# ANNEX I

# SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Tildrakizumab is a humanised IgG1/k monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection (injection)

The solution is clear to slightly opalescent and colourless to slightly yellow. The solution pH is in the range of 5.7 - 6.3 and the osmolality is between 258 and 311 mOsm/kg.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Ilumetri is indicated for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy.

### 4.2 Posology and method of administration

Ilumetri is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of plaque psoriasis.

Posology

The recommended dose of Ilumetri is 100 mg by subcutaneous injection at weeks 0, and 4 and every 12 weeks thereafter.
In patients with certain characteristics (e.g. high disease burden, body weight ≥ 90 kg) 200 mg may provide greater efficacy.

Consideration should be given to discontinuing treatment in patients who have shown no response after 28 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 28 weeks.

*Special populations*

*Elderly*
No dose adjustment is required (see section 5.2).

*Renal or hepatic impairment*
Ilumetri has not been studied in these patient populations. No dose recommendations can be made. For further information on elimination of tildrakizumab, see section 5.2.

*Paediatric population*
The safety and efficacy of Ilumetri in children and adolescents below the age of 18 years have not yet been established. No data are available.

Method of administration

Ilumetri is administered by subcutaneous injection. Injection sites should be alternated. Ilumetri should not be injected into areas where the skin is affected by plaque psoriasis or is tender, bruised, red, hard, thick, or scaly. The pre-filled syringe must not be shaken. Each pre-filled syringe is for single use only.

Inject the full amount of tildrakizumab according to the instructions for use provided in the package leaflet.

After proper training in subcutaneous injection technique, patients may self-inject Ilumetri if a physician determines that it is appropriate. However, the physician should ensure appropriate follow-up of patients. Patients should be instructed to inject the full amount of Ilumetri according to the instructions provided in the package leaflet. Comprehensive instructions for administration are given in the package leaflet.

## 4.3 Contraindications

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

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

## 4.4 Special warnings and precautions for use

Traceability

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

Infections

Ilumetri has the potential to increase the risk of infection (see section 4.8).
Caution should be exercised when considering the use of Ilumetri in patients with a chronic infection or a history of recurrent or recent serious infection.
Patients should be instructed to seek medical advice if signs or symptoms suggestive of a clinically relevant chronic or acute infection occur. If a patient develops a serious infection, the patient should be closely monitored and Ilumetri should not be administered until the infection resolves.

Pre-treatment evaluation for tuberculosis

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

Hypersensitivity

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

Vaccinations

Prior to initiating treatment with tildrakizumab, consider completion of all appropriate immunisations according to current immunisation guidelines. If a patient has received live viral or bacterial vaccination it is recommended to wait at least 4 weeks prior to starting treatment with tildrakizumab. Patients treated with Ilumetri should not receive live vaccines during treatment and for at least 17 weeks after treatment (see section 4.5).

## 4.5 Interaction with other medicinal products and other forms of interaction

Vaccines

No data are available on the response to live or inactivated vaccines. Live vaccines should not be given concurrently with Ilumetri (see section 4.4).

Interactions with cytochrome p450

Concomitant medicines affecting Ilumetri pharmacokinetics are not expected since it is cleared from the body by general protein catabolism processes with no contribution of cytochrome P450 (CYP450) enzymes, and it is not eliminated by renal or hepatic pathways. Furthermore, Ilumetri does not impact the pharmacokinetics of concomitant medicines metabolized by CYP450 enzymes either through direct or indirect mechanisms (see section 5.2).

Interactions with other immunosuppressive agents or phototherapy

The safety and efficacy of Ilumetri in combination with other immunosupressive agents, including biologics, or phototherapy has not been evaluated.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use an effective method of contraception during treatment and for at least 17 weeks after treatment.

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of tildrakizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effect with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Ilumetri during pregnancy.

Breast-feeding

It is unknown whether tildrakizumab is excreted in human milk. Available toxicological data in cynomolgus monkey have shown negligible levels of Ilumetri in milk on postnatal day 28 (see section 5.3). In humans, during the first few days after birth antibodies may be transferred to the newborns

through milk. In this short period, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Ilumetri therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of Ilumetri on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are upper respiratory tract infections, headache, gastroenteritis, nausea, diarrhoea, injection site pain and back pain.

Tabulated list of adverse reactions

Three placebo-controlled studies (Phase 2b and two Phase 3) were integrated to evaluate the safety of Ilumetri in comparison to placebo. A total of 1,768 patients were evaluated (705 patients on 100 mg, 708 patients on 200 mg and 355 patients on placebo). These 355 patients on placebo were subsequently crossed over to tildrakizumab.
Adverse reactions (Table 1) are listed by MedDRA system organ class (SOC) and frequency, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from available data).

**Table 1. List of adverse reactions**

| MedDRA System Organ Class | Preferred term | Frequency category |
|---|---|---|
| Infections and infestations | Upper respiratory tract infections[a] | Very common |
| Nervous system disorders | Headache | Common |
| Gastrointestinal disorders | Gastroenteritis | Common |
| | Nausea | Common |
| | Diarrhoea | Common |
| General disorders and administration site conditions | Injection site pain | Common |
| | Back pain | Common |

[a]Including nasopharyngitis.

Description of selected adverse reaction

*Immunogenicity*

In pooled Phase 2b and Phase 3 analyses 7.3% of Ilumetri-treated patients developed antibodies to Ilumetri. No apparent association between the development of antibodies to Ilumetri to lower efficacy and the development of treatment emergent adverse events was observed.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

Doses up to 10 mg/kg intravenously have been safely administered in clinical trials.
In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and that appropriate symptomatic treatment be instituted immediately.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC17

Mechanism of action

Tildrakizumab is a humanized IgG1/k monoclonal antibody that specifically binds to the p19 protein subunit of the interleukin-23 (IL-23) cytokine without binding to IL-12 and inhibits its interaction with the IL-23 receptor.

IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses. Tildrakizumab inhibits the release of proinflammatory cytokines and chemokines.

Clinical efficacy and safety

The multicentre, randomised, double-blind, placebo-controlled trials reSURFACE 1 and reSURFACE 2 studies enrolled a total of 1,862 patients 18 years of age and older with plaque psoriasis who had a minimum body surface area involvement of 10%, a Physician Global Assessment (PGA) score of ≥3 in the overall assessment (plaque thickness, erythema, and scaling) of psoriasis on a severity scale of 0 to 5, a Psoriasis Area and Severity Index (PASI) score ≥12, and who were candidates for phototherapy or systemic therapy.

In these studies, patients were randomised to either placebo or tildrakizumab (including 200 mg and 100 mg at 0, 4 and every twelve weeks thereafter [Q12W]), up to 52 or 64 weeks. In the active comparator study (reSURFACE 2), patients were also randomised to receive etanercept 50 mg twice weekly for 12 weeks, and weekly thereafter up to 28 weeks.

Overall demographic and baseline characteristics in reSURFACE1 and reSURFACE2 studies were consistent across individual trials. Patients were 18 to 82 years old, with a mean age of 45.9. The median baseline PASI score ranged from 17.7 to 18.4 across treatment groups. Baseline PGA score was marked or severe in 33.4% of patients. Of all patients, 35.8% had received prior phototherapy, 41.1% had received prior conventional systemic therapy, 16.7% had received prior biologic therapy for the treatment of plaque psoriasis. A total of 15.4% of study patients had a history of psoriatic arthritis. Mean baseline Dermatology Life Quality Index (DLQI) ranged from 13.0 to 14.8.

Studies reSURFACE 1 and reSURFACE 2 assessed the changes from baseline at Week 12 in the two co-primary endpoints: 1) PASI 75 and 2) PGA of "0" (cleared) or "1" (minimal), with at least a 2-point improvement from baseline. Other evaluated outcomes included the proportion of patients who achieved PASI 90, PASI 100, the proportion of patients with DLQI 0 or 1, and maintenance of efficacy up to 52/64 weeks.

Results obtained at weeks 12, 28 and beyond (up to week 64 in reSURFACE 1 and up to week 52 in reSURFACE 2) are presented in Table 2 and Table 3.

**Table 2. Summary of Response Rates in Studies reSURFACE 1 and reSURFACE 2**

| | Week 12 (2 doses)* | | | | Week 28 (3 doses)* | | |
|---|---|---|---|---|---|---|---|
| | 200 mg | 100 mg | Placebo | Etanercept | 200 mg | 100 mg | Etanercept |
| **reSURFACE1** | | | | | | | |
| Number of patients | 308 | 309 | 154 | - | 298 | 299 | - |
| PASI 75[a] (%) | 62.3[†b] | 63.8[†b] | 5.8[b] | - | 81.9[c] | 80.4[c] | - |
| PGA of "clear" or "minimal" with ≥2 grade improvement from Baseline[a] (%) | 59.1[†b] | 57.9[†b] | 7.1[b] | - | 69.1[c] | 66.0[c] | - |
| PASI 90 (%) | 35.4[†b] | 34.6[†b] | 2.6[b] | - | 59.0[c] | 51.6[c] | - |
| PASI 100 (%) | 14.0[†b] | 13.9[†b] | 1.3[b] | - | 31.5[c] | 23.5[c] | - |
| DLQI Score 0 or 1 (%) | 44.2[†] | 41.5[†] | 5.3 | - | 56.7[c] | 52.4[c] | - |
| **reSURFACE2** | | | | | | | |
| Number of patients | 314 | 307 | 156 | 313 | 299 | 294 | 289 |
| PASI 75[a] (%) | 65.6[†‡b] | 61.2[†‡b] | 5.8[b] | 48.2[b] | 72.6[‡b] | 73.5[‡b] | 53.6[b] |
| PGA of "clear" or "minimal" with ≥2 grade improvement from Baseline[a] (%) | 59.2[†¥b] | 54.7[†b] | 4.5[b] | 47.6[b] | 69.2[‡b] | 64.6[‡b] | 45.3[b] |
| PASI 90 (%) | 36.6[†‡b] | 38.8[†‡b] | 1.3[b] | 21.4[b] | 57.7[‡c] | 55.5[‡c] | 29.4[c] |
| PASI 100 (%) | 11.8[†‡b] | 12.4[†‡b] | 0 | 4.8[b] | 27.0[‡c] | 22.8[‡c] | 10.7[c] |
| DLQI Score 0 or 1 (%) | 47.4[†¥] | 40.2[†] | 8.0 | 35.5 | 65.0[‡c] | 54.1[‡c] | 39.4[c] |

[a] Co-primary efficacy endpoint at week 12.
[b] Non responder imputation for missing data.
[c] No imputation for missing data.
*The number of doses administered refers only to tildrakizumab groups.
n = number of patients in the full analysis set for which data was available, after imputation when applicable.
p-values calculated using the Cochran-Mantel-Haenszel (CMH) test stratified by body weight (≤90 kg, >90 kg) and prior exposure to biologic therapy for psoriasis (yes/no).
[†] p≤0.001 versus placebo; [‡] p≤0.001 versus etanercept; [¥] p≤0.05 versus etanercept.

Maintenance of Response

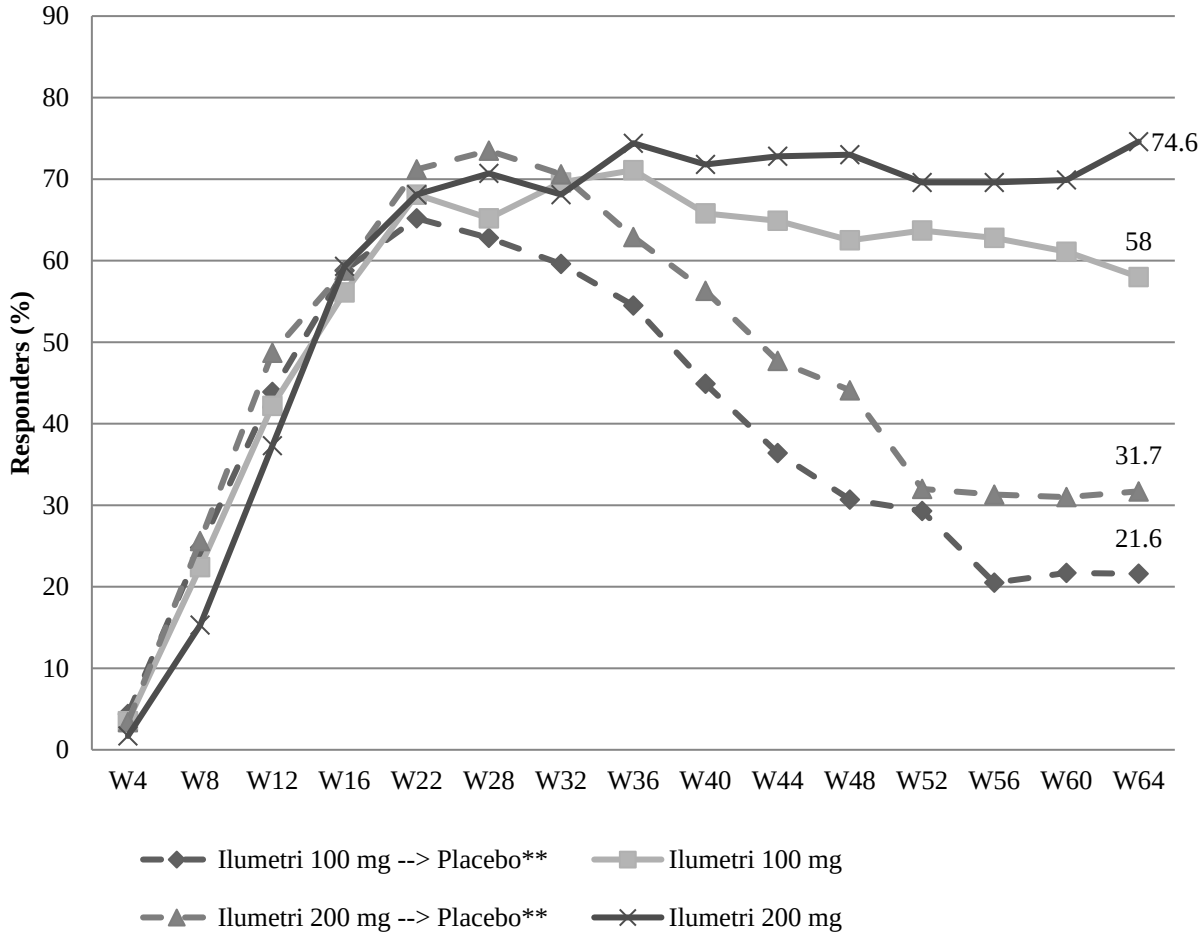
The maintenance of response in studies reSURFACE1 and reSURFACE2 are presented in Table 3. Maintenance and durability of PASI 90 response over time is presented in Figure 1.

**Table 3. Maintenance of Response in Studies reSURFACE 1 and reSURFACE 2**

| | Long term response[a,b] | | | |
|---|---|---|---|---|
| | 200 mg | | 100 mg | |
| **reSURFACE 1** | **Week 28** | **Week 64** | **Week 28** | **Week 64** |
| Number of patients | 116 | 114 | 115 | 112 |
| PGA of "clear" or "minimal" with ≥2 grade improvement from Baseline (%) | 80.2 | 76.3 | 80.9 | 61.6 |
| PASI 90 (%) | 70.7 | 74.6 | 65.2 | 58.0 |
| PASI 100 (%) | 38.8 | 40.4 | 25.2 | 32.1 |
| **reSURFACE 2** | **Week 28** | **Week 52** | **Week 28** | **Week 52** |
| Number of patients | 108 | 105 | 213 | 204 |
| PGA of "clear" or "minimal" with ≥2 grade improvement from Baseline (%) | 88.0 | 84.8 | 84.0 | 79.4 |
| PASI 90 (%) | 75.0 | 81.9 | 74.2 | 78.4 |
| PASI 100 (%) | 34.3 | 46.7 | 30.2 | 35.3 |

[a] Long-term response in patients who were responders (had achieved at least PASI 75) to tildrakizumab at week 28.
[b] No imputation for missing data.

**Figure 1. Maintenance and durability of PASI 90 Response. Proportion of Patients with PASI 90 response over time up to Week 64 (Full Analysis Set Part 3[*])**




Patients randomised to tildrakizumab 100 mg or tildrakizumab 200 mg in Part 1 who were PASI 75 responders at week 28 (reSURFACE1).
[*]No imputation of missing data.
[**]These patients were switched to placebo at week 28.

Quality of Life/Patient-reported Outcomes

At week 12 and across studies, tildrakizumab was associated with statistically significant improvement in Health-related Quality of Life as assessed by the DLQI (Table 2). Improvements were maintained over time with at week 52, 63.7% (100 mg) and 73.3% (200 mg) in reSURFACE 1, and 68.8% (100 mg) and 72.4% (200 mg) in reSURFACE 2 of patients who were PASI 75 responders at week 28 having a DLQI of 0 or 1.

Paediatric population

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

## 5.2 Pharmacokinetic properties

Absorption

The subcutaneous formulation of tildrakizumab showed an absolute bioavailability ranging from 73% (90% CI: 46% - 115%, 200 mg SC vs. 3 mg/kg IV) to 80% (90% CI: 62% - 103%, 50 mg SC vs. 0.5 mg/kg IV) in healthy subjects, as a result of cross study single dose comparison. Maximum concentration was reached at 6.2 days after injection. Population PK analysis indicated a 31% higher bioavailability in healthy subjects compared to patients.

At steady state, following administration of 100 mg of tildrakizumab in subjects with moderate to severe plaque psoriasis geometric means (% CV) of $AUC_{0-\tau}$ and $C_{max}$ values were respectively 305 µg·day/mL (41%) and 8.1 µg/mL (34%), whereas they were 612 µg·day/mL (40%) and 16.3 µg/mL (33%) following administration of 200 mg.

Distribution

Tildrakizumab has limited extravascular distribution with volume of distribution (Vd) values ranging from 76.9 to 106 mL/kg.

Biotransformation

Tildrakizumab is catabolized into component amino acids by general protein degradation processes. Small-molecule metabolic pathways (e.g., CYP450 enzymes, glucuronosyltransferases) do not contribute to its clearance.

Elimination

Clearance values range from 2.04 to 2.52 mL/day/kg and the half-life was 23.4 days (23% CV) in subjects with plaque psoriasis.

Linearity/non-linearity

Tildrakizumab exhibited dose-proportional pharmacokinetics in subjects with plaque psoriasis over a dose range from 50 mg to 400 mg following subcutaneous administration, with clearance being independent of dose.

Steady-state is achieved by 16 weeks with the clinical regimen of 0, 4, and every 12 weeks thereafter, with 1.1-fold accumulation in exposure between week-1 and week-12 independent of dose.

Body weight

Population pharmacokinetic modelling indicated that exposure decreased as body weight increased. The geometric mean exposure ($AUC_{0-\tau}$ at steady state) in adult patients weighing >90 kg following a 100 mg or 200 mg SC dose was predicted to be about 30% lower than in an adult patient weighing ≤90 kg (see section 4.2).

Pharmacokinetics in special populations

*Elderly*
Population pharmacokinetic analysis indicated that age did not have a clinically significant influence on the clearance of tildrakizumab in adult subjects with plaque psoriasis. Following administration of 100 mg or 200 mg of tildrakizumab, subjects who are 65 years or older (n=81 and n=82, respectively) had a similar tildrakizumab clearance as compared to subjects less than 65 years old (n=884).

*Renal and Hepatic impairment*
No formal trial of the effect of hepatic or renal impairment on the pharmacokinetics of tildrakizumab was conducted. Tildrakizumab is catabolized into component amino acids by general protein degradation processes and is not eliminated by renal or hepatic pathways.

Drug interactions

Results from a drug-drug interaction study conducted in plaque psoriasis subjects suggest that tildrakizumab had no clinically relevant effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Therefore, tildrakizumab does not impact the pharmacokinetics of concomitant medicines metabolized by CYP enzyme (see section 4.5).

## 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, and repeated dose toxicity.

Animal carcinogenicity studies have not been conducted with tildrakizumab. Studies in mouse tumor models showed that selective inhibition of IL-23p19 does not increase carcinogenic risk.

In cynomolgus monkeys, there was negligible secretion of the product into breast milk. One month after birth, the milk/serum ratio was ≤0.002. Tildrakizumab was shown to distribute across the placental barrier. After repeated dosing to pregnant cynomolgus monkeys, serum concentrations were quantifiable in the fetus, but the reproduction toxicity studies did not reveal any untoward effects.

No effects on fertility parameters such as reproductive organs, menstrual cycle length, and/or hormones were observed in male and female cynomolgus monkeys that were administered tildrakizumab at doses resulting in >100 times the human exposure at the recommended clinical dose based on AUC.

In a pre- and postnatal development toxicity study in monkeys, no related increase in pregnancy loss was observed at exposures up to 85 times the human exposure at the recommended dose. No harmful effects were noted in neonates at maternal exposures up to 9 times the human exposure at the recommended dose. Two neonatal deaths from monkeys administered tildrakizumab at maternal exposure of 85 times the human exposure at the recommended dose were attributed to possible viral infection and considered of uncertain relationship to the treatment. The clinical significance of these findings is unknown.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

L-Histidine
L-Histidine hydrochloride monohydrate
Polysorbate 80
Sucrose
Water for injections

### 6.2 Incompatibilities

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

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Unopened pre-filled syringe of Ilumetri may be removed from the refrigeration and stored up to 25°C for a single period of up to 30 days. Once removed from the refrigerator and stored under these conditions, discard after 30 days or by the expiry date printed on the container, whichever occurs first. A field for the date is provided on the carton to record the removal from refrigerator date.
Keep the pre-filled syringes in the outer carton in order to protect from light until the time of use.
Do not shake.

### 6.5 Nature and contents of container

1 mL solution in a type I glass pre-filled syringe with stainless steel 29G x ½" needle, covered with a needle shield and rigid needle shield of polypropylene with a fluropolymer lamination, plunger stopper assembled in a passive safety device.

Pack size of 1 pre-filled syringe or 2 pre-filled syringes.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Ilumetri is a sterile solution for injection in pre-filled syringe. The pre-filled syringes are for single use only.

Do not shake or freeze the pre-filled syringe. The pre-filled syringe should be taken out of the refrigerator 30 minutes before injecting to allow it to reach room temperature (up to 25ºC).
Prior to use, a visual inspection of the pre-filled syringe is recommended. The liquid should be clear. Its colour may vary from colourless to slightly yellow. A small air bubble may be apparent: this is normal.
Do not use if the liquid contains easily visible particles, is cloudy or is distinctly brown.

The instructions for using the pre-filled syringes, included with the package leaflet, must be followed carefully.

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

## 7. MARKETING AUTHORISATION HOLDER

Almirall, S.A.
Ronda General Mitre, 151
08022 Barcelona
Spain

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1323/001
EU/1/18/1323/002

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 september 2018

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

N.V. Organon
Veersemeer 4
5347 JN Oss
The Netherlands

Samsung BioLogics Co., Ltd.
300, Songdo Bio Way (Daero)
Yeonsu-gu Incheon, 21987
Korea

Name and address of the manufacturer(s) responsible for batch release

SUN Pharmaceutical Industries (Europe) B.V.
Polarisavenue 87
2132JH Hoofddorp
The Netherlands

Industrias Farmacéuticas Almirall, S.A.
Ctra. Nacional II, Km. 593
08740 Sant Andreu de la Barca
Barcelona
Spain

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE

## USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON – PACK SIZE 1 PRE-FILLED SYRINGE**

## 1. NAME OF THE MEDICINAL PRODUCT

Ilumetri 100 mg solution for injection in pre-filled syringe
tildrakizumab

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

## 3. LIST OF EXCIPIENTS

Excipients: L-Histidine, L-Histidine hydrochloride monohydrate, polysorbate 80, sucrose and water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled syringe

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
Single use only.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

Removal from refrigerator date:

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.
Do not shake.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Almirall, S.A.
Ronda General Mitre, 151
08022 Barcelona
Spain

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1323/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Ilumetri

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:

NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON – PACK SIZE 2 PRE-FILLED SYRINGES**

## 1. NAME OF THE MEDICINAL PRODUCT

Ilumetri 100 mg solution for injection in pre-filled syringe
tildrakizumab

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

## 3. LIST OF EXCIPIENTS

Excipients: L-Histidine, L-Histidine hydrochloride monohydrate, polysorbate 80, sucrose and water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

2 pre-filled syringes

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.
Single use only.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled syringes in the outer carton in order to protect from light.
Do not shake.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Almirall, S.A.
Ronda General Mitre, 151
08022 Barcelona
Spain

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1323/002 2 pre-filled syringes

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Ilumetri

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:

NN:

**SMALL IMMEDIATE PACKAGING UNITS**

**LABEL - PRE-FILLED SYRINGE**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ilumetri 100 mg injection
tildrakizumab
SC

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

## 6. OTHER

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the user**

**Ilumetri 100 mg solution for injection in pre-filled syringe**
tildrakizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Ilumetri is and what it is used for

Ilumetri contains the active substance tildrakizumab. Tildrakizumab belongs to a group of medicines called interleukin (IL) inhibitors.
This medicine works by blocking the activity of a protein called IL-23, a substance found in the body which is involved in normal inflammatory and immune responses and which is present at increased levels in diseases such as psoriasis.

Ilumetri is used to treat a skin condition called plaque psoriasis, in adults with moderate to severe disease. Using Ilumetri will benefit you by improvements of skin clearance and reducing your symptoms.

## 2. What you need to know before you use Ilumetri

**Do not use Ilumetri:**
- If you are allergic to tildrakizumab or any of the other ingredients of this medicine (listed in section 6).
- If you have an infection which your doctor thinks is important, for example, active tuberculosis which is an infectious disease affecting mainly the lungs.

**Warnings and precautions**
Talk to your doctor, pharmacist or nurse before using Ilumetri:
- If you experience allergic reactions with symptoms such as chest tightness, wheezing, swelling of the face, lips or throat do not inject more Ilumetri and contact your doctor immediately.
- If you currently have an infection or if you have long-term or repeated infections.

- If you have recently had or plan to have a vaccination.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Ilumetri.

*Look out for infections and allergic reactions*
Ilumetri can potentially cause serious side effects, including infections and allergic reactions. You must look out for signs of these conditions while you are taking Ilumetri.
Stop using Ilumetri and tell your doctor or seek medical help immediately if you notice any signs indicating a possible serious infection or an allergic reaction (see 4. Possible side effects).

**Children and adolescents**
Ilumetri is not recommended for use in children and adolescents under 18 years of age. This is because it has not yet been evaluated in this group of patients.

**Other medicines and Ilumetri**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. These include vaccines and immunosuppressants (medicines that affect the immune system).

You should not be given certain types of vaccines (live vaccines) while using Ilumetri. No data are available with the concomitant use of Ilumetri and live vaccines.

**Pregnancy, breastfeeding and fertility**
It is preferable to avoid the use of Ilumetri in pregnancy. The effects of this medicine in pregnant women are not known.

If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use an effective method of contraception whilst having treatment with Ilumetri and for at least 17 weeks after treatment.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

**Driving and using machines**
Ilumetri has no or little effect on the ability to drive and use machines.

## 3. How to use Ilumetri

Ilumetri is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis.

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. This medicine is for single use only.

The recommended dose of Ilumetri is 100 mg by subcutaneous injection at weeks 0, and 4 and every 12 weeks thereafter.
In patients with certain characteristics (e.g. high disease burden, body weight ≥ 90 kg) 200 mg may provide greater efficacy.

Your doctor will decide for how long you need to take Ilumetri.

After proper training in subcutaneous injection technique, you may inject Ilumetri yourself if your doctor determines that it is appropriate.

For instructions on how to inject Ilumetri yourself, see ‘Instructions for use’ at the end of this leaflet.

Talk to your doctor about when you will have your injections and follow-up appointments.

**Use in children and adolescents**
The safety and efficacy of Ilumetri in children and adolescents under 18 years of age has not yet been established and therefore Ilumetri is not recommended for use in children or adolescents.

**If you use more Ilumetri than you should**
If you have administered more Ilumetri than you should or the dose has been administered sooner than according to your doctor’s prescription, tell your doctor.

**If you forget to use Ilumetri**
If you have forgotten or missed an Ilumetri injection, administer the dose as soon as possible. Thereafter, resume dosing at the regularly scheduled interval.

**If you stop using Ilumetri**
The decision to stop using Ilumetri should be discussed with your doctor. Your symptoms may return upon discontinuation.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

## 4. Possible side effects

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

**Serious side effects**
If you notice any of the following, **contact your doctor immediately**:
- Swelling of the face, lips or throat
- Breathing difficulties

As these may be signs of an allergic reaction.

**Other side effects**
Most of the following side effects are mild. If any of these side effects becomes severe, tell your doctor or pharmacist.

**Very common side effects** (may affect more than 1 in 10 people):
- Upper respiratory infections

**Common side effects** (may affect up to 1 in 10 people):
- Gastroenteritis
- Nausea
- Diarrhoea
- Injection site pain
- Back pain
- Headache

**Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Ilumetri

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the label of the pre-filled syringe after EXP. The expiry date refers to the last day of that month.

Keep the product in the original carton in order to protect from light until the time of use. Do not shake.

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

After taking a pre-filled syringe from the refrigerator, wait approximately 30 minutes to allow the Ilumetri solution in the syringe to reach room temperature (up to 25ºC). Do not warm in any other way.

Do not use if the liquid contains visible particles, is cloudy or is distinctly brown.

Once taken out of the refrigerator, do not store tildrakizumab above 25ºC or refrigerate it again.
Write down the date of removal from the refrigerator in the space provided on the outer carton and appropriate discard date. Use the syringe within 30 days after taking it out of the refrigerator or by the expiry date whichever occurs first.

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 to protect the environment.

## 6. Contents of the pack and other information

**What Ilumetri contains**

- The active substance is tildrakizumab. Each pre-filled syringe contains 100 mg of tildrakizumab.
- The other ingredients are L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sucrose and water for injections.

**What Ilumetri looks like and contents of the pack**
Ilumetri is a clear to slightly opalescent and colourless to slightly yellow solution.
Ilumetri is available in unit packs containing 1 pre-filled syringe and packs comprising 2 pre-filled syringes.
Not all pack sizes may be marketed.

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08022 Barcelona, Spain

**Manufacturer**
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Industrias Farmacéuticas Almirall, S.A.
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**This leaflet was last revised in**

**Other sources of information**
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

## INSTRUCTIONS FOR USE

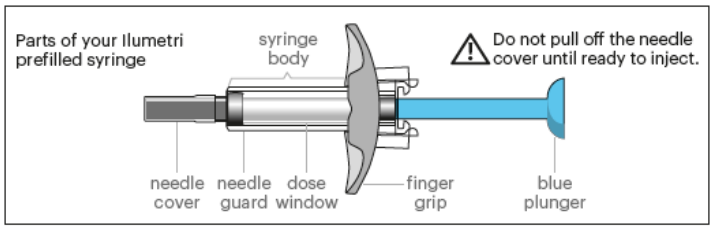
Before using the pre-filled syringes:

**Important points to know**

- Before you use Ilumetri pre-filled syringes, read and carefully follow all the step-by-step instructions. Keep the instructions for use and refer to them as needed.
- The pre-filled syringes must not be shaken.
- Read the Ilumetri Package Leaflet to learn more about your medicine.

## PRODUCT DESCRIPTION

This is what Ilumetri pre-filled syringe looks like:




## PREPARATION

**1. Take a pack from the refrigerator (if stored in the refrigerator)**

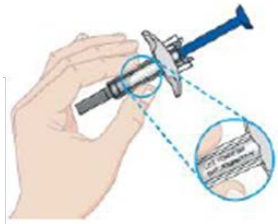
- Take a carton pack out of the refrigerator and place the original and unopened carton pack on a clean and flat working surface.

**2. Wait for 30 minutes (if stored in the refrigerator)**

- Leave the pre-filled syringe in the Ilumetri carton (with the lid closed) and let it sit at room temperature for 30 minutes.


**3. Inspect the medicine**

- Remove the pre-filled syringe from the carton when ready to inject.
  - Check the expiration date on the carton and pre-filled syringe and discard if the date has passed.
  - DO NOT pull off the needle cover until you are ready to inject.
- Inspect Ilumetri visually for particulate matter and discoloration prior to administration.
  - Ilumetri is a clear to slightly opalescent and colourless to slightly yellow solution.
  - DO NOT use if the liquid contains visible particles or the syringe is damaged. **Air bubbles may be present; there is no need to remove them.**



**4. Collect all the materials you need**

- On a clean, well-lit work surface, place the:
  - alcohol wipes
  - cotton ball or gauze pad

- sticking plaster
- sharps disposal container

**5. Wash your hands**

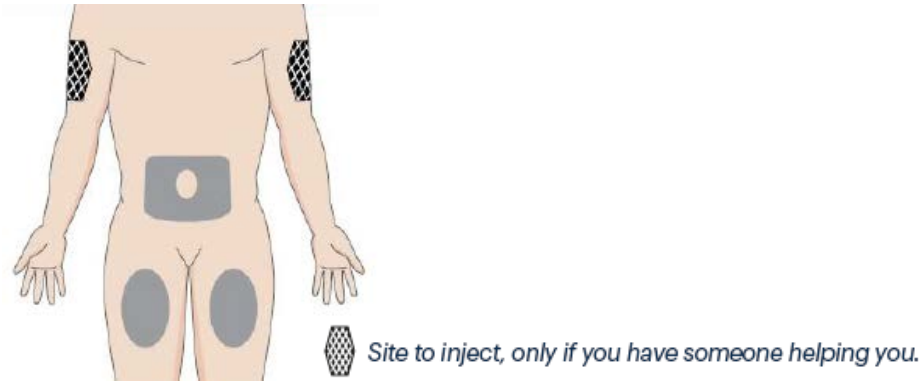
- Wash your hands thoroughly with soap and water.

**6. Choose an injection site**

- Choose an injection site with **clear skin** and easy access such as **abdomen, thighs or upper arm.**
  - DO NOT administer 5 cm around the navel or where the skin is tender, bruised, abnormally red, hardened or affected by psoriasis.
  - DO NOT inject into scars, stretch marks, or blood vessels.
  - The upper arm is only suitable when someone else is injecting you.
  - **Choose a different location for the second injection.**

**7. Clean injection site**

- Clean the injection site with an alcohol wipe and allow the skin to dry.
  - Do not touch this area again before giving the injection.




**INJECTION**

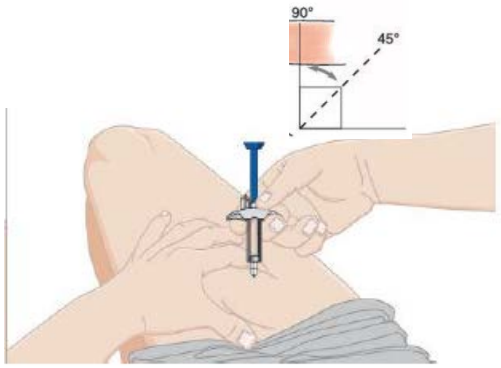
In case your dose is 200 mg, you will need to use 2 pre-filled syringes each time you administer the product.

**8. Pull off the needle cover**

- While holding the body of the pre-filled syringe, remove the needle cover as shown and discard. You may see 1 or 2 drops of liquid and that is okay.
  - DO NOT touch the blue plunger yet.
  - DO NOT use if pre-filled syringe or needle is bent.


**9. Pinch skin & insert needle**

- Gently pinch your skin at the chosen injection site.
  - Insert the entire needle into the pinched skin between your fingers **at a 45- to 90-degree angle.**
    - DO NOT place your finger on the plunger while inserting the needle.
- Hold the pre-filled syringe steady.

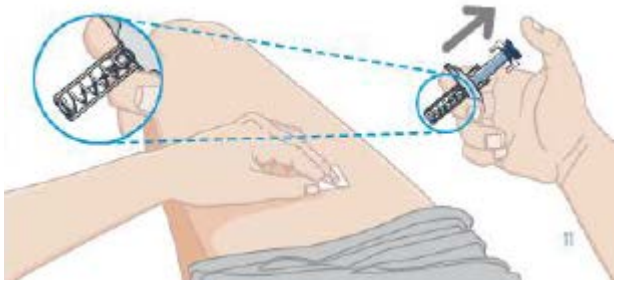



**10. Inject**

- After inserting the needle, let go of the skin gently.
- Press down the blue plunger until it can go no further. This activates the safety mechanism that will ensure full retraction of the needle after the injection is given.
  - A complete dose is administered if the blue plunger cannot go any further, and there are no spills.

**11. Remove the used syringe**

- Remove the needle from the skin entirely before letting go of the blue plunger.
  - After the blue plunger is released, the safely lock will draw the needle inside the needle guard.



- Dispose of used syringe in a sharps disposal container right away after use and before injecting a second syringe.
- If there is some residual fluid or a tiny bit of blood, clean the injection site with a cotton ball or gauze pad WITHOUT applying any pressure. If you feel the need, you can use a sticky plaster to cover the injection site.
- Repeat the procedure with the second syringe in a different location of your skin if you are administering a dose of 200 mg.