.5%	36.0 %[e]	19.7 %	58.8 %[e]

IGA = Investigator's Global Assessment scale; EASI = Eczema Area and Severity Index; NRS = pruritus Numerical Rating Scale; Q2W = every other week

[a] Full analysis set (FAS) includes all patients randomized.

[b] Responder was defined as a patient with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥ 2 points on a 0-4 IGA scale.

[c] Patients who received rescue treatment or with missing data were considered as non-responders.

[d] a significantly greater proportion of patients on DUPIXENT had improvement in pruritus NRS of ≥ 4 points compared to placebo at week 2 ($p<0.01$)

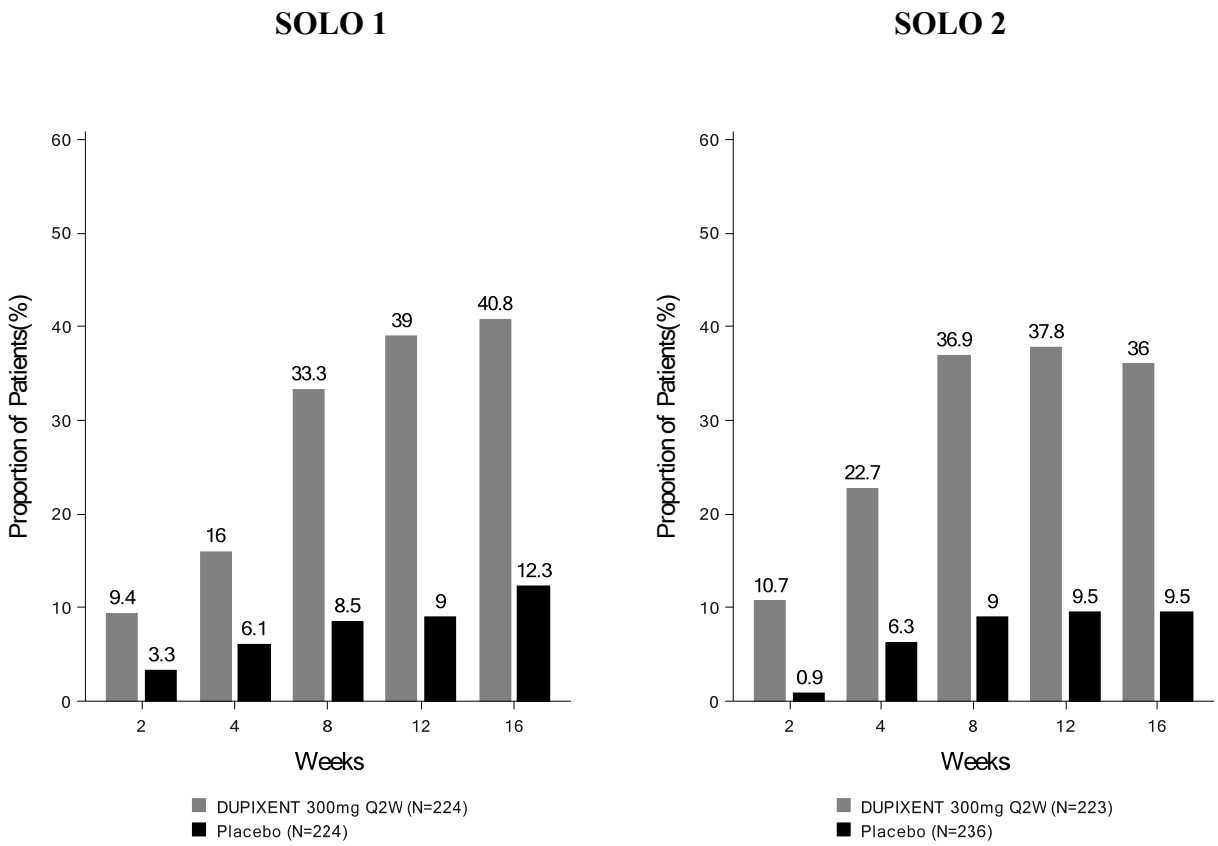
[e] p-value <0.0001

[f] All patients were on background TCS therapy and patients were permitted to use topical calcineurin inhibitors.

The primary and key secondary efficacy endpoints (categorical) were analyzed using the Cochran-Mantel-Haenszel test. To control the total type 1 error rate at 0.05, each dose regimen was tested at $\alpha=0.025$ and a hierarchical testing procedure was used for the multiple endpoints within each dose regimen. Results are based on patient considered non-responder after rescue treatment use.

A significantly greater proportion of patients randomized to DUPIXENT achieved a rapid improvement in the pruritus NRS compared to placebo (defined as ≥4-point improvement as early as week 2; $p<0.01$) and the proportion of patients responding on the pruritus NRS continued to increase through the treatment period (see Figure 1).

Figure 1- Proportion of patients with ≥ 4-point Improvement on the Pruritus NRS in SOLO 1[a] and SOLO 2[a] (FAS)[b]



[a] In the primary analyses of the efficacy endpoints, subjects who received rescue treatment or with missing data were considered non-responders.
[b] Full Analysis Set (FAS) includes all subjects randomized.

Treatment effects in subgroups (weight, age, gender, race, and background treatment, including immunosuppressants) in SOLO 1 and SOLO 2 were in general consistent with the results in the overall study population.

In studies SOLO 1, SOLO 2, and CHRONOS, a third randomized treatment arm of DUPIXENT 300 mg QW did not demonstrate additional treatment benefit over DUPIXENT 300 mg Q2W.

52-Week Concomitant TCS Study (CHRONOS)

Trial CHRONOS is ongoing. In this trial, of the 421 subjects, 353 had been on study for 52 weeks at the time of data analysis. Of these 353 subjects, responders at Week 52 represent a mixture of subjects who maintained their efficacy from Week 16 (e.g., 53% of DUPIXENT IGA 0 or 1 responders at Week 16 remained responders at Week 52) and subjects who were non-responders at Week 16 who later responded to treatment. Results of supportive analyses of the 353 subjects in the CHRONOS trial are presented in Table 4.

Table 4 - The Percentage of Responders in Clinical Trial CHRONOS by Treatment Arm and Responder Status at Week 16 and Week 52

	DUPIXENT 300 mg Q2W + TCS	**Placebo + TCS**
Number of Subjects[a]	89	264
Responder[b,c] at Week 16 and 52	22%	7%
Responder at Week 16 but Non-responder at Week 52	20%	7%
Non-responder at Week 16 and Responder at Week 52	13%	6%
Non-responder at Week 16 and 52	44%	80%
Overall Responder[b,c] Rate at Week 52	36%	13%

[a] In CHRONOS, of the 421 randomized and treated subjects, 68 subjects (16%) had not been on study for 52 weeks at the time of data analysis.
[b] Responder was defined as a subject with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥2 points on a 0-4 IGA scale.
[c] Subjects who received rescue treatment or with missing data were considered as non-responders.

Additional Secondary Endpoints

Patient reported outcomes in both monotherapy studies (SOLO1 and SOLO2) and in the Dupixent +TCS study (CHRONOS) were consistent with significant improvements observed in the physician reported outcomes.

A larger proportion of patients treated with DUPIXENT had ≥4 points improvement (corresponding to minimal clinically important difference) in POEM and DLQI in SOLO1, SOLO2, and CHRONOS studies compared to placebo.

In SOLO 1, the proportion of DUPIXENT-treated responders for POEM and DLQI was 67.6% and 64.1%, respectively, compared to 26.9% and 30.5% for placebo at week 16.

In SOLO 2, the proportion of DUPIXENT-treated responders for POEM and DLQI was 71.7% and 73.1%, respectively, compared to 24.4% and 27.6% for placebo at week 16.

In CHRONOS, the proportion of DUPIXENT-treated responders for POEM and DLQI was 76.4% and 80.0%, respectively, compared to 26.1% and 30.3% for placebo at week 52.

DETAILED PHARMACOLOGY

Dupilumab binds specifically to human IL-4Rα and does not react with any other animal species. Pivotal toxicology studies were therefore conducted using surrogate antibodies against the IL-4Rα of cynomolgus monkeys and CD-1 mice.

Animal Pharmacology

Dupilumab binds with high affinity to human IL-4Rα and inhibits both IL-4 and IL-13 mediated signaling in vitro and in vivo. Administration of dupilumab leads to a reduction in type 2 (including Th2) inflammation in different mouse models using mice that express human IL-4Rα and human IL-4. In the house dust mite (HDM) allergen inflammation model, dupilumab decreases circulating levels of IgE and allergen-specific IgG1, reduces pulmonary infiltration of eosinophils, and reduces goblet cell metaplasia in this model of type 2 (including Th2)-driven inflammation.

TOXICOLOGY

No significant adverse effects were observed in cynomolgus monkeys when administered a surrogate antibody against IL-4Rα by subcutaneous or intravenous injection up to dose levels of 100 mg/kg/week for 6 months (approximately 25-times the steady state exposure for the maximum recommended clinical dose). Serum drug levels achieved at these dosages were sufficient to have fully saturated the monkey IL-4Rα.

No juvenile toxicology studies have been conducted with dupilumab or any of its surrogates.

Carcinogenesis, Mutagenesis and Impairment of Fertility and Reproduction

Carcinogenicity studies have not been conducted with dupilumab.

No significant adverse embryofetal, morphological, functional or immunological developmental effects were observed in offspring of pregnant cynomolgus monkeys exposed to a surrogate antibody against IL-4Rα by subcutaneous injection from the beginning of organogenesis through parturition up to dose levels of 100 mg/kg/week. The overall rate of embryofetal loss during gestation was 5 of 20 (25%) in control animals, 10 of 20 (50%) in animals treated with 25 mg/kg/week, and 3 of 18 (17%) in animals treated with 100 mg/kg/week. Concentrations of the surrogate antibody observed in the infant monkeys at birth were comparable to those observed in maternal serum, indicating placental transfer.

No effects on fertility parameters, including reproductive organs, menstrual cycle length, or sperm analyses were observed in sexually mature mice receiving a murine surrogate antibody against IL-4Rα by subcutaneous injection up to dose levels of 200 mg/kg/week.

REFERENCES

1. Simpson EL et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. N Engl J Med. 2016; 375(24):2335-2348.

2. Blauvelt A et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1 year, randomized, double-blinded, placebo-controlled phase 3 trial. Lancet 2017;389:2287-303.

3. Thaçi D, Simpson EL, Beck LA et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. Lancet. 2016 Jan 2; 387(10013):40-52. doi: 10.1016/S0140-6736(15)00388-8. Epub 2015 Oct 8.

4. McGregor S, Farhangian ME, Feldman SR. Dupilumab for the treatment of atopic dermatitis: a clinical trial review. Expert Opin Biol Ther. 2015; 15(11):1657-60.

5. Blakely K, Gooderham M, Papp K. Dupilumab, A Monoclonal Antibody for Atopic Dermatitis: A Review of Current Literature. Skin Therapy Lett. 2016 Mar;21(2):1-5.

6. Hamilton JD, Suárez-Fariñas M, Dhingra N et al. Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis. J Allergy Clin Immunol. 2014 Dec;134(6):1293-300. doi: 10.1016/j.jaci.2014.10.013.

7. Beck LA, Thaçi D, Hamilton JD et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med. 2014 Jul 10;371(2):130-9. doi: 10.1056/NEJMoa1314768.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

Pr DUPIXENT™

Dupilumab solution for subcutaneous injection

Read this carefully before you start taking DUPIXENT 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 DUPIXENT.

What is DUPIXENT used for?

DUPIXENT is an injectable prescription medicine used to treat adult patients with moderate-to-severe atopic dermatitis, also known as atopic eczema. DUPIXENT can be used with or without topical corticosteroids.

It is not known if DUPIXENT is safe and effective in children below age of 18 years.

How does DUPIXENT work?

DUPIXENT contains the active substance dupilumab.

Dupilumab is a monoclonal antibody (a type of specialized protein) that blocks the action of proteins called IL-4 and IL-13. IL-4 and IL-13 play a major role in the symptoms of atopic dermatitis.

Using DUPIXENT for atopic dermatitis will benefit you by improving the condition of your skin and reducing itch.

What are the ingredients in DUPIXENT?

Medicinal ingredients: dupilumab
Non-medicinal ingredients: acetic acid, L-arginine hydrochloride, L-histidine, polysorbate 80, sodium acetate, sucrose, water for injection.

DUPIXENT comes in the following dosage forms:

DUPIXENT comes as a single-dose (1 time use) pre-filled syringe with or without needle shield. Your healthcare provider will prescribe the type that is best for you.

Do not use DUPIXENT if:

Do not use DUPIXENT if you are allergic to dupilumab or to any of the ingredients in DUPIXENT.

DUPIXENT can potentially cause serious side effects, including generalized allergic (hypersensitivity) reactions. You must look for signs of these conditions while you are taking DUPIXENT. Stop taking DUPIXENT and tell your doctor or seek medical help immediately if you notice any signs of an allergic reaction (see also the table "Serious side effects and what to do about them" below).

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

- have a parasitic (intestinal parasites) infection . DUPIXENT may weaken your resistance to infections caused by parasites. If you already have a parasitic infection, it should be treated before you start treatment with DUPIXENT. If you live in a region where these infections are common or if you are travelling to such a region, check with your doctor.
- are pregnant or plan to become pregnant. It is not known if DUPIXENT will harm your unborn baby. Tell your healthcare provider if you become pregnant while taking DUPIXENT.
- are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will take DUPIXENT or breastfeed. You should not do both without talking to your healthcare provider first.
- have other allergic conditions such as asthma.
- are scheduled to receive a vaccination
- have eye problems (e.g., itching, redness)

Other warnings you should know about:

There is no experience with DUPIXENT in children and adolescents less than 18 years of age. Therefore, the use of DUPIXENT is not recommended in this age group.

DUPIXENT is unlikely to influence your ability to drive and use machines.

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

The following may interact with DUPIXENT:

Inform your healthcare professional that you are taking DUPIXENT if you recently received a vaccine or if you are about to receive a vaccine. DUPIXENT should not be used concomitantly with certain types of vaccines.

How to take DUPIXENT:

Always check the label of your pre-filled syringe before each injection to make sure you have the correct product.

DUPIXENT should be allowed to reach room temperature by waiting for 45 minutes after removing from the refrigerator before injecting.

DUPIXENT is injected under the skin (subcutaneous use) of your upper leg (thigh), stomach area (abdomen, except 5 cm around your belly button); if somebody else gives you the injection, you can also use the upper arm. Choose a different spot each time you inject (e.g. right thigh then left thigh, or right abdomen then left abdomen). Do not inject into skin that is tender, damaged or has bruises or scars.

Do not inject DUPIXENT together with other injectable medicines at the same injection site.

It is important that you do not stop using DUPIXENT without talking with your healthcare provider. Prior to discontinuing DUPIXENT check with your doctor if you need to adjust your treatment or need to manage other allergic and or atopic conditions.

Do not use DUPIXENT for a condition for which it was not prescribed. Do not give DUPIXENT to other people, even if they have the same symptoms that you have. It may harm them.

Learning how to use the pre-filled syringe (with or without needle shield)

- Before you use the pre-filled syringe for the first time, your doctor, pharmacist or nurse will show you or your caregiver how to inject DUPIXENT. Do not try to inject DUPIXENT until you or your caregiver have been shown the correct way by your healthcare provider.
- Always read and use the pre-filled syringe as described in the "Instructions for Use" provided in the box.

Usual dose:

Use DUPIXENT exactly as prescribed by your healthcare provider.

The first time you will start DUPIXENT you will receive 600 mg (two (2) injections of 300 mg each). Thereafter, DUPIXENT is given as an injection (300 mg) once every other week.

Overdose:

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

Missed Dose:
If you miss a dose of DUPIXENT, give the injection within 7 days from the missed dose, and then continue with the original schedule. If the missed dose is not given within 7 days, wait until the next scheduled dose to give your DUPIXENT injection.

What are possible side effects from using DUPIXENT?

DUPIXENT may cause allergic reactions. Stop taking DUPIXENT and tell your doctor or seek medical help immediately if you notice any signs of an allergic reaction, such as:

- fever
- feeling ill
- swollen lymph nodes
- hives
- skin rash
- skin or eyelid itching
- joint pain

These are not all the possible side effects you may feel when taking DUPIXENT. If you experience any side effects not listed here, contact your healthcare professional. Please also see "Do not use DUPIXENT if" section above.

The most common side effects of DUPIXENT include:

- injection site reactions
- eye dryness, redness or itching
- eyelid itching, redness and/or swelling
- oral herpes (cold sores)

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON Allergic reactions			✓

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;
- 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 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

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:

Keep out of reach and sight of children.

Do not use this medicine after the expiry date which is stated on the label and carton.

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

Keep the syringe in the outer carton in order to protect from light.

Do not expose to extreme heat.

DUPIXENT should be allowed to reach room temperature by waiting for 45 minutes after removing from the refrigerator before injecting.

If necessary, pre-filled syringes may be kept at room temperature up to 25°C, away from direct heat and light, for a maximum of 14 days. Do not store above 25°C. After removal from the refrigerator, DUPIXENT must be used within 14 days or discarded.

Do not use this medicine if the solution is discolored or cloudy, or if it contains visible flakes or particles.

After use, put the syringe into a puncture-resistant container. Always keep the container out of the reach of children. Ask your health care provider or pharmacist how to throw away the container. Do not recycle the container.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how

to throw away medicines you no longer use. These measures will help protect the environment.

If you want more information about DUPIXENT:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.sanofigenzyme.ca, or by calling 1-800-589-6215.

This leaflet was prepared by Sanofi-aventis Canada Inc.

Last Revised: November 28, 2017

INSTRUCTIONS FOR USE

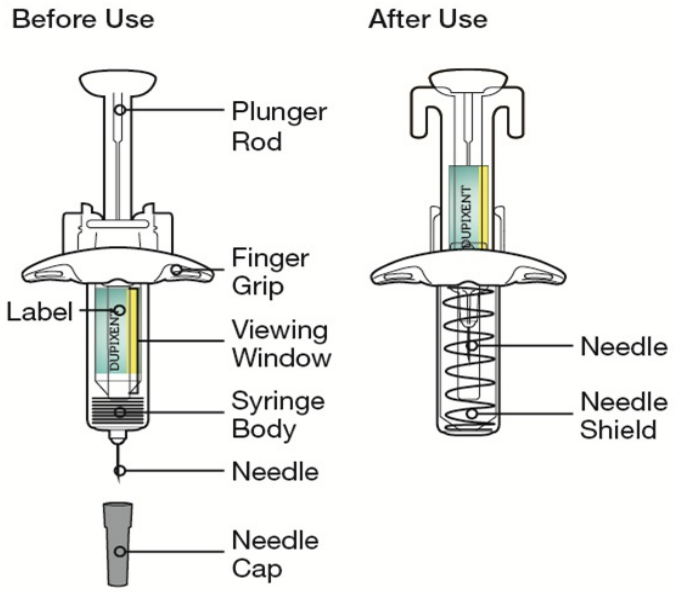
DUPIXENT SINGLE-DOSE PRE-FILLED SYRINGE WITH NEEDLE SHIELD

Read the Instructions for Use before using the DUPIXENT Pre-filled Syringe.

This device is a **Single-dose** Pre-filled Syringe (called "Syringe" in these instructions). It contains 300 mg of DUPIXENT for injection under the skin (subcutaneous injection).

Keep these instructions for future use. If you have any further questions, you should ask your healthcare provider or call 1-800-589-6215.

The parts of the DUPIXENT syringe are shown in this picture.



Important Information

- It is important that you do not try to give yourself or someone else the injection unless you have received training from your healthcare provider.
- Read all of the instructions carefully before using the Syringe.
- Ask your healthcare provider how often you will need to inject the medicine.
- Ask your healthcare provider to show you the right way to use the Syringe before you inject for the first time.
- Rotate the injection site each time you inject.
- To reduce the risk of accidental needle sticks, each pre-filled syringe has a needle shield that is automatically activated to cover the needle after you have given your injection

- **Do not** use the Syringe if it has been damaged.
- **Do not** use the Syringe if the Needle Cap is missing or not securely attached.
- **Do not** touch the Plunger Rod until you are ready to inject.
- **Do not** inject through clothes.
- **Do not** get rid of any air bubbles in the Syringe.
- **Do not** pull back on the Plunger Rod at any time.
- **Do not** re-use the Syringe.

How to Store DUPIXENT:

- Keep the Syringe(s) out of the reach of children.
- Keep unused Syringes in the original carton and store in the refrigerator between 2ºC and 8ºC.
- Remove the Syringe from the refrigerator at least 45 minutes before your injection so that it reaches room temperature.
- **Do not** keep DUPIXENT at room temperature for more than 14 days.
- **Do not** shake the Syringe at any time.
- **Do not** heat the Syringe.
- **Do not** freeze the Syringe.
- **Do not** put the Syringe into direct sunlight.

How to Dispose of (Throw Away) Used Syringes

Put your used Needles and Syringes in a-puncture-resistant container right away after use.

Do not dispose of (throw away) the Syringes in your household trash.

If you do not have a puncture-resistant container, you may use a household container that is:

- made of a heavy-duty plastic;
- can be closed with a tightfitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,

- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container

When your puncture-resistant container is almost full, you will need to follow your provincial or local regulations for the correct way to dispose of it.

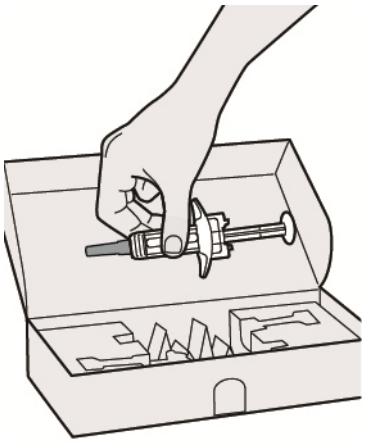
Step 1: Remove

Remove the Syringe from the carton by holding the middle of the Syringe Body:

Do not pull off the Needle Cap until you are ready to inject.

Do not use the Syringe if it has been damaged.

Do not keep DUPIXENT at room temperature for more than 14 days.



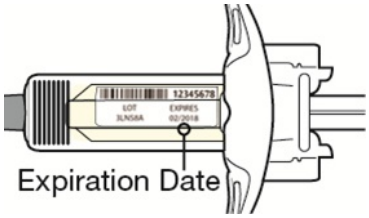
Step 2: Prepare

Ensure you have the following:
- the DUPIXENT Pre-filled Syringe
- 1 alcohol wipe*
- 1 cotton ball or gauze*
- a puncture-resistant container* (See Step 13)

**Items not included in the carton*

Look at the label:
- Check the expiration date
- Check that you have the correct product and dose

Do not use the Syringe if the expiration date has passed.



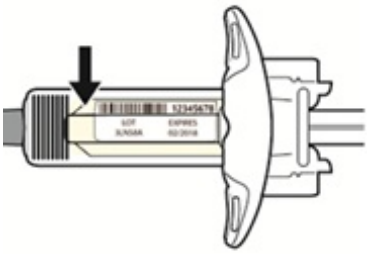
Step 3: Inspect

Look at the medicine through the viewing window on the Syringe:

Check if the liquid is clear and colorless to pale yellow.

Note: You may see an air bubble; this is normal.

Do not use the Syringe if the liquid is discolored or cloudy, or if it contains visible flakes or particles.



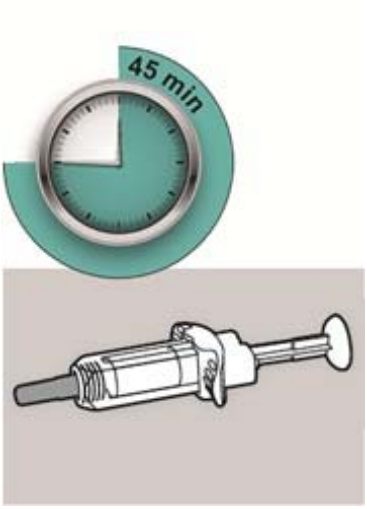
Step 4: Wait 45 minutes

Lay the Syringe on a flat surface and let it naturally warm to room temperature for at least 45 minutes.

Do not heat the Syringe.

Do not put the Syringe into direct sunlight.

Do not keep DUPIXENT at room temperature for more than 14 days.

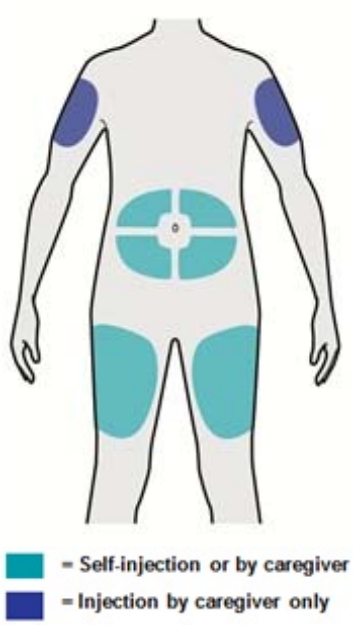


Step 5: Select

Select the injection site.

- You can inject into your thigh or stomach, except for the 5 cm (2 inches) around your navel (belly-button)
- If somebody else gives you the injection, you can also use the upper arm.

Do not inject into skin that is tender, damaged or has bruises or scars.



Step 6: Clean

Wash your hands.

Clean the injection site with an alcohol wipe.

Let your skin dry before injecting.

Do not touch the injection site again or blow on it before the injection.

Step 7: Pull

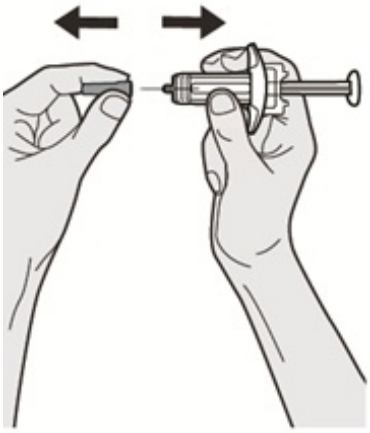
Hold the Syringe in the middle of the Syringe Body with the Needle pointing away from you and pull off the Needle Cap.

Do not put the Needle Cap back on.

Do not touch the Needle.

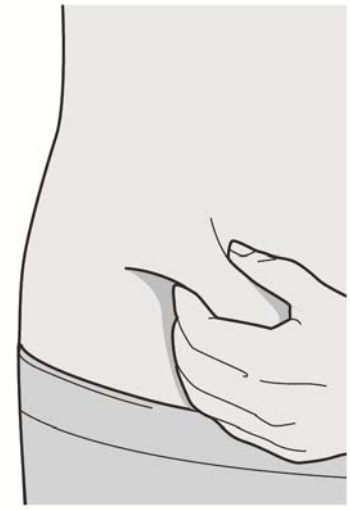
Do not inject if the Needle is damaged

Inject your medicine immediately after removing the Needle Cap.



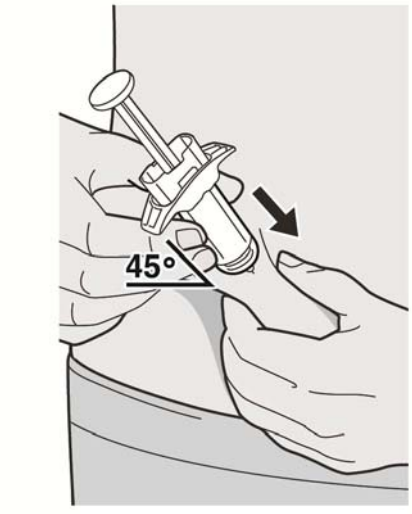
Step 8: Pinch

Pinch a fold of skin at the injection site, as shown in the picture.



Step 9: Insert

Insert the Needle completely into the fold of the skin at roughly a 45º angle.



Step 10: Push

Relax the pinch.

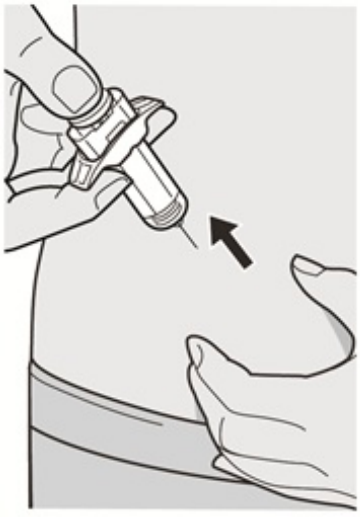
Push the Plunger Rod down slowly and steadily as far as it will go until the Syringe is empty.

Note: You will feel some resistance. This is normal.

Step 11: Remove

Keep pressing down on the Plunger and remove the Needle from the skin at the same angle it was inserted.

Do not put the Needle Cap back on.

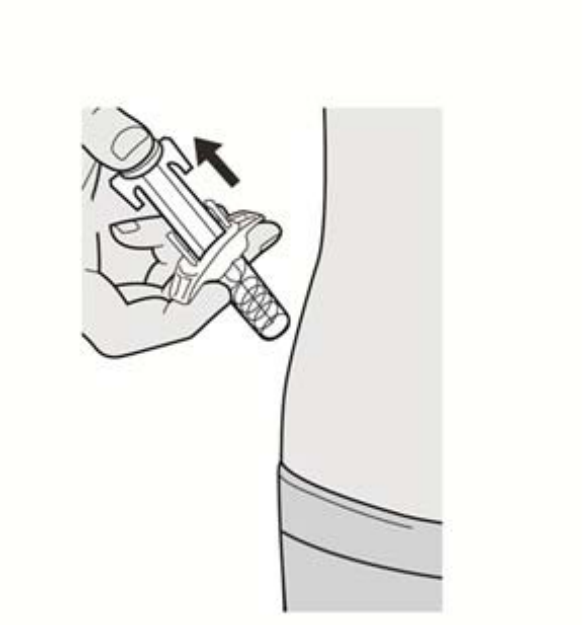


Step 12: Release

Once the Needle is out of the skin, lift your thumb to retract the Needle up into the Needle Shield.

Lightly press a cotton ball or gauze on the injection site if you see any blood.

Do not rub your skin after the injection.



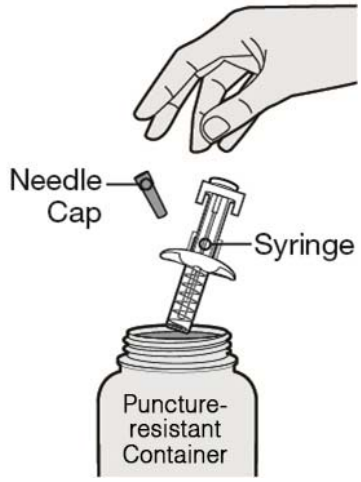
Step 13: Dispose

Dispose of the Syringe and the Needle Cap in a puncture-resistant container.

Do not put the Needle Cap back on.

Always keep the container out of the reach of children.

See “How to Dispose of (Throw Away) Used Syringes”.



DUPIXENT SINGLE-DOSE PRE-FILLED SYRINGE

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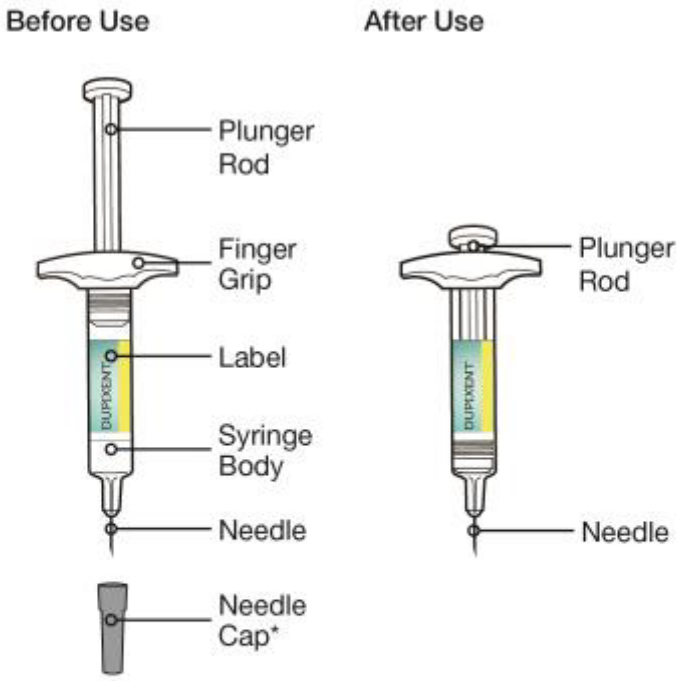
This device is a **Single-dose** Pre-filled Syringe (called "Syringe" in these instructions). It contains 300 mg of DUPIXENT for injection under the skin (subcutaneous injection).

Keep these instructions for future use. If you have any further questions, you should ask your healthcare provider or call 1-800-589-6215.

The parts of the DUPIXENT syringe are shown in this picture.



*The device may have either a soft or hard Needle Cap.

Important Information

- It is important that you do not try to give yourself or someone else the injection unless you have received training from your healthcare provider.
- Read all of the instructions carefully before using the Syringe.
- Ask your healthcare provider how often you will need to inject the medicine.
- Ask your healthcare provider to show you the right way to use the Syringe before you inject for the first time.
- Rotate the injection site each time you inject.

- **Do not** use the Syringe if it has been damaged.
- **Do not** use the Syringe if the Needle Cap is missing or not securely attached.
- **Do not** touch the Plunger Rod until you are ready to inject.
- **Do not** inject through clothes.
- **Do not** get rid of any air bubbles in the Syringe.
- **Do not** pull back on the Plunger Rod at any time.
- **Do not** re-use the Syringe.

How to Store DUPIXENT:

- Keep the Syringe(s) out of the reach of children.
- Keep unused Syringes in the original carton and store in the refrigerator between 2ºC and 8ºC.
- Remove the Syringe from the refrigerator at least 45 minutes before your injection so that it reaches room temperature.
- **Do not** keep DUPIXENT at room temperature for more than 14 days.
- **Do not** shake the Syringe at any time.
- **Do not** heat the Syringe.
- **Do not** freeze the Syringe.
- **Do not** put the Syringe into direct sunlight.

How to Dispose of (Throw Away) Used Syringes

Put your used Needles and Syringes in a-puncture-resistant container right away after use.

Do not dispose of (throw away) the Syringes in your household trash.

If you do not have a puncture-resistant container, you may use a household container that is:

- made of a heavy-duty plastic;
- can be closed with a tightfitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container

When your puncture-resistant container is almost full, you will need to follow your provincial or local regulations for the correct way to dispose of it.

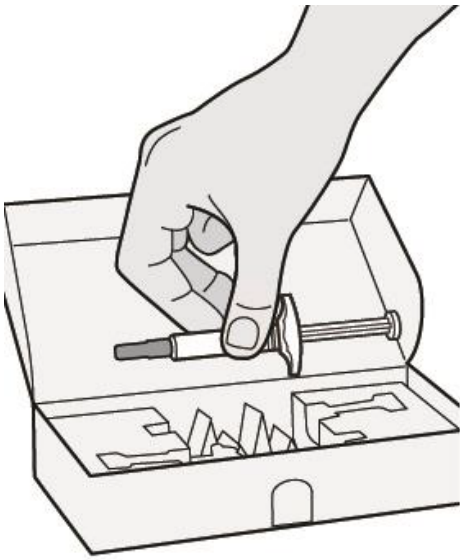
Step 1: Remove

Remove the Syringe from the carton by holding the middle of the Syringe Body:

Do not pull off the Needle Cap until you are ready to inject.

Do not use the Syringe if it has been damaged.

Do not keep DUPIXENT at room temperature for more than 14 days



Step 2: Prepare

Ensure you have the following:

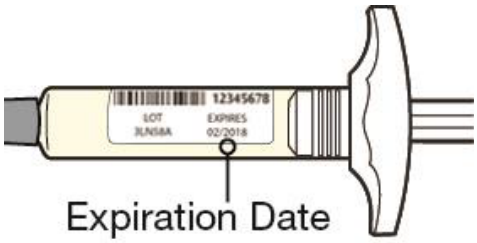
- the DUPIXENT Pre-filled Syringe
- 1 alcohol wipe*
- 1 cotton ball or gauze*
- a puncture-resistant container* (See Step 12)

**Items not included in the carton*

Look at the label:

- Check the expiration date
- Check that you have the correct product and dose

⚠ **Do not use the Syringe if the expiration date has passed.**



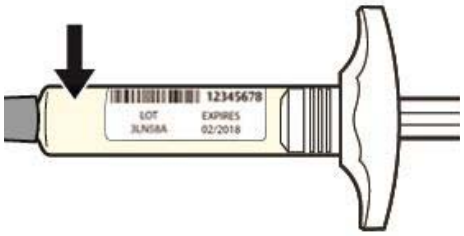
Step 3: Inspect

Look at the medicine in the Syringe:

Check if the liquid is clear and colorless to pale yellow.

Note: You may see an air bubble; this is normal.

⚠ **Do not use the Syringe if the liquid is discolored or cloudy, or if it contains visible flakes or particles.**



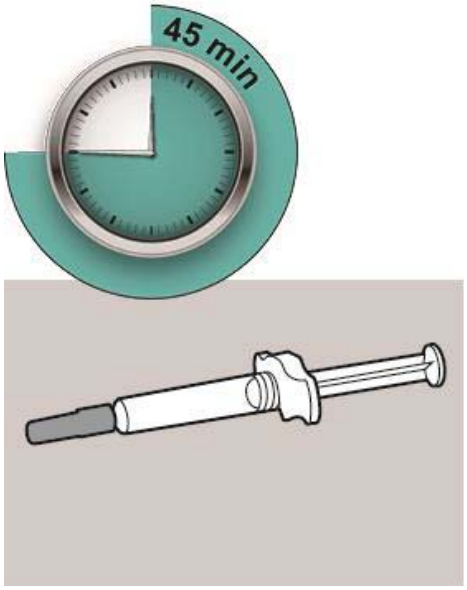
Step 4: Wait 45 minutes

Lay the Syringe on a flat surface and let it naturally warm to room temperature for at least 45 minutes.

⚠ **Do not heat the Syringe.**

⚠ **Do not put the Syringe into direct sunlight.**

⚠ **Do not keep DUPIXENT at room temperature for more than14 days.**

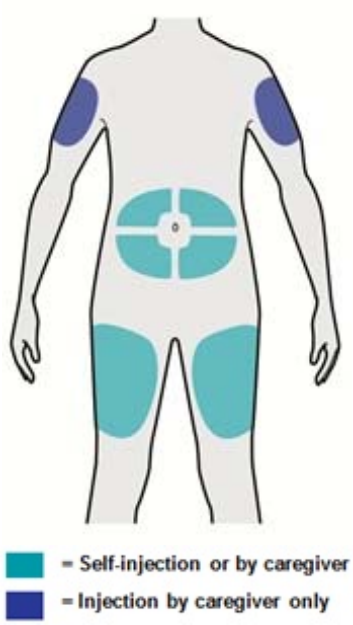


Step 5: Select

Select the injection site.

- You can inject into your thigh or stomach, except for the 5 cm (2 inches) around your navel (belly-button).
- If somebody else gives you the injection, you can also use the upper arm.

⚠ **Do not inject into skin that is tender, damaged or has bruises or scars.**



Step 6: Clean

Wash your hands.

Clean the injection site with an alcohol wipe.

Let your skin dry before injecting.

⚠ **Do not touch the injection site again or blow on it before the injection.**

Step 7: Pull

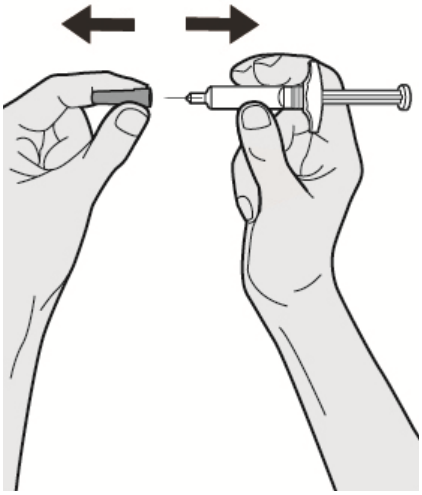
Hold the Syringe in the middle of the Syringe Body with the Needle pointing away from you and pull off the Needle Cap.

Do not put the Needle Cap back on.

Do not touch the Needle.

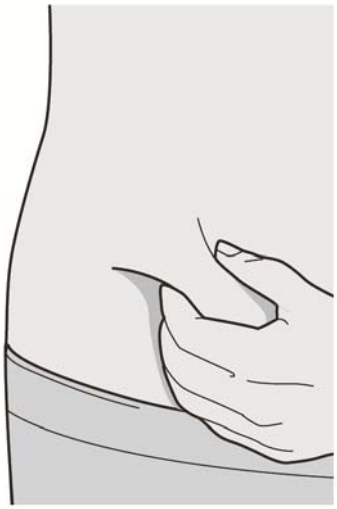
Do not inject if the Needle is damaged

Inject your medicine immediately after removing the Needle Cap.



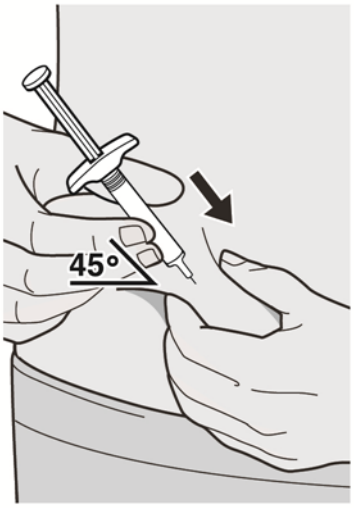
Step 8: Pinch

Pinch a fold of skin at the injection site, as shown in the picture.



Step 9: Insert

Insert the Needle into the fold of the skin at roughly a 45º angle.

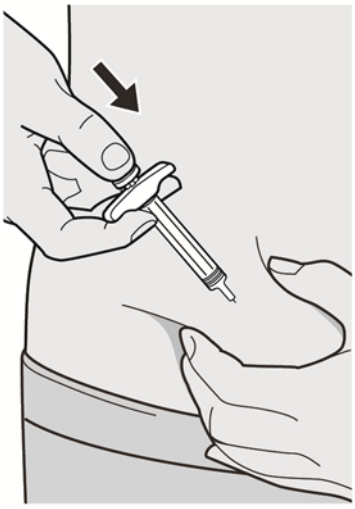


Step 10: Push

Relax the pinch.

Push the Plunger Rod down slowly and steadily as far as it will go until the Syringe is empty.

Note: You will feel some resistance. This is normal.



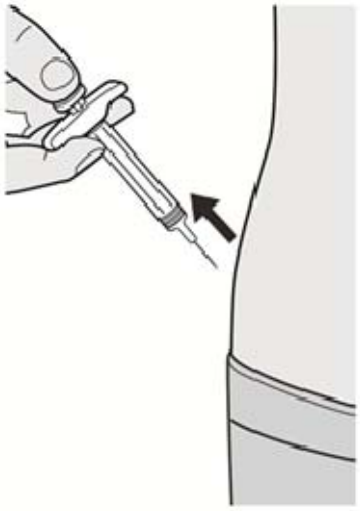
Step 11: Remove

Pull the Needle out of the skin at the same angle it was inserted.

⚠ **Do not put the Needle Cap back on.**

Lightly press a cotton ball or gauze on the injection site if you see any blood.

Do not rub your skin after the injection.



Step 12: Dispose

Dispose of the Syringe and the Needle Cap in a puncture-resistant container.

Do not put the Needle Cap back on.

Always keep the container out of the reach of children.

See “How to Dispose of (Throw Away) Used Syringes”.