

STELARA[®]

DATA SHEET

NAME OF THE MEDICINE

Ustekinumab (rnc). CAS Registry Number: 815610-63-0.

DESCRIPTION

STELARA (ustekinumab) is a human IgG1kappa monoclonal antibody with an approximate molecular weight of 148,600 daltons. STELARA is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

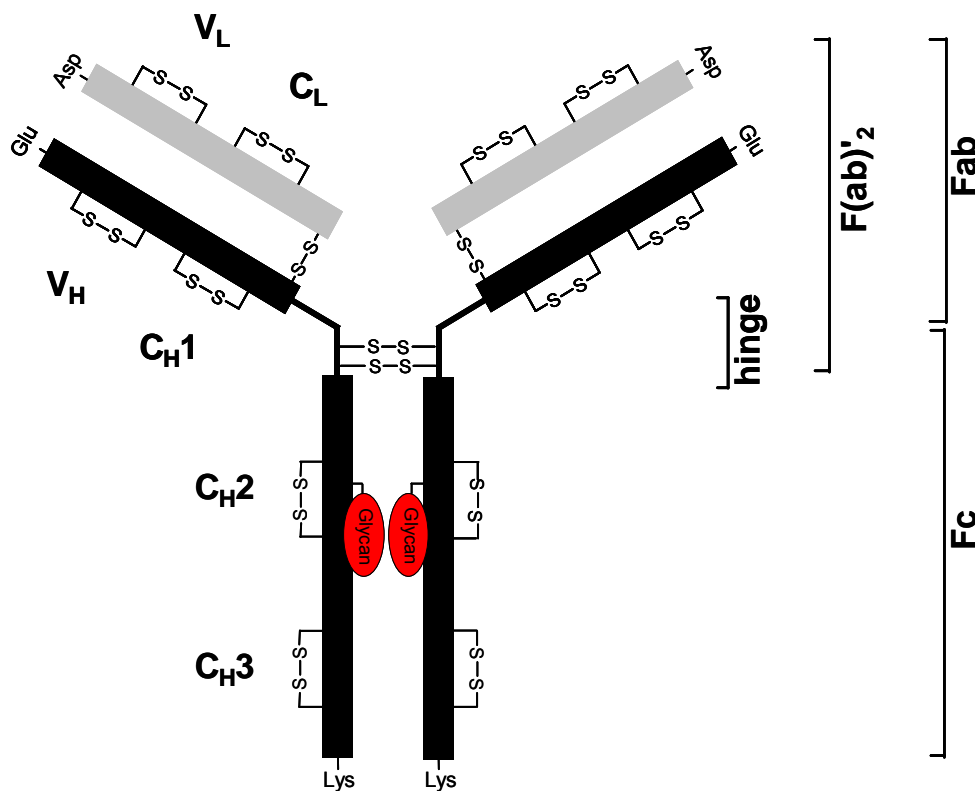


Figure 1. General structure of ustekinumab.

STELARA (ustekinumab) solution for subcutaneous injection is available in the following presentations:

Pre-filled Syringe:

- 45 mg / 0.5 mL
- 90 mg / 1.0 mL

Single-use Vial:

- 45 mg / 0.5 mL
- 90 mg / 1.0 mL (not currently marketed).

Each mL of STELARA contains 90 mg of ustekinumab, 1.0 mg histidine/histidine hydrochloride, 76 mg sucrose, 0.04 mg polysorbate 80, and water for injections.

PHARMACOLOGY

Mechanism of action

STELARA is a human IgG1kappa monoclonal antibody that specifically binds to the p40 protein subunit of the human cytokines interleukin (IL)-12 and IL-23. STELARA inhibits the bioactivity of human IL-12 and IL-23 by preventing these cytokines from binding to their IL-12Rbeta1 receptor protein expressed on the surface of immune cells. STELARA cannot bind to IL-12 or IL-23 that is pre-bound to IL-12Rbeta1 cell surface receptors. Thus, STELARA is not expected to contribute to complement- or antibody-mediated cytotoxicity of the receptor-bearing cell.

IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells. IL-12 and IL-23 participate in immune function by contributing to NK cell activation and CD4+ T cell differentiation and activation. However, abnormal regulation of IL-12 and IL-23 has been associated with immune-mediated diseases, such as psoriasis. STELARA prevents IL-12 and IL-23 contributions to immune cell activation, such as intracellular signalling and cytokine secretion. Thus, STELARA may interrupt signalling and cytokine cascades that are central to psoriasis pathology.

Pharmacodynamics

Treatment with STELARA resulted in significant improvement in histological measures of psoriasis including epidermal hyperplasia and cell proliferation. These results are consistent with the clinical efficacy observed.

STELARA had no apparent effect on the percentages of circulating immune cell populations including memory and naive T cell subsets or circulating cytokine levels.

Clinical response (improvement in Psoriasis Area and Severity Index [PASI]) appeared to be related to serum ustekinumab levels. Patients with psoriasis with higher clinical responses as measured by PASI response had higher median serum concentrations of ustekinumab than those with lower clinical responses. Overall, the proportion of patients with psoriasis who achieved PASI 75 response increased with increasing serum levels of ustekinumab. The proportion of patients who achieved PASI 75 response at Week 28 increased with increasing serum ustekinumab trough levels at Week 28.

Pharmacokinetics

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 (V_z) 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 psoriasis, ranging from 15 to 32 days across all psoriasis 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 vs. Multiple Doses

Serum concentration-time profiles of ustekinumab were generally predictable after single or multiple subcutaneous dose administrations. 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. The median steady-state trough concentration ranged from 0.21 microgram/mL to 0.26 microgram/mL (45 mg dose) and from 0.47 microgram/mL to 0.49 microgram/mL (90 mg dose). There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

Impact of Weight on Pharmacokinetics

Serum ustekinumab concentrations were affected by patient weight. Within each dose (45 or 90 mg), patients of higher weight (> 100 kg) had lower median serum ustekinumab concentrations compared with those in patients of lower weight (\leq 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 (\leq 100 kg) in the 45 mg group.

Population Pharmacokinetic Analysis

In a population pharmacokinetic analysis, the apparent clearance (CL/F) and apparent volume of distribution (V/F) were 0.465 L/d and 15.7 L, respectively, and the $t_{1/2}$ was approximately 3 weeks in patients with psoriasis. The CL/F of ustekinumab was not impacted by sex, age, or race. The CL/F was impacted by body weight, with a trend toward higher CL/F in patients with higher body weight. The median CL/F in patients with weight > 100 kg was approximately 55% higher compared with patients with weight < 100 kg. The median V/F in patients with weight > 100 kg was approximately 37% higher as compared with patients with weight < 100 kg.

In the population pharmacokinetic analysis, the effect of comorbidities (past and current history of diabetes, hypertension, and hyperlipidaemia) on pharmacokinetics of ustekinumab was evaluated. The pharmacokinetics of ustekinumab were impacted by the comorbidity of diabetes, with a trend towards higher CL/F in patients with diabetes. The mean CL/F in patients with diabetes was approximately 29% higher compared with patients without diabetes.

No specific drug-drug interaction studies have been conducted in healthy subjects or patients with psoriasis.

In the population pharmacokinetic analysis, the effect of the most frequently used concomitant medications in patients with psoriasis (including paracetamol/acetaminophen, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, naproxen, thyroxine, hydrochlorothiazide, and influenza vaccine) on pharmacokinetics of ustekinumab was explored and none of the concomitant medications exerted significant impact. The pharmacokinetics of ustekinumab was not impacted by the prior use of methotrexate, cyclosporin, or other biological therapeutics for the treatment of psoriasis.

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 (see **Interactions with Other Medicines**)).

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

No specific studies have been conducted in elderly patients. The population pharmacokinetic analysis indicated there were no apparent changes in CL/F and V/F estimates in patients > 65 years.

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

CLINICAL TRIALS

The safety and efficacy of STELARA was assessed in 2 Phase 3 studies (A Phase 3 multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of CNTO 1275 in the treatment of subjects with moderate to severe plaque-type psoriasis followed by long-term extension [PHOENIX] 1 and PHOENIX 2). A total of 1996 patients were enrolled in these studies.

The studies enrolled adults (≥ 18 years) with chronic (> 6 months) plaque psoriasis who had a minimum body surface area (BSA) involvement of 10%, and PASI score ≥ 12 and who were candidates for systemic therapy or phototherapy. Patients with guttate, erythrodermic, or pustular psoriasis were excluded from the studies. No concomitant anti-psoriatic therapies were allowed during the study with the exception of low-potency topical corticosteroids on the face and groin after week 12.

The Psoriasis Area and Severity Index (PASI) is a composite score that assesses the fraction of body surface area involved with psoriasis and the severity of psoriatic changes within the affected regions (plaque thickness/induration, erythema, and scaling). PASI numeric scores range from 0 to 72, with higher scores representing more severe disease.

Patients achieving $\geq 75\%$ improvement in PASI from baseline (PASI 75) were considered PASI 75 responders. Patients originally randomized to STELARA who were PASI 75 responders at both Weeks 28 and 40 were considered long-term PASI 75 responders. Patients achieving $\geq 90\%$ improvement in PASI from baseline (PASI 90) were considered PASI 90 responders and patients with $\geq 50\%$ improvement in PASI from baseline (PASI 50) were considered PASI 50 responders. Patients who achieved $\geq 50\%$ but less than 75% improvement in PASI from baseline were considered partial responders. Patients with $< 50\%$ improvement in PASI from baseline were considered non-responders.

Other key efficacy assessments included:

- The Physician's Global Assessment (PGA), a 6-category scale focusing on plaque thickness/induration, erythema, and scaling.
- The Dermatology Life Quality Index (DLQI), a dermatology-specific quality of life instrument, with a lower score indicating an improved quality of life.
- The SF-36, a health survey questionnaire consisting of multi-item scales measuring 8 health concepts (PHOENIX 1 only).
- The Nail Psoriasis Severity Index (NAPSI), a physician-assessed score that measures the severity of nail involvement (PHOENIX 1 only).
- The Hospital Anxiety and Depression Scale (HADS), a self-rating tool developed to evaluate psychological measures in patients with physical ailments (PHOENIX 2 only).
- The Work Limitations Questionnaire (WLQ), a 25-item, self-administered questionnaire that was used to measure the impact of chronic health conditions on job performance and work productivity among employed populations (PHOENIX 2 only).

- The Itch Visual Analogue Scale, (Itch VAS) used to assess the severity of itch at the time of the assessment (PHOENIX 1 only).

PHOENIX 1

PHOENIX 1 evaluated the safety and efficacy of STELARA versus placebo in 766 patients with plaque psoriasis and the efficacy of every 12 week dosing for patients who were PASI 75 responders. Patients randomized to STELARA received 45 mg or 90 mg doses at Weeks 0 and 4 followed by the same doses every 12 weeks. Patients randomized to receive placebo at Weeks 0 and 4 crossed over to receive STELARA (either 45 mg or 90 mg) at Weeks 12 and 16 followed by the same dose every 12 weeks.

Maintenance dosing (every 12 weeks)

To evaluate the therapeutic benefit of maintenance dosing with STELARA, patients originally randomized to STELARA who were PASI 75 responders at both Weeks 28 and 40 were re-randomized to either maintenance dosing of STELARA every 12 weeks or to placebo (i.e., withdrawal of therapy). Patients who were re-randomized to placebo at Week 40 reinitiated STELARA at their original dosing regimen when they experienced at least a 50% loss of their PASI improvement obtained at Week 40.

Dose Adjustment (every 8 weeks)

At Week 28, patients who were non-responders discontinued treatment and patients who were partial responders were adjusted to every-8-week dosing. PASI 75 responders at week 28 who became partial responders or non-responders at Week 40 were adjusted to every-8-week dosing. All patients were followed for at least 52 weeks following first administration of study treatment.

PHOENIX 2

PHOENIX 2 evaluated the safety and efficacy of STELARA versus placebo in 1230 patients with plaque psoriasis. Patients randomized to STELARA received 45 mg or 90 mg doses at Weeks 0 and 4 followed by an additional dose at Week 16. Patients randomized to receive placebo at Weeks 0 and 4 crossed over to receive STELARA (either 45 mg or 90 mg) at Weeks 12 and 16. Patients were followed for 28 weeks.

Baseline disease characteristics: PHOENIX 1 and 2

Baseline disease characteristics across PHOENIX 1 and 2 were similar (Table 1).

Table 1. Baseline Disease Characteristics

| | PHOENIX 1 | | PHOENIX 2 | |
|--|-----------|-----------|-----------|-----------|
| | Placebo | STELARA | Placebo | STELARA |
| Patients randomized at Week 0 | N = 255 | N = 511 | N = 410 | N = 820 |
| Median BSA | 22.0 | 21.0 | 20.0 | 21.0 |
| Patients with BSA \geq 20% | 145 (57%) | 276 (54%) | 217 (53%) | 445 (54%) |
| Median PASI | 17.80 | 17.40 | 16.90 | 17.60 |
| PASI \geq 20 | 91 (36%) | 169 (33%) | 133 (32%) | 300 (37%) |
| PGA of marked or severe | 112 (44%) | 223 (44%) | 160 (39%) | 328 (40%) |
| History of psoriatic arthritis | 90 (35%) | 168 (33%) | 105 (26%) | 200 (24%) |
| Prior phototherapy | 150 (59%) | 342 (67%) | 276 (67%) | 553 (67%) |
| Prior conventional systemic therapy excluding biologics | 142 (56%) | 282 (55%) | 241 (59%) | 447 (55%) |
| Prior conventional systemic or biologic therapy | 189 (74%) | 364 (71%) | 287 (70%) | 536 (65%) |
| Failed to respond to, had contraindication for, or intolerant to \geq 1 conventional therapy | 139 (55%) | 270 (53%) | 254 (62%) | 490 (60%) |
| Failed to respond to, had contraindication for, or intolerant to \geq 3 conventional therapies | 30 (12%) | 54 (11%) | 66 (16%) | 134 (16%) |

Efficacy at the Primary Endpoint, PHOENIX 1 and 2

In both the PHOENIX 1 and PHOENIX 2 studies, a significantly greater proportion of patients randomized to treatment with STELARA were PASI 75 responders compared with placebo at Week 12 (Table 2). In the PHOENIX 1 study, 67% and 66% of patients receiving STELARA 45 mg and 90 mg, respectively, achieved a PASI 75 response at Week 12 compared with 3% of patients receiving placebo. In the PHOENIX 2 study, 67% and 76% of patients receiving STELARA 45 mg and 90 mg respectively achieved a PASI 75 response at Week 12 compared with 4% of patients receiving placebo.

All 3 components of the PASI (plaque thickness/induration, erythema, and scaling) contributed comparably to the improvement in PASI.

The efficacy of STELARA was significantly superior ($p < 0.001$) to placebo across all subgroups defined by baseline demographics, clinical disease characteristics (including patients with a history of psoriatic arthritis) and prior medication usage. While pharmacokinetic modelling suggested a trend towards higher CL/F in patients with diabetes, a consistent effect on efficacy was not observed.

Other efficacy measures at Week 12

In both PHOENIX 1 and PHOENIX 2, compared with placebo, significantly greater proportions of patients randomized to 45 mg or 90 mg STELARA achieved a cleared or minimal PGA score, and significantly greater proportions of patients randomized to 45 mg or 90 mg STELARA were PASI 90 and PASI 50 responders at Week 12 (Table 2). In the PHOENIX 1 study, 60% and 62% of the patients treated with 45 mg and 90 mg STELARA, respectively, achieved PGA scores of cleared or minimal compared with 4% of placebo-treated patients. In PHOENIX 2, 68% and 73 % of patients receiving 45 mg or 90 mg STELARA, respectively, had cleared or minimal PGA scores compared with 5% of the placebo patients. In PHOENIX 1, PASI 90 was achieved by 42% and 37% of the patients treated with 45 mg and 90 mg STELARA, respectively, compared with 2% of placebo-treated patients. In PHOENIX 2, the percentage of patients achieving PASI 90 was 42% in the 45 mg STELARA group, 51% in the 90 mg STELARA group and 1% in the placebo group. The percentage of patients achieving PASI 50 in PHOENIX 1 was 84% and 86% in the 45 mg and 90 mg STELARA groups, respectively, compared with 10% in the placebo group. Similarly, 84% of patients treated with 45 mg STELARA, 89% of patients treated with 90 mg STELARA and 10% of patients treated with placebo reached PASI 50 in PHOENIX 2 (Table 2).

Table 2. Key psoriasis endpoints – PHOENIX 1 and PHOENIX 2

| Response | PHOENIX 1 STELARA | | | | | PHOENIX 2 STELARA | | | | |
|-------------------------------------|----------------------|-----------------------|-----------------------|-----------------------|-----------------------|----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| | Placebo | 45 mg | | 90 mg | | Placebo | 45 mg | | 90 mg | |
| | n=255 Week 12 | n=255 Week 12 | n=250 Week 28 | n=256 Week 12 | n=243 Week 28 | n=410 Week 12 | n=409 Week 12 | n=397 Week 28 | n=411 Week 12 | n=400 Week 28 |
| PASI response | | | | | | | | | | |
| PASI 50 (%) | 26 (10) | 213 (84) ^a | 228 (91) ^b | 220 (86) ^a | 234 (96) ^b | 41 (10) | 342 (84) ^a | 369 (93) ^b | 367 (89) ^a | 380 (95) ^b |
| PASI 75 (%) | 8 (3) | 171 (67) ^a | 178 (71) ^b | 170 (66) ^a | 191 (79) ^b | 15 (4) | 273 (67) ^a | 276 (70) ^b | 311 (76) ^a | 314 (79) ^b |
| PASI 90 (%) | 5 (2) | 106 (42) ^a | 123 (49) ^b | 94 (37) ^a | 135 (56) ^b | 3 (1) | 173 (42) ^a | 178 (45) ^b | 209 (51) ^a | 217 (54) ^b |
| PGA Cleared or Minimal ^a | 10 (4) | 151 (59) ^a | 146 (58) ^b | 156 (61) ^a | 160 (66) ^b | 18 (4) | 277 (68) ^a | 241 (61) ^b | 300 (73) ^a | 279 (70) ^b |
| PASI 75 response by weight | | | | | | | | | | |
| ≤ 100 kg | | | | | | | | | | |
| n | 166 | 168 | 164 | 164 | 153 | 290 | 297 | 287 | 289 | 280 |
| PASI 75 (%) | 6 (4) | 124 (74) | 130 (79) | 107 (65) | 124 (81) | 12 (4) | 218 (73) | 217 (76) | 225 (78) | 226 (81) |
| >100 kg | | | | | | | | | | |
| n | 89 | 87 | 86 | 92 | 90 | 120 | 112 | 110 | 121 | 119 |
| PASI 75 (%) | 2 (2) | 47 (54) | 48 (56) | 63 (68) | 67 (74) | 3 (3) | 55 (49) | 59 (54) | 86 (71) | 88 (74) |
| PGA Cleared or Minimal by weight | | | | | | | | | | |
| ≤ 100 kg | | | | | | | | | | |
| n | 166 | 168 | 164 | 164 | 153 | 290 | 297 | 287 | 289 | 280 |
| PGA response (%) | 7 (4) | 108 (64) | 106 (65) | 103 (63) | 106 (70) | 14 (5) | 220 (74) | 192 (67) | 216 (74) | 207 (74) |
| >100 kg | | | | | | | | | | |
| n | 89 | 87 | 86 | 92 | 90 | 120 | 112 | 110 | 121 | 119 |
| PGA response (%) | 3 (3) | 44 (51) | 40 (47) | 54 (59) | 54 (60) | 4 (3) | 59 (53) | 49 (45) | 85 (70) | 71 (60) |

^a p < 0.001 for 45 mg or 90 mg comparison with placebo at Week 12. ^b No statistical comparisons to placebo were made at Week 28 because the original placebo group began receiving STELARA at Week 12.

Response over time

In PHOENIX 1, significantly greater proportions of STELARA-treated patients had PASI 50 responses (9% and 10% for the 45 mg and 90 mg groups, respectively) compared with placebo (2%) by Week 2 (p < 0.001). Significantly greater proportions of patients treated with STELARA achieved PASI 75 responses (9% and 12% for the 45 mg and 90 mg STELARA groups, respectively) compared with placebo (0.4%) by Week 4 (p < 0.001). Maximum response was generally achieved by Week 24 in the 45 mg and 90 mg STELARA treatment groups, and response rates were generally sustained through Week 36 (Figure 2). In PHOENIX 1, PASI 75 rates at Week 24 were 76% for the 45 mg group, and 85% for the 90 mg group. Higher response rates were observed in patients receiving STELARA 90 mg than in those receiving STELARA 45 mg by Week 16 and these higher response rates were sustained through Week 36 (Figure 2). Similar results were observed in the PHOENIX 2 study through Week 28.

In pre-specified analyses of efficacy by body weight in PHOENIX 1 and PHOENIX 2, no consistent pattern of dose response was seen in patients ≤ 100 kg. In patients who weighed >100 kg, higher PASI 75 response rates were seen with 90 mg dosing compared with 45 mg dosing, and a higher proportion of patients receiving 90 mg dosing had PGA scores of cleared or minimal compared with patients receiving 45 mg dosing (Table 2). Figure 2 shows PASI 75 response over time in PHOENIX 1 and 2.

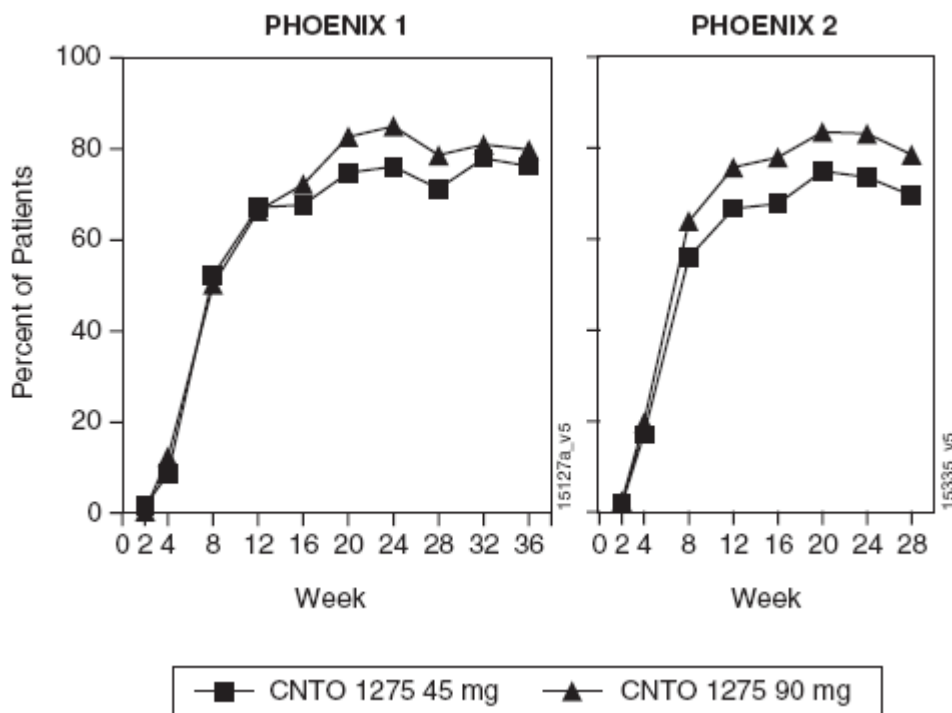


Figure 2. PASI 75 response over time in PHOENIX 1 and 2.

Therapeutic benefit of long-term continuous use

At Week 40 in PHOENIX 1, 162 patients were randomized to receive STELARA (maintenance) and 160 were randomized to receive placebo (treatment withdrawal). Maintenance of PASI 75 was significantly superior with continuous treatment compared with treatment withdrawal ($p < 0.001$). Similar results were seen with each dose of STELARA. At Week 52, 89% of patients re-randomized to maintenance treatment were PASI 75 responders compared with 63% of patients re-randomized to placebo (treatment withdrawal) ($p < 0.001$).

Efficacy of retreatment

In PHOENIX 1, after withdrawal from therapy, patients re-initiated their original STELARA treatment regimen after loss of $\geq 50\%$ of PASI improvement. Retreatment with STELARA resulted in 76% of evaluated patients regaining PASI 75 response within 8 weeks after reinitiating therapy.

Dosing Interval Adjustment

In PHOENIX 1, Week 28 and Week 40 partial responders and Week 40 non-responders were adjusted from every 12 week to every 8 week dosing. Approximately 40%-50% of Week 28 partial responders to every 12 week dosing achieved PASI 75 response after adjustment to every 8 week dosing and this proportion of PASI 75 responders was maintained through Week 52. A similar proportion of patients who were PASI 75 responders at Week 28 and subsequently became partial responders or non-responders at Week 40 achieved PASI 75 response following a dosing interval adjustment to every 8 weeks.

Quality of Life

In PHOENIX 1 and 2, the mean baseline DLQI scores ranged from 11 to 12. In PHOENIX 1, the mean baseline SF-36 Physical Component ranged from 47-49 and the mean baseline SF-36 Mental Component was approximately 50. Quality of life improved significantly in patients randomized to 45 mg or 90 mg ustekinumab compared with patients randomized to placebo as evaluated by DLQI in PHOENIX 1 and 2 and SF-36 in PHOENIX 1. Quality of life improvements were significant as early as 2 weeks in patients treated with ustekinumab ($p < 0.001$) and these improvements were maintained over time with continued dosing.

In PHOENIX 1, 65% and 71% of patients treated with 45 mg and 90 mg of ustekinumab, respectively, showed a clinically meaningful reduction (5 or more points) in DLQI from baseline at week 12 compared to 18% in placebo group ($p < 0.001$ for both groups compared with placebo). Furthermore, 33% and 34% of patients treated with 45 mg and 90 mg of ustekinumab, respectively, showed a DLQI score of 0 compared to 1% in the placebo group ($p < 0.001$ for both groups compared with placebo), indicating no impairment in QOL from disease or treatment in these patients. In PHOENIX 2, 72% and 77% of patients treated with 45 mg and 90 mg of ustekinumab, respectively, showed a clinically meaningful reduction (5 or more points) in DLQI from baseline at Week 12 compared to 21% in placebo group ($p < 0.001$ for both groups compared with placebo). In addition, 37% and 39% of patients treated with 45 mg and 90 mg of ustekinumab, respectively, showed a DLQI score of 0 compared to 1% in the placebo group ($p < 0.001$ for both groups compared with placebo).

In PHOENIX 1, the median baseline NAPSI score for nail psoriasis was 4.0 and the median number of fingernails involved with psoriasis was 8.0. Nail psoriasis improved significantly in patients randomized to 45 mg or 90 mg ustekinumab compared with patients randomized to placebo when measured by the NAPSI score ($p \leq 0.001$). Improvements in physical and mental component summary scores of the SF-36 and in the Itch Visual Analogue Scale (VAS) were also significant in each ustekinumab treatment group compared with placebo ($p < 0.001$). In PHOENIX 2, the Hospital Anxiety and Depression Scale (HADS) and Work Limitations Questionnaire (WLQ) were also significantly improved in each ustekinumab treatment group compared with placebo ($p < 0.001$).

ACCEPT

A multicentre, randomized, single-blind, active-controlled study (ACCEPT) compared the safety and efficacy of ustekinumab and etanercept in patients 18 years of age and older with chronic (>6 months) plaque psoriasis who had a minimum BSA involvement of 10%, PASI score ≥ 12 , Physician Global Assessment (PGA) score ≥ 3 , who were candidates for phototherapy or systemic therapy, and who had had an inadequate response to, intolerance to, or contraindication to cyclosporin, methotrexate, or PUVA therapy. A total of 903 patients were enrolled in the study.

The ACCEPT trial compared the efficacy of ustekinumab to etanercept and evaluated the safety of ustekinumab and etanercept in moderate to severe psoriasis patients. The active-controlled portion of the study was from Week 0 to Week 12, during which patients were randomized to receive etanercept (50 mg twice a week) ustekinumab 45 mg at Weeks 0 and 4, or ustekinumab 90 mg at Weeks 0 and 4. This trial was powered to test the superiority of each ustekinumab dose to etanercept on the primary endpoint of the proportion of patients who achieved a PASI 75 at Week 12.

Significantly greater proportions of subjects treated with ustekinumab 45 mg (67%; $p = 0.012$) or 90 mg (74%; $p < 0.001$) were PASI 75 responders at Week 12 compared with the etanercept group (56.8%). PASI 90 response was observed in 36% and 45 % of patients in the ustekinumab 45 mg and 90 mg groups, respectively, compared with 23% of patients receiving etanercept ($p < 0.001$ for each comparison versus etanercept). PASI 100 response was observed in 12% and 21% of patients in the ustekinumab 45 mg and 90 mg groups, respectively, compared to 6% of patients receiving etanercept. In addition, a greater proportion of patients in the ustekinumab 45 mg and 90 mg treatment groups achieved a PGA score of “cleared” or “minimal” (65% and 71%, respectively) compared with patients in the etanercept treatment group (49%) ($p < 0.001$ for each comparison versus etanercept).

In pre-specified analyses of efficacy by body weight in ACCEPT, minimal dose response to ustekinumab was evident in patients ≤ 100 kg. In patients who weighed >100 kg, higher PASI 75 response rates were seen with 90 mg dosing compared with 45 mg dosing, and a higher proportion of patients receiving 90 mg dosing had PGA scores of cleared or minimal compared with patients receiving 45 mg dosing (Table 3).

Table 3 Key psoriasis endpoints at Week 12: ACCEPT

| | ACCEPT | | |
|--|---------------------------------|---------------------------------|--------------------------|
| | Etanercept (50 mg twice a week) | Ustekinumab (week 0 and week 4) | |
| | | 45 mg | 90 mg |
| Patients randomized | 347 | 209 | 347 |
| PASI RESPONSE | | | |
| PASI 50 response | 286 (82%) | 181 (87%) | 320 (92%) ^a |
| PASI 75 response | 197 (57%) | 141 (67%) ^b | 256 (74%) ^a |
| PASI 90 response | 80 (23%) | 76 (36%) ^a | 155 (45%) ^a |
| PASI 100 response | 22 (6%) | 25 (12%) ^c | 74 (21%) ^a |
| PGA of Cleared or Minimal^a | 170 (49%) | 136 (65%) ^a | 245 (71%) ^a |
| PASI 75 RESPONSE BY WEIGHT | | | |
| < 100 kg | | | |
| N | 251 | 151 | 244 |
| PASI 75 response | 154 (61.4%) | 109 (72.2%) | 189 (77.5%) |
| >100 kg | | | |
| N | 96 | 58 | 103 |
| PASI 75 response | 43 (44.8%) | 32 (55.2%) | 67 (65.0%) |
| PGA of Cleared or Minimal by weight | | | |
| ≤ 100 kg | | | |
| N | 251 | 151 | 244 |
| PGA response | 131 (52.2%) | 110 (72.8%) | 185 (75.8%) |
| >100 kg | | | |
| N | 96 | 58 | 103 |
| PGA response | 39 (40.6%) | 26 (44.8%) | 60 (58.3%) |
| PASI 75 RESPONSE BY NUMBER OF UNSUITABLE CONVENTIONAL SYSTEMIC AGENTS^g | | | |
| -at least one therapy | | | |
| N | 347 | 209 | 346 |
| PASI 75 Response | 197 (56.8%) | 141 (67.5%) ^b | 256 (74.0%) ^a |
| -at least two therapies | | | |
| N | 186 | 118 | 185 |
| PASI 75 Response | 94 (50.5%) | 79 (66.9%) ^d | 137 (74.1%) ^a |
| -at least three therapies | | | |
| N | 52 | 31 | 47 |
| PASI 75 Response | 20 (38.5%) | 17 (54.8%) ^e | 34 (72.3%) ^f |

^a p <0.001 for ustekinumab 45 mg or 90 mg comparison with etanercept.

^b p =0.012 for ustekinumab 45 mg comparison with etanercept.

^c p =0.020 for ustekinumab 45 mg comparison with etanercept

^d p=0.004 for ustekinumab 45 mg comparison with etanercept.

^e p=0.303 for ustekinumab 45 mg comparison with etanercept.

^f p=0.001 for ustekinumab 90 mg comparison with etanercept.

^g Conventional systemic agents include psoralen plus ultraviolet A, methotrexate, and cyclosporin. Unsuitable conventional systemic agents are defined as those to which patients had had an inadequate response, were intolerant, or had a contraindication.

INDICATIONS

Plaque Psoriasis

STELARA is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

CONTRAINDICATIONS

Severe hypersensitivity to ustekinumab or to any of the excipients (see **PRECAUTIONS**).

PRECAUTIONS

Serious 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 have been observed in patients receiving STELARA. 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. 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 (see **ADVERSE EFFECTS**).

Malignancies

STELARA is a selective immunosuppressant. Immunosuppressive agents have the potential to increase the risk of malignancy. Some patients who received STELARA in clinical studies developed cutaneous and non-cutaneous malignancies (see **ADVERSE EFFECTS**).

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.

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, administration of STELARA should be discontinued immediately and appropriate therapy instituted (see **ADVERSE EFFECTS**).

Immunisations

It is recommended that live viral or live bacterial vaccines 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.

Immunosuppression

The safety and efficacy of STELARA in combination with other systemic agents used in psoriasis or with phototherapy have not been evaluated. STELARA should not be used in combination with such agents.

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.

General

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

Effects on fertility

In a male fertility study in cynomolgus monkeys, no ustekinumab-related effects on mating behaviour, sperm parameters, or serum concentrations of male hormones were observed following twice weekly subcutaneous administration of ustekinumab at doses up to 45 mg/kg.

The effect of STELARA on female fertility has not been evaluated. A female fertility toxicity study was conducted in mice using an analogous antibody that binds to and inhibits IL-12 and IL-23 activity in mice. Twice weekly subcutaneous administration of the anti-mouse IL-12/23 antibody was well tolerated at doses up to 50 mg/kg and no adverse effects on female fertility parameters were observed.

Use in Pregnancy

Category B1.

It is not known whether STELARA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. STELARA should be given to a pregnant woman only if the benefit clearly outweighs the risk.

Developmental toxicity studies of STELARA were conducted in cynomolgus monkeys. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed at doses up to 45 mg/kg following weekly or twice weekly administration via the IV or SC routes, respectively, during the period of organogenesis. However, animal reproductive and developmental studies are not always predictive of human response.

Use in Lactation

Ustekinumab is excreted in the milk of lactating monkeys administered ustekinumab. It is not known if STELARA is absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from STELARA, a decision should be made whether to discontinue nursing or to discontinue the drug.

Maternal treatment of monkeys with STELARA at doses up to 45 mg/kg twice weekly SC from gestation Day 20 to post-partum Day 33 had no adverse effects on offspring development. However, animal reproductive and developmental studies are not always predictive of human response.

Paediatric Use

Specific studies of STELARA in paediatric patients have not been conducted. There are no safety or efficacy data in children or adolescents < 18 years of age.

Use in the Elderly

No major age-related differences in clearance or volume of distribution were observed in clinical studies. No overall differences in efficacy or safety in patients aged 65 and older [n=131] who received STELARA were observed compared with younger patients.

Carcinogenicity

STELARA has not been evaluated for carcinogenic potential. STELARA is a selective immunosuppressant agent. Immunosuppressive agents have the potential to increase the risk of malignancy (See PRECAUTIONS – Malignancies).

Genotoxicity

STELARA has not been evaluated for genotoxic potential.

Interactions with Other Medicines

Drug interaction studies have not been conducted in humans with STELARA (See PHARMACOLOGY - Pharmacokinetics).

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). These results do not suggest the need for dose adjustments in patients who are receiving concomitant CYP450 substrate (See PHARMACOLOGY - Pharmacokinetics).

Live vaccines should not be given concurrently with STELARA (see PRECAUTIONS).

Effect on Ability to Drive and Operate Machinery

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

ADVERSE EFFECTS

Psoriasis Clinical Studies Experience

The safety data described below reflect exposure to STELARA in 3 adequate and well-controlled studies of 2266 patients, including 1970 exposed for at least 6 months, 1285 exposed for at least 1 year and 373 for at least 18 months.

The following serious adverse reactions were reported:

- Serious Infections
- Malignancies

The most common adverse reactions (>10%) in controlled and uncontrolled portions of the psoriasis clinical studies with STELARA were nasopharyngitis and upper respiratory tract infection. Most were considered to be mild and did not necessitate drug discontinuation.

Table 3 provides a summary of Adverse Drug Reactions from psoriasis clinical studies. The adverse drug reactions are ranked by frequency, using the following convention:

Very common ($\geq 1/10$)

Common (frequent) ($\geq 1/100$, $< 1/10$)

Uncommon (infrequent) ($\geq 1/1,000$, $< 1/100$)

Rare ($\geq 1/10,000$, $< 1/1,000$)

Table 4. Summary of ADRs in Psoriasis Clinical Studies

| | |
|--|--|
| Infections and infestations | Very common: Upper respiratory tract infection, nasopharyngitis Common: Cellulitis, viral upper respiratory tract infection. Uncommon: Herpes zoster |
| Psychiatric disorders | Common: Depression |
| Nervous system disorders | Common: Dizziness, headache |
| Respiratory, thoracic and mediastinal disorders | Common: Pharyngolaryngeal pain, nasal congestion |
| Gastrointestinal disorders | Common: Diarrhoea |
| Skin and subcutaneous tissue disorders | Common: Pruritus |
| Musculoskeletal and connective tissue disorders | Common: Back pain, myalgia |
| General disorders and administration site conditions | Common: Fatigue, injection site erythema Uncommon: Injection site reactions (including pain, swelling, pruritus, induration, hemorrhage, bruising and irritation) |

Infections

In controlled studies of psoriasis patients, the rates of infection or serious infection were similar between STELARA-treated patients and those treated with placebo. In the placebo-controlled period of clinical studies of psoriasis patients, the rate of infection was 1.39 per patient-year of follow-up in STELARA-treated patients, and 1.21 per patient-year of follow-up in placebo-treated patients. Serious infections occurred in 0.01 per patient-year of follow-up in STELARA-treated patients (5 serious infections in 407 patient-years of follow-up) and 0.02 per patient-year of follow-up in placebo-treated patients (3 serious infections in 177 patient-years of follow-up) (see PRECAUTIONS).

In the controlled and non-controlled portions of psoriasis clinical studies, the rate of infection was 1.24 per patient-year of follow-up in STELARA-treated patients. The incidence of serious infections was 0.01 per patient-year of follow-up in STELARA-treated patients (24 serious infections in 2251 patient-years of follow-up) and included cellulitis, diverticulitis, osteomyelitis, viral infections, gastroenteritis, pneumonia, and urinary tract infections.

Among 3117 patients treated in 4 psoriasis clinical trials of STELARA representing 6791 patient-years of exposure (1129 patients treated for at least 3 years, and 619 patients for at least 4 years), the rates of infection or serious infection were similar to those described above.

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

Malignancies

In the controlled period of the 3 placebo-controlled psoriasis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.25 per 100 patient-years of follow-up for STELARA-treated patients (1 patient in 406 patient-years of follow-up) compared with 0.57 per 100 patient-years of follow-up for placebo-treated patients (1 patient in 177 patient-years of follow-up).

The incidence of non-melanoma skin cancer was 0.74 per 100 patient-years of follow-up for STELARA-treated patients (3 patients in 406 patient-years of follow-up) compared with 1.13 per

100 patient-years of follow-up for placebo-treated patients (2 patients in 176 patient-years of follow-up).

Among 3117 patients treated in 4 psoriasis clinical trials of STELARA (1129 patients treated for at least 3 years, and 619 patients for at least 4 years), malignancies excluding nonmelanoma skin cancers were reported in 42 patients in 6779 patient-years of follow-up (incidence of 0.62 per 100 patient-years of follow-up for STELARA-treated patients). This rate of malignancies reported in STELARA-treated patients was comparable to the rate expected in the general population (standardized incidence ratio = 1.1 [95% confidence interval: 0.76, 1.43]). The most frequently observed malignancies, other than nonmelanoma skin cancer, were prostate, colorectal, melanoma *in situ* and breast. The incidence of nonmelanoma skin cancer was 0.61 per 100 patient-years of follow-up for STELARA-treated patients (41 patients in 6770 patient-years of follow-up).

Hypersensitivity Reactions

In clinical studies of STELARA, rash and urticaria have each been observed in <2% of patients.

Immunogenicity

Approximately 5% of patients treated with STELARA developed antibodies to ustekinumab, which were generally low-titre. No apparent correlation of antibody development to injection site reactions was seen. Patients positive for antibodies to STELARA tended to have lower efficacy, however, antibody positivity does not preclude a clinical response.

Adverse Events

The following adverse events have been reported in patients treated with STELARA. A causal relationship to STELARA is uncertain.

In psoriasis clinical trials of STELARA, serious cardiovascular events, including cardiovascular death, myocardial infarction, and stroke, were reported in 0.3% of patients who received STELARA compared with 0% of patients treated with placebo, during the placebo-controlled period. Individuals with chronic inflammatory diseases, such as psoriasis, have higher rates of cardiovascular risk factors and cardiovascular events. Rates of myocardial infarction and stroke reported in STELARA-treated patients were comparable to rates expected in the general population.

Adverse events of depression were reported in some patients who received STELARA in psoriasis clinical trials, including rare events of suicidality. Individuals with psoriasis have higher rates of depression, and it is not known if STELARA may have contributed to these events since STELARA also resulted in improvements of the Hospital Anxiety and Depression Scale (see CLINICAL TRIALS).

Post Marketing Experience

The adverse drug reactions in Table 4 are ranked by frequency* using the following convention:

- Very common: $\geq 1/10$
- Common: $\geq 1/100$ and $< 1/10$
- Uncommon: $\geq 1/1,000$ and $< 1/100$
- Rare: $\geq 1/10,000$ and $< 1/1000$
- Very rare: $< 1/10,000$, including isolated reports

Table 5. Post-Marketing Reports

| | |
|-------------------------|---|
| Immune system disorders | Common: Hypersensitivity reactions (including rash, urticaria) Rare: Serious hypersensitivity reactions (including |
|-------------------------|---|

| | |
|--|-----------------------------|
| | anaphylaxis and angioedema) |
|--|-----------------------------|

*Post-marketing adverse reaction frequency is derived from clinical trials if the adverse reaction was observed during trials, or is estimated to be lower than a certain frequency given the exposure in adequately designed clinical trials where the adverse reaction was not observed.

DOSAGE AND ADMINISTRATION

Dosing

STELARA is administered by subcutaneous injection. The recommended dose of STELARA is 45 mg administered at Weeks 0 and 4, then every 12 weeks thereafter. Alternatively, 90 mg administered over Weeks 0 and 4, then every 12 weeks thereafter may be used in patients with a body weight greater than 100 kg.

Dose Adjustment

For patients who inadequately respond to dosing every 12 weeks, consideration may be given to treating as often as every 8 weeks. Treatment should be discontinued in patients who have shown no response after 28 weeks of treatment.

Re-treatment

After interruption of therapy, re-treatment with a dosing regimen of Weeks 0 and 4, then every 12 weeks thereafter has been shown to be safe and effective.

Administration

STELARA injections are for single use in one patient only.

STELARA is intended for use under the guidance and supervision of a health care professional. A patient may self-inject with STELARA if a physician determines that it is appropriate and with medical follow-up as necessary, after proper training in subcutaneous injection technique.

Comprehensive instructions for the administration of STELARA are given in the Consumer Medicine Information. Patients should be instructed to inject the full amount of STELARA according to the directions provided in the Consumer Medicine Information.

Following administration of STELARA, the syringe should be disposed of in accordance with accepted medical practices for used syringes.

OVERDOSAGE

Single doses up to 4.5 mg/kg intravenously have been administered in clinical studies without dose-limiting toxicity. In case of overdose, 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. Contact the Poisons Information Centre (telephone 0800 POISON or 0800 764 766) for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS

STELARA is supplied as a sterile solution in a single-use (Type 1) glass vial. The vial is stoppered with a coated stopper.

STELARA is also supplied as a single-use, sterile solution in a Type 1 glass syringe with a fixed 27G, half-inch needle and needle cover. The needle cover is manufactured using a dry natural rubber containing latex (see PRECAUTIONS). The syringe is fitted with a passive safety guard.

The solution is clear to slightly opalescent, colourless to light yellow with a pH of approximately 6.0. STELARA does not contain preservatives.

There are two strengths of STELARA available: 45 mg of ustekinumab (rmc) in 0.5 mL, or 90 mg of ustekinumab (rmc) in 1.0 mL (the 90 mg vial is not currently marketed).

STELARA is available in packs of:

- 1 single use vial (45 mg)
- 1 pre-filled syringe (45 mg and 90 mg).

Store at 2°C to 8°C. Refrigerate. Do not freeze.

Protect from light by storing in original carton until time of use. Do not shake.

Shelf life

12 months (vial) and 18 months (pre-filled syringe).

MEDICINE CLASSIFICATION

Prescription Only Medicine

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DATE OF PREPARATION

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