SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

IMULDOSA® 130 mg concentrate for solution for infusion

ustekinumab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 130 mg ustekinumab in 26 mL (5 mg/mL).

Ustekinumab is a fully human IgG1κ monoclonal antibody to interleukin (IL)-12/23 produced in a murine myeloma cell line using recombinant DNA technology.

Excipients with known effect

Sodium

Each dose contains less than 1 mmol sodium (23 mg).

Polysorbate

Each unit volume contains 11.1 mg polysorbate 80, which is equivalent to 10.4 mg per 130 mg dose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (solution for infusion).

The solution is colourless to slightly yellow and clear to slightly opalescent.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adult Crohn's Disease
IMULDOSA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist.

Paediatric Crohn's Disease
IMULDOSA is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients weighing at least 40 kg, who have had an inadequate response to, or were intolerant to either conventional or biologic therapy.

Ulcerative colitis
IMULDOSA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic.

4.2 Posology and method of administration

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

Posology

Adults

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

Table 1: Initial intravenous dosing of IMULDOSA

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

[a] Approximately 6 mg/kg

The first subcutaneous dose should be given at week 8 following the intravenous dose. For the posology of the subsequent subcutaneous dosing regimen, see section 4.2 of the IMULDOSA solution for injection (vial) and solution for injection in pre-filled syringe SmPC.

Elderly (≥ 65 years)
No dose adjustment is needed for elderly patients (see section 4.4).

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

Paediatric population

Paediatric Crohn's disease (patients weighing at least 40 kg)
IMULDOSA treatment is to be initiated with a single intravenous dose based on body weight. The infusion solution is to be composed of the number of vials of IMULDOSA 130 mg as specified in Table 2 (see section 6.6 for preparation).

Table 2 Initial intravenous dosing of IMULDOSA

Body weight of patient at the time of dosing	**Recommended dose[a]**	**Number of 130 mg IMULDOSA Vials**
≥ 40 kg to ≤ 55 kg	260 mg	2
> 55 kg to ≤ 85 kg	390 mg	3
> 85 kg	520 mg	4

[a]Approximately 6 mg/kg

The first subcutaneous dose should be given at week 8 following the intravenous dose. For the posology of the subsequent subcutaneous dosing regimen, see section 4.2 of the IMULDOSA solution for injection (vial) and solution for injection in pre-filled syringe SmPC.

The safety and efficacy of IMULDOSA for the treatment of Crohn's disease in paediatric patients weighing less than 40 kg have not yet been established. No data are available.

Method of administration
IMULDOSA 130 mg is for intravenous use only. It should be administered over at least one hour.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Clinically important, active infection (e.g. active tuberculosis; see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infections

Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. In clinical studies and a post-marketing observational study in patients with psoriasis, serious bacterial, fungal, and viral infections have been observed in patients receiving ustekinumab (see section 4.8).

Opportunistic infections including reactivation of tuberculosis, other opportunistic bacterial infections (including atypical mycobacterial infection, listeria meningitis, pneumonia legionella, and nocardiosis), opportunistic fungal infections, opportunistic viral infections (including encephalitis caused by herpes simplex 2), and parasitic infections (including ocular toxoplasmosis) have been reported in patients treated with ustekinumab.

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

Prior to initiating treatment with IMULDOSA, patients should be evaluated for tuberculosis infection. IMULDOSA must not be given to patients with active tuberculosis (see section 4.3). Treatment of latent tuberculosis infection should be initiated prior to administering IMULDOSA. Anti-tuberculosis therapy should also be considered prior to initiation of IMULDOSA in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving IMULDOSA 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 IMULDOSA 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 ustekinumab in clinical studies and in a post-marketing observational study in patients with psoriasis developed cutaneous and non-cutaneous malignancies (see section 4.8). The risk of malignancy may be higher in psoriasis patients who have been treated with other biologics during the course of their disease.

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

All patients, in particular those greater than 60 years of age, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be monitored for the appearance of skin cancer (see section 4.8).

Systemic and respiratory hypersensitivity reactions

Systemic

Serious hypersensitivity reactions have been reported in the post-marketing setting, in some cases several days after treatment. Anaphylaxis and angioedema have occurred. If an anaphylactic or other serious hypersensitivity reaction occurs, appropriate therapy should be instituted and administration of IMULDOSA should be discontinued (see

section 4.8).

Infusion-related reactions
Infusion-related reactions were observed in clinical trials (see section 4.8). Serious infusion-related reactions including anaphylactic reactions to the infusion have been reported in the post-marketing setting. If a serious or life-threatening reaction is observed, appropriate therapy should be instituted and ustekinumab should be discontinued.

Respiratory
Cases of allergic alveolitis, eosinophilic pneumonia, and non-infectious organising pneumonia have been reported during post-approval use of ustekinumab. Clinical presentations included cough, dyspnoea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalisation. Improvement has been reported after discontinuation of ustekinumab and also, in some cases, administration of corticosteroids. If infection has been excluded and diagnosis is confirmed, discontinue ustekinumab and institute appropriate treatment (see section 4.8).

Cardiovascular events
Cardiovascular events including myocardial infarction and cerebrovascular accident have been observed in patients with psoriasis exposed to ustekinumab in a post-marketing observational study. Risk factors for cardiovascular disease should be regularly assessed during treatment with IMULDOSA.

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 IMULDOSA. Specific studies have not been conducted in patients who had recently received live viral or live bacterial vaccines. No data are available on the secondary transmission of infection by live vaccines in patients receiving ustekinumab. Before live viral or live bacterial vaccination, treatment with IMULDOSA 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.

Administration of live vaccines (such as the BCG vaccine) to infants exposed *in utero* to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.5 and 4.6). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable. Patients receiving IMULDOSA may receive concurrent inactivated or non-live vaccinations.

Long term treatment with ustekinumab does not suppress the humoral immune response to pneumococcal polysaccharide or tetanus vaccines (see section 5.1).

Concomitant immunosuppressive therapy
In psoriasis studies, the safety and efficacy of ustekinumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of ustekinumab. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of ustekinumab. Caution should be exercised when considering concomitant use of other immunosuppressants and IMULDOSA or when transitioning from other immunosuppressive biologics (see section 4.5).

Immunotherapy
Ustekinumab has not been evaluated in patients who have undergone allergy immunotherapy. It is not known whether ustekinumab may affect allergy immunotherapy.

Serious skin conditions
In patients with psoriasis, exfoliative dermatitis has been reported following ustekinumab treatment (see section 4.8). Patients with plaque psoriasis may develop erythrodermic psoriasis, with symptoms that may be clinically indistinguishable from exfoliative dermatitis, as part of the natural course of their disease. As part of the monitoring of the patient's psoriasis, physicians should be alert for symptoms of erythrodermic psoriasis or exfoliative dermatitis. If these symptoms occur, appropriate therapy should be instituted. IMULDOSA should be discontinued if a drug reaction is suspected.

Lupus-related conditions
Cases of lupus-related conditions have been reported in patients treated with ustekinumab, including cutaneous lupus erythematosus and lupus-like syndrome. If lesions occur, especially in sun exposed areas of the skin or if accompanied by arthralgia, the patient should seek medical attention promptly. If the diagnosis of a lupus-related condition is confirmed, ustekinumab should be discontinued and appropriate treatment initiated.

Special populations
Elderly (≥ 65 years)
No overall differences in efficacy or safety in patients age 65 and older who received ustekinumab were observed compared to younger patients in clinical studies in approved indications, however the number of patients aged 65 and older is not sufficient to determine whether they respond differently from younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Sodium content
IMULDOSA contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'. IMULDOSA is however, diluted in sodium chloride 9 mg/mL (0.9%) solution for infusion. This should be taken into consideration for patients on a controlled sodium diet (see section 6.6).

Polysorbate 80
IMULDOSA contains 11.1 mg polysorbate 80 (E433) in each unit volume, which is equivalent to 10.4 mg per 130 mg dose.
Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Live vaccines should not be given concurrently with IMULDOSA.

Administration of live vaccines (such as the BCG vaccine) to infants exposed *in utero* to ustekinumab is not recommended for twelve months following birth or until ustekinumab infant serum levels are undetectable (see sections 4.4 and 4.6). If there is a clear clinical benefit for the individual infant, administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab serum levels are undetectable.

In the population pharmacokinetic analyses of the phase 3 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. The pharmacokinetics of ustekinumab was not impacted by concomitant use of MTX, NSAIDs, 6-mercaptopurine, azathioprine and oral corticosteroids in patients with psoriatic arthritis, Crohn's disease or ulcerative colitis, or prior exposure to anti-TNFα agents, in patients with psoriatic arthritis or Crohn's disease or by prior exposure to biologics (i.e. anti-TNFα agents and/or vedolizumab) in patients with ulcerative colitis.

The results of an *in vitro* study and a phase 1 study in subjects with active Crohn's disease do not suggest the need for dose adjustments in patients who are receiving concomitant CYP450 substrates (see section 5.2).

In psoriasis studies, the safety and efficacy of ustekinumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of ustekinumab. In Crohn's disease and ulcerative colitis studies, concomitant use of immunosuppressants or corticosteroids did not appear to influence the safety or efficacy of ustekinumab (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective methods of contraception during treatment and for at least 15 weeks after treatment.

Pregnancy

Data from a moderate number of prospectively collected pregnancies following exposure to IMULDOSA with known outcomes, including more than 450 pregnancies exposed during the first trimester, do not indicate an increased risk of major congenital malformations in the newborn.

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). However, the available clinical experience is limited. As a precautionary measure, it is preferable to avoid the use of IMULDOSA in pregnancy.

Ustekinumab crosses the placenta and has been detected in the serum of infants born to female patients treated with ustekinumab during pregnancy. The clinical impact of this is unknown, however, the risk of infection in infants exposed in utero to ustekinumab may be increased after birth.

Administration of live vaccines (such as the BCG vaccine) to infants exposed *in utero* to ustekinumab

is not recommended for twelve months following birth or until ustekinumab infant serum levels are

undetectable (see sections 4.4 and 4.5). If there is a clear clinical benefit for the individual infant,

administration of a live vaccine might be considered at an earlier timepoint, if infant ustekinumab

serum levels are undetectable.

Breast-feeding

Limited data from published literature suggests that ustekinumab is excreted in human breast milk in very small amounts. 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 IMULDOSA must be made taking into account the benefit of breast-feeding to the child and the benefit of IMULDOSA therapy to the woman.

Fertility

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

4.7 Effects on ability to drive and use machines

IMULDOSA has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions (> 5%) in controlled periods of the adult psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies with ustekinumab were nasopharyngitis and headache. Most were considered to be mild and did not necessitate discontinuation of study treatment. The most serious adverse reaction that has been reported for ustekinumab is serious hypersensitivity reactions including anaphylaxis (see section 4.4). The overall safety profile was similar for patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

Tabulated list of adverse reactions

The safety data described below reflect exposure in adults to ustekinumab in 14 phase 2 and phase 3 studies in 6,710 patients (4,135 with psoriasis and/or psoriatic arthritis, 1,749 with Crohn's disease and 826 patients with ulcerative colitis). This includes exposure to ustekinumab in the controlled and non-controlled periods of the clinical studies in patients with psoriasis, psoriatic arthritis, Crohn's disease or ulcerative colitis for at least 6 months (4,577 patients) or at least 1 year (3,648 patients). 2,194 patients with psoriasis, Crohn's disease or ulcerative colitis were exposed for at least 4 years while 1,148 patients with psoriasis or Crohn's disease were exposed for at least 5 years.

Table 3 provides a list of adverse reactions from adult psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies as well as adverse reactions reported from post-marketing experience. 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) and Not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: List of adverse reactions

System Organ Class	**Frequency: Adverse reaction**
Infections and infestations	Common: Upper respiratory tract infection, nasopharyngitis, sinusitis Uncommon: Cellulitis, dental infections, herpes zoster, lower respiratory tract infection, viral upper respiratory tract infection, vulvovaginal mycotic infection
Immune system disorders	Uncommon: Hypersensitivity reactions (including rash, urticaria) Rare: Serious hypersensitivity reactions (including anaphylaxis, angioedema)
Psychiatric disorders	Uncommon: Depression
Nervous system disorders	Common: Dizziness, headache Uncommon: Facial palsy
Respiratory, thoracic and mediastinal disorders	Common: Oropharyngeal pain Uncommon: Nasal congestion Rare: Allergic alveolitis, eosinophilic pneumonia Very rare: Organising pneumonia*
Gastrointestinal disorders	Common: Diarrhoea, nausea, vomiting
Skin and subcutaneous tissue disorders	Common: Pruritus Uncommon: Pustular psoriasis, skin exfoliation, acne Rare: Exfoliative dermatitis, hypersensitivity vasculitis Very rare: Bullous pemphigoid, cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Common: Back pain, myalgia, arthralgia Very rare: Lupus-like syndrome
General disorders and administration site conditions	Common: Fatigue, injection site erythema, injection site pain Uncommon: Injection site reactions (including haemorrhage, haematoma, induration, swelling and pruritus), asthenia

*See section 4.4, Systemic and respiratory hypersensitivity reactions.

Description of selected adverse reactions Infections

In the placebo-controlled studies of patients with psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis, the rates of infection or serious infection were similar between ustekinumab-treated patients and those treated with placebo. In the placebo-controlled period of these clinical studies, the rate of infection was 1.36 per patient-year of follow-up in ustekinumab-treated patients, and 1.34 in placebo-treated patients. Serious infections occurred at the rate of 0.03 per patient-year of follow-up in ustekinumab-treated patients (30 serious infections in 930 patient-years of follow-up) and 0.03 in placebo-treated patients (15 serious infections in 434 patient-years of follow-up) (see section 4.4).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 15,227 patient years of ustekinumab exposure in 6,710 patients, the median follow-up was 1.2 years; 1.7 years for psoriatic disease studies, 0.6 year for Crohn's disease studies, and 2.3 years for ulcerative colitis studies. The rate of infection was 0.85 per patient year of follow up in ustekinumab treated patients, and the rate of serious infections was 0.02 per patient year of follow up in ustekinumab treated patients (289 serious infections in 15,227 patient years of follow up) and serious infections reported included pneumonia, anal abscess, cellulitis, diverticulitis, gastroenteritis and viral infections.

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

Malignancies

In the placebo-controlled period of the psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, the incidence of malignancies excluding non-melanoma skin cancer was 0.11 per 100 patient-years of follow-up for ustekinumab-treated patients (1 patient in 929 patient-years of follow-up) compared with 0.23 for placebo-treated patients (1 patient in 434 patient-years of follow-up). The incidence of non-melanoma skin cancer was 0.43 per 100 patient-years of follow-up for ustekinumab-treated patients (4 patients in 929 patient-years of follow-up) compared to 0.46 for placebo-treated patients (2 patients in 433 patient-years of follow-up).

In the controlled and non-controlled periods of psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis clinical studies, representing 15,205 patient years of ustekinumab exposure in 6,710 patients, the median follow-up was 1.2 years; 1.7 years for psoriatic disease studies, 0.6 year for Crohn's disease studies and 2.3 years for ulcerative colitis studies. Malignancies excluding non-melanoma skin cancers were reported in 76 patients in 15,205 patient years of follow up (incidence of 0.50 per 100 patient-years of follow-up for ustekinumab treated patients). The incidence of malignancies reported in ustekinumab treated patients was comparable to the incidence expected in the general population (standardised incidence ratio = 0.94 [95% confidence interval: 0.73, 1.18], adjusted for age, gender and race). The most frequently observed malignancies, other than non-melanoma skin cancer, were prostate, melanoma, colorectal, and breast cancers. The incidence of non-melanoma skin cancer was 0.46 per 100 patient years of follow up for ustekinumab treated patients (69 patients in 15,165 patient years of follow up). The ratio of patients with basal versus squamous cell skin cancers (3:1) is comparable with the ratio expected in the general population (see section 4.4).

Hypersensitivity and infusion reactions

In Crohn's disease and ulcerative colitis intravenous induction studies, no events of anaphylaxis or other serious infusion reactions were reported following the single intravenous dose. In these studies, 2.2% of 785 placebo-treated patients and 1.9% of 790 patients treated with the recommended dose of ustekinumab reported adverse events occurring during or within an hour of the infusion. Serious infusion-related reactions including anaphylactic reactions to the infusion have been reported in the post-marketing setting (see section 4.4).

Paediatric population

Paediatric patients 6 years and older with plaque psoriasis

The safety of ustekinumab has been studied in two phase 3 studies of paediatric patients with moderate to severe plaque psoriasis. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks and the second study was in 44 patients from 6 to 11 years of age treated for up to 56 weeks. In general, the adverse events reported in these two studies with safety data up to 1 year were similar to those seen in previous studies in adults with plaque psoriasis.

Paediatric patients weighing at least 40 kg with Crohn's disease

The safety of Ustekinumab has been studied in one phase 1 and one phase 3 study of paediatric patients with moderately to severely active Crohn's disease up to week 240 and week 52, respectively. In general, the safety profile in this cohort (n = 71) was similar to that seen in previous studies in adults with Crohn's disease.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Single doses up to 6 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: Immunosuppressants, interleukin inhibitors, ATC code: L04AC05.

IMULDOSA is a biosimilar medicinal product. Detailed information is available on the

MHRA website.Mechanism of action
Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12R□1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12R□1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23 receptors. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells, and both cytokines participate in immune functions; IL-12 stimulates natural killer (NK) cells and drives the differentiation of CD4+ T cells toward the T helper 1 (Th1) phenotype, IL-23 induces the T helper 17 (Th17) pathway. However, abnormal regulation of IL 12 and IL 23 has been associated with immune mediated diseases, such as psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis.

By binding the shared p40 subunit of IL-12 and IL-23, ustekinumab may exert its clinical effects in psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis through interruption of the Th1 and Th17 cytokine pathways, which are central to the pathology of these diseases.

In patients with Crohn's disease, treatment with ustekinumab resulted in a decrease in inflammatory markers including C-Reactive Protein (CRP) and faecal calprotectin during the induction phase, which were then maintained throughout the maintenance phase. CRP was assessed during the study extension and the reductions observed during maintenance were generally sustained through week 252.

In patients with ulcerative colitis, treatment with ustekinumab resulted in a decrease in inflammatory markers including CRP and faecal calprotectin during the induction phase, which was maintained throughout the maintenance phase and study extension through week 200.

Immunisation
During the long term extension of Psoriasis Study 2 (PHOENIX 2), adult patients treated with ustekinumab for at least 3.5 years mounted similar antibody responses to both pneumococcal polysaccharide and tetanus vaccines as a non-systemically treated psoriasis control group. Similar proportions of adult patients developed protective levels of anti-pneumococcal and anti-tetanus antibodies and antibody titres were similar among ustekinumab-treated and control patients.

Clinical efficacy

Crohn's Disease
The safety and efficacy of ustekinumab was assessed in three randomised, double-blind, placebo-controlled, multicentre studies in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of ≥ 220 and ≤ 450). The clinical development program consisted of two 8-week intravenous induction studies (UNITI-1 and UNITI-2) followed by a 44 week subcutaneous randomised withdrawal maintenance study (IM-UNITI) representing 52 weeks of therapy.

The induction studies included 1409 (UNITI-1, n = 769; UNITI-2 n = 640) patients. The primary endpoint for both induction studies was the proportion of subjects in clinical response (defined as a reduction in CDAI score of ≥ 100 points) at week 6. Efficacy data were collected and analysed through week 8 for both studies. Concomitant doses of

oral corticosteroids, immunomodulators, aminosalicylates and antibiotics were permitted and 75% of patients continued to receive at least one of these medications. In both studies, patients were randomised to receive a single intravenous administration of either the recommended tiered dose of approximately 6 mg/kg (see Table 1, section 4.2), a fixed dose of 130 mg ustekinumab, or placebo at week 0.

Patients in UNITI-1 had failed or were intolerant to prior anti-TNFα therapy. Approximately 48% of the patients had failed 1 prior anti-TNF therapy and 52% had failed 2 or 3 prior anti-TNFα therapies. In this study, 29.1% of the patients had an inadequate initial response (primary non-responders), 69.4% responded but lost response (secondary non-responders), and 36.4% were intolerant to anti-TNFα therapies.

Patients in UNITI-2 had failed at least one conventional therapy, including corticosteroids or immunomodulators, and were either anti-TNF-α naïve (68.6%) or had previously received but not failed anti-TNFα therapy (31.4%).

In both UNITI-1 and UNITI-2, a significantly greater proportion of patients were in clinical response and remission in the ustekinumab treated group compared to placebo (Table 4). Clinical response and remission were significant as early as week 3 in ustekinumab treated patients and continued to improve through week 8. In these induction studies, efficacy was higher and better sustained in the tiered dose group compared to the 130 mg dose group, and tiered dosing is therefore the recommended intravenous induction dose.

Table 4: Induction of Clinical Response and Remission in UNITI-1 and UNITI-2

	UNITI-1*		**UNITI-2****	
	Placebo N = 247	**Recommended dose of ustekinumab N = 249**	**Placebo N = 209**	**Recommended dose of ustekinumab N = 209**
Clinical Remission, week 8	18 (7.3%)	52 (20.9%)[a]	41 (19.6%)	84 (40.2%)[a]
Clinical Response (100 point), week 6	53 (21.5%)	84 (33.7%)[b]	60 (28.7%)	116 (55.5%)[a]
Clinical Response (100 point), week 8	50 (20.2%)	94 (37.8%)[a]	67 (32.1%)	121 (57.9%)[a]
70 Point Response, week 3	67 (27.1%)	101 (40.6%)[b]	66 (31.6%)	106 (50.7%)[a]
70 Point Response, week 6	75 (30.4%)	109 (43.8%)[b]	81 (38.8%)	135 (64.6%)[a]

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission

70 point response is defined as reduction in CDAI score by at least 70 points

* Anti-TNFα failures

** Conventional therapy failures

[a] $p < 0.001$

[b] $p < 0.01$

The maintenance study (IM-UNITI), evaluated 388 patients who achieved 100 point clinical response at week 8 of induction with ustekinumab in studies UNITI-1 and UNITI-2. Patients were randomised to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, 90 mg ustekinumab every 12 weeks or placebo for 44 weeks (for recommended maintenance posology, see section 4.2 of the IMULDOSA solution for injection (vial) and solution for injection in pre-filled syringe SmPC).

Significantly higher proportions of patients maintained clinical remission and response in the ustekinumab treated groups compared to the placebo group at week 44 (see Table 5).

Table 5: Maintenance of Clinical Response and Remission in IM-UNITI (week 44; 52 weeks from initiation of the induction dose)

	Placebo* N = 131†	**90 mg ustekinumab every 8 weeks** N = 128†	**90 mg ustekinumab every 12 weeks** N = 129†
Clinical Remission	36%	53%[a]	49%[b]
Clinical Response	44%	59%[b]	58%[b]
Corticosteroid-Free Clinical Remission	30%	47%[a]	43%[c]
Clinical Remission in patients:			
in remission at the start of maintenance therapy	46% (36/79)	67% (52/78)[a]	56% (44/78)
who entered from study CRD3002‡	44% (31/70)	63% (45/72)[c]	57% (41/72)
who are Anti-TNFα naïve	49% (25/51)	65% (34/52)[c]	57% (30/53)
who entered from study CRD3001§	26% (16/61)	41% (23/56)	39% (22/57)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission

* The placebo group consisted of patients who were in response to ustekinumab and were randomised to receive placebo at the start of maintenance therapy.

† Patients who were in 100 point clinical response to ustekinumab at start of maintenance therapy

‡ Patients who failed conventional therapy but not anti-TNFα therapy

§ Patients who are anti-TNFα refractory/intolerant

[a] $p < 0.01$

[b] $p < 0.05$

[c] nominally significant ($p < 0.05$)

In IM-UNITI, 29 of 129 patients did not maintain response to ustekinumab when treated every 12 weeks and were allowed to dose adjust to receive ustekinumab every 8 weeks. Loss of response was defined as a CDAI score ≥ 220 points and a ≥ 100 point increase from the CDAI score at baseline. In these patients, clinical remission was achieved in 41.4% of patients 16 weeks after dose adjustment.

Patients who were not in clinical response to ustekinumab induction at week 8 of the UNITI-1 and UNITI-2 induction studies (476 patients) entered into the non-randomised portion of the maintenance study (IM-UNITI) and received a 90 mg subcutaneous injection of ustekinumab at that time. Eight weeks later, 50.5% of the patients achieved clinical response and continued to receive maintenance dosing every 8 weeks; among these patients with continued maintenance dosing, a majority maintained response (68.1%) and achieved remission (50.2%) at week 44, at proportions that were similar to the patients who initially responded to ustekinumab induction.

Of 131 patients who responded to ustekinumab induction, and were randomised to the placebo group at the start of the maintenance study, 51 subsequently lost response and received 90 mg ustekinumab subcutaneously every 8 weeks. The majority of patients who lost response and resumed ustekinumab did so within 24 weeks of the induction infusion. Of these 51 patients, 70.6% achieved clinical response and 39.2% percent achieved clinical remission 16 weeks after receiving the first subcutaneous dose of ustekinumab.

In IM-UNITI, patients who completed the study through week 44 were eligible to continue treatment in a study extension. Among the 567 patients who entered on and were treated with ustekinumab in the study extension, clinical remission and response were generally maintained through week 252 for both patients who failed TNF-therapies and those who failed conventional therapies.

No new safety concerns were identified in this study extension with up to 5 years of treatment in patients with Crohn's Disease.

Endoscopy
Endoscopic appearance of the mucosa was evaluated in 252 patients with eligible baseline endoscopic disease activity in a substudy. The primary endpoint was change from baseline in Simplified Endoscopic Disease Severity Score for Crohn's Disease (SES-CD), a composite score across 5 ileo- colonic segments of presence/size of ulcers, proportion of mucosal surface covered by ulcers, proportion of mucosal surface affected by any other lesions and presence/type of narrowing/strictures. At week 8, after a single intravenous induction dose, the change in SES-CD score was greater in the ustekinumab group (n = 155, mean change = -2.8) than in the placebo group (n = 97, mean change = -0.7, p = 0.012).

Fistula Response
In a subgroup of patients with draining fistulas at baseline (8.8%; n = 26), 12/15 (80%) of ustekinumab-treated patients achieved a fistula response over 44 weeks (defined as ≥ 50% reduction from baseline of the induction study in the number of draining fistulas) compared to 5/11 (45.5%) exposed to placebo.

Health-related quality of life
Health-related quality of life was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ) and SF-36 questionnaires. At week 8, patients receiving ustekinumab showed statistically significantly greater and clinically meaningful improvements on IBDQ total score and SF-36 Mental Component Summary Score in both UNITI-1 and UNITI-2, and SF-36 Physical Component Summary Score in UNITI-2, when compared to placebo. These improvements were generally better maintained in ustekinumab-treated patients in the IM-UNITI study through week 44 when compared to placebo.
Improvement in health-related quality of life was generally maintained during the extension through week 252.

Immunogenicity
Antibodies to ustekinumab may develop during ustekinumab treatment and most are neutralising. The formation of anti-ustekinumab antibodies is associated with increased clearance of ustekinumab in patients with Crohn's disease or ulcerative colitis. No reduced efficacy was observed. There is no apparent correlation between the presence of anti-ustekinumab antibodies and the occurrence of injection site reactions.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with ustekinumab in one or more subsets of the paediatric population in Crohn's Disease and ulcerative colitis (see section 4.2 for information on paediatric use).

Paediatric Crohn's disease
The safety and efficacy of ustekinumab was evaluated in 48 paediatric patients weighing at least 40 kg, in an interim analysis of a multicentre phase 3 study (UNITI-Jr) for paediatric patients with moderately to severely active Crohn's disease (defined by a Paediatric Crohn's Disease Activity Index [PCDAI] score >30) through 52 weeks of treatment (8 weeks of induction and 44 weeks of maintenance treatment). Patients included in the study either had not adequately responded to or had not tolerated prior biologic therapy or conventional therapy for Crohn's disease. The study included an

open-label induction treatment with a single ustekinumab intravenous dose, of approximately 6 mg/kg (see section 4.2), followed by a randomised double-blind subcutaneous maintenance regimen of 90 mg ustekinumab administered either every 8 weeks or every 12 weeks.

Efficacy results
The primary endpoint of the study was clinical remission at induction week 8 (defined as PCDAI score ≤ 10). The proportion of patients who achieved clinical remission was 52.1% (25/48) and is comparable to that observed in the adult ustekinumab phase 3 studies.

Clinical response was observed as early as week 3. The proportion of patients in clinical response at week 8 (defined as a reduction from baseline in the PCDAI score of >12.5 points with a total PCDAI score not more than 30) was 93.8% (45/48).

Table 6 presents the analyses for the secondary endpoints through maintenance week 44.

Table 6: Summary of Secondary endpoints through Maintenance week 44

	90 mg ustekinumab every 8 weeks N = 23	**90 mg ustekinumab every 12 weeks N = 25**	**Total number of patients N = 48**
Clinical Remission [*]	43.5% (10/23)	60.0% (15/25)	52.1% (25/48)
Corticosteroid-free Clinical Remission [§]	43.5% (10/23)	60.0% (15/25)	52.1% (25/48)
Clinical remission for patients who were in clinical remission at induction week 8 [*]	64.3% (9/14)	54.5% (6/11)	60.0% (15/25)
Clinical Response [†]	52.2% (12/23)	60.0% (15/25)	56.3% (27/48)
Endoscopic response [£]	22.7% (5/22)	28.0% (7/25)	25.5% (12/47)

[*] Clinical remission is defined as PCDAI score ≤10 points.

[§] Corticosteroid-free remission is defined as PCDAI score of ≤10 points and not receiving corticosteroids for at least 90 days prior to Week M-44.

[†] Clinical response is defined as a reduction from baseline in the PCDAI score of ≥12.5 points with a total PCDAI score not more than 30.

[£] Endoscopic response is defined as a reduction in the SES-CD score of ≥50% or SES-CD score ≤2, in patients with a baseline SES-CD score of ≥3.

Dosing frequency adjustment
Patients who entered the maintenance regimen and experienced loss of response (LOR) based on PCDAI score were eligible for dose adjustment. Patients were either switched from treatment every 12 weeks to every 8 weeks or stayed on treatment every 8 weeks (sham adjustment). 2 patients were dose adjusted to the shorter dosing interval. In these patients, clinical remission was achieved in 100% (2/2) of patients 8 weeks after dose adjustment.

The safety profile of the induction dose regimen and both maintenance dose regimens in the paediatric population weighing at least 40 kg is comparable with that established in the adult Crohn's disease population (see Section 4.8).

Serum and faecal inflammatory biomarkers

The mean change from baseline at maintenance week 44 in C-Reactive protein (CRP) and faecal calprotectin concentrations were -11.17 mg/L (24.159) and -538.2 mg/kg (1271.33), respectively.

Health-related quality of life
The total IMPACT-III scores and all subdomains (bowel symptoms, fatigue-related systemic symptoms, and well-being) demonstrated clinically meaningful improvements after 52 weeks.

5.2 Pharmacokinetic properties

Following the recommended intravenous induction dose, median peak serum ustekinumab concentration, observed 1 hour after the infusion, was 126.1 μg/mL in patients with Crohn's disease and 127.0 μg/mL in patients with ulcerative colitis.

Distribution
Median volume of distribution during the terminal phase (Vz) following a single intravenous administration to patients with psoriasis ranged from 57 to 83 mL/kg.

Biotransformation
The exact metabolic pathway for ustekinumab is unknown.

Elimination
Median systemic clearance (CL) following a single intravenous administration to patients with psoriasis ranged from 1.99 to 2.34 mL/day/kg. Median half-life ($t_{1/2}$) of ustekinumab was approximately 3 weeks in patients with ulcerative colitis, Crohn's disease, psoriasis and/or psoriatic arthritis, ranging from 15 to 32 days across all psoriasis and psoriatic arthritis studies.

Dose linearity
The systemic exposure of ustekinumab (C_{max} and AUC) increased in an approximately dose-proportional manner after a single intravenous administration at doses ranging from 0.09 mg/kg to 4.5 mg/kg.

Special populations
No pharmacokinetic data are available in patients with impaired renal or hepatic function. No specific studies have been conducted with intravenous ustekinumab in elderly or paediatric patients weighing less than 40 kg.

In patients with Crohn's disease and ulcerative colitis, variability in ustekinumab clearance was affected by body weight, serum albumin level, sex, and antibody to ustekinumab status while body weight was the main covariate affecting the volume of distribution. Additionally in Crohn's disease, clearance was affected by C-reactive protein, TNF antagonist failure status and race (Asian versus non-Asian). The impact of these covariates was within ±20% of the typical or reference value of the respective PK parameter, thus dose adjustment is not warranted for these covariates. Concomitant use of immunomodulators did not have a significant impact on ustekinumab disposition.

Regulation of CYP450 enzymes
The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro* study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4; see section 4.5).

A phase 1, open-label, drug interaction study, Study CNTO1275CRD1003, was conducted to evaluate the effect of ustekinumab on cytochrome P450 enzyme activities following induction and maintenance dosing in patients with active Crohn's disease (n=18). No clinically significant changes in exposure of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), or midazolam (CYP3A substrate) were observed when used concomitantly with ustekinumab at the approved recommended dosing in patients with Crohn's disease (see section 4.5).

Paediatric population

Serum ustekinumab concentrations in paediatric Crohn's disease patients weighing at least 40 kg, treated with the recommended weight-based dose were generally comparable to those in the adult Crohn's disease population treated with the adult weight-based dose.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard (e.g. organ toxicity) for humans based on studies of repeated-dose toxicity and developmental and reproductive toxicity, including safety pharmacology evaluations. In developmental and reproductive toxicity studies in cynomolgus monkeys, neither adverse effects on male fertility indices nor birth defects or developmental toxicity were observed. No adverse effects on female fertility indices were observed using an analogous antibody to IL-12/23 in mice.

Dose levels in animal studies were up to approximately 45-fold higher than the highest equivalent dose intended to be administered to psoriasis patients and resulted in peak serum concentrations in monkeys that were more than 100-fold higher than observed in humans.

Carcinogenicity studies were not performed with ustekinumab due to the lack of appropriate models for an antibody with no cross-reactivity to rodent IL-12/23 p40.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

EDTA disodium salt dihydrate L-histidine

L-histidine hydrochloride monohydrate

L-methionine

Polysorbate 80 Sucrose

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. IMULDOSA should only be diluted with sodium chloride 9 mg/mL (0.9%) solution.

IMULDOSA should not be administered concomitantly in the same intravenous line with other medicinal products.

6.3 Shelf life

3 years.

Do not freeze.

Chemical and physical in-use stability has been demonstrated for 8 hours at 15-25°C.

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

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.

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

6.5 Nature and contents of container

26 mL solution in a type I glass 30 mL vial closed with a coated butyl rubber stopper. IMULDOSA is available in a 1 vial pack.

6.6 Special precautions for disposal

The solution in the IMULDOSA vial should not be shaken. The solution should be visually inspected for particulate matter or discolouration prior to administration. The solution is colourless to slightly yellow and clear to slightly opalescent. The

medicinal product should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present.

Dilution

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

1. Calculate the dose and the number of IMULDOSA vials needed based on patient weight (see section 4.2, Table 1). Each 26 mL vial of IMULDOSA contains 130 mg of ustekinumab. Only use complete vials of IMULDOSA.
2. Withdraw and discard a volume of the sodium chloride 9 mg/mL (0.9%) solution from the 250 mL infusion bag equal to the volume of IMULDOSA to be added. (Discard 26 mL sodium chloride for each vial of IMULDOSA needed, for 2 vials-discard 52 mL, for 3 vials- discard 78 mL, for 4 vials-discard 104 mL.)
3. Withdraw 26 mL of IMULDOSA from each vial needed and add it to the 250 mL infusion bag. The final volume in the infusion bag should be 250 mL. Gently mix.
4. Visually inspect the diluted solution before administration. Do not use if visibly opaque particles, discolouration or foreign particles are observed.
5. Administer the diluted solution over a period of at least one hour. Once diluted, the infusion should be completed within eight hours of the dilution in the infusion bag.
6. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.2 micrometre).
7. Each vial is for single use only and any unused medicinal product should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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