Johnson&Johnson

Professional Information (PI)

SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

STELARA® 45 mg solution for subcutaneous injection

STELARA® 90 mg solution for subcutaneous injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains:

- 45 mg ustekinumab in 0,5 mL

- 90 mg ustekinumab in 1,0 mL

Each pre-filled pen (for adult use) contains:

- 45 mg ustekinumab in 0,5 mL

- 90 mg ustekinumab in 1,0 mL

Each vial contains:

- 45 mg ustekinumab in 0,5 mL

Ustekinumab is a fully human IgG1κ monoclonal antibody to interleukin (IL)-12/23 produced in a murine myeloma cell line using recombinant DNA technology.

For the full list of excipients, see section 6.1.

Contains sugar (sucrose).

STELARA 45 mg subcutaneous dose contains 38 mg of sucrose.

STELARA 90 mg subcutaneous dose contains 76 mg of sucrose.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear to slightly opalescent, colourless to light yellow. The solution may contain a few small translucent or white protein particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Plaque psoriasis

STELARA is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for phototherapy or systemic therapy.

Paediatric plaque psoriasis

STELARA is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

Psoriatic Arthritis (PsA)

STELARA, alone or in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active psoriatic arthritis in adults as second line treatment, when the response to previous Disease-Modifying Antirheumatic Drugs (DMARDS) was inadequate.

Crohn's Disease

STELARA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies.

Ulcerative colitis

STELARA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies.

4.2 Posology and method of administration

Posology

STELARA is intended for use under the guidance and supervision of medical practitioners experienced in the diagnosis and treatment of conditions for which STELARA is indicated.

Posology

Plaque psoriasis and psoriatic arthritis

For the treatment of plaque psoriasis and psoriatic arthritis, STELARA is administered by subcutaneous injection.

Adults (18-64 years):

The recommended dose of STELARA is 45 mg administered subcutaneously at Weeks 0 and 4, then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight greater than 100 kg (see section 5.2, Pharmacokinetic Properties). In patients weighing > 100 kg, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy in these patients.

For patients with plaque psoriasis, who inadequately respond to dosing every 12 weeks, consideration may be given to treating every 8 weeks.

Consideration should be given to discontinuing treatment in patients who have

shown no response up to 28 weeks of treatment.

Re-treatment:

For patients with psoriasis, re-treatment with a dosing regimen of Weeks 0 and 4 after interruption of therapy has been shown to be safe and effective.

Crohn's Disease and Ulcerative Colitis

In the treatment regimen, the first dose of STELARA is administered intravenously. For the posology of the intravenous dosing regimen, see section 4.2 of the STELARA 130 mg Concentrate for solution for infusion Professional information.

The first subcutaneous administration of 90 mg STELARA should take place at week 8 after the intravenous dose. After this, dosing every 12 weeks is recommended.

Patients who have not shown adequate response at 8 weeks after the first subcutaneous dose, may receive a second subcutaneous dose at this time.

Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks.

Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgement.

Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit 16 weeks after the IV induction dose or 16 weeks after switching to the 8-weekly maintenance dose.

Immunomodulators and/or corticosteroids may be continued during treatment with STELARA.

In patients who have responded to treatment with STELARA, corticosteroids may be reduced or discontinued in accordance with standard of care.

In Crohn's disease or ulcerative colitis, if therapy is interrupted, resumption of treatment with subcutaneous dosing every 8 weeks is safe and effective.

Elderly (≥ 65 years)

In clinical studies, no major age-related differences in clearance or volume of distribution were observed and no overall differences in safety and efficacy in patients age 65 and older who received STELARA were observed compared to younger patients. The number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

No dose adjustment is needed for elderly patients (see section 4.4).

Renal and hepatic impairment

STELARA has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population

The safety and efficacy of STELARA in children with psoriasis less than 6 years of age or in children with psoriatic arthritis less than 18 years of age have not yet been established.

The safety and efficacy of STELARA in treatment of Crohn's disease or ulcerative colitis in children less than 18 years of age have not been established.

Paediatric plaque psoriasis (6 years and older)

For the treatment of plaque psoriasis, STELARA should be administered by subcutaneous

injection. The recommended dose of STELARA based on body weight is shown below (Tables 1 and 2). STELARA should be administered at Weeks 0 and 4, then every 12 weeks thereafter. The pre-filled pen is not recommended for use in paediatric patients.

Table 1: Recommended dose of STELARA for paediatric psoriasis

Weight	Recommended dose	Dosage form
< 60 kg	0,75 mg/kg*	Vial
≥ 60 to ≤ 100 kg	45 mg	Pre-filled syringe, vial
>100 kg	90 mg	Pre-filled syringe

* To calculate the volume of injection (mL) for patients < 60 kg, use the following formula: *body weight* (kg) x *0,0083* (mL/kg) or see Table 2. The calculated volume should be rounded to the nearest 0,01 mL and administered using a 1 mL graduated syringe. A 45 mg vial is available for paediatric patients who need to receive less than the full 45 mg dose.

Table 2 Injection volumes of STELARA for paediatric psoriasis patients < 60 kg

Body weight at time of dosing (kg)	Dose (mg)	Volume of injection (mL)
15	11.3	0.12
16	12.0	0.13
17	12.8	0.14
18	13.5	0.15
19	14.3	0.16
20	15.0	0.17
21	15.8	0.17
22	16.5	0.18
23	17.3	0.19
24	18.0	0.20
25	18.8	0.21
26	19.5	0.22
27	20.3	0.22
28	21.0	0.23
29	21.8	0.24

30	22.5	0.25
31	23.3	0.26
32	24.0	0.27
33	24.8	0.27
34	25.5	0.28
35	26.3	0.29
36	27.0	0.30
37	27.8	0.31
38	28.5	0.32
39	29.3	0.32
40	30.0	0.33
41	30.8	0.34
42	31.5	0.35
43	32.3	0.36
44	33.0	0.37
45	33.8	0.37
46	34.5	0.38
47	35.3	0.39
48	36.0	0.40
49	36.8	0.41
50	37.5	0.42
51	38.3	0.42
52	39.0	0.43
53	39.8	0.44
54	40.5	0.45
55	41.3	0.46
56	42.0	0.46
57	42.8	0.47
58	43.5	0.48
59	44.3	0.49

Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.

Method of administration

STELARA 45 mg vials or 45 mg and 90 mg pre-filled syringes or pre-filled pens are for subcutaneous injection only. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

After proper training in subcutaneous injection technique, patients or their caregivers may inject STELARA if a medical practitioner determines that it is appropriate. However, the medical practitioner should ensure appropriate follow-up of patients.

The pre-filled pen has not been studied in the paediatric population and is not recommended for use in paediatric patients.

Patients or their caregivers should be instructed to inject the prescribed amount of STELARA subcutaneously according to the directions provided in the Professional information. Comprehensive instructions for administration are given in the Patient Information Leaflet.

For further instructions on the preparation and special precautions for handling, see section 6.6.

4.3 Contraindications

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

Active tuberculosis (see section 4.4).

4.4 Special warnings and precautions for use

Infections

STELARA is a selective immunosuppressant and may have the potential to increase the risk of infections and reactivate latent infections.

In clinical studies, serious bacterial, fungal, and viral infections were observed in patients receiving STELARA (see section 4.8: Infections).

STELARA should not be given to patients with a clinically important, active infection.

Caution should be exercised when considering the use of STELARA in patients with a chronic infection or a history of recurrent infection.

Prior to initiating treatment with STELARA, patients should be evaluated for tuberculosis infection. STELARA should not be given to patients with active tuberculosis (see section 4.3). Treatment of latent tuberculosis infection should be initiated prior to administering STELARA. Anti-tuberculosis therapy should also be considered prior to initiation of STELARA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving STELARA should be monitored closely for signs and symptoms of active tuberculosis during and after treatment.

Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, they should be closely monitored and STELARA should not be administered until the infection resolves.

Malignancies

STELARA is a selective immunosuppressant. Immunosuppressive medicines, such as STELARA, have the potential to increase the risk of malignancy. Some patients who received STELARA in clinical studies developed cutaneous and non-cutaneous malignancies (see section 4.8: Malignancies).

STELARA has not been studied in patients with a history of malignancy. Caution should be exercised when considering the use of STELARA in patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

All patients, in particular those older than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of skin cancer (see section 4.8: Malignancies).

Hypersensitivity reactions

In post-marketing experience, serious hypersensitivity reactions, including anaphylaxis and

angioedema, have been reported. If an anaphylactic or other serious hypersensitivity reaction occurs, institute appropriate therapy and administration of STELARA should be discontinued (see section 4.8: Hypersensitivity reactions).

Latex sensitivity

The needle cover on the pre-filled syringe and the needle cover inside the bottom cap of the pre-filled pen contain dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Immunisations

Live viral or live bacterial vaccines (such as Bacillus of Calmette and Guérin (BCG)) should not be given concurrently with STELARA.

No data are available on the secondary transmission of infection by live vaccines in patients receiving STELARA. Caution is advised when administering some live vaccines to household contacts of patients receiving STELARA because of the potential risk for shedding from the household contact and transmission to the patient.

Patients receiving STELARA may receive concurrent inactivated or non-live vaccinations.

Long term treatment with STELARA does not suppress the humoral immune response to pneumococcal polysaccharide or tetanus vaccines.

Infant exposure *in utero*

For infants exposed *in utero* to ustekinumab, a six month waiting period following birth is recommended before the administration of live vaccines. Administration of a live vaccine prior to 6 months of age may be considered if ustekinumab dosing was limited to the first trimester of pregnancy when placental transport is minimal, or ustekinumab serum levels are

undetectable in the infant, or the benefit of the vaccination clearly outweighs the theoretical risk of administration of live vaccines to the infant (see section 4.6 - Fertility, pregnancy and lactation).

Immunosuppression

In psoriasis studies, the safety and efficacy of STELARA in combination with immunosuppressive medicines or phototherapy have not been evaluated.

In psoriatic arthritis studies, concomitant methotrexate (MTX) use did not appear to influence the safety or efficacy of STELARA.

In Crohn's disease and ulcerative colitis studies, concomitant use of immunomodulators (6-mercaptopurine (6-MP), azathioprine (AZA), methotrexate (MTX) or corticosteroids did not appear to influence the safety or efficacy of STELARA.

Caution should be exercised when considering concomitant use of immunosuppressive medicines and STELARA or when transitioning from other biologic medicines. (see section 4.5).

Immunotherapy

STELARA has not been evaluated in patients who have undergone allergy immunotherapy. STELARA may affect allergy immunotherapy. Caution should be exercised in patients receiving or who have received allergy immunotherapy particularly for anaphylaxis.

Serious skin conditions

In patients with psoriasis, exfoliative dermatitis has been reported following ustekinumab treatment (see section 4.8). Patients with plaque psoriasis may develop erythrodermic psoriasis, with symptoms that may be clinically indistinguishable from exfoliative dermatitis, as part of the natural course of

their disease. As part of the monitoring of the patient's psoriasis, physicians should be alert for symptoms of erythrodermic psoriasis or exfoliative dermatitis. If these symptoms occur, appropriate therapy should be instituted. STELARA should be discontinued if a drug reaction is suspected.

Sucrose

STELARA contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not use STELARA. In addition, sucrose may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicinal products and other forms of interaction

Live vaccines should not be given concurrently with STELARA. Recommendations for infants exposed to ustekinumab *in utero* are provided (see section 4.4).

The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an in vitro study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4).

Results from a Phase 1 study in subjects with active Crohn's disease suggest no clinically relevant drug interactions are likely. These results do not suggest the need for dose adjustments in patients who are receiving concomitant CYP450 substrates (see *5.2)*.

In a population pharmacokinetic analysis, the effect of the most frequently

used concomitant medicines in patients with psoriasis (including paracetamol, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, naproxen, levothyroxine, hydrochlorothiazide, and influenza vaccine) on pharmacokinetics of ustekinumab was explored. There were no indications of an interaction with these concomitantly administered medicines.

The pharmacokinetics of STELARA was not impacted by the prior use of MTX, NSAIDs, and oral corticosteroids, or prior exposure to anti-TNFα medicines in patients with psoriatic arthritis, Crohn's disease or in patients with ulcerative colitis.

In psoriasis studies, the safety and efficacy of STELARA in combination with immunosuppressive medicines, including biologics, or phototherapy have not been evaluated.

Caution should be exercised when considering concomitant use of immunosuppressive medicines and STELARA.

4.6 Fertility, pregnancy and lactation

Pregnancy

Data from prospectively collected pregnancies following exposure to STELARA resulting in live birth with known outcomes, including more than 450 pregnancies exposed during the first trimester, do not indicate an increased risk of malformations in the newborn.

Overall, data from observational studies, pharmacovigilance, and published case reports and cohort studies do not indicate an increase in the risk of major birth defects, pattern of major or minor anomalies, miscarriage, or adverse infant outcomes.

STELARA should not be given to a pregnant woman except if the benefit clearly outweighs the risk.

Lactation

Limited data from published literature suggests that ustekinumab is excreted in human breast milk in very small amounts. While systemic exposure to the breastfed infant is expected to be low because ustekinumab is a large molecule and is degraded in the gastrointestinal tract, it is not known if STELARA is absorbed systemically after ingestion.

Because of the potential for adverse reactions in breastfeeding infants from STELARA, a decision should be made whether to discontinue breastfeeding or to discontinue STELARA.

Fertility

The effect of STELARA on human fertility has not been evaluated (see section 5.3).

It is not known whether STELARA can affect reproductive potential.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical studies experience in adult patients

Summary of safety profile

The most common adverse reactions (> 5 %) in controlled periods of the adult psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies with STELARA were nasopharyngitis and headache. Most were considered to be mild and did not necessitate discontinuation of study treatment. The most serious adverse reaction that has been reported for STELARA is serious hypersensitivity reactions including anaphylaxis (see section 4.4).

The overall safety profile was similar for patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

Tabulated list of adverse reactions

The safety data described below reflect exposure in adults to STELARA in 14 phase 2 and phase 3 studies in 6 710 patients (4 135 with psoriasis and/or psoriatic arthritis, 1 749 with Crohn's disease and 826 patients with ulcerative colitis). This includes exposure to STELARA in the controlled and non-controlled periods of the clinical studies for at least 6 months or 1 year (4 577 and 3648 patients respectively with psoriasis, psoriatic arthritis, Crohn's disease or ulcerative colitis) and exposure for at least 4 or 5 years (2194 and 1148 patients with psoriasis respectively).

Table 3 provides a list of adverse reactions from adult psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies. The adverse reactions are classified by System Organ Class 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), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: Summary of Adverse Reactions in Clinical Studies

System Organ Class	Frequency: Adverse reaction
Infections and infestations	*Common*: Upper respiratory tract infection, nasopharyngitis, sinusitis *Uncommon*: Cellulitis, dental infections, herpes zoster, viral upper respiratory tract infection, vulvovaginal mycotic infection
Psychiatric disorders	*Uncommon*: Depression
Nervous system disorders	*Common*: Dizziness, headache Uncommon: Facial Palsy
Respiratory, thoracic and mediastinal disorders	*Common*: Oropharyngeal pain *Uncommon*: Nasal congestion
Gastrointestinal disorders	*Common*: Diarrhoea, nausea, vomiting
Skin and subcutaneous tissue disorders	*Common*: Pruritus *Uncommon*: Acne *Rare :* Exfoliative dermatits
Musculoskeletal and connective tissue disorders	*Common:* Back pain, myalgia, arthralgia
General disorders and administration site conditions	*Common:* Fatigue, injection site erythema, injection site pain *Uncommon*: Injection site reactions (including haemorrhage, haematoma, induration, swelling and pruritus), asthenia

Physicians should consider the local disease background when treating patients with STELARA (see section 4.4).

Description of selected adverse reactions

Infections

In the placebo-controlled period of clinical studies of patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis, the rate of infection was 1,36 per patient-year of follow-up in STELARA-treated patients, and 1,34 per patient follow-up in placebo-treated patients. Serious infections occurred at the same rate of 0,03 per patient-year of follow-up in STELARA and placebo treated patients (see section 4.4: Infections).

In the controlled and non-controlled portions of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, the rates of infection and serious infection were 0,85 and 0,02 , respectively, per patient-year of follow-up in STELARA-treated patients. Serious infections included anal abscess, cellulitis, pneumonia, diverticulitis, gastroenteritis and viral infections.

In clinical studies, patients with latent tuberculosis who were concurrently treated with isoniazid did not develop tuberculosis.

Malignancies

In the placebo controlled period of the psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0,11 per 100 patient-years of follow-up for STELARA-treated patients compared with 0,23 per 100 patient years of follow up for placebo-treated patients.

The incidence of non-melanoma skin cancer was 0,43 per 100 patient-years of follow-up for

STELARA-treated patients compared with 0,46 per 100 patient-years of follow up for placebo-treated patients.

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies malignancies, excluding non-melanoma skin cancers were reported with an incidence of 0,50 per 100 patient-years of follow-up for STELARA-treated patients. This was comparable to the incidence expected in the general population (standardised incidence ratio = 0,94 [95% confidence interval: 0,73, 1,18]).

The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, melanoma, colorectal and breast. The incidence of non-melanoma skin cancer was 0,49 per 100 patient-years of follow-up for STELARA-treated patients (see section 4.4: Malignancies).

The ratio of patients with basal versus squamous cell skin cancers (3:1) is comparable with the ratio expected in the general population.

Hypersensitivity

During the controlled periods of psoriasis and psoriatic arthritis clinical studies of STELARA, rash and urticaria have each been observed in < 1 % of patients.

Clinical studies experience in paediatric patients with psoriasis

The safety of STELARA has been studied in two Phase 3 studies of paediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks (CADMUS) and the second study was in 44 patients from 6 to 11 years of age treated for up to 56 weeks (CADMUS Jr.). In general, the adverse events reported in these two studies were similar to those seen in previous studies in adults with

plaque psoriasis.

Postmarketing experience

Table 4: Adverse Reactions Identified During Postmarketing Experience with STELARA

Immune system disorders	Hypersensitivity reactions (including rash, urticaria) Serious hypersensitivity reactions (including anaphylaxis, angioedema)
Infections and infestations	Lower respiratory tract infection
Respiratory, thoracic and mediastinal disorders	Allergic alveolitis, eosinophilic pneumonia
Skin and subcutaneous tissue disorders	Pustular psoriasis, exfoliative dermatitis, erythrodermic psoriasis, hypersensitivity vasculitis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product

is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In case of overdose, although no dose-dependent toxicity has been observed, theoretically, side effects could be exacerbated or exaggerated. It is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC05.

Mechanism of action

Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to complement or antibody mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors.

IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells. IL-12 stimulates natural killer (NK) cells and drives

the differentiation of CD4+ cells toward the T-helper 1 (Th1) phenotype and stimulates interferon gamma (IFNγ) production. IL-23 induces the T helper 17 (Th17) pathway and promotes secretion of IL-17A, IL-21, and IL-22.

By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.

In patients with psoriasis and /or psoriatic arthritis, ustekinumab had no apparent effect on the percentages of circulating immune cell populations including memory and naive T cell subsets or circulating cytokine levels. Systemic markers of inflammation were measurable in the serum at baseline and 4 markers (MDC,VEGF, MCSF-1 and YKL-40) showed modest differences in concentration post-treatment in ustekinumab-treated patients as compared to placebo.

In psoriasis and psoriatic arthritis studies, clinical response (improvement in Psoriasis Area and Severity Index [PASI] or ACR measurements, respectively) appeared to be related to serum ustekinumab levels. Patients with psoriasis with higher PASI response had higher median serum concentrations of ustekinumab than those with lower clinical responses.

In patients with Crohn's disease and ulcerative colitis, treatment with ustekinumab resulted in a decrease in inflammatory markers including C-Reactive Protein (CRP) and faecal calprotectin during the induction phase, which were then maintained throughout the maintenance phase.

5.2 Pharmacokinetic properties

Absorption

The median time to reach the maximum serum concentration (t_{max}) was 8,5 days after a single 90 mg subcutaneous administration in healthy subjects. The median t_{max} values of ustekinumab following a single subcutaneous administration of either 45 mg or 90 mg in patients with psoriasis were comparable to that observed in healthy subjects.

The absolute bioavailability of ustekinumab following a single subcutaneous administration was estimated to be 57,2 % in patients with psoriasis.

Distribution

Median volume of distribution during the terminal phase (Vz) following a single intravenous administration to patients with psoriasis ranged from 57 to 83 mL/kg.

Metabolism

The exact metabolic pathway for ustekinumab is unknown.

Elimination

Median systemic clearance (CL) following a single intravenous administration to patients with psoriasis ranged from 1,99 to 2,34 mL/day/kg. Median half-life ($t_{1/2}$) of ustekinumab was approximately 3 weeks in patients with ulcerative colitis,
Crohn's disease, psoriasis and/or psoriatic arthritis, ranging from 15 to 32 days
across all psoriasis and psoriatic arthritis studies.

Dose linearity

The systemic exposure of ustekinumab (C_{max} and AUC) increased in an approximately dose-proportional manner after a single intravenous administration at doses ranging from 0,09 mg/kg to 4,5 mg/kg or following a single subcutaneous administration at doses ranging from approximately 24 mg to 240 mg in patients with psoriasis.

Single dose versus multiple doses

Serum concentration-time profiles of ustekinumab were generally predictable after single or multiple subcutaneous dose administrations. In patients with psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week 28 after initial subcutaneous doses at Weeks 0 and 4 followed by doses every 12 weeks. There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

In patients with Crohn's disease and ulcerative colitis, following the recommended IV induction dose, median peak serum ustekinumab concentration was 126,1 mcg/mL in patients with Crohn's disease and 127,0 mcg/mL in patients with ulcerative colitis. Starting at Week 8, subcutaneous maintenance dosing of
90 mg ustekinumab was administered every 8 or 12 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose. Median steady-state trough concentrations ranged from 1,97 mcg/mL to 2,24 mcg/mL and from 0,61 mcg/mL to 0,76 mcg/mL for 90 mg ustekinumab every 8 weeks or every 12 weeks respectively.

Impact of weight on pharmacokinetics

Serum ustekinumab concentrations were affected by weight in patients with psoriasis and/or psoriatic arthritis. Within each dose (45 mg or 90 mg), patients of higher weight (>100 kg) had lower median serum ustekinumab concentrations compared with those in patients of lower weight (≤ 100 kg). However, across doses, the median trough serum concentrations of ustekinumab in patients with higher weight (> 100 kg) in the 90 mg group were comparable to those in patients with lower weight (≤ 100 kg) in the 45 mg group.

Special populations

No pharmacokinetic data are available in patients with impaired renal or hepatic function.

No specific studies have been conducted in elderly patients.

A population pharmacokinetic analysis indicated there was no apparent changes in CL/F and V/F estimates in patients ≥ 65 years.

Paediatrics (17 years of age and younger)

The pharmacokinetics of ustekinumab in paediatric psoriasis patients, 6 to 17 years of age, treated with the recommended dose was generally comparable to that in the adult psoriasis population.

The pharmacokinetics of ustekinumab were not affected by the use of tobacco or alcohol.

Regulation of CYP450 enzymes

The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4).

No clinically significant changes in exposure of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), or midazolam (CYP3A substrate) were observed when used concomitantly with ustekinumab at the approved recommended dosing in subjects with Crohn's disease (the same dose as ulcerative colitis and higher than approved recommended dosing for plaque psoriasis and psoriatic arthritis).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard (e.g. organ toxicity) for humans based on studies of repeated-dose toxicity and developmental and reproductive toxicity, including safety pharmacology evaluations. In developmental and reproductive toxicity studies in cynomolgus monkeys, neither adverse effects on male fertility indices nor birth defects or

developmental toxicity were observed. No adverse effects on female fertility indices were observed using an analogous antibody to IL-12/23 in mice.

Dose levels in animal studies were up to approximately 45-fold higher than the highest equivalent dose intended to be administered to psoriasis patients and resulted in peak serum concentrations in monkeys that were more than 100-fold higher than observed in humans.

Carcinogenicity studies were not performed with ustekinumab due to the lack of appropriate models for an antibody with no cross-reactivity to rodent IL-12/23 p40.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine

L-histidine monohydrochloride monohydrate

Polysorbate 80

Sucrose

Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

45 mg vial : 24 months

Pre-filled Syringe and Pre-filled pen : 36 months

6.4 Special precautions for storage

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

Keep the vial or pre-filled syringe in the outer carton until time of use in order to

protect from light.

Do not freeze. Do not shake.

6.5 Nature and contents of container

STELARA 45 mg solution for injection 0,5 mL solution in a type I glass 2 mL vial closed with a coated butyl rubber stopper.

STELARA 45 mg solution for injection in pre-filled syringe 0,5 mL solution in a type I glass 1 mL syringe with a fixed stainless steel needle and a needle shield containing dry natural rubber (a derivative of latex). The syringe is fitted with the Ultrasafe Passive Needle Guard.

STELARA 90 mg solution for injection in pre-filled syringe 1 mL solution in a type I glass 1 mL syringe with a fixed stainless steel needle and a needle shield containing dry natural rubber (a derivative of latex). The syringe is fitted with the Ultrasafe Passive Needle Guard.

STELARA 45 mg solution for injection in pre-filled pen 0,5 mL solution in a type I glass 1 mL syringe with a fixed stainless steel needle and a rigid needle shield containing dry natural rubber (a derivative of latex). The syringe is fitted with the pre-filled pen device.

STELARA 90 mg solution for injection in pre-filled syringe 1 mL solution in a type I glass 1 mL syringe with a fixed stainless steel needle and a rigid needle shield containing dry natural rubber (a derivative of latex). The syringe is fitted with the pre-filled pen device.

STELARA is available in a 1 vial pack or a pack of 1 pre-filled syringe or 1 pre-filled pen.

6.6 Special precautions for disposal and other handling

The solution in the STELARA vial; pre-filled syringe or pre-filled pen should not be shaken.

The solution should be visually inspected for particulate matter or discolouration prior to

subcutaneous administration. The solution is clear to slightly opalescent, colourless to light yellow and may contain a few small translucent or white particles of protein. This appearance is not unusual for proteinaceous solutions. The medicine should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present. Before injection, remove STELARA from the refrigerator and allow STELARA to reach room temperature (30 minutes) without removing the needle cap.

Detailed instructions for use are provided in the Patient Information Leaflet.

STELARA does not contain preservatives; therefore any unused medicine remaining in the vial and the syringe should not be used. STELARA is supplied as a sterile, single-use vial or single-use pre-filled syringe. The syringe, needle and vial must never be re-used. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION



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8. REGISTRATION NUMBER(S)

STELARA 45 mg: 43/30.1/0727

STELARA 90 mg: 43/30.1/0728

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration of STELARA 45 mg and 90 mg: 27 July 2012

10. DATE OF REVISION OF THE TEXT

15 May 2026