ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

STELARA 45 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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 a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear to slightly opalescent, colourless to light yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

STELARA is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA (see section 5.1).

4.2 Posology and method of administration

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

Posology
The recommended posology of STELARA is an initial dose of 45 mg administered subcutaneously at week 0, followed by a 45 mg dose at week 4, then every 12 weeks thereafter.

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

Patients with body weight > 100 kg
For patients with a body weight > 100 kg the dose is 90 mg administered subcutaneously at week 0, followed by a 90 mg dose at week 4, then every 12 weeks thereafter (see section 5.1). In patients weighing > 100 kg, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy in these patients.

Elderly patients (≥ 65 years)
No dose adjustment is needed for elderly patients.

Children and adolescents (< 18 years)
STELARA is not recommended for use in children below age 18 due to a lack of data on safety and efficacy.

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

Method of administration
STELARA is for subcutaneous injection. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

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

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

Clinically important, active infection.

4.4 Special warnings and precautions for use

Infections
Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. In clinial studies, serious bacterial, fungal, and viral infections have been observed in patients receiving STELARA (see section 4.8).

Caution should be exercised when considering the use of STELARA in patients with a chronic infection or a history of recurrent infection (see section 4.3).

Prior to initiating treatment with STELARA, patients should be evaluated for tuberculosis infection. STELARA must 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 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, the patient should be closely monitored and STELARA should not be administered until the infection resolves.

Malignancies
Immunosuppressants like ustekinumab 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).

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving STELARA. Thus, caution should be exercised when considering the use of STELARA in these patients.

Hypersensitivity reactions
If an anaphylactic or other serious allergic reaction occurs, administration of STELARA should be discontinued immediately and appropriate therapy instituted (see section 4.8).

Vaccinations
It is recommended that live viral or live bacterial vaccines (such as Bacillus of Calmette and Guérin (BCG)) should not be given concurrently with STELARA. Specific studies have not been conducted in patients who had recently received live viral or live bacterial vaccines. Before live viral or live bacterial vaccination, treatment with STELARA should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination. Prescribers should consult the Summary of Product Characteristics for the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.

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

Concomitant immunosuppressive therapy
The safety and efficacy of STELARA in combination with other immunosuppressants, including biologics, or phototherapy have not been evaluated. Caution should be exercised when considering concomitant use of other immunosuppressants and STELARA or when transitioning from other immunosuppressive biologics (see section 4.5).

Special populations
Children and adolescents (< 18 years)
STELARA is not recommended for use in children below age 18 due to a lack of data on safety and efficacy.

Elderly patients (≥ 65 years)
No overall differences in efficacy or safety in patients age 65 and older who received STELARA were observed compared to younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Hepatic and renal impairment
Specific studies have not been conducted in patients with hepatic and renal impairment (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. In the population pharmacokinetic analysis of the phase III studies, the effect of the most frequently used concomitant medicinal products in patients with psoriasis (including paracetamol, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, levothyroxine) on pharmacokinetics of ustekinumab was explored. There were no indications of an interaction with these concomitantly administered medicinal products. The basis for this analysis was that at least 100 patients (> 5% of the studied population) were treated concomitantly with these medicinal products for at least 90% of the study period.

Live vaccines should not be given concurrently with STELARA (see section 4.4).

The safety and efficacy of STELARA in combination with other immunosuppressants, including biologics, or phototherapy have not been evaluated (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of ustekinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of STELARA in pregnancy. Women of childbearing potential should use effective methods of contraception during treatment and up to 15 weeks after treatment.

Lactation
It is unknown whether ustekinumab is excreted in human breast milk. Animal studies have shown excretion of ustekinumab at low levels in breast milk. It is not known if ustekinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from ustekinumab, a decision on whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with STELARA must be made taking into account the benefit of breast-feeding to the child and the benefit of STELARA therapy to the woman.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The safety data described below reflect exposure to ustekinumab in 3 studies of 2,266 patients, including 1,970 exposed for at least 6 months and 1,285 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 ustekinumab were nasopharyngitis and upper respiratory tract infection. Most were considered to be mild and did not necessitate discontinuation of study treatment.

Table 1 provides a summary of adverse reactions from psoriasis 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 1 Summary of adverse reactions in psoriasis clinical studies

System Organ Class	**Frequency: Adverse reaction**
Infections and infestations	Very common: Upper respiratory tract infection, nasopharyngitis Common: Cellulitis, viral upper respiratory tract infection
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, haemorrhage, bruising and irritation)

Infections
In controlled studies of psoriasis patients, the rates of infection or serious infection were similar between ustekinumab-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 ustekinumab-treated patients, and 1.21 in placebo-treated patients. Serious infections occurred in 0.01 per patient-year of follow-up in ustekinumab-treated patients (5 serious infections in 407 patient-years of follow-up) and 0.02 in placebo-treated patients (3 serious infections in 177 patient-years of follow-up) (see section 4.4).

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 ustekinumab-treated patients, and the incidence of serious infections was 0.01 per patient-year of follow-up in ustekinumab-treated patients (24 serious infections in 2,251 patient-years of follow-up) and serious infections reported included cellulitis, diverticulitis, osteomyelitis, viral infections, gastroenteritis, pneumonia, and urinary tract 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 clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.25 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in 406 patient-years of follow-up) compared with 0.57 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 ustekinumab-treated patients (3 patients in 406 patient-years of follow-up) compared to 1.13 for placebo-treated patients (2 patients in 176 patient-years of follow-up).

In the controlled and non-controlled portions of psoriasis clinical studies, the incidence of malignancies excluding non-melanoma skin cancers was 0.36 per 100 patient-years of follow-up for ustekinumab-treated patients (8 patients in 2,249 patient-years of follow-up) and malignancies reported included breast, colon, head and neck, kidney, prostate, and thyroid cancers. The rate of malignancies reported in ustekinumab-treated patients was comparable to the rate expected in the general population (standardised incidence ratio = 0.68 [95% confidence interval: 0.29, 1.34]). The incidence of non-melanoma skin cancer was 0.80 per 100 patient-years of follow-up for ustekinumab-treated patients (18 patients in 2,245 patient-years of follow-up) (see section 4.4).

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

Immunogenicity
Approximately 5% of ustekinumab-treated patients developed antibodies to ustekinumab, which were generally low-titer. No apparent correlation of antibody development to injection site reactions was seen. Efficacy tended to be lower in patients positive for antibodies to ustekinumab; however, antibody positivity does not preclude a clinical response.

4.9 Overdose

No cases of overdose have been reported.

Single doses up to 4.5 mg/kg have been administered intravenously 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 and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Interleukin inhibitors, ATC code: L04AC05.

Mechanism of action
Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with high affinity and specificity to the p40 protein subunit of the human cytokines IL-12 and IL-23. Ustekinumab inhibits the activity of human IL-12 and IL-23 by preventing these cytokines from binding to their IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is pre-bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely 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 natural killer (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. Ustekinumab prevents IL-12 and IL-23 contributions to immune cell activation, such as intracellular signaling and cytokine secretion. Thus, ustekinumab is believed to interrupt signaling and cytokine cascades that are relevant to psoriasis pathology.

Clinical efficacy and safety
The safety and efficacy of ustekinumabwas assessed in 1,996 patients in two randomised, double-blind, placebo-controlled studies in patients with moderate to severe plaque psoriasis and who were candidates for phototherapy or systemic therapy.

Psoriasis Study 1 (PHOENIX 1) evaluated 766 patients. 53% of these patients were either non-responsive, intolerant, or had a contraindication to other systemic therapy. Patients randomised to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4 and followed by the same dose every 12 weeks. Patients randomised to receive placebo at Weeks 0 and 4 crossed over to receive ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16 followed by dosing every 12 weeks. Patients originally randomised to ustekinumab who achieved Psoriasis Area and Severity Index 75 response (PASI improvement of at least 75% relative to baseline) at both Weeks 28 and 40 were re-randomised to receive ustekinumab every 12 weeks or to placebo (i.e., withdrawal of therapy). Patients who were re-randomised to placebo at Week 40 reinitiated ustekinumab at their original dosing regimen when they experienced at least a 50% loss of their PASI improvement obtained at Week 40. All patients were followed for up to 76 weeks following first administration of study treatment.

Psoriasis Study 2 (PHOENIX 2) evaluated 1230 patients. 61% of these patients were either non-responsive, intolerant, or had a contraindication to other systemic therapy. Patients randomised to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4 followed by an additional dose at 16 weeks. Patients randomised to receive placebo at Weeks 0 and 4 crossed over to receive ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16. All patients were followed for up to 52 weeks following first administration of study treatment.

In both studies, baseline disease characteristics were generally consistent across all treatment groups with a median baseline PASI score from 17 to 18 and median baseline Body Surface Area (BSA) ≥ 20, median Dermatology Life Quality Index (DLQI) range from 10 to 12. Approximately one third (PHOENIX 1) and one quarter (PHOENIX 2) of subjects had Psoriatic Arthritis (PsA).

The primary endpoint in both studies was the proportion of patients who achieved PASI 75 response from baseline at Week 12 (see Table 2).

Table 2 Summary of clinical response in Psoriasis Study 1 (PHOENIX 1) and Psoriasis Study 2 (PHOENIX 2)

	Week 12 (2 injections)			Week 28 (3 injections)	
	PBO	45 mg	90 mg	45 mg	90 mg
Psoriasis Study 1					
Number of patients randomised	255	255	256	250	243
PASI 50 response N (%)	26 (10%)	213 (84%) [a]	220 (86%) [a]	228 (91%)	234 (96%)
PASI 75 response N (%)	8 (3%)	171 (67%) [a]	170 (66%) [a]	178 (71%)	191 (79%)
PASI 90 response N (%)	5 (2%)	106 (42%) [a]	94 (37%) [a]	123 (49%)	135 (56%)
PGA[b] of cleared or minimal N (%)	10 (4%)	151 (59%) [a]	156 (61%) [a]	146 (58%)	160 (66%)
Psoriasis Study 2					
Number of patients randomised	410	409	411	397	400
PASI 50 response N (%)	41 (10%)	342 (84%) [a]	367 (89%) [a]	369 (93%)	380 (95%)
PASI 75 response N (%)	15 (4%)	273 (67%) [a]	311 (76%) [a]	276 (70%)	314 (79%)
PASI 90 response N (%)	3 (1%)	173 (42%) [a]	209 (51%) [a]	178 (45%)	217 (54%)
PGA[b] of cleared or minimal N (%)	18 (4%)	277 (68%) [a]	300 (73%) [a]	241 (61%)	279 (70%)
[a] $p < 0.001$ for 45 mg or 90 mg in comparison with placebo (PBO).					
[b] PGA = Physician Global Assessment					

In Psoriasis Study 1 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 ustekinumab. At Week 52, 89% of patients re-randomised to maintenance treatment were PASI 75 responders compared with 63% of patients re-randomised to placebo (treatment withdrawal) ($p < 0.001$). At week 76, 84% of patients re-randomised to maintenance treatment were PASI 75 responders compared with 19% of patients re-randomised to placebo (treatment withdrawal).

In patients re-randomised to placebo, and who reinitiated their original ustekinumab treatment regimen after loss of ≥ 50% of PASI improvement 85% regained PASI 75 response within 12 weeks after re-initiating therapy.

In Psoriasis Study 1, at Week 2 and Week 12, significantly greater improvements from baseline were demonstrated in the DLQI in each ustekinumab treatment group compared with placebo. The improvement was sustained through Week 28. Similarly, significant improvements were seen in Psoriasis Study 2 at Week 4 and 12, which were sustained through Week 24. In Psoriasis Study 1, improvements in nail psoriasis (Nail Psoriasis Severity Index), in the 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. In Psoriasis Study 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.

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 those 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 psoriasis, ranging from 15 to 32 days across all psoriasis studies. In a population pharmacokinetic analysis, the apparent clearance (CL/F) and apparent volume of distribution (V/F) were 0.465 l/day and 15.7 l, respectively, in patients with psoriasis. The CL/F of ustekinumab was not impacted by gender. Population pharmacokinetic analysis showed that there was a trend towards a higher clearance of ustekinumab in patients who tested positive for antibodies to ustekinumab.

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 µg/ml to 0.26 µg/ml (45 mg) and from 0.47 µg/ml to 0.49 µg/ml (90 mg). There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

Impact of weight on pharmacokinetics
In a population pharmacokinetic analysis, body weight was found to be the most significant covariate affecting the clearance of ustekinumab. The median CL/F in patients with weight > 100 kg was approximately 55% higher compared to patients with weight ≤ 100 kg. The median V/F in patients with weight > 100 kg was approximately 37% higher as compared to patients with weight ≤ 100 kg. 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.

In the population pharmacokinetic analysis, there were no indications of an effect of tobacco or alcohol on the pharmacokinetics of ustekinumab.

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

Sucrose
L-histidine
L-histidine monohydrochloride monohydrate
Polysorbate 80
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

12 months

6.4 Special precautions for storage

Store in a refrigerator (2ºC - 8ºC). Do not freeze.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

STELARA is supplied as a sterile solution in a single-use type I glass 2 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 discoloration 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 product should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present. Before administration, STELARA should be allowed to reach a comfortable temparature for injection (approximately half an hour). STELARA does not contain preservatives; therefore any unused product

remaining in the vial and the syringe should not be used. Detailed instructions for use are provided in the package leaflet.

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

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

STELARA 90 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 90 mg ustekinumab in 1 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 a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear to slightly opalescent, colourless to light yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

STELARA is indicated for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and PUVA (see section 5.1).

4.2 Posology and method of administration

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

Posology
The recommended posology of STELARA is an initial dose of 45 mg administered subcutaneously at week 0, followed by a 45 mg dose at week 4, then every 12 weeks thereafter.

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

Patients with body weight > 100 kg
For patients with a body weight > 100 kg the dose is 90 mg administered subcutaneously at week 0, followed by a 90 mg dose at week 4, then every 12 weeks thereafter (see section 5.1). In patients weighing > 100 kg, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy in these patients.

Elderly patients (≥ 65 years)
No dose adjustment is needed for elderly patients.

Children and adolescents (< 18 years)
STELARA is not recommended for use in children below age 18 due to a lack of data on safety and efficacy.

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

Method of administration
STELARA is for subcutaneous injection. If possible, areas of the skin that show psoriasis should be avoided as injection sites.

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

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

Clinically important, active infection.

4.4 Special warnings and precautions for use

Infections
Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. In clinial studies, serious bacterial, fungal, and viral infections have been observed in patients receiving STELARA (see section 4.8).

Caution should be exercised when considering the use of STELARA in patients with a chronic infection or a history of recurrent infection (see section 4.3).

Prior to initiating treatment with STELARA, patients should be evaluated for tuberculosis infection. STELARA must 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 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, the patient should be closely monitored and STELARA should not be administered until the infection resolves.

Malignancies
Immunosuppressants like ustekinumab 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).

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving STELARA. Thus, caution should be exercised when considering the use of STELARA in these patients.

Hypersensitivity reactions
If an anaphylactic or other serious allergic reaction occurs, administration of STELARA should be discontinued immediately and appropriate therapy instituted (see section 4.8).

Vaccinations
It is recommended that live viral or live bacterial vaccines (such as Bacillus of Calmette and Guérin (BCG)) should not be given concurrently with STELARA. Specific studies have not been conducted in patients who had recently received live viral or live bacterial vaccines. Before live viral or live bacterial vaccination, treatment with STELARA should be withheld for at least 15 weeks after the last dose and can be resumed at least 2 weeks after vaccination. Prescribers should consult the Summary of Product Characteristics for the specific vaccine for additional information and guidance on concomitant use of immunosuppressive agents post-vaccination.

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

Concomitant immunosuppressive therapy
The safety and efficacy of STELARA in combination with other immunosuppressants, including biologics, or phototherapy have not been evaluated. Caution should be exercised when considering concomitant use of other immunosuppressants and STELARA or when transitioning from other immunosuppressive biologics (see section 4.5).

Special populations
Children and adolescents (< 18 years)
STELARA is not recommended for use in children below age 18 due to a lack of data on safety and efficacy.

Elderly patients (≥ 65 years)
No overall differences in efficacy or safety in patients age 65 and older who received STELARA were observed compared to younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Hepatic and renal impairment
Specific studies have not been conducted in patients with hepatic and renal impairment (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. In the population pharmacokinetic analysis of the phase III studies, the effect of the most frequently used concomitant medicinal products in patients with psoriasis (including paracetamol, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, levothyroxine) on pharmacokinetics of ustekinumab was explored. There were no indications of an interaction with these concomitantly administered medicinal products. The basis for this analysis was that at least 100 patients (> 5% of the studied population) were treated concomitantly with these medicinal products for at least 90% of the study period.

Live vaccines should not be given concurrently with STELARA (see section 4.4).

The safety and efficacy of STELARA in combination with other immunosuppressants, including biologics, or phototherapy have not been evaluated (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of ustekinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of STELARA in pregnancy. Women of childbearing potential should use effective methods of contraception during treatment and up to 15 weeks after treatment.

Lactation
It is unknown whether ustekinumab is excreted in human breast milk. Animal studies have shown excretion of ustekinumab at low levels in breast milk. It is not known if ustekinumab is absorbed systemically after ingestion. Because of the potential for adverse reactions in nursing infants from ustekinumab, a decision on whether to discontinue breast-feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with STELARA must be made taking into account the benefit of breast-feeding to the child and the benefit of STELARA therapy to the woman.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The safety data described below reflect exposure to ustekinumab in 3 studies of 2,266 patients, including 1,970 exposed for at least 6 months and 1,285 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 ustekinumab were nasopharyngitis and upper respiratory tract infection. Most were considered to be mild and did not necessitate discontinuation of study treatment.

Table 1 provides a summary of adverse reactions from psoriasis 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 1 Summary of adverse reactions in psoriasis clinical studies

System Organ Class	**Frequency: Adverse reaction**
Infections and infestations	Very common: Upper respiratory tract infection, nasopharyngitis Common: Cellulitis, viral upper respiratory tract infection
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, haemorrhage, bruising and irritation)

Infections
In controlled studies of psoriasis patients, the rates of infection or serious infection were similar between ustekinumab-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 ustekinumab-treated patients, and 1.21 in placebo-treated patients. Serious infections occurred in 0.01 per patient-year of follow-up in ustekinumab-treated patients (5 serious infections in 407 patient-years of follow-up) and 0.02 in placebo-treated patients (3 serious infections in 177 patient-years of follow-up) (see section 4.4).

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 ustekinumab-treated patients, and the incidence of serious infections was 0.01 per patient-year of follow-up in ustekinumab-treated patients (24 serious infections in 2,251 patient-years of follow-up) and serious infections reported included cellulitis, diverticulitis, osteomyelitis, viral infections, gastroenteritis, pneumonia, and urinary tract 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 clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.25 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in 406 patient-years of follow-up) compared with 0.57 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 ustekinumab-treated patients (3 patients in 406 patient-years of follow-up) compared to 1.13 for placebo-treated patients (2 patients in 176 patient-years of follow-up).

In the controlled and non-controlled portions of psoriasis clinical studies, the incidence of malignancies excluding non-melanoma skin cancers was 0.36 per 100 patient-years of follow-up for ustekinumab-treated patients (8 patients in 2,249 patient-years of follow-up) and malignancies reported included breast, colon, head and neck, kidney, prostate, and thyroid cancers. The rate of malignancies reported in ustekinumab-treated patients was comparable to the rate expected in the general population (standardised incidence ratio = 0.68 [95% confidence interval: 0.29, 1.34]). The incidence of non-melanoma skin cancer was 0.80 per 100 patient-years of follow-up for ustekinumab-treated patients (18 patients in 2,245 patient-years of follow-up) (see section 4.4).

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

Immunogenicity
Approximately 5% of ustekinumab-treated patients developed antibodies to ustekinumab, which were generally low-titer. No apparent correlation of antibody development to injection site reactions was seen. Efficacy tended to be lower in patients positive for antibodies to ustekinumab; however, antibody positivity does not preclude a clinical response.

4.9 Overdose

No cases of overdose have been reported.

Single doses up to 4.5 mg/kg have been administered intravenously 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 and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Interleukin inhibitors, ATC code: L04AC05.

Mechanism of action
Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with high affinity and specificity to the p40 protein subunit of the human cytokines IL-12 and IL-23. Ustekinumab inhibits the activity of human IL-12 and IL-23 by preventing these cytokines from binding to their IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is pre-bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely 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 natural killer (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. Ustekinumab prevents IL-12 and IL-23 contributions to immune cell activation, such as intracellular signaling and cytokine secretion. Thus, ustekinumab is believed to interrupt signaling and cytokine cascades that are relevant to psoriasis pathology.

Clinical efficacy and safety
The safety and efficacy of ustekinumabwas assessed in 1,996 patients in two randomised, double-blind, placebo-controlled studies in patients with moderate to severe plaque psoriasis and who were candidates for phototherapy or systemic therapy.

Psoriasis Study 1 (PHOENIX 1) evaluated 766 patients. 53% of these patients were either non-responsive, intolerant, or had a contraindication to other systemic therapy. Patients randomised to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4 and followed by the same dose every 12 weeks. Patients randomised to receive placebo at Weeks 0 and 4 crossed over to receive ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16 followed by dosing every 12 weeks. Patients originally randomised to ustekinumab who achieved Psoriasis Area and Severity Index 75 response (PASI improvement of at least 75% relative to baseline) at both Weeks 28 and 40 were re-randomised to receive ustekinumab every 12 weeks or to placebo (i.e., withdrawal of therapy). Patients who were re-randomised to placebo at Week 40 reinitiated ustekinumab at their original dosing regimen when they experienced at least a 50% loss of their PASI improvement obtained at Week 40. All patients were followed for up to 76 weeks following first administration of study treatment.

Psoriasis Study 2 (PHOENIX 2) evaluated 1230 patients. 61% of these patients were either non-responsive, intolerant, or had a contraindication to other systemic therapy. Patients randomised to ustekinumab received 45 mg or 90 mg doses at Weeks 0 and 4 followed by an additional dose at 16 weeks. Patients randomised to receive placebo at Weeks 0 and 4 crossed over to receive ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16. All patients were followed for up to 52 weeks following first administration of study treatment.

In both studies, baseline disease characteristics were generally consistent across all treatment groups with a median baseline PASI score from 17 to 18 and median baseline Body Surface Area (BSA) ≥ 20, median Dermatology Life Quality Index (DLQI) range from 10 to 12. Approximately one third (PHOENIX 1) and one quarter (PHOENIX 2) of subjects had Psoriatic Arthritis (PsA).

The primary endpoint in both studies was the proportion of patients who achieved PASI 75 response from baseline at Week 12 (see Table 2).

Table 2 Summary of clinical response in Psoriasis Study 1 (PHOENIX 1) and Psoriasis Study 2 (PHOENIX 2)

	Week 12 (2 injections)			Week 28 (3 injections)	
	PBO	45 mg	90 mg	45 mg	90 mg
Psoriasis Study 1					
Number of patients randomised	255	255	256	250	243
PASI 50 response N (%)	26 (10%)	213 (84%) [a]	220 (86%) [a]	228 (91%)	234 (96%)
PASI 75 response N (%)	8 (3%)	171 (67%) [a]	170 (66%) [a]	178 (71%)	191 (79%)
PASI 90 response N (%)	5 (2%)	106 (42%) [a]	94 (37%) [a]	123 (49%)	135 (56%)
PGA[b] of cleared or minimal N (%)	10 (4%)	151 (59%) [a]	156 (61%) [a]	146 (58%)	160 (66%)
Psoriasis Study 2					
Number of patients randomised	410	409	411	397	400
PASI 50 response N (%)	41 (10%)	342 (84%) [a]	367 (89%) [a]	369 (93%)	380 (95%)
PASI 75 response N (%)	15 (4%)	273 (67%) [a]	311 (76%) [a]	276 (70%)	314 (79%)
PASI 90 response N (%)	3 (1%)	173 (42%) [a]	209 (51%) [a]	178 (45%)	217 (54%)
PGA[b] of cleared or minimal N (%)	18 (4%)	277 (68%) [a]	300 (73%) [a]	241 (61%)	279 (70%)
[a] $p < 0.001$ for 45 mg or 90 mg in comparison with placebo (PBO).					
[b] PGA = Physician Global Assessment					

In Psoriasis Study 1 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 ustekinumab. At Week 52, 89% of patients re-randomised to maintenance treatment were PASI 75 responders compared with 63% of patients re-randomised to placebo (treatment withdrawal) ($p < 0.001$). At week 76, 84% of patients re-randomised to maintenance treatment were PASI 75 responders compared with 19% of patients re-randomised to placebo (treatment withdrawal).

In patients re-randomised to placebo, and who reinitiated their original ustekinumab treatment regimen after loss of ≥ 50% of PASI improvement 85% regained PASI 75 response within 12 weeks after re-initiating therapy.

In Psoriasis Study 1, at Week 2 and Week 12, significantly greater improvements from baseline were demonstrated in the DLQI in each ustekinumab treatment group compared with placebo. The improvement was sustained through Week 28. Similarly, significant improvements were seen in Psoriasis Study 2 at Week 4 and 12, which were sustained through Week 24. In Psoriasis Study 1, improvements in nail psoriasis (Nail Psoriasis Severity Index), in the 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. In Psoriasis Study 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.

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 those 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 psoriasis, ranging from 15 to 32 days across all psoriasis studies. In a population pharmacokinetic analysis, the apparent clearance (CL/F) and apparent volume of distribution (V/F) were 0.465 l/day and 15.7 l, respectively, in patients with psoriasis. The CL/F of ustekinumab was not impacted by gender. Population pharmacokinetic analysis showed that there was a trend towards a higher clearance of ustekinumab in patients who tested positive for antibodies to ustekinumab.

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 µg/ml to 0.26 µg/ml (45 mg) and from 0.47 µg/ml to 0.49 µg/ml (90 mg). There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

Impact of weight on pharmacokinetics
In a population pharmacokinetic analysis, body weight was found to be the most significant covariate affecting the clearance of ustekinumab. The median CL/F in patients with weight > 100 kg was approximately 55% higher compared to patients with weight ≤ 100 kg. The median V/F in patients with weight > 100 kg was approximately 37% higher as compared to patients with weight ≤ 100 kg. 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.

In the population pharmacokinetic analysis, there were no indications of an effect of tobacco or alcohol on the pharmacokinetics of ustekinumab.

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

Sucrose
L-histidine
L-histidine monohydrochloride monohydrate
Polysorbate 80
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

12 months

6.4 Special precautions for storage

Store in a refrigerator (2ºC - 8ºC). Do not freeze.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

STELARA is supplied as a sterile solution in a single-use type I glass 2 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 discoloration 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 product should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present. Before administration, STELARA should be allowed to reach a comfortable temparature for injection (approximately half an hour). STELARA does not contain preservatives; therefore any unused product

remaining in the vial and the syringe should not be used. Detailed instructions for use are provided in the package leaflet.

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

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Manufacturer of the active substance

Centocor Biologics, LLC
4777 LeBourget Drive
St. Louis, MO 63134
USA

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

Centocor BV
Einsteinweg 101
NL-2333 CB Leiden
The Netherlands

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

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

The Marketing authorisation Holder (MAH) shall ensure that, at launch, all healthcare professionals who are experienced to prescribe/use Stelara are provided with educational materials containing the following:

The objectives of this Health Care Professional educational program will be focused on:
- Local Guidance for TB screening (see draft materials in RMP Appendix 1).
- The potential risks will be the focus of this EM
- Serious infections including salmonella, TB, and non-tuberculous mycobacterial infections-
- Malignancies

Patient information pack will be focused on:
- Potential risks/side effects as described in the Patient Information Sheet.
- Serious infections, including salmonella infections, TB, and non-tuberculous mycobacterial infections.
- Malignancies

- Appropriate techniques for administration of ustekinumab.

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 002 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1.6 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

VIAL CARTON TEXT (45 mg)

1. NAME OF THE MEDICINAL PRODUCT

STELARA 45 mg solution for injection
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 45 mg of ustekinumab in 0.5 ml.

3. LIST OF EXCIPIENTS

Excipients: Sucrose, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
45 mg/0.5 ml
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Subcutaneous use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

STELARA 45 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL TEXT (45 mg)

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

STELARA 45 mg solution for injection
ustekinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

45 mg/0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

VIAL CARTON TEXT (90 mg)

1. NAME OF THE MEDICINAL PRODUCT

STELARA 90 mg solution for injection
ustekinumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 90 mg of ustekinumab in 1 ml.

3. LIST OF EXCIPIENTS

Excipients: Sucrose, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
90 mg/1 ml
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake.
Subcutaneous use
Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

STELARA 90 mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL TEXT (90 mg)

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

STELARA 90 mg solution for injection
ustekinumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

90 mg/1 ml

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

STELARA 45 mg solution for injection
Ustekinumab

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT STELARA IS AND WHAT IT IS USED FOR

STELARA belongs to a group of medicines called immunosuppressants (medicines that inhibit your immune system). STELARA contains the active substance ustekinumab, a monoclonal antibody.

STELARA is used to treat moderate to severe plaque psoriasis in patients who cannot use or did not respond to other medicines and phototherapy. This disease causes inflammation of skin and nails. STELARA will reduce the inflammation and other signs of the disease.

2. BEFORE YOU USE STELARA

Do not use STELARA
- If you are allergic (hypersensitive) to ustekinumab or to any of the other ingredients of STELARA (listed in section 6 'What STELARA contains').
- If you have an active infection which your doctor considers important (see also below 'Take special care with STELARA').

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

Take special care with STELARA
Your doctor will assess your health before treatment. Make sure you tell your doctor about any illness you have. Check with your doctor before using STELARA if you have:

- **Infections**
  - **You must tell your doctor if you have any kind of infection**
    STELARA may make you less able to fight infections. Some infections could also become serious.
  - Tell your doctor if you have any signs of infection, even if it is very minor. Signs may include fever, feeling tired, cough, flu-like symptoms, diarrhoea, dental problems and burning when urinating. If you are not sure, talk to your doctor straight away
  - It is particularly important to tell your doctor if you have an infection that will not go away or keeps coming back
  - Tell your doctor if you have any open cuts or sores – they might get infected.

  - **Tuberculosis (TB)**
    - Tell your doctor if you have had tuberculosis. Also tell him or her if you have recently been near anyone who might have tuberculosis
    - Your doctor will examine you for tuberculosis and perform a test to see if you have tuberculosis, before you are given STELARA
    - If your doctor thinks that you are at risk of tuberculosis, you may be given medicines for tuberculosis. This will be before you begin treatment with STELARA, and during treatment with STELARA.

- **Cancer.** Immunosuppressants like STELARA decrease the activity of the immune system. This may increase the risk of cancer. Tell your doctor if you have ever had any type of cancer.

- **Vaccinations.** Tell your doctor if you have recently had or are going to have a vaccine.

- **Other therapies for psoriasis.** Tell your doctor if you are receiving any other immunosuppressant or phototherapy (when your body is treated with specific ultraviolet (UV) light) while using STELARA, which may also decrease the activity of your immune system. The combination of these therapies has not been investigated and it may increase the risk of diseases related to a weakened immune system.

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

Using other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

You should not be given certain types of vaccines while on treatment with STELARA.

Pregnancy and breast-feeding
Talk to your doctor before using STELARA:

- If you are pregnant or are planning to become pregnant while using STELARA. The effects of this medicine in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using STELARA and for at least 15 weeks after the last STELARA treatment.
- If you are breast-feeding or if you plan to breast-feed while using STELARA. Your doctor will decide whether you should use this medicine.

Driving and using machines
It is not known if STELARA can affect the ability to drive or use machines.

3. HOW TO USE STELARA

Always use STELARA exactly as your doctor has told you. You should check with your doctor if you are not sure. Make sure you discuss with your doctor when you will have your injections and your follow-up appointments.

How much STELARA is given
- Your doctor will decide how much STELARA you need and for how long
- This may depend on your weight
- The usual starting dose is 45 mg ustekinumab. After the starting dose, you will receive the next dose 4 weeks later, and then every 12 weeks
- Patients who weigh more than 100 kg may be given 90 mg instead of 45 mg.

Children and adolescents (under 18 years)
STELARA is not recommended for children and adolescents (under 18 years old) because it has not been studied in this age group.

How STELARA is given
- STELARA is given by injection under your skin (subcutaneously)
- At the start, medical or nursing staff may inject STELARA. However, you and your doctor may decide that you may inject STELARA yourself. In this case you will get training on how to inject STELARA yourself.

Talk to your doctor if you have any questions about giving yourself an injection. See below in section 'Instructions for administration' for further information about how to inject STELARA.

If you use more STELARA than you should
If you have used or been given too much STELARA, talk to a doctor or pharmacist straight away. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use STELARA
If you forget a dose, contact your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose.

If you stop using STELARA
It is not dangerous to stop using STELARA. However, the symptoms for which STELARA was prescribed may come back.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, STELARA can cause side effects, although not everybody gets them.
Most side effects are mild to moderate. However, some patients may experience serious side effects and may require treatment.

Tell your doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:

- **Signs of an allergic reaction** such as swelling of the face, lips, mouth or throat which may make it difficult to swallow or breathe; skin rash; hives; swelling of the hands, feet or ankles
- **Signs of infection (including tuberculosis)** such as fever, feeling tired or short of breath, cough which will not go away, flu-like symptoms, night sweats, diarrhoea, wounds, dental problems and burning when urinating.

Side effects may occur with certain frequencies, which are defined as follows:
- very common: affects more than 1 user in 10

- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data.

The following side effects have been observed with STELARA:

Very common:
- Infection of the throat or airways.

Common:
- Depression
- Feeling dizzy
- Headache
- Sore throat
- Blocked or stuffy nose
- Diarrhoea
- Itching
- Back or muscle pain
- Feeling tired
- Redness of the injection site
- Inflammation of tissue under the skin. The signs include warmth, swelling, redness and pain.

Uncommon:
- Pain, swelling, itching, hardness, bleeding, bruising and irritation where the injection is given.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE STELARA

Keep out of the reach and sight of children.

Store in a refrigerator (2°C–8°C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.

Do not shake STELARA vials. Prolonged vigorous shaking may damage the medicine.

Do not use STELARA
- After the expiry date which is stated on the label and the carton after "EXP". The expiry date refers to the last day of that month
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see further section 6 'What STELARA looks like and contents of the pack')
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated)
- If the product has been shaken vigorously
- If the seal is broken.

STELARA is for single use only. Any unused product remaining in the vial and the syringe should be disposed of.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What STELARA contains
- The active substance is ustekinumab. Each vial contains 45 mg ustekinumab (45 mg in 0.5 ml).
- The other ingredients are sucrose, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80 and water for injections.

What STELARA looks like and contents of the pack
STELARA is a clear to slightly opalescent, colourless to light yellow solution for injection. The solution may contain a few small translucent or white particles of protein. It is supplied as a carton pack containing 1 single-dose, glass 2 ml vial. Each vial contains 45 mg ustekinumab in 0.5 ml of solution for injection.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
2340 Beerse
Belgium

Manufacturer
Centocor B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
JANSSEN-CILAG NV
Roderveldlaan 1
B-2600 Berchem
Tél/Tel: + 32 3 280 54 11

Luxembourg/Luxemburg
JANSSEN-CILAG NV
Roderveldlaan 1
B-2600 Berchem
Belgique/Belgien
Tél: +32 3 280 54 11

България
Johnson & Johnson d.o.o.
Бизнес Парк София,
Младост 4, сграда 4, етаж 3
София 1715
Тел.: +359 2 489 94 00

Magyarország
JANSSEN-CILAG Kft.
H-2045 Törökbálint, Tó Park
Tel: +36 23-510-919

Česká republika
JANSSEN-CILAG s.r.o.
Karla Engliše 3201/6
15000 Praha 5
Česká republika
Tel: +420 227 012 222

Malta
A.M. Mangion Ltd.
Mangion Building
Triq ġdida fi triq Valletta
Luqa LQA 6000
Malta
TEL: 00356 2397 6000/6412

Danmark
JANSSEN-CILAG A/S
Hammerbakken 19
DK-3460 Birkerød
Tlf: +45 45 94 82 82

Nederland
JANSSEN-CILAG B.V.
Dr. Paul Janssenweg 150
5026 RH Tilburg
Tel: +31 13 583 73 73

Deutschland
JANSSEN-CILAG GmbH
Raiffeisenstrasse 8
D-41470 Neuss
Tel: +49 2137-955-955

Eesti
Janssen-Cilag Polska Sp. z o.o.
Eesti filiaal
Lõõtsa 2
EE-11415 Tallinn
Tel: +372 617 7410

Ελλάδα
JANSSEN-CILAG Φαρμακευτική Α.Ε.Β.Ε.
Λεωφόρος Ειρήνης 56
GR-151 21 Πεύκη
Αθήνα
Τηλ: +30 210 61 40 061

España
JANSSEN-CILAG, S.A.
Paseo de las Doce Estrellas, 5-7
Campo de las Naciones
E-28042 Madrid
Tel: +34 91 722 81 00

France
JANSSEN-CILAG S.A.
1, rue Camille Desmoulins
TSA 91003
92787 Issy Les Moulineaux
Cedex 9
Tél: 0800 25 50 75 or +33 1 55 00 44 44

Ireland
JANSSEN-CILAG Ltd.
50 -100 Holmers Farm Way,
High Wycombe,
Buckinghamshire, HP12 4EG
Tel: +44 1 494 567 567

Ísland
JANSSEN-CILAG
c/o Vistor hf.
Hörgatún 2
IS-210 Garðabær
Sími: +354 535 7000

Italia
JANSSEN-CILAG SpA
Via M.Buonarroti, 23
I-20093 Cologno Monzese MI
Tel: +39 02/2510.1

Norge
JANSSEN-CILAG A.S.
Drammensveien 288
NO-0283 Oslo
Tlf: + 47 24 12 65 00

Österreich
JANSSEN-CILAG Pharma GmbH
Pfarrgasse 75
A-1232 Wien
Tel: +43 1 610 300

Polska
JANSSEN–CILAG
POLSKA Sp. z o.o.
ul.Iłżecka 24
02–135 Warszawa
Tel.: + 48 22 237 60 00

Portugal
JANSSEN-CILAG FARMACÊUTICA, LDA.
Estrada Consiglieri Pedroso, 69 A
Queluz de Baixo
P-2734-503 Barcarena
Tel: +351 21 43 68 835

România
Johnson & Johnson d.o.o.
Str. Tipografilor nr. 11-15,
Clădirea S-Park,
Corp A2, Etaj 5
013714 Bucureşti
Tel : +40 21 207 18 00

Slovenija
Johnson & Johnson d.o.o.
Šmartinska 53
SI-1000, Ljubljana
Tel. +386 1 401 18 30

Slovenská republika
Johnson & Johnson, s.r.o.
Plynárenská 7/B
824 78 Bratislava
Tel: +421 233 552 600

Suomi/Finland
JANSSEN-CILAG OY
Vaisalantie/Vaisalavägen 2
FI-02130 Espoo/Esbo
Puh/Tel: +358 207 531 300

Κύπρος
Βαρνάβας Χατζηπαναγής Λτδ
7 Ανδροκλέους
CY-1060 Λευκωσία
Τηλ: +357 22 755 214

Latvija
Janssen-Cilag Polska Sp. z o.o.
filiāle Latvijā
Matrožu iela 15
LV-1048, Rīga
Tel: +371 678 93561

Lietuva
UAB "Johnson & Johnson"
Geležinio Vilko g. 18A
LT-08104 Vilnius
Tel: +370 5 278 68 88

Sverige
JANSSEN-CILAG AB
Box 7073
192 07 Sollentuna
Tel +46 8 626 50 00

United Kingdom
JANSSEN-CILAG Ltd.
50 -100 Holmers Farm Way,
High Wycombe,
Buckinghamshire, HP12 4EG
Tel: +44 1 494 567 567

This leaflet was last approved in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/.

<----------

INSTRUCTIONS FOR ADMINISTRATION

At the start of treatment, medical or nursing staff assists you with your first injection. However, you and your doctor may decide that you may inject STELARA yourself. If this happens, you will get training on how to inject STELARA. Talk to your doctor if you have any questions about giving yourself an injection.

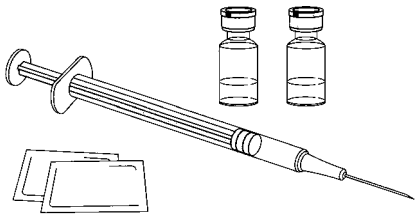
- Do not mix STELARA with other liquids for injection
- Do not shake STELARA vials. This is because strong shaking may damage the medicine. Do not use the medicine if it has been shaken strongly.

1. Check the number of vials and prepare the materials:

Take the vial(s) out of the refrigerator and check the vial(s) to make sure

- the number of vials and strength is correct
    - If your dose is 45 mg you will get one 45 mg vial of STELARA
    - If your dose is 90 mg you will get two 45 mg vials of STELARA and you will need to give yourself two injections. Choose two different sites for these injections (e.g. one injection in the right thigh and the other injection in the left thigh), and give the injections one right after the other. Use a new needle and syringe for each injection.
- it is the right medicine
- it has not passed its expiry date
- the vial is not damaged and the seal is not broken
- the solution is not discoloured, cloudy or contains any foreign particles
- the solution is not frozen.

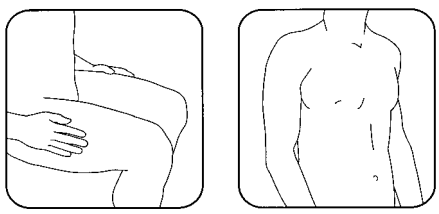
- Let the vial stand for about half an hour. This will let the liquid come to a comfortable temperature for injection.
- Wash your hands very well with soap and warm water
- Get everything together that you need and lay out on a clean surface. This includes a syringe, needle and antiseptic swabs.



2. Choose and prepare the injection site:

Choose an injection site

- STELARA is given by injection under your skin (subcutaneously)
- Good places for the injection are the upper thigh or around the belly (abdomen) at least 5 cm away from the navel (belly button)
- If possible, do not use areas of skin that show signs of psoriasis
- If someone will assist in giving you the injection, then he or she may also choose the upper arms or buttocks as an injection site.

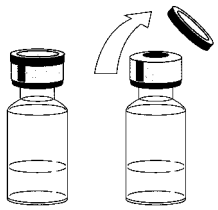


Prepare the injection site

- Wipe the injection site on the skin with an alcohol swab
- **Do not** touch this area again before giving the injection.

3. Prepare the dose:

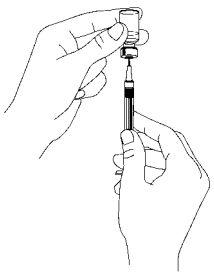
- Take the cap off the top of the vial



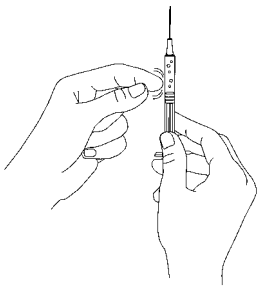
- Do not remove the stopper
- Clean the stopper with an antiseptic swab
- Put the vial on a flat surface.

Remove the needle cover

- Do not touch the needle or let the needle touch anything
- Push the needle through the rubber stopper
- Turn the vial and the syringe upside down
- Pull on the syringe plunger to fill the syringe with the amount of liquid in the vial
- It is important that the needle is always in the liquid. This stops air bubbles forming in the syringe



- Remove the needle from the vial
- Hold the syringe with the needle pointing up to see if it has any air bubbles inside
- If there are air bubbles, tap the side gently until the air bubbles go to the top of the syringe



- Then press the plunger until all of the air (but none of the liquid) has been removed
- Do not lay the syringe down or allow the needle to touch anything.

4. Inject the dose:

- Gently pinch the cleaned skin between your thumb and index finger. Do not squeeze it tightly
- Push the needle into the pinched skin
- Push the plunger with your thumb as far as it will go to inject all of the liquid. Push it slowly and evenly, keeping the skin gently pinched
- When the plunger is pushed as far as it will go, take out the needle and let go of the skin
- Press an antiseptic swab over the injection site for a few seconds after the injection.

5. Disposal:

- Used syringes and needles should be placed in a puncture-resistant container, like a sharps container. Dispose of your sharps container according to your local regulations
- Empty vials, antiseptic wipes, and other supplies can be disposed in your garbage.

PACKAGE LEAFLET: INFORMATION FOR THE USER

STELARA 90 mg solution for injection
Ustekinumab

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT STELARA IS AND WHAT IT IS USED FOR

STELARA belongs to a group of medicines called immunosuppressants (medicines that inhibit your immune system). STELARA contains the active substance ustekinumab, a monoclonal antibody.

STELARA is used to treat moderate to severe plaque psoriasis in patients who cannot use or did not respond to other medicines and phototherapy. This disease causes inflammation of skin and nails. STELARA will reduce the inflammation and other signs of the disease.

2. BEFORE YOU USE STELARA

Do not use STELARA
- If you are allergic (hypersensitive) to ustekinumab or to any of the other ingredients of STELARA (listed in section 6 'What STELARA contains').
- If you have an active infection which your doctor considers important (see also below 'Take special care with STELARA').

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

Take special care with STELARA
Your doctor will assess your health before treatment. Make sure you tell your doctor about any illness you have. Check with your doctor before using STELARA if you have:

- **Infections**
  - **You must tell your doctor if you have any kind of infection**
    STELARA may make you less able to fight infections. Some infections could also become serious.
  - Tell your doctor if you have any signs of infection, even if it is very minor. Signs may include fever, feeling tired, cough, flu-like symptoms, diarrhoea, dental problems and burning when urinating. If you are not sure, talk to your doctor straight away
  - It is particularly important to tell your doctor if you have an infection that will not go away or keeps coming back
  - Tell your doctor if you have any open cuts or sores – they might get infected.

  - **Tuberculosis (TB)**
    - Tell your doctor if you have had tuberculosis. Also tell him or her if you have recently been near anyone who might have tuberculosis
    - Your doctor will examine you for tuberculosis and perform a test to see if you have tuberculosis, before you are given STELARA
    - If your doctor thinks that you are at risk of tuberculosis, you may be given medicines for tuberculosis. This will be before you begin treatment with STELARA, and during treatment with STELARA.

- **Cancer.** Immunosuppressants like STELARA decrease the activity of the immune system. This may increase the risk of cancer. Tell your doctor if you have ever had any type of cancer.

- **Vaccinations.** Tell your doctor if you have recently had or are going to have a vaccine.

- **Other therapies for psoriasis.** Tell your doctor if you are receiving any other immunosuppressant or phototherapy (when your body is treated with specific ultraviolet (UV) light) while using STELARA, which may also decrease the activity of your immune system. The combination of these therapies has not been investigated and it may increase the risk of diseases related to a weakened immune system.

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

Using other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

You should not be given certain types of vaccines while on treatment with STELARA.

Pregnancy and breast-feeding
Talk to your doctor before using STELARA:

- If you are pregnant or are planning to become pregnant while using STELARA. The effects of this medicine in pregnant women are not known. If you are a woman of childbearing potential, you are advised to avoid becoming pregnant and must use adequate contraception while using STELARA and for at least 15 weeks after the last STELARA treatment.
- If you are breast-feeding or if you plan to breast-feed while using STELARA. Your doctor will decide whether you should use this medicine.

Driving and using machines
It is not known if STELARA can affect the ability to drive or use machines.

3. HOW TO USE STELARA

Always use STELARA exactly as your doctor has told you. You should check with your doctor if you are not sure. Make sure you discuss with your doctor when you will have your injections and your follow-up appointments.

How much STELARA is given
- Your doctor will decide how much STELARA you need and for how long
- This may depend on your weight
- The usual starting dose is 45 mg ustekinumab. After the starting dose, you will receive the next dose 4 weeks later, and then every 12 weeks
- Patients who weigh more than 100 kg may be given 90 mg instead of 45 mg.

Children and adolescents (under 18 years)
STELARA is not recommended for children and adolescents (under 18 years old) because it has not been studied in this age group.

How STELARA is given
- STELARA is given by injection under your skin (subcutaneously)
- At the start, medical or nursing staff may inject STELARA. However, you and your doctor may decide that you may inject STELARA yourself. In this case you will get training on how to inject STELARA yourself.

Talk to your doctor if you have any questions about giving yourself an injection. See below in section 'Instructions for administration' for further information about how to inject STELARA.

If you use more STELARA than you should
If you have used or been given too much STELARA, talk to a doctor or pharmacist straight away. Always have the outer carton of the medicine with you, even if it is empty.

If you forget to use STELARA
If you forget a dose, contact your doctor or pharmacist. Do not take a double dose to make up for a forgotten dose.

If you stop using STELARA
It is not dangerous to stop using STELARA. However, the symptoms for which STELARA was prescribed may come back.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, STELARA can cause side effects, although not everybody gets them.
Most side effects are mild to moderate. However, some patients may experience serious side effects and may require treatment.

Tell your doctor straight away if you notice any of the following serious side effects – you may need urgent medical treatment:

- **Signs of an allergic reaction** such as swelling of the face, lips, mouth or throat which may make it difficult to swallow or breathe; skin rash; hives; swelling of the hands, feet or ankles
- **Signs of infection (including tuberculosis)** such as fever, feeling tired or short of breath, cough which will not go away, flu-like symptoms, night sweats, diarrhoea, wounds, dental problems and burning when urinating.

Side effects may occur with certain frequencies, which are defined as follows:
- very common: affects more than 1 user in 10

- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data.

The following side effects have been observed with STELARA:

Very common:
- Infection of the throat or airways.

Common:
- Depression
- Feeling dizzy
- Headache
- Sore throat
- Blocked or stuffy nose
- Diarrhoea
- Itching
- Back or muscle pain
- Feeling tired
- Redness of the injection site
- Inflammation of tissue under the skin. The signs include warmth, swelling, redness and pain.

Uncommon:
- Pain, swelling, itching, hardness, bleeding, bruising and irritation where the injection is given.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE STELARA

Keep out of the reach and sight of children.

Store in a refrigerator (2°C–8°C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.

Do not shake STELARA vials. Prolonged vigorous shaking may damage the medicine.

Do not use STELARA
- After the expiry date which is stated on the label and the carton after "EXP". The expiry date refers to the last day of that month
- If the liquid is discoloured, cloudy or you can see other foreign particles floating in it (see further section 6 'What STELARA looks like and contents of the pack')
- If you know, or think that it may have been exposed to extreme temperatures (such as accidentally frozen or heated)
- If the product has been shaken vigorously
- If the seal is broken.

STELARA is for single use only. Any unused product remaining in the vial and the syringe should be disposed of.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What STELARA contains
- The active substance is ustekinumab. Each vial contains 90 mg ustekinumab (90 mg in 1 ml).
- The other ingredients are sucrose, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80 and water for injections.

What STELARA looks like and contents of the pack
STELARA is a clear to slightly opalescent, colourless to light yellow solution for injection. The solution may contain a few small translucent or white particles of protein. It is supplied as a carton pack containing 1 single-dose, glass 2 ml vial. Each vial contains 90 mg ustekinumab in 1 ml of solution for injection.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
2340 Beerse
Belgium

Manufacturer
Centocor B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
JANSSEN-CILAG NV
Roderveldlaan 1
B-2600 Berchem
Tél/Tel: + 32 3 280 54 11

Luxembourg/Luxemburg
JANSSEN-CILAG NV
Roderveldlaan 1
B-2600 Berchem
Belgique/Belgien
Tél: +32 3 280 54 11

България
Johnson & Johnson d.o.o.
Бизнес Парк София,
Младост 4, сграда 4, етаж 3
София 1715
Тел.: +359 2 489 94 00

Magyarország
JANSSEN-CILAG Kft.
H-2045 Törökbálint, Tó Park
Tel: +36 23-510-919

Česká republika
JANSSEN-CILAG s.r.o.
Karla Engliše 3201/6
15000 Praha 5
Česká republika
Tel: +420 227 012 222

Malta
A.M. Mangion Ltd.
Mangion Building
Triq ġdida fi triq Valletta
Luqa LQA 6000
Malta
TEL: 00356 2397 6000/6412

Danmark
JANSSEN-CILAG A/S
Hammerbakken 19
DK-3460 Birkerød
Tlf: +45 45 94 82 82

Nederland
JANSSEN-CILAG B.V.
Dr. Paul Janssenweg 150
5026 RH Tilburg
Tel: +31 13 583 73 73

Deutschland
JANSSEN-CILAG GmbH
Raiffeisenstrasse 8
D-41470 Neuss
Tel: +49 2137-955-955

Eesti
Janssen-Cilag Polska Sp. z o.o.
Eesti filiaal
Lõõtsa 2
EE-11415 Tallinn
Tel: +372 617 7410

Ελλάδα
JANSSEN-CILAG Φαρμακευτική Α.Ε.Β.Ε.
Λεωφόρος Ειρήνης 56
GR-151 21 Πεύκη
Αθήνα
Τηλ: +30 210 61 40 061

España
JANSSEN-CILAG, S.A.
Paseo de las Doce Estrellas, 5-7
Campo de las Naciones
E-28042 Madrid
Tel: +34 91 722 81 00

France
JANSSEN-CILAG S.A.
1, rue Camille Desmoulins
TSA 91003
92787 Issy Les Moulineaux
Cedex 9
Tél: 0800 25 50 75 or +33 1 55 00 44 44

Ireland
JANSSEN-CILAG Ltd.
50 -100 Holmers Farm Way,
High Wycombe,
Buckinghamshire, HP12 4EG
Tel: +44 1 494 567 567

Ísland
JANSSEN-CILAG
c/o Vistor hf.
Hörgatún 2
IS-210 Garðabær
Sími: +354 535 7000

Italia
JANSSEN-CILAG SpA
Via M.Buonarroti, 23
I-20093 Cologno Monzese MI
Tel: +39 02/2510.1

Norge
JANSSEN-CILAG A.S.
Drammensveien 288
NO-0283 Oslo
Tlf: + 47 24 12 65 00

Österreich
JANSSEN-CILAG Pharma GmbH
Pfarrgasse 75
A-1232 Wien
Tel: +43 1 610 300

Polska
JANSSEN–CILAG
POLSKA Sp. z o.o.
ul.Iłżecka 24
02–135 Warszawa
Tel.: + 48 22 237 60 00

Portugal
JANSSEN-CILAG FARMACÊUTICA, LDA.
Estrada Consiglieri Pedroso, 69 A
Queluz de Baixo
P-2734-503 Barcarena
Tel: +351 21 43 68 835

România
Johnson & Johnson d.o.o.
Str. Tipografilor nr. 11-15,
Clădirea S-Park,
Corp A2, Etaj 5
013714 Bucureşti
Tel : +40 21 207 18 00

Slovenija
Johnson & Johnson d.o.o.
Šmartinska 53
SI-1000, Ljubljana
Tel. +386 1 401 18 30

Slovenská republika
Johnson & Johnson, s.r.o.
Plynárenská 7/B
824 78 Bratislava
Tel: +421 233 552 600

Suomi/Finland
JANSSEN-CILAG OY
Vaisalantie/Vaisalavägen 2
FI-02130 Espoo/Esbo
Puh/Tel: +358 207 531 300

Κύπρος
Βαρνάβας Χατζηπαναγής Λτδ
7 Ανδροκλέους
CY-1060 Λευκωσία
Τηλ: +357 22 755 214

Latvija
Janssen-Cilag Polska Sp. z o.o.
filiāle Latvijā
Matrožu iela 15
LV-1048, Rīga
Tel: +371 678 93561

Lietuva
UAB "Johnson & Johnson"
Geležinio Vilko g. 18A
LT-08104 Vilnius
Tel: +370 5 278 68 88

Sverige
JANSSEN-CILAG AB
Box 7073
192 07 Sollentuna
Tel +46 8 626 50 00

United Kingdom
JANSSEN-CILAG Ltd.
50 -100 Holmers Farm Way,
High Wycombe,
Buckinghamshire, HP12 4EG
Tel: +44 1 494 567 567

This leaflet was last approved in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/.

<----------

INSTRUCTIONS FOR ADMINISTRATION

At the start of treatment, medical or nursing staff assists you with your first injection. However, you and your doctor may decide that you may inject STELARA yourself. If this happens, you will get training on how to inject STELARA. Talk to your doctor if you have any questions about giving yourself an injection.

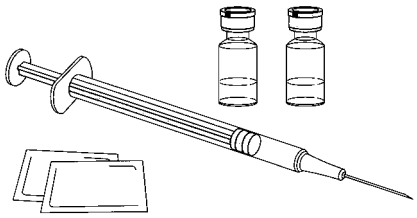
- Do not mix STELARA with other liquids for injection
- Do not shake STELARA vials. This is because strong shaking may damage the medicine. Do not use the medicine if it has been shaken strongly.

1. Check the number of vials and prepare the materials:

Take the vial(s) out of the refrigerator and check the vial(s) to make sure

- the number of vials and strength is correct
    - If your dose is 90 mg you will get one 90 mg vial of STELARA.
- it is the right medicine
- it has not passed its expiry date
- the vial is not damaged and the seal is not broken
- the solution is not discoloured, cloudy or contains any foreign particles
- the solution is not frozen.

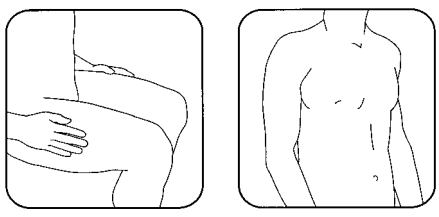
- Let the vial stand for about half an hour. This will let the liquid come to a comfortable temperature for injection.
- Wash your hands very well with soap and warm water
- Get everything together that you need and lay out on a clean surface. This includes a syringe, needle and antiseptic swabs.



2. Choose and prepare the injection site:

Choose an injection site

- STELARA is given by injection under your skin (subcutaneously)
- Good places for the injection are the upper thigh or around the belly (abdomen) at least 5 cm away from the navel (belly button)
- If possible, do not use areas of skin that show signs of psoriasis
- If someone will assist in giving you the injection, then he or she may also choose the upper arms or buttocks as an injection site.

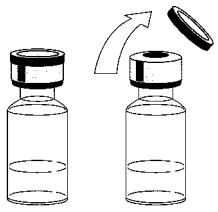


Prepare the injection site

- Wipe the injection site on the skin with an alcohol swab
- **Do not** touch this area again before giving the injection.

3. Prepare the dose:

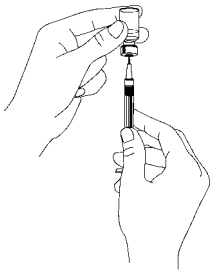
- Take the cap off the top of the vial



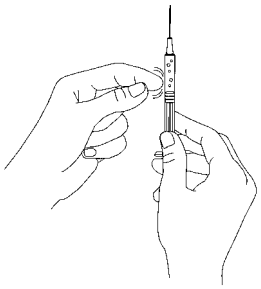
- Do not remove the stopper
- Clean the stopper with an antiseptic swab
- Put the vial on a flat surface.

Remove the needle cover

- Do not touch the needle or let the needle touch anything
- Push the needle through the rubber stopper
- Turn the vial and the syringe upside down
- Pull on the syringe plunger to fill the syringe with the amount of liquid in the vial
- It is important that the needle is always in the liquid. This stops air bubbles forming in the syringe



- Remove the needle from the vial
- Hold the syringe with the needle pointing up to see if it has any air bubbles inside
- If there are air bubbles, tap the side gently until the air bubbles go to the top of the syringe



- Then press the plunger until all of the air (but none of the liquid) has been removed
- Do not lay the syringe down or allow the needle to touch anything.

4. Inject the dose:

- Gently pinch the cleaned skin between your thumb and index finger. Do not squeeze it tightly
- Push the needle into the pinched skin
- Push the plunger with your thumb as far as it will go to inject all of the liquid. Push it slowly and evenly, keeping the skin gently pinched
- When the plunger is pushed as far as it will go, take out the needle and let go of the skin
- Press an antiseptic swab over the injection site for a few seconds after the injection.

5. Disposal:

- Used syringes and needles should be placed in a puncture-resistant container, like a sharps container. Dispose of your sharps container according to your local regulations
- Empty vials, antiseptic wipes, and other supplies can be disposed in your garbage.