Approved Professional Information (PI)

SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

STELARA® 130 mg concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 130 mg ustekinumab in 26 mL (5 mg/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 130 mg intravenous loading dose contains 2 210 mg sucrose per vial.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

The solution is clear and colourless to light yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 concentrate for solution for infusion is intended for use under the guidance and supervision of medical practitioners experienced in the diagnosis and treatment of Crohn's disease or ulcerative colitis. STELARA concentrate for solution for infusion should only be used for the intravenous induction dose.

Posology

Crohn's Disease and Ulcerative Colitis

STELARA treatment is to be initiated with a single intravenous dose based on body weight. The infusion solution is to be composed of the number of vials of STELARA 130 mg as specified in Table 1 (see section 6.6 for preparation).

Table 1 Initial intravenous dosing of STELARA

Body weight of patient at the time of dosing	**Recommended dose** [a]	**Number of 130 mg STELARA vials**
≤ 55 kg	260 mg	2
> 55 kg to ≤ 85 kg	390 mg	3
> 85 kg	520 mg	4

[a] Approximately 6 mg/kg

The first subcutaneous dose should be given at week 8 following the intravenous dose.

For the posology of the subsequent subcutaneous dosing regimen, see section 4.2 of the STELARA solution for injection (vial) and solution for injection in pre-filled syringe Professional Information.

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 for the treatment of Crohn's disease or ulcerative colitis in children less than 18 years have not yet been established. No data are available.

Method of administration

STELARA 130 mg is for intravenous use only. It should be administered over at least one hour.

For instructions on dilution of the medicinal product before administration, 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 non-melanoma 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).

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.

Immunosuppression

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.

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

No specific interaction studies have been performed in humans. 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

The safety of STELARA has not been established during pregnancy or lactation. STELARA should not be given to a pregnant woman except if the benefit clearly outweighs the risk.

Lactation

It is unknown whether STELARA is excreted in human breast milk. Women are advised against breastfeeding while receiving STELARA.

Fertility

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

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 6 709 patients (4 135 with psoriasis and/or psoriatic arthritis, 1 749

with Crohn's disease and 825 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 3 253 patients respectively with psoriasis, psoriatic arthritis, Crohn's disease or ulcerative colitis) and exposure for at least 4 or 5 years (1 482 and 838 patients with psoriasis respectively).

Table 2 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 2: 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
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
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 0,91 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 0,54 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 = 0,93 [95% confidence interval: 0,71, 1,20]).

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 and infusion reactions

In Crohn's disease and ulcerative colitis intravenous induction studies, no events of anaphylaxis or other serious infusion reactions were reported following the single intravenous dose. In these studies, 2,2 % of 785 placebo treated patients and 1,9 % of 790 patients treated with the recommended dose of STELARA reported adverse events occurring during or within an hour of the infusion.

Postmarketing experience

Table 3: 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

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 :**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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

Following the recommended intravenous induction dose, median peak serum ustekinumab concentration, observed 1 hour after the infusion, was 126,1 µg/mL in patients with Crohn's disease and 127,0 µg/mL in patients with ulcerative colitis.

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. 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.

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).

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

EDTA disodium salt dihydrate

L-histidine

L-histidine monohydrochloride monohydrate

L-methionine

Polysorbate 80

Sucrose

Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines. STELARA should only be diluted with sodium chloride 9 mg/mL (0,9 %) solution. STELARA should not be administered concomitantly in the same intravenous line with other medicinal products.

6.3 Shelf life

3 years.

Do not freeze.

Chemical and physical in-use stability has been demonstrated for 4 hours at 15-25 °C.

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user.

6.4 Special precautions for storage

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

Keep the vial in the outer carton until time of use in order to protect from light.

Do not freeze. Do not shake.

For storage conditions after dilution of the medicinal product, see section 6.3

6.5 Nature and contents of container

26 mL solution in a type I glass 30 mL vial closed with a coated butyl rubber stopper.

STELARA is available in a 1 vial pack.

6.6 Special precautions for disposal and other handling

The solution in the STELARA vial should not be shaken. The solution should be visually inspected for particulate matter or discolouration prior to administration. The solution is clear, colourless to light yellow. The medicine should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present.

Dilution

STELARA concentrate for solution for infusion must be diluted and prepared by a healthcare professional using aseptic technique.

1. Calculate the dose and the number of STELARA vials needed based on patient's body weight (see section 4.2, Table 1). Each 26 mL vial of STELARA contains 130 mg of ustekinumab. Only use complete vials of STELARA.
2. Withdraw and discard a volume of the sodium chloride 9 mg/mL (0,9%) solution from the 250 mL infusion bag equal to the volume of STELARA to be added. (discard 26 mL sodium chloride for each vial of STELARA needed, for 2 vials- discard 52 mL, for 3 vials- discard 78 mL, for 4 vials- discard 104 mL)
3. Withdraw 26 mL of STELARA from each vial needed and add it to the 250 mL infusion bag. The final volume in the infusion bag should be 250 mL. Gently mix.
4. Visually inspect the diluted solution before administration. Do not use if visibly opaque particles, discolouration or foreign particles are observed.
5. Administer the diluted solution over a period of at least one hour. Once diluted, the infusion should be completed within four hours of the dilution in the infusion bag.
6. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.2 micrometer).
7. Do not infuse STELARA concomitantly in the same intravenous line with other medicines.
8. Each vial is for single use only and any unused medicine should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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