資料３－⑧　ウステキヌマブ（ustekinumab）

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 $\geq$ 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 (2°C - 8°C). 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

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For a full list of excipients, see section 6.1.

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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.

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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.

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

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Special populations
Children and adolescents (< 18 years)
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Elderly patients (≥ 65 years)
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Hepatic and renal impairment
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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 $\geq$ 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.