Summary of Product Characteristics

ILUMYA®

1. NAME OF THE MEDICINAL PRODUCT

Ilumya

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.
Excipient with known effect:
Each pre-filled syringe of Ilumya 100 mg contains 0.5 mg of polysorbate 80.

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

Ilumya is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

4.2 Posology and method of administration

Ilumya 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 Ilumya is 100 mg by subcutaneous injection at weeks 0, and 4 and every 12 weeks thereafter.

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.

Missed dose

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

Special populations

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

Renal or hepatic impairment
Ilumya 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 Ilumya in children and adolescents below the age of 18 years have not yet been established. No data are available.

Method of administration
Ilumya is administered by subcutaneous injection. Injection sites should be alternated. Ilumya 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.

After proper training in subcutaneous injection technique, patients may self-inject Ilumya 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 tildrakizumab 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

Tildrakizumab has the potential to increase the risk of infection (see section 4.8). Caution should be exercised when considering the use of tildrakizumab 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 tildrakizumab should not be administered until the infection resolves (see section 4.3).

Pre-treatment evaluation for tuberculosis

Prior to initiating treatment, patients should be evaluated for tuberculosis (TB) infection. Patients receiving tildrakizumab should be closely monitored for signs and symptoms of active TB during and after treatment. Anti-TB therapy should be considered prior to initiating treatment 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 hypersensitivity reaction occurs, administration of tildrakizumab should be discontinued immediately and appropriate therapy initiated (see section 4.3).

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 tildrakizumab should not receive live vaccines during treatment and for at least 17 weeks after treatment (see section 4.5).

Excipients

Ilumya contains 0.5 mg of polysorbate 80 in each pre-filled syringe of 100 mg, which is equivalent to 0.5mg/ml. Polysorbate may cause allergic reactions.

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 tildrakizumab (see section 4.4).

Interactions with cytochrome P450

Concomitant medicines affecting tildrakizumab 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, tildrakizumab does not impact the pharmacokinetics of concomitant medicines metabolised 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 tildrakizumab in combination with other immunosuppressive 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 Ilumya 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 Ilumya 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 Ilumya therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of Ilumya 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

Ilumya 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 (12.6%), headache (4.0%), diarrhoea (1.6%), gastroenteritis (1.5%), back pain (1.5%), nausea (1.3%) and injection site pain (1.3%).

Tabulated list of adverse reactions

Adverse reactions from clinical studies (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). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

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
	Diarrhoea	Common
	Nausea	Common
	Back pain	Common
General disorders and administration site conditions	Injection site pain	Common

[a]Including nasopharyngitis.

Long-term Safety

The safety profile of tildrakizumab observed during the long-term extensions periods of resurface 1 and resurface 2 was consistent with that of the double-blind periods.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

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 humanised 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. Patients who did not respond to etanercept treatment (<75% reduction in PASI from baseline) were switched to tildrakizumab 200 mg Q12W up to 52 weeks, while patients who responded to etanercept were discontinued from the study.

Eligible patients who completed the double-blind periods of reSURFACE 1 and reSURFACE 2 with ≥ 50% improvement in PASI from baseline could participate in open-label extension phases of these studies in order to evaluate the long-term safety and maintenance of efficacy of continuous tildrakizumab treatment. Patients entering the extension periods of reSURFACE 1 and reSURFACE 2 continued treatment at the same

dose of tildrakizumab, 100 mg or 200 mg, that they were receiving at week 64 or 52, respectively. Up to 6 years of follow-up data are available.

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 years old. 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

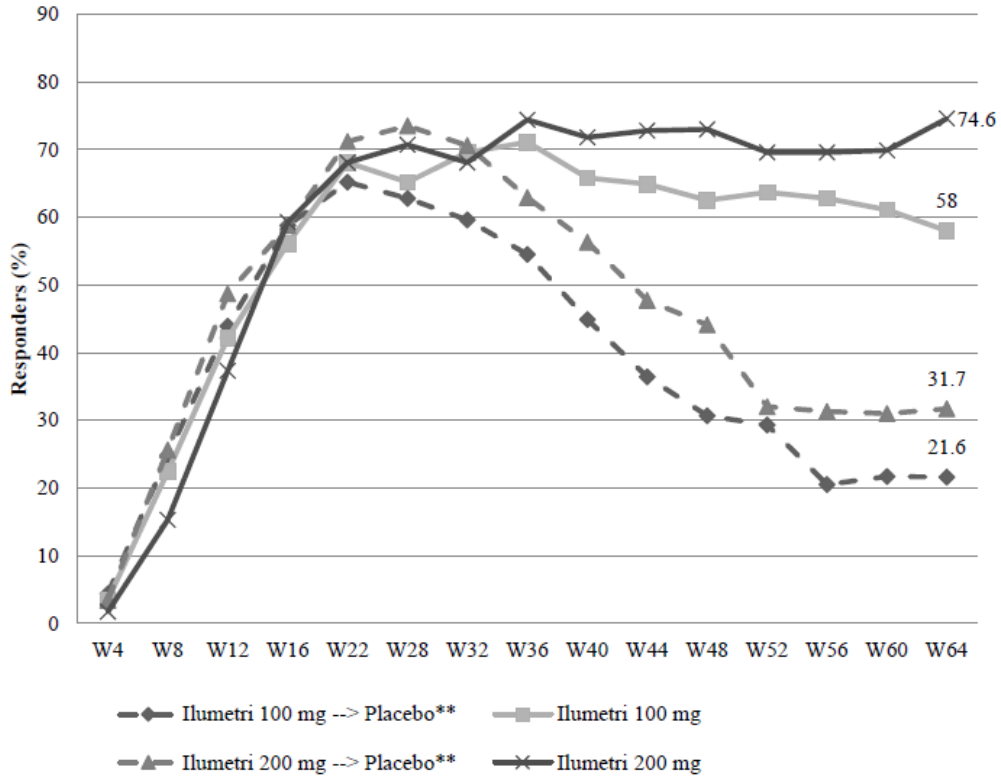
The maintenance of response in studies reSURFACE1 and reSURFACE2 are presented in Table 3. Maintenance and durability of PASI 90 response over time is presented in Figure 1.

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.

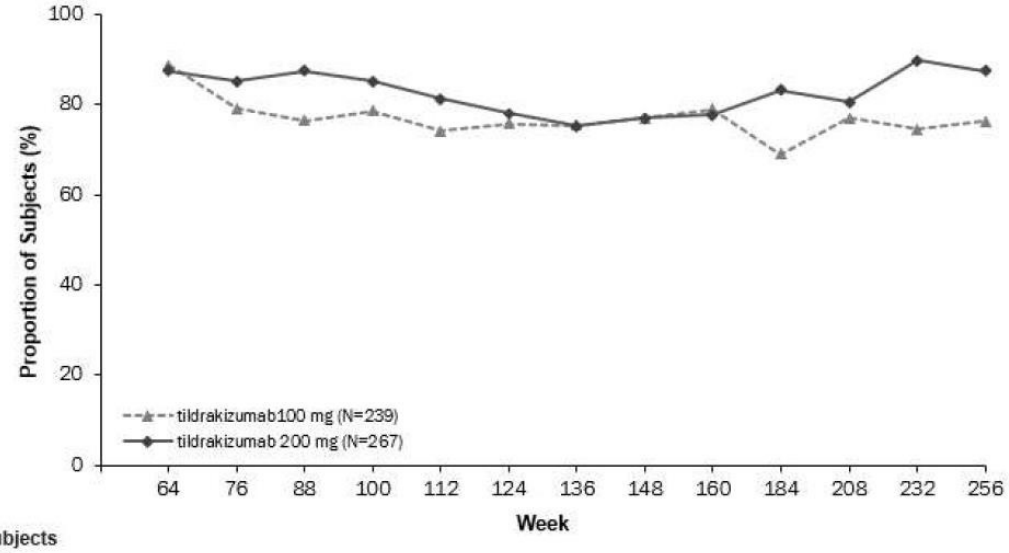
Figure 1. Maintenance and durability of PASI 90 response. Proportion of patients with PASI 90 response over time up to week 64 (full analysis set part 3*)



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.

Of the patients who completed the double-blind period, 506 (79%) in reSURFACE 1 and 730 (97%) in reSURFACE 2 entered the extension period. Across studies, at least 76% of patients who had a PASI 90 response at the end of double-blind period, maintained a PASI 90 response during the extension period, when tildrakizumab 100 mg or 200 mg treatment was continued during a period of 192 weeks (Figure 2 and Figure 3).

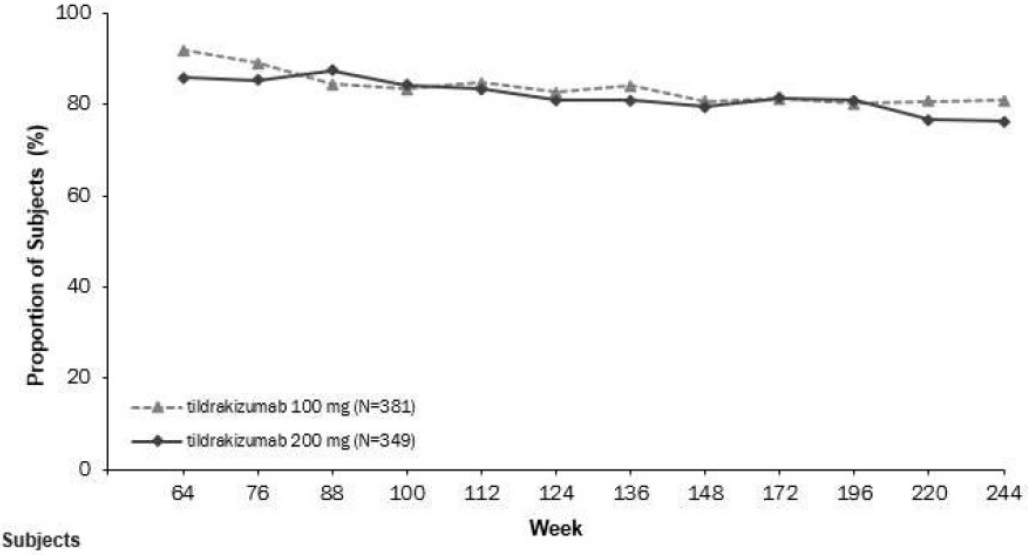
Figure 2. Percentage of patients who maintained a PASI 90 response by visit in the openlabel extension of reSURFACE 1 (Full Analysis Set, Extension Period*)



Number of Subjects													
Tildrakizumab 100 mg	125	125	124	122	120	120	118	118	115	110	105	102	97
Tildrakizumab 200 mg	137	136	136	129	134	133	133	131	130	125	124	118	113

*Among PASI 90 responders at the end of the double-blind study period. No imputation of missing data.
Note: Visit week is nominal, as study participants had a window of up to approximately 12 weeks from week 64 to
begin the extension.

Figure 3. Percentage of patients who maintained a PASI 90 response by visit in the openlabel extension of reSURFACE 2 (Full Analysis Set, Extension Period*)



Number of Subjects												
Tildrakizumab 100 mg	258	258	251	249	245	244	239	234	234	227	218	211
Tildrakizumab 200 mg	192	192	192	191	188	184	184	181	178	173	171	169

*Among PASI 90 responders at the end of the double-blind study period. No imputation of missing data.

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.

Immunogenicity

In pooled Phase 2b and Phase 3 analyses, 7.3% of tildrakizumab-treated patients developed antibodies to tildrakizumab up to week 64. Of the subjects who developed antibodies to tildrakizumab, 38% (22/57 patients) had neutralizing antibodies. This represents 2.8% of all subjects receiving tildrakizumab.

In pooled phase 3 analyses, 8.3% of tildrakizumab-treated patients developed antibodies to tildrakizumab up to 420 weeks of treatment. Of the tildrakizumab-treated patients who developed antibodies to tildrakizumab, 35% (36/102 patients) had antibodies that were classified as neutralizing, which represents 2.9% of all tildrakizumab-treated patients.

The development of neutralizing antibodies to tildrakizumab was associated with lower serum tildrakizumab concentrations.

5.2 Pharmacokinetic properties

Absorption

The subcutaneous formulation of tildrakizumab showed an absolute bioavailability ranging from 73% (90% CI: 46% - 115%, 200 mg subcutaneous vs. 3 mg/kg intravenous) to 80% (90% CI: 62% - 103%, 50 mg subcutaneous vs. 0.5 mg/kg intravenous) in healthy subjects, as a result of cross study single dose comparison. Maximum concentration was reached at 6.2 days after injection. Population pharmacokinetic 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 (% coefficient of variation [%CV]) of AUC_0-τ and Cmax 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 catabolised 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.

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 catabolised into component amino acids by general protein degradation processes and is not eliminated by renal or hepatic pathways.

Body weight

Population pharmacokinetic modelling indicated that exposure decreased as body weight increased. The geometric mean exposure (AUC0-τ at steady state) in adult patients weighing >90 kg following a 100 mg or 200 mg subcutaneous dose was predicted to be about 30% lower than in an adult patient weighing ≤90 kg (see section 4.2).

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 metabolised 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 mutagenicity and 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

Sucrose
L-Histidine hydrochloride monohydrate
Polysorbate 80
L-Histidine
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

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

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Unopened pre-filled syringe of Ilumya 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.
Store the pre-filled syringes in the outer carton in order to protect from light.
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 fluoropolymer lamination, plunger stopper assembled in a passive safety device.
Pack size of 1 pre-filled syringe.

6.6 Special precautions for disposal and other handling

Ilumya 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. 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 use 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. MANUFACTURER:

Sun Pharmaceutical Industries Europe B.V.
Polaris Avenue 87, 2132 JH Hoofddorp, The Netherlands

8. MARKETING AUTHORISATION HOLDER

Taro International Ltd.
14 Hakitor St., Haifa Bay 2624761

9. MARKETING AUTHORISATION NUMBER

167-49-36455-00

Revised in August 2024 according to the MOH guidelines.