## 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/

# 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.