EU Risk Management Plan for Hukyndra (adalimumab)

RMP version to be assessed as part of this application:

RMP Version number:	2.0
Data lock point for this RMP:	15 May 2024
Date of final sign-off:	22 May 2024
Rationale for submitting an updated RMP:	Line extension to include the following presentations: 20 mg solution for injection in pre-filled syringe (20 SD).
Summary of significant changes in this RMP:	Part I: Product overview has been updated to include the new presentation of Hukyndra. Alignment to innovator's latest published RMP: deletion of "Patients with Immune Compromised Conditions" from missing information; alignment to innovator's RMP Part VI (public summary)
Other RMP versions under evaluation:	Not applicable
Details of the currently approved RMP:	Version number: 0.3 (1.0) Approved with procedure: EMEA/H/C/005548 Date of approval (opinion date): 15/November/2021
QPPV name:	Dr. Andreas Iwanowitsch
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Adalimumab.
Pharmacotherapeutic group(s) (ATC Code)	Pharmacotherapeutic group: Immunosuppressants — Tumour Necrosis Factor alpha (TNF-α) inhibitors. ATC code: L04AB04.
Marketing Authorisation Holder	STADA Arzneimittel AG
Medicinal products to which this RMP refers	2.
Invented name(s) in the European Economic Area (EEA)	Hukyndra.
Marketing authorisation procedure	Centralised procedure.
Brief description of the product	Chemical class Immunosuppressants — Tumour Necrosis Factor alpha (TNF-α) inhibitors.
	Summary of mode of action Adalimumab binds specifically to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of 0.1-0.2 nM).
	Important information about its composition Adalimumab is a recombinant human monoclonal antibody produced in Chinese Hamster Ovary cells.
Hyperlink to the Product Information	Please refer to Module 1.3.1.

Indication(s) in the EEA	Current: **Hukyndra 40 mg solution for injection in pre-filled syringe, Hukyndra 40 mg solution for injection in pre-filled pen:** Rheumatoid arthritis (RA) Hukyndra in combination with methotrexate, is indicated for: • The treatment of moderate to severe, active RA in adult patients when the response to disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate has been inadequate. • The treatment of severe, active and progressive RA in adults not previously treated with methotrexate. Hukyndra can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Juvenile idiopathic arthritis (JIA) • Polyarticular JIA: Hukyndra in combination with methotrexate is indicated for the treatment of active polyarticular JIA, in patients from the age of 2 years who have had an inadequate response to one or more DMARD. Hukyndra can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. • Enthesitis-related arthritis: Hukyndra is indicated for the treatment of active enthesitis-related arthritis in patients, ≥6 years of age, who have had an inadequate response to, or who are intolerant of, conventional therapy. Axial spondyloarthritis • Ankylosing spondylitis: Hukyndra is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy. • Axial spondyloarthritis without radiographic evidence of ankylosing spondylitis: Hukyndra is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs. Psoriatic arthritis

	Hukyndra is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate. Psoriasis (Ps) Hukyndra is indicated for the treatment of moderate to severe chronic plaque Ps in adult patients who are candidates for systemic therapy. Paediatric plaque Ps Hukyndra is indicated for the treatment of severe chronic plaque Ps in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies. Hidradenitis suppurativa Hukyndra is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic hidradenitis suppurativa therapy. Crohn's disease (CD) Hukyndra is indicated for treatment of moderately to severely active CD, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. Paediatric CD Hukyndra is indicated for the treatment of moderately to severely active CD in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies. Ulcerative colitis (UC) Hukyndra is indicated for treatment of moderately to severely active UC in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies. Paediatric UC Hukyndra is indicated for the treatment of moderately to severely active ulcerative colitis in paediatric patients (from 6 years of age)

	who have had an inadequate response to conventional therapy including corticosteroids and/or 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies. Uveitis Hukyndra is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate. Paediatric uveitis Hukyndra is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.
	Proposed: **Hukyndra 20 mg solution for injection in pre-filled syringe:** Juvenile idiopathic arthritis *Polyarticular juvenile idiopathic arthritis* Hukyndra in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Hukyndra can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Adalimumab has not been studied in patients aged less than 2 years. *Enthesitis-related arthritis* Hukyndra is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy. Paediatric plaque psoriasis Hukyndra is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

	Paediatric Crohn's disease Hukyndra is indicated for the treatment of moderately to severely active Crohn's disease in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or an immunomodulator, or who are intolerant to or have contraindications for such therapies. Paediatric Uveitis Hukyndra is indicated for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.
Dosage in the EEA	Current: **Hukyndra 40 mg solution for injection in pre-filled syringe, Hukyndra 40 mg solution for injection in pre-filled pen:** **Adults:** RA The recommended dose of Hukyndra for adult patients with RA is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection. Methotrexate should be continued during treatment with Hukyndra. In monotherapy, some patients who experience a decrease in their response to Hukyndra 40 mg every other week may benefit from an increase in dose to 40 mg adalimumab every week or 80 mg every other week. Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be reconsidered in a patient not responding within this time period. Ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis and psoriatic arthritis The recommended dose of Hukyndra for patients with ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis and for patients with psoriatic arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection. Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should

	be reconsidered in a patient not responding within this time period. Ps The recommended dose of Hukyndra for adult patients is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week starting one week after the initial dose. Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period. Beyond 16 weeks, patients with inadequate response to Hukyndra 40 mg every other week may benefit from an increase in dose to 40 mg every week or 80 mg every other week. The benefits and risks of continued 40 mg weekly or 80 mg every other week therapy should be carefully reconsidered in a patient with an inadequate response after the increase in dose. If adequate response is achieved with 40 mg every week or 80 mg every other week, the dose may subsequently be reduced to 40 mg every other week. Hidradenitis suppurativa The recommended Hukyndra dose regimen for adult patients with hidradenitis suppurativa is 160 mg initially at Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later at Day 15 (given as two 40 mg injections in one day). Two weeks later (Day 29) continue with a dose of 40 mg every week or 80 mg every other week (given as two 40 mg injections in one day). Antibiotics may be continued during treatment with Hukyndra if necessary. It is recommended that the patient should use a topical antiseptic wash on their hidradenitis suppurativa lesions on a daily basis during treatment with Hukyndra. Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period. Should treatment be interrupted, Hukyndra 40 mg every week or 80 mg every other week may be re-introduced. The benefit and risk of continued long-term treatment should be periodically evaluated. CD The recommended Hukyndra induction dose regimen for adult patients with moderately to severely active CD is 80 mg at Week 0 followed by 40 mg at Week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at Week 0 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg at Week 2

	(given as two 40 mg injections in one day), can be used with the awareness that the risk for adverse events (Aes) is higher during induction. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Alternatively, if a patient has stopped Hukyndra and signs and symptoms of disease recur, Hukyndra may be re-administered. There is little experience from re-administration after more than 8 weeks since the previous dose. During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines. Some patients who experience decrease in their response to Hukyndra 40 mg every other week may benefit from an increase in dose to 40 mg Hukyndra every week or 80 mg every other week. Some patients who have not responded by Week 4 may benefit from continued maintenance therapy through Week 12. Continued therapy should be carefully reconsidered in a patient not responding within this time period. <u>UC</u> The recommended Hukyndra induction dose regimen for adult patients with moderate to severe UC is 160 mg at Week 0 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days) and 80 mg at Week 2 (given as two 40 mg injections in one day). After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines. Some patients who experience decrease in their response to 40 mg every other week may benefit from an increase in dose to 40 mg Hukyndra every week or 80 mg every other week. Available data suggest that clinical response is usually achieved within 2-8 weeks of treatment. Hukyndra therapy should not be continued in patients failing to respond within this time period. <u>Uveitis</u> The recommended dose of Hukyndra for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. There is limited experience in the initiation of treatment with adalimumab alone. Treatment with Hukyndra can be initiated in combination with corticosteroids and/or with other non-biologic immunomodulatory agents. Concomitant corticosteroids may be

	tapered in accordance with clinical practice starting two weeks after initiating treatment with Hukyndra. It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis. **Paediatric population:** <u>JIA</u> • Polyarticular JIA from 2 years of age: the recommended dose of Hukyndra for patients with polyarticular JIA from 2 years of age is based on body weight. Hukyndra is administered every other week via subcutaneous injection. Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period. • Enthesitis-related arthritis: the recommended dose of Hukyndra for patients with enthesitis-related arthritis from 6 years of age is based on body weight. Hukyndra is administered every other week via subcutaneous injection. <u>Paediatric plaque Ps</u> The recommended Hukyndra dose for patients with plaque Ps from 4 to 17 years of age is based on body weight. Hukyndra is administered via subcutaneous injection. Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this time period. The safety of adalimumab in paediatric patients with plaque Ps has been assessed for a mean of 13 months. <u>Adolescent hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)</u> The recommended Hukyndra dose is 80 mg at Week 0 followed by 40 mg every other week starting at Week 1 via subcutaneous injection. In adolescent patients with inadequate response to Hukyndra 40 mg every other week, an increase in dose to 40 mg every week or 80 mg every other week may be considered. Antibiotics may be continued during treatment with Hukyndra if necessary. It is recommended that the patient should use a topical antiseptic wash on their hidradenitis suppurativa lesions on a daily basis during treatment with Hukyndra. Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period. Should treatment be interrupted, Hukyndra may be re-introduced as appropriate.

	The benefit and risk of continued long-term treatment should be periodically evaluated. Paediatric CD The recommended dose of Hukyndra for patients with CD from 6 to 17 years of age is based on body weight. Hukyndra is administered via subcutaneous injection. Patients who experience insufficient response may benefit from an increase in dose: • <40 kg: 20 mg every week. • ≥40 kg: 40 mg every week or 80 mg every other week. Continued therapy should be carefully considered in a subject not responding by Week 12. Paediatric UC The recommended dose of Hukyndra for patients from 6 to 17 years of age with ulcerative colitis is based on body weight. Hukyndra is administered via subcutaneous injection: Patient weight Induction dose Maintenance dose starting at Week 4* < 40 kg • 80 mg at Week 0 (given as two 40 mg injections in one day) and • 40 mg at Week 2 (given as one 40 mg injection) • 40 mg every other week ≥ 40 kg • 160 mg at Week 0 (given as four 40 mg injections in one day or two 40 mg injections per day for two consecutive days) and • 80 mg at Week 2 (given as two 40 mg injections in one day) • 80 mg every other week Continued therapy beyond 8 weeks should be carefully considered in patients not showing signs of response within this time period. There is no relevant use of Hukyndra in children aged less than 6 years in this indication. Hukyndra may be available in different strengths and/or presentations depending on the individual treatment needs.

	Paediatric uveitis The recommended dose of Hukyndra for paediatric patients with uveitis from 2 years of age is based on body weight. Hukyndra is administered via subcutaneous injection. In paediatric uveitis, there is no experience in the treatment with adalimumab without concomitant treatment with methotrexate. When Hukyndra therapy is initiated, a loading dose of 40 mg for patients <30 kg or 80 mg for patients ≥30 kg may be administered one week prior to the start of maintenance therapy. No clinical data are available on the use of an adalimumab loading dose in children <6 years of age. It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis.
	Proposed: **Hukyndra 20 mg solution for injection in pre-filled syringe:** Paediatric population *Juvenile idiopathic arthritis* *Polyarticular juvenile idiopathic arthritis from 2 years of age* The recommended dose of Hukyndra for patients with polyarticular juvenile idiopathic arthritis from 2 years of age is based on body weight. Hukyndra is administered every other week via subcutaneous injection. Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period. *Enthesitis-related arthritis* The recommended dose of Hukyndra for patients with enthesitis-related arthritis from 6 years of age is based on body weight. Hukyndra is administered every other week via subcutaneous injection. *Paediatric plaque psoriasis* The recommended Hukyndra dose for patients with plaque psoriasis from 4 to 17 years of age is based on body weight. Hukyndra is administered via subcutaneous injection. Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this time period.

	If retreatment with adalimumab is indicated, the above guidance on dose and treatment duration should be followed. The safety of adalimumab in paediatric patients with plaque psoriasis has been assessed for a mean of 13 months. *Paediatric Crohn's disease* The recommended dose of Hukyndra for patients with Crohn's disease from 6 to 17 years of age is based on body weight. Hukyndra is administered via subcutaneous injection. Patients who experience insufficient response may benefit from an increase in dose: • < 40 kg: 20 mg every week • ⩾ 40 kg: 40 mg every week or 80 mg every other week Continued therapy should be carefully considered in a subject not responding by week 12. There is no relevant use of adalimumab in children aged less than 6 years for this indication. *Paediatric Uveitis* The recommended dose of Hukyndra for paediatric patients with uveitis from 2 years of age is based on body weight. Hukyndra is administered via subcutaneous injection. In paediatric uveitis, there is no experience in the treatment with adalimumab without concomitant treatment with methotrexate. When Hukyndra therapy is initiated, a loading dose of 40 mg for patients < 30 kg or 80 mg for patients ⩾ 30 kg may be administered one week prior to the start of maintenance therapy. No clinical data are available on the use of an adalimumab loading dose in children < 6 years of age.
Pharmaceutical form(s) and strengths	Current: • 40 mg solution for injection in pre-filled syringe: each 0.4 ml single dose pre-filled syringe contains 40 mg adalimumab. • 40 mg solution for injection in pre-filled pen: each 0.4 ml single dose pre-filled pen contains 40 mg adalimumab.
	Proposed: • 20 mg solution for injection in pre-filled syringe: each 0.2 ml single dose pre-filled syringe contains 20 mg of adalimumab.

Is/will the product be subject to additional monitoring in the EU?	Yes.

Part II: Safety specification

Part II: Module SI — Epidemiology of the indication(s) and target population(s)

Not applicable. Omitted module for biosimilar products.

Part II: Module SII — Non-clinical part of the safety specification

Hukyndra (adalimumab) has been developed as a proposed biosimilar to US-licensed Humira and to EU-approved Humira (the originator). The non-clinical development program for Hukyndra has been designed in accordance with the current regulatory requirements for the non-clinical development of biosimilar monoclonal antibodies:

- Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues [EMA/CHMP/BMWP/403543/2010].
- Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product [FDA Guidance for Industry, 2016].

Physicochemical and functional pharmacological data generally indicated similarity among multiple batches of Hukyndra and EU-authorised and US-licensed Humira. No animal *in vivo* studies evaluating efficacy, toxicity, pharmacology or drug interactions of Hukyndra were neither deemed necessary nor requested by the agencies European Medicines Agency (EMA) and United States Food Drug Administration (FDA) in the scientific advice meetings to support the clinical studies [EMA, 2018]. Although no regulatory requirement per se, an exploratory an exploratory study was conducted comparing the pharmacokinetics and injection site reactions of two batches of Hukyndra versus EU-Humira in Cynomolgus monkeys [AVT02-PC-001].

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity

- Key issues identified from acute or repeat-dose toxicity studies

  No single-dose toxicity study and no repeat-dose toxicity study have been conducted with Hukyndra. Non-clinical data obtained during the development of the originator revealed no special hazard for humans based on single- and repeat-dose toxicity studies [SmPC Humira 80 mg/0.8 mL].

- Reproductive/developmental toxicity

  No reproductive and developmental toxicity study has been conducted with Hukyndra. Based on a large amount of published data, it is evident that TNFα is involved in embryonic development. Thus, inhibition of TNFα may affect the development of the embryo and/or foetus, and the risk of use of adalimumab in pregnant women is unknown.

  Generally, fertility studies are performed in rodents. However, neither the rat nor the mouse was considered to be a relevant model for human safety assessment. Long-term animal studies with Humira have not been conducted to evaluate its effect on fertility [Prescribing Information Humira, 2002].

  Cynomolgus monkeys were chosen as a model for developmental and prenatal toxicity testing during the development of the originator. This embryo-foetal developmental toxicity/perinatal developmental study in Cynomolgus monkeys at 0, 30 and 100 mg/kg (9-17 monkeys/group) revealed no evidence of harm to the foetuses due to adalimumab [SmPC Humira 80 mg/0.8 mL].

  In summary, the animal studies revealed no foetal harm or malformations with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose [Drugs.com, 2019].

However, these data are not sufficient to support the safe use of adalimumab in pregnant women.

- Genotoxicity

  No genotoxicity studies have been conducted with Hukyndra. Non-clinical data obtained during the development of the originator revealed no special hazard for humans based on genotoxicity studies [SmPC Humira 80 mg/0.8 mL].

  Generally, the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed. It is not expected that these substances would interact directly with DNA or other chromosomal material. Furthermore, the use of standard genotoxicity studies for assessing the genotoxic potential of process contaminants is not considered appropriate as mentioned in the ICH guideline S6 (R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

- Carcinogenicity

  No carcinogenicity studies have been conducted with Hukyndra. Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals as per ICH guideline S6 (R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

  No carcinogenicity studies with the originator have been conducted to evaluate the carcinogenic potential due to the lack of appropriate models for an antibody with limited cross-reactivity to rodent TNF and to the development of neutralising antibodies in rodents [Prescribing Information Humira, 2002; SmPC Humira 80 mg/0.8 mL].

Other toxicity-related information or data

- Local tolerance

  No formal local tolerance study has been conducted with Hukyndra.

  Local tolerability was investigated in one exploratory non-clinical *in vivo* study in Cynomolgus monkeys. The study compared two Hukyndra batches versus EU-Humira by a subcutaneous single dose. Six animals were included in each treatment group. All animals appeared healthy prior to dosing and throughout the duration of the study. The few reported observations included non-formed/liquid faeces, mucoid faeces, discoloured faeces, orange discoloured skin, scab on left shoulder, prolapsed rectum and body weight loss. However, any reported body weight losses were minor and were considered unlikely to be related to ATV02 administration. For each treatment group, the mean body weight generally remained stable throughout the study. Five injection site observations were detected in 3 of the 18 treated animals and 2 of the animals belonged to the control group treated with reference product EU Humira. They comprised 4 cases of very slight erythema (barely perceptible) and one case of very slight oedema (barely perceptible). Thus, the local tolerability of a single subcutaneous administration of ATV02 to the mid-scapular region of Cynomolgus monkeys was good [AVT02-PC-001].

- Immunogenicity

  An immune response by an organism against a therapeutic antigen such as a monoclonal antibody might lead to production of anti-drug antibodies interfering with or inactivating the therapeutic effects of the treatment and, in rare cases, inducing adverse effects [De Groot, 2007]. A challenge in biotherapy is predicting the immunogenic potential of novel protein therapeutics [Baker, 2010].

In general, an immune response to human or humanised proteins is expected to be greater in animals than in humans due to species differences in protein structure and the perceived foreignness of the drug construct in the animal model. As a result, animal models tend to have low predictive value and often over-estimate biopharmaceutical immunogenicity rates and the incidence of adverse immune-mediated events in the human subjects [Ponce, 2009], which is also taken into account in the regulatory guidelines. Thus, the EMA Guideline on similar biological products containing monoclonal antibodies [EMA/CHMP/BMWP/403543/2010] and the EMA Guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use [EMA/CHMP/BMWP/86289/2010] highlights that immunogenicity assessment in animals is generally not predictive for immunogenicity in humans.

Nevertheless, immunogenicity data derived from non-clinical studies have important utility. Specifically, data from anti-drug antibody evaluations in animal studies are crucial for their adequate interpretation, especially when alterations in drug pharmacokinetics or pharmacodynamic parameters are observed [Ponce, 2009].

No information on the development of anti-drug antibodies to Hukyndra has been gained in the non-clinical study in Cynomolgus monkeys [AVT02-PC-001], as immunogenicity assessment in animals is generally not predictive for immunogenicity in humans [EMA/CHMP/BMWP/403543/2010].

Part II: Module SIII — Clinical trial exposure

An abbreviated clinical program is proposed in accordance with EMA biosimilar guidance's (Guideline on similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues [EMA/CHMP/BMWP/403543/2010]). Four (4) clinical studies have been conducted (2 completed and 2 ongoing):

- Two phase I clinical trials: one of these studies is aimed to compare the pharmacokinetics, safety and tolerability of Hukyndra versus the originator (EU-approved and US-licensed Humira). The second study is aimed to compare the pharmacokinetics, safety and tolerability of Hukyndra administered subcutaneously via prefilled syringe or autoinjector.
- Two phase III clinical trials: one of these studies is aimed to compare the efficacy, safety, and Immunogenicity of Hukyndra versus Humira in patients with moderate-to-severe chronic plaque psoriasis (Ps). The second study is aimed to assess the real-life patient handling experience of Hukyndra administered subcutaneously with an autoinjector in patients with moderate to severe active rheumatoid arthritis (RA).

Table SIII.1: Estimated cumulative subject exposure from clinical trials

Treatment	Number of subjects
Hukyndra	649
EU-approved and US-licensed Humira	467
Total	**1,116**
Total	**649**

Table SIII.2: Cumulative subject exposure to Hukyndra from clinical trials by age

Age range	Number of subjects
<18 years	0
18-64 years	623
≥65 years	26
Total	**649**

Table SIII.3: Cumulative subject exposure to Hukyndra from clinical trials by sex

Sex	Number of subjects
Male	284
Female	365
Total	**649**

Table SIII.4: Cumulative subject exposure to Hukyndra from clinical trials by race

Sex	Number of subjects
Asian	52
Black or African American	2
Caucasian/White	538
Native Hawaiian or other Pacific Islander	9
Multiple	14
Other	34
Total	**649**

Part II: Module SIV — Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Chronic and/or recurrent infections

Reason for exclusion: Criterion to avoid a potential safety bias.

Is it considered to be included as missing information?: No.

Rationale: Comprehensive wording concerning infections (including chronic infections) is currently in section 4.4 “Special warnings and precautions for use” of the summary of product characteristics (SmPC).

History of demyelinating disease or neurologic symptoms suggestive of demyelinating disease

Reason for exclusion: Adalimumab use in patients with a history of or symptoms and/or diagnostic findings suggestive of demyelinating disease is not recommended due to the known association of anti-TNF agents with demyelinating disorders.

Is it considered to be included as missing information?: No.

Rationale: Demyelination is currently addressed in section 4.4 “Special warnings and precautions for use” of the SmPC. Further information for the uveitis specific patient population is also included in section 4.4.

History of human immunodeficiency virus (HIV) or HIV positive test

Reason for exclusion: In patients with HIV, which results in an immunocompromised state, is not recommended.

Is it considered to be included as missing information?: Yes.

Rationale: Not applicable.

Hepatitis B (HB): HBs antigen positive (+) or detected sensitivity on the Hepatitis B virus DNA PCR qualitative test for HBc Ab/HBs ab positive subjects

Reason for exclusion: Reactivation of hepatitis B has occurred in patients receiving TNF-antagonists.

Is it considered to be included as missing information?: No.

Rationale: Reactivation of hepatitis B is currently addressed in section 4.4 “Special warnings and precautions for use” of the SmPC.

Evidence of history of malignancy increasing the subject’s risks, or that would interfere with the study evaluation, procedures, or study completion

Reason for exclusion: Patients with a history of malignancy, though treated, may have an elevated risk of recurrence. These patients have not been studied on adalimumab and, therefore, there is no information for guidance.

Is it considered to be included as missing information?: No.

Rationale: Comprehensive wording concerning malignancy is currently in section 4.4 “Special warnings and precautions for use” of the SmPC.

Women who are pregnant, nursing, or who plan to become pregnant

Reason for exclusion: Pregnant women are rarely enrolled in a clinical trial unless a product is specifically indicated for a pregnancy-related indication.

Is it considered to be included as missing information?: No.

Rationale: Comprehensive wording concerning use in pregnancy and lactation is currently in section 4.6 “Fertility, pregnancy and lactation” of the SmPC.

History of clinically significant drug or alcohol abuse

Reason for exclusion: Criterion to avoid a potential safety bias.

Is it considered to be included as missing information?: Yes.

Rationale: Not applicable.

Known hypersensitivity to adalimumab or its excipients

Reason for exclusion: Patients with known hypersensitivity to adalimumab or excipients should not use.

Is it considered to be included as missing information?: No.

Rationale: Use in this population is contraindicated in section 4.3 “Contraindications” of the SmPC.

Active tuberculosis (TB) or other severe infections

Reason for exclusion: To avoid any possible impact by adalimumab, in relationship with its immunosuppressant effect, on the treatment of a current or recent infection.

Is it considered to be included as missing information?: No.

Rationale: Use in this population is contraindicated in section 4.3 “Contraindications” of the SmPC.

History of congestive heart failure

Reason for exclusion: Therapy with adalimumab for patients with congestive heart failure is not recommended based on studies performed in patients with congestive heart failure and other TNF inhibitors, which showed an increase in the risk for worsening of congestive heart failure.

Is it considered to be included as missing information?: No.

Rationale: Use in this population (moderate to severe heart failure) is contraindicated in section 4.3 “Contraindications” of the SmPC.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Asian: 52 Black or African American: 2 Caucasian/White: 52 Native Hawaiian or other Pacific Islander: 9 Multiple: 14 Other: 34
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program

Part II: Module SV — Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable since the product is not commercialised.

Part II: Module SVI — Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Adalimumab is not structurally or pharmacologically related to any drug known to cause abuse or dependence, and it is not expected to have a potential for misuse as a recreational drug.

Part II: Module SVII — Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not all adverse reactions are necessarily considered a risk for the medicinal product in a given therapeutic context and not all risks qualify as important to be included in the list of safety concerns for the purpose of risk management planning.

The information available for adalimumab has been analysed and those risks not considered important for inclusion in the list of safety concerns in the RMP (along with the reason of not inclusion) are detailed below:

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Eye disorders: Blepharitis, Conjunctivitis, Eye swelling.
- Gastrointestinal disorders: Abdominal pain, Nausea and vomiting.
- General disorders and administration site conditions: Injection site reaction (including injection site erythema).
- Nervous system disorders: Headache, Migraine.
- Psychiatric disorders: Anxiety, Insomnia, Mood alterations (including depression).
- Respiratory, thoracic and mediastinal disorders: Asthma, Cough.
- Skin and subcutaneous tissue disorders: Alopecia, Dermatitis (including eczema), Hyperhidrosis, Onychoclasis, Pruritus, Rash (including exfoliative rash), Urticaria.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- Blood and the lymphatic system disorders: Idiopathic thrombocytopenic purpura, Pancytopenia.
- Cardiac disorders: Arrhythmia, Cardiac arrest.
- Ear and labyrinth disorders: Deafness, Tinnitus.
- Eye disorders: Diplopia.
- Gastrointestinal disorders: Dysphagia, Face oedema.
- General disorders and administration site conditions: Inflammation.
- Hepatobiliary disorders: Bilirubin increased, Cholecystitis and cholelithiasis.
- Musculoskeletal and connective tissue disorders: Rhabdomyolysis, Systemic lupus erythematosus.
- Nervous system disorders: Neuropathy, Tremor.
- Renal and urinary disorders: Nocturia.

- Reproductive system and breast disorders: Erectile dysfunction.
- Respiratory, thoracic and mediastinal disorders: Chronic obstructive pulmonary disease, Pleural effusion, Pneumonitis, Pulmonary embolism, Pulmonary fibrosis.
- Skin and subcutaneous tissue disorders: Angioedema, Night sweats, Scar.
- Vascular disorders: Aortic aneurysm, Thrombophlebitis, Vascular arterial occlusion.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Blood and the lymphatic system disorders: Anaemia, Leucocytosis, Leukopenia (including neutropenia and agranulocytosis), Thrombocytopenia.
- Cardiac disorders: Congestive heart failure, Myocardial infarction, Tachycardia.
- Eye disorders: Visual impairment.
- Ear and labyrinth disorders: Vertigo.
- Gastrointestinal disorders: Dyspepsia, Gastrointestinal haemorrhage, Gastroesophageal reflux disease, Intestinal perforation, Sicca syndrome, Pancreatitis.
- General disorders and administration site conditions: Chest pain, Oedema, Pyrexia.
- Hepatobiliary disorders: Autoimmune hepatitis, Elevated liver enzymes, Hepatic steatosis, Hepatitis, Liver failure, Reactivation of hepatitis B.
- Immune system disorder: Allergies (including seasonal allergy), Anaphylaxis, Hypersensitivity, Sarcoidosis, Vasculitis.
- Investigations: Autoantibody test positive (including double stranded DNA antibody), Blood lactate dehydrogenase increased, Coagulation and bleeding disorders (including activated partial thromboplastin time prolonged), Impaired healing.
- Metabolism and nutrition disorders: Blood sodium abnormal, Dehydration, Hyperglycaemia, Hypocalcaemia, Hypokalaemia, Hypophosphataemia, Lipids increased, Uric acid increased.
- Musculoskeletal and connective tissue disorders: Lupus-like syndrome, Muscle spasms (including blood creatine phosphokinase increased), Musculoskeletal pain.
- Nervous system disorders: Cerebrovascular accident, Nerve root compression, Paraesthesias (including hypoesthesia).
- Renal and urinary disorders: Haematuria, Renal impairment.
- Respiratory, thoracic and mediastinal disorders: Dyspnoea, Interstitial lung disease.
- Skin and subcutaneous tissue disorders: Bruising (including purpura), Cutaneous vasculitis, Erythema multiforme, Worsening or new onset of psoriasis (including palmoplantar pustular psoriasis), Stevens-Johnson syndrome.
- Vascular disorders: Flushing, Haematoma, Hypertension.

Known risks that do not impact the risk-benefit profile:

- Lichenoid skin reaction.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk 1: Serious infections

As anti-tumour necrosis factor alpha (TNF-α) may alter T-cell mediated immunity some impact on host defence against infections might be expected.

Risk-benefit impact:

Considering the safety measures described in the SmPC and the patient reminder card, it is expected that the risk-benefit balance of the product will be favourable.

Important Identified Risk 2: Tuberculosis (TB)

As anti-TNFs may alter T-cell mediated immunity some impact on host defence against infections including TB might be expected.

Risk-benefit impact:

Considering the safety measures described in the SmPC and the patient reminder card, it is expected that the risk-benefit balance of the product will be favourable.

Important Identified Risk 3: Malignancies

As anti-TNFs may alter T-cell mediated immunity there may be influence on the occurrence of malignancy, but the mechanism is unknown.

Risk-benefit impact:

Considering the safety measures described in the SmPC and the patient reminder card, it is expected that the risk-benefit balance of the product will be favourable.

Important Identified Risk 4: Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis)

The mechanisms by which anti TNFs may induce demyelination remain to be clearly established.

Risk-benefit impact:

Considering the safety measures described in the SmPC and the patient reminder card, it is expected that the risk-benefit balance of the product will be favourable.

Important Identified Risk 5: Bacillus Calmette–Guérin (BCG) disease following live BCG vaccination in infants with *in utero* exposure to adalimumab

As requested by the EMA to the originator per the Type II variation (EMENH/C/000481/11/0170).

Risk-benefit impact:

Considering the safety measures described in the SmPC and the patient reminder card, it is expected that the risk-benefit balance of the product will be favourable.

Important Potential Risk 1: Progressive multifocal leukoencephalopathy (PML)

PML is a rare disorder that damages the material (myelin) that covers and protects nerves in the brain. The potential mechanism for PML is reactivation of polyomavirus John Cunningham (JC) in the brain that is believed to be started by severe immunosuppression as in HIV infection. There is no known association of PML with the use of adalimumab or other TNF inhibitors, however,

because PML is rare and often fatal its appearance in patients on biologic medications including adalimumab is under observation.

Risk-benefit impact:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Important Potential Risk 2: Reversible posterior leukoencephalopathy syndrome (RPLS)

RPLS is a syndrome characterised by headache, confusion, seizures and visual loss. This syndrome appears in patients who become severely immunosuppressed by drugs like those used for anti-rejection. Stopping the drug(s) makes the condition reverse. There is no known association of this event with adalimumab use; however, rare RPLS post-marketing reports in patients using adalimumab have been received and although most have other causes, the reports are under observation for a possible association.

Risk-benefit impact:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Important Potential Risk 3: Adenocarcinoma of colon in ulcerative colitis (UC) patients

There is a known increased risk of adenocarcinoma of colon in UC patients that increases with amount of bowel inflammation as well as the length of time a patient has the disease. Since early detection can limit the bad outcomes from adenocarcinoma of colon, patients with UC, regardless of the therapy used, should receive routine adenocarcinoma of colon screening (colonoscopy) more frequently than that recommended for the general population according to current practice guidelines. Since there may be an increased risk of cancer in patients receiving adalimumab, it is not known if this therapy increases the risk of adenocarcinoma of colon even more in UC patients, thus, the reports of this cancer are under observation in this patient group.

Risk-benefit impact:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Missing information 1: Patients with Immune Compromised conditions

Insufficient data on efficacy and safety are available for this population group.

Risk-benefit impact

Since there is scarce experience with the use of adalimumab in patients with immune compromised conditions, this population needs to be further studied.

Missing information 2: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD

Insufficient data on long-term safety are available for this population group.

Risk-benefit impact:

Since there is scarce experience with the use of adalimumab in long-term use in the treatment of children aged from 6 years to less than 18 years with CD, this use needs to be further studied.

Missing information 3: Episodic treatment in Ps, UC, and juvenile idiopathic arthritis (JIA)

Insufficient data on efficacy and safety are available for this population group.

Risk-benefit impact:

Since there is scarce experience with the use of adalimumab in Episodic treatment in Ps, UC and JIA, this use needs to be further studied.

Missing information 4: Long-term safety information in the treatment of children with uveitis

Insufficient data on long-term safety are available for this population group.

Risk-benefit impact:

Since there is scarce experience with the use of adalimumab in long-term use in the treatment of children with uveitis, this use needs to be further studied.

Missing information 5: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis.

Insufficient data on long-term safety are available for this population group.

Risk-benefit impact:

Since there is scarce experience with the use of adalimumab in long-term use in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis, this use needs to be further studied.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Safety concerns have been updated in this RMP (version 1.1) to align to that of the reference product, Humira:

Removal of Missing Information:

- Patients with immune compromised conditions

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk 1: Serious infections

Potential mechanisms:

Adalimumab may alter T-cell mediated immunity through modulation of TNF-α.

Evidence source(s) and strength of evidence:

Serious infections, including sepsis, due to bacterial, mycobacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis have been reported in patients receiving adalimumab. Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicaemia. Opportunistic infections, including invasive fungal infections have been observed in patients receiving adalimumab.

Data from adalimumab trials and registries as described below and from the Humira's post-marketing safety database.

Characterisation of the risk:

- Frequency by incidence

In controlled trials, the rate of serious infection in subjects treated with adalimumab was between 0/100 patient-years (Pys) in the non-radiographic axial spondylarthritis (nr-axSpA) and peripheral spondylarthritis indication and 5.2/100 Pys in the JIA indication.

- Seriousness/Outcomes

In all clinical trials with adalimumab (non-registry and registry trials), 335 deaths with associated fatal adverse events (Aes) occurred among 46,537 (0.7%) subjects. Of the 335 deaths with associated fatal Aes, 55/56 were due at least in part to serious infection.

- Severity and nature of risk

Risk severity ranges from mild infectious processes to sepsis and death.

- Background incidence/prevalence/mortality

RA

The incidence of infections per 100 person-years in Olmsted County, Minnesota (MN) residents ages ≥18 years of age was 19.64 among those with rheumatoid arthritis (RA) and 12.87 among those without RA (risk ratio (RR) = 1.53 [95% confidence interval (CI): 1.41-1.65]. The incidence of infections requiring hospitalisation was also greater in for RA patients than non-RA patients, 9.57 per 100 person years versus 5.09 per 100 person years (RR = 1.88 [95% CI: 1.71-2.07]) [Doran, 2002a].

In the North American Rheumatism Association Medical Information System (ARAMIS) database, the rate of serious infection requiring hospitalisation among individuals with RA equalled 3.1 per 100 person-years. The rate among RA patients receiving no treatment equalled 1.1 per 100 person years, while the rate among those receiving DMARDs equalled 2.9 (RR= 2.7 [95% CI: not reported]) [Singh, 1999].

Among 609 RA patients in Olmsted County, MN, 64% had at least one infection and 48% had at least one infection requiring hospitalisation (mean 12.7 years per patient follow-up time) [Doran, 2002b].

Infection was a common cause of death in an Olmsted County, MN RA cohort with 15.2% of death certificates listing infection as the primary cause of death [Doran, 2002c].

The standardised mortality rate (SMR) for non-pulmonary infection was 6.2 in a cohort of 898 RA patients from the North American ARAMIS database whose cause of death was known; the SMR for pneumonia was 5.3 [Wolfe, 1994].

Ps

In Ps patients not treated with biologics, the incidence rates of serious infections ranged from approximately 0.3 to 2.1 per 100 person-years [Wakkee, 2011; Gottlieb, 2014; Kimball, 2014; Kalb,2015; Reich 2015].

Among Swedish inpatients hospitalised with Ps, the mortality rate due to infective disease was increased compared to the general population (unadjusted SMR = 2.25 [95% CI: 1.5-3.3]). This risk decreased and was no longer significant when the analysis was restricted to Ps patients hospitalised for Ps only [Boffetta, 2001].

UC

Multiple studies have suggested that *Helicobacter pylori* (*H. pylori*) infection is less prevalent in patients with inflammatory bowel disease (IBD) than in controls. This finding has been associated with 5-aminosalicylic acid (5-ASA) [Piodi, 2003] and sulfasalazine therapy [el-Omar, 1994].

Risk factors and risk groups:

Risk factors for infection, in general, may include increased age, impaired immune function, presence of comorbidities, and duration of exposure to and the number of concomitant immunosuppressive therapies. Infections that present a serious risk to those with advanced age include respiratory infections (e.g. pneumonia, influenza, and tuberculosis), bacteraemia, urinary tract infections, salmonellosis, hepatitis, and nosocomial infections [Institute of Medicine, 1992].

While taking adalimumab, patient's risk for infection might increase, particularly if the patient is over 65 years of age, takes immunosuppressive treatment (e.g. mercaptopurine (6-MP), azathioprine (AZA)), is a heavy smoker, or has a history of decreased lung function. Infections may be serious and, in rare cases, life threatening.

Preventability:

Having a high degree of suspicion with prompt treatment of signs or symptoms of infection, even in the absence of fever.

Using the minimum amount of immunosuppressive drugs to accomplish and sustain remission.

According to the SmPC, patients taking TNF-antagonists are more susceptible to serious infections. Impaired lung function may increase the risk for developing infections. Patients must therefore be monitored closely for infections, before, during and after treatment with adalimumab. Because the elimination of adalimumab may take up to four months, monitoring should be continued throughout this period. Treatment with adalimumab should not be initiated in patients with active infections including chronic or localised infections until infections are controlled. Patients who develop a new infection while undergoing treatment with adalimumab should be monitored closely and undergo a complete diagnostic evaluation. Administration of adalimumab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled. Physicians should exercise caution when considering the use of adalimumab in patients with a history of recurring infection or with underlying conditions which may predispose patients to infections, including the use of concomitant immunosuppressive medications.

The SmPC also states that, for patients who develop the signs and symptoms such as fever, malaise, weight loss, sweats, cough, dyspnoea, and/or pulmonary infiltrates or other serious systemic illness with or without concomitant shock an invasive fungal infection should be suspected and administration of adalimumab should be promptly discontinued. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections.

In addition, in order to minimise the risk, a patient reminder card will be distributed (see Part V.2 and Annex 6 for further information).

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC and the patient reminder card, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

There is no potential public health risk or impact.

Important Identified Risk 2: Tuberculosis (TB)

Potential mechanisms:

Adalimumab may alter T-cell mediated immunity through modulation of TNF-α.

Evidence source(s) and strength of evidence:

Tuberculosis, including reactivation and new onset of tuberculosis, has been reported in patients receiving adalimumab. Reports included cases of pulmonary and extra-pulmonary (i.e. disseminated) tuberculosis.

Data from adalimumab trials and registries as described below and from the Humira's post-marketing safety database.

Characterisation of the risk:

- Frequency by incidence

Only clinically active TB infections are presented (TB test positivity alone, or latent TB, are not included).

In controlled trials, the rate of TB in subjects treated with adalimumab was between 0/100 Pys in the JIA, psoriatic arthritis, ankylosing spondylitis, Crohn's disease (CD), Ps, paediatric Ps, hidradenitis suppurativa, and peripheral spondylarthritis indications and 3.0/100 Pys in the uveitis indication.

- Seriousness/Outcomes

In all clinical trials with adalimumab (non-registry and registry trials), 335 deaths with associated fatal Aes occurred among 46,537 (0.7%) subjects. Of the 335 deaths with associated fatal Aes, 2 were due at least in part to TB.

- Severity and nature of risk

Risk severity ranges from mild infectious processes to sepsis and death.

- Background incidence/prevalence/mortality

In the United States of America (USA), TB incidence was significantly higher among RA patients on traditional DMARD and corticosteroid therapies compared to RA patients not treated with these therapies (RR = 1.2 [95% CI: 1.0-1.5] and RR= 1.7 [95% CI: 1.3-2.2], respectively) [Brassard, 2006].

In Sweden, the incidence of hospitalisation due to TB among RA inpatients was two-times higher than the incidence among referent inpatients (RR= 2.0 [95% CI: 1.2-3.4]) [Askling, 2005].

In South Korea, the rate of TB among RA patients not taking TNF a inhibitors equalled 257 per 100,000 person-years, representing an 8-fold increase in TB risk compared to general population (RR = 8.9 [95% CI: 4.6-17.2]) [Seong, 2007].

Risk factors and risk groups:

Risk factors for infection, in general, may include increased age, impaired immune function, presence of comorbidities, and duration of exposure to and the number of concomitant immunosuppressive therapies. Infections that present a serious risk to those at advanced age include

respiratory infections (e.g. pneumonia, influenza, and tuberculosis), bacteraemia, urinary tract infections, salmonellosis, hepatitis, and nosocomial infections [Institute of Medicine, 1992].

Preventability:

According to the SmPC, before initiation of therapy with adalimumab, all patients must be evaluated for both active or inactive ("latent") TB infection. This evaluation should include a detailed medical assessment of patient history of TB or possible previous exposure to people with active TB and previous and/or current immunosuppressive therapy. Appropriate screening tests (i.e. tuberculin skin test and chest X-ray) should be performed in all patients (local recommendations may apply). Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised. If active TB is diagnosed, adalimumab therapy must not be initiated.

If latent TB is suspected, a physician with expertise in the treatment of TB should be consulted. In addition, appropriate treatment must be started with anti-TB prophylaxis treatment before the initiation of adalimumab, and in accordance with local recommendations.

Use of anti-TB prophylaxis treatment should also be considered before the initiation of adalimumab in patients with several or significant risk factors for TB despite a negative test for TB and in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed.

Patients should be instructed to seek medical advice if signs/symptoms suggestive of a TB infection (e.g. persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with adalimumab.

In addition, in order to minimise the risk, a patient reminder card will be distributed (see Part V.2 and Annex 6 for further information).

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC and the patient reminder card, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

The potential public health issue is that of increased rates of TB and, therefore, increased possible risk of contagion. TB is highly contagious via airborne bacteria, unlike other infections which are not likely to be transmitted by casual contact with an infected individual.

Important Identified Risk 3: Malignancies

Potential mechanisms:

Adalimumab may alter T-cell mediated immunity, which may influence the appearance of malignancy, but the mechanism is unknown.

Evidence source(s) and strength of evidence:

Data from adalimumab trials as described below.

Rare cases of certain types of cancer in children and adults have been reported in patients taking TNF blockers. Patients who have severe, long-standing RA are at higher than average risk of getting lymphoma or leukaemia. This risk is independent of adalimumab usage.

If taking adalimumab, the risk of getting lymphoma, leukaemia, or other cancers may increase. The risk can increase if taking AZA or 6-MP.

No reports of hepatosplenic T-cell lymphoma (HSTCL) were received from any clinical trial, open-label (OL) or controlled.

Information from the Humira's post-marketing safety database.

On rare occasions, a specific and severe type of lymphoma, called HSTCL, has been seen in patients on adalimumab. This is a very rare specific form of lymphoma involving the blood cells, liver, and spleen.

Some patients who developed HSTCL were also treated with AZA or 6-MP.

Cases of NMSC have been observed in patients taking Humira.

Characterisation of the risk:

- Frequency by incidence

In controlled trials, the rate of malignancy in subjects treated with adalimumab was between 0/100 Pys in the JIA, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, paediatric Ps, nr-axSpA, and peripheral spondylarthritis indications and 2.4/100 Pys in the uveitis indication.

- Seriousness/Outcomes

In all clinical trials with adalimumab (non-registry and registry trials), 335 deaths with associated fatal Aes occurred among 46,537 (0.7%) subjects. Of the 335 deaths with associated fatal Aes, 80 (0.2%) were due at least in part to malignancy.

- Severity and nature of risk

The risk for lymphoma, leukaemia, and HSTCL includes death. The risk for NMSC includes disfigurement, and possibly death in rare cases of metastatic squamous cell skin cancer. The risk for melanoma includes disfigurement, death, and metastatic disease. The risk for MCC includes metastatic disease and death.

- Background incidence/prevalence/mortality

Lymphoma:

RA

The incidence of Non-Hodgkin's lymphoma (NHL) in a cohort of 789 Spanish RA patients was 13 per 10,000 Pys (95% CI: 4-41), and was greater than seen in the general population (standardised incidence ratio (SIR) 5.24 [95% CI: 1.1-15.7]) [Abasolo, 2008].

Compared to malignancy rates in the general population, the RR for NHL and Hodgkin's lymphoma (HL) were 2.4 (95% CI: 1.9-2.9) and 3.4 (95% CI: 1.8-5.6), respectively, among 20,699 Denmark RA inpatients followed 1 to 15 years after initial hospitalisation [Mellemkjaer, 1996].

The SIR of NHL and HL developing 1 to 4 years after initial RA hospitalisation in a study of 42,262 Swedish RA inpatients was 2.42 (95% CI: 1.94-2.98) and 2.76 (95% CI: 1.25-5.26), respectively [Hemminki, 2008b].

The SIR for NHL was 2.39 (95% CI: 1.61-3.41) for males and 2.04 (95% CI: 1.60-2.58) for females among 124,143 Scottish RA inpatients, excluding events occurring ≤3 months after initial hospitalisation. The reported SIR in this study for HL was 5.49 (95% CI: 2.36-10.8) for males and 3.04 (95% CI: 1.39-5.78) for females [Thomas, 2000b].

In Sweden, the SIR for lymphoma was 1.98 (95% CI: 1.5-2.6), the SIR for NHL was 1.88 (95% CI: 1.3-2.6), and the SIR of HL was 2.34 (95% CI: 1.2-4.1) among 11,683 RA patients with inpatient records between 1965 and 1983 and followed-up through 1984 [Gridley, 1993].

A case-control study of 378 Swedish inpatients with RA and 378 matched controls found the risk of lymphoma was increased in those with medium (OR= 7.7 [4.8-12.3]) and high RA inflammatory activity (OR= 71.3 [24.1-211.4]) in comparison with those with mild inflammation [Baecklund, 2006].

A study using inpatient records for patients with RA from California hospitals linked to the California Cancer Registry reported the standardised incidence ratio (SIR) for HL for males was 2.76 (95% CI: 1.32-5.08) and 1.62 (95% CI: 0.91-2.68) for females.

For NHL, the SIR for males was 2.07 (95% CI: 1.71-2.48) and 1.37 (95% CI: 1.19-1.57) for females. The study included 84,475 patients with a diagnosis of RA recorded on a hospital discharge record between 1991 and 2002 and excluded events occurring ≤6 months after initial hospitalisation [Parikh-Patel, 2009].

Among 459 RA patients treated with methotrexate and receiving care at rheumatology clinics in Melbourne, Australia, the SIR for NHL was 5.1 (95% CI: 2.2-10.0) and the SIR for HL was 8.9 (95% CI: 0.2-49.8). Methotrexate treatment began prior to June 1986 for all patients and follow-up spanned 1983 to 1998 [Buchbinder, 2008].

The period prevalence (March 1999 through June 2005) of HL in a cohort of 221 male Spanish RA patients was 0.45% (95% CI: 0.011-2.5) [Abasolo, 2008]. The period prevalence (March 1999 through June 2005) of NHL in a cohort of 568 females Spanish RA patients was 0.17% (95% CI: 0.004-0.98) [Abasolo, 2008].

The pooled analyses of four National Data Bank for Rheumatic Diseases sites estimated the SMR of NHL to be 2.04 (no 95% CI reported) [Wolfe, 2003b].

AS

A Swedish population-based case control study of hospitalised patients with AS found no increased risk of lymphoma (OR 1.0 (95% CI: 0.6-1.7) [Askling, 2006].

CD

Authors of a meta-analysis estimated the incidence of lymphoma in CD to be 1.77 per 10,000 PY (95% CI: 0.75-2.78) based on 7 studies involving 15,579 CD patients. The pooled RR of lymphoma from 8 studies with 36,576 patients was 1.42 (95% CI: 1.16-1.73) compared to the general population [von Roon, 2007].

The adjusted incidence of lymphoma was 47.2 per 100,000 PY in a population-based cohort of 2,857 CD patients in Manitoba, Canada. In this study, the incidence rate ratio (IRR) of lymphoma for CD patients compared to individuals without IBD was 2.40 (95% CI: 1.17-4.97) [Bernstein, 2001b].

United Kingdom (UK) database: The SIR of NHL among 21,788 Swedish CD patients hospitalised with a CD diagnosis between 1964 and 2004 was 4.01 (95% CI: 2.59-5.92) 1 to 4 years after hospitalisation [Hemminki, 2009].

The adjusted RR of NHL and HL occurring at least 1 year after initial hospitalisation for CD in 5,127 English inpatients was 1.01 (95% CI: 0.61-18.7) and 0.69 (0.2-3.91), respectively [Goldacre, 2008].

A study of 2,645 Danish patients starting 1 year subsequent to hospitalisation with CD between 1977 and 1989 and followed until the end of 1993 reported the SIR of NHL as 1.5 (95% CI: 0.4-3.7) [Mellemkjaer, 2000].

The standard morbidity ratio for lymphoma was 1.35 (95% CI: 0.37-3.45) in a population of 1,251 CD patients diagnosed in Stockholm from 1955-1984 and followed until 1989 [Persson, 1994].

The incidence of lymphoma equalled 0.42 per 1,000 person-years (0.33-0.54) among patients identified in the UK General Practice Research Database (GPRD) database with a first diagnosis of Ps during the period 1994 through 2004. The incidence of lymphoma among patients without Ps equalled 0.24 per 1,000 person-years (95% CI: 0.17-0.33). The IRR was 1.76 (95% CI: 1.19-2.58) [Brauchli, 2009b].

UC

The age-adjusted incidence of lymphoma was 29.8 per 100,000 PY in a population-based cohort of 2,672 UC patients in Manitoba, Canada [Bernstein, 2001b]. In this study, the IRR of lymphoma for UC patients compared to individuals without IBD was 1.03 (95% CI: 0.47-2.24) [Bernstein, 2001b].

Compared to patients hospitalised for other conditions, the adjusted RR of NHL and HL occurring at least 1 year after to initial hospitalisation for UC in 6,990 English inpatients was 1.19 (95% CI: 0.64-2.01) and 1.60 (95% CI: 0.33-4.78) [Goldacre, 2008]. Similarly, analyses of the GPRD (1988-1997) in the UK found no increased incidence in lymphoma in UC patients (lymphoma SIR 1.11, 95% CI: 0.51-2.19) [Lewis, 2001]. A case-control study conducted using Swedish and Danish registry data found no increased risk of HL in UC patients compared to matched controls without UC (OR: 0.8, 95% CI: 0.3-2.5) [Landgren, 2006]. A study conducted in Florence, Italy yielded results inconsistent with those presented above. UC cases identified in Florence, Italy from 1978-1992 and followed through 1997 experienced much higher rates of Hodgkin's disease (SIR: 9.3, 95% CI: 2.5-23.82) but not NHL (SIR: 1.8 95% CI: 0.20-6.5) than would be expected [Palli, 2000].

In Sweden, the SIR for NHL occurring at least 1 year after the first hospitalisation with a UC diagnosis was 1.34 (95% CI: 1.03-1.71) among 27,656 patients between 1964-2004 [Hemminki, 2008a].

The SMR for NHL was 2.27 (95% CI: 0.03-12.6) in a population-based cohort of 689 UC patients in Florence, Italy diagnosed between 1978 and 1992 and followed through 1996 [Palli, 1998].

A study conducted in 1,160 UC cases diagnosed in Copenhagen from 1962-1987 found no increase in risk of lymphoma (standardised morbidity ratio = 0.51 [95% CI: 0.06-1.82]) [Winther, 2004].

HSTCL:

The frequency of this aggressive form of lymphoma is exceedingly rare. Accurate incidence rates are not available.

For Humira-indicated populations, the background prevalence and mortality of HSTCL are not well described.

Leukaemia:

RA

The incidence rate of leukaemia per 10,000 Pys as shown in a cohort of 789 Spanish RA patients was 17.0 (95% CI: 7.0-50.0) for the time period 1999 to 2005. The SIR was 8.8 (95% CI: 2.4-22.6) [Abasolo, 2008].

In Sweden, the SIR for leukaemia was 1.23 (95% CI: 0.8-1.8) among 11,683 patients with a diagnosis of RA on inpatient hospital records from 1965 through 1983 and followed through 1984. The period at risk excluded the 60 days after the first admission date [Gridley, 1993].

The SIR of leukaemia developing 1 to 4 years after initial RA hospitalisation in a study of Swedish RA patients first hospitalised with a diagnosis of RA ranged from 1.65 (95% CI: 1.08-2.42) for the period 1990-1999 to 2.03 (95% CI: 1.05-3.56) for the period 2000-2004 respectively [Hemminki, 2008b]. The SIR for acute myeloid leukaemia ranged from 2.51 (95% CI: 1.14-4.8) to 6.9 (95% CI: 2.95-13.66), respectively [Hemminki, 2008b].

CD

Authors of a meta-analysis of 4 studies involving 5,901 patients with CD reported the incidence of leukaemia per 10,000 Pys as 0.82 (95% CI: 0.11-2.25) [von Roon, 2007]. Utilising 6 studies involving 27,272 patients with CD, the authors reported the RR of leukaemia as 1.15 (95% CI: 0.69-1.92) compared to the general population [von Roon, 2007].

The SIR of leukaemia among 21,788 Swedish CD patients hospitalised with a diagnosis of CD recorded on the discharge between 1964 and 2004 was 1.35 (95% CI: 0.54-2.80) 1 to 4 years after initial hospitalisation [Hemminki, 2009].

A study of 5,127 hospitalised English CD patients reported an adjusted RR of lymphoid leukaemia compared to a non IBD reference cohort occurring at least 1 year after initial hospitalisation of 0.97 (95% CI: 0.12-3.53) [Goldacre, 2008]. The adjusted RR of myeloid leukaemia was 2.0 (95% CI: 0.73-4.41) [Goldacre, 2008].

A follow-up study of 2,645 Danish patients starting 1 year subsequent to hospitalisation with CD between 1977-1989 reported the SIR of leukaemia as 1.2 (95% CI: 0.2-3.4) [Mellemkjaer, 2000].

The standard morbidity ratio for leukaemia was 0.70 (95% CI: 0.02-3.93) in a population of 1,251 CD patients in Stockholm County with inpatient hospital records from 1955-1984 and followed until 1989 [Persson, 1994].

The age-adjusted incidence rate of leukaemia/multiple myeloma per 100,000 Pys as shown in a population-based cohort of 2,857 CD patients in Manitoba, Canada was 18.0 (95% CI not reported) from 1984-1997 [Bernstein 2001b]. The IRR of leukaemia/multiple myeloma in CD patients compared to non-IBD residents of Manitoba by age, sex, and postal area of residence was 0.79 (95% CI: 0.24-2.54) [Bernstein 2001b].

Ps

The SIR for leukaemia cancers among 15,858 Swedish patients with a Ps diagnosis on inpatient hospital records between 1965 and 2004 was 1.47 (95% CI: 0.97-2.14) ≥1 year after last Ps hospitalisation [Ji, 2009].

The SIR for leukaemia among 6,910 Danish patients with a Ps diagnosis on inpatient hospital records between 1977 and 1987 and followed-up through 1993 was 0.9 (95% CI: 0.5-1.6) [Frentz, 1999].

The incidence of leukaemia equalled 0.33 per 1,000 person years (95% CI: 0.25-0.43) among patients identified in the UK GPRD database with a first diagnosis of Ps during the period 1994 through 2004. The incidence of leukaemia among patients without Ps equalled 0.17 per 1,000 person-years (95% CI: 0.12-0.25). The IRR was 1.89 (1.21-2.94) [Brauchli, 2009b].

UC

The age-adjusted incidence rate of leukaemia/multiple myeloma per 100,000 Pys as shown in a population-based cohort of 2,672 UC patients in Manitoba, Canada was 19.6 (95% CI not reported) from 1984-1997 [Bernstein 2001b]. The IRR of leukaemia/multiple myeloma in UC patients compared to non-IBD residents of Manitoba by age, sex, and postal area of residence was 1.02 (95% CI: 0.37-2.86) [Bernstein 2001b].

A study of 6,990 hospitalised English UC patients reported an adjusted RR of lymphoid leukaemia compared to reference cohort occurring at least 1 year after initial hospitalisation of 0.31 (95% CI: 0.001-1.75) from 1963 through March 1999 [Goldacre, 2008]. The adjusted RR of myeloid leukaemia was 2.15 (95% CI: 1.02-4.03) [Goldacre, 2008].

In Sweden, the SIR for leukaemia occurring at least 1 year after the first hospitalisation with a UC diagnosis equalled 0.98 (95% CI: 0.70-1.35) among 27,606 patients between 1964 and 2004 [Hemminki, 2008a].

The SMR for leukaemia was 1.43 (95% CI: 0.02-7.9) in a population-based cohort of 689 UC patients in Florence, Italy diagnosed between 1978 and 1992 and followed through 1996 [Palli, 1998].

For Humira-indicated populations, the background prevalence of leukaemia is not well described.

Non-melanoma skin cancer (NMSC):

RA

The SIR for NMSC was 0.97 (95% CI: 0.77-1.20) for males and 1.06 (95% CI: 0.92-1.21) for females among 26,623 Scottish RA patients hospitalised between 1981 and 1996, excluding events occurring ≤3 months after initial hospitalisation [Thomas, 2000b].

In Sweden, the SIR for NMSC was 1.17 (95% CI: 0.8-1.7) among 11,683 patients with a hospital diagnosis of RA between 1965 and 1983 and followed up through 1984 [Gridley, 1993].

Excluding the first year of follow-up, the RR for basal cell carcinoma was 1.3 (95% CI: 1.1-1.4) among 20,699 Denmark patients with an RA inpatient diagnosis during 1977-1987 and followed up through 1991 compared to that of the general Danish population. The RR for squamous cell carcinoma was 1.4 (95% CI: 1.1-1.9) for the same cohort [Mellemkjaer, 1996].

The SIR of squamous cell carcinoma after initial RA hospitalisation occurring in 2000-2004 and followed up through 2004 equalled 3.93 (95% CI: 2.78-5.4) in Danish RA patients [Hemminki, 2008b].

The period prevalence (March 1999 through June 2005) of NMSC among male and female Spanish RA patients was 0.90% (0.01-3.2) and 0.53% (0.1-1.5), respectively [Abasolo, 2008].

AS

Excluding the first year of follow-up, the SIR for NMSC among 6,621 Swedish patients with an AS inpatient diagnosis during 1965-1995 and followed up through 1995 equalled 0.76 (95% CI: 0.33-1.37) [Feltelius, 2003].

CD

The SIR of squamous cell carcinoma among 21,788 Swedish patients with a CD inpatient diagnosis occurring from 1964-2004 was 2.14 (95% CI: 1.13-3.67) for the period 1 to 4 years after hospitalisation [Hemminki, 2009].

Excluding the first year following first hospitalisation for CD, the SIR for NMSC equalled 1.2 (95% CI: 0.7-1.8) in a follow-up study of 2,645 Danish CD patients with hospitalisation occurring during 1977-1989 and followed through December 1993 [Mellemkjaer, 2000].

The standard morbidity ratio for NMSC was 1.53 (95% CI: 0.19-5.52) in a population of 1,251 CD patients in Stockholm County, Sweden diagnosed during 1955-1984 and followed until 1989 [Persson, 1994].

Ps

The SIR for squamous cell carcinoma among 5,687 Finnish Ps patients with an inpatient PS diagnosis during 1973-1984 and followed up through 1995 was 3.2 (95% CI: 2.3-4.4) excluding the first 6 months following initial Ps hospitalisation. In the same cohort, the SIR for basal cell carcinoma equalled 1.2 (95% CI: 1.0-1.5) [Hannuksela-Svahn, 2000].

The SIR for NMSC among 6,905 Danish Ps patients with an inpatient Ps diagnosis between 1977 and 1987 and followed up through 1993 was 2.46 (95% CI: 2.13-2.83) [Frentz, 1999].

Excluding the first year of follow-up after initial hospitalisation for Ps, the SIR for squamous cell skin cancer among 15,858 Swedish Ps patients hospitalised between 1965 and 2004 and followed-up through 2004 equalled 2.08 (95% CI: 1.67-2.55) [Ji, 2009].

UC

Results from the Danish cancer registry data (1977-1989) found a slight increase in NMSC in UC patients compared to the general Danish population (RR = 1.4 [95% CI: 1.0-1.9]) [Mellemkjaer, 1995].

In Sweden, the SIR for squamous cell skin cancer occurring at least 1 year after the first hospitalisation with a squamous cell skin cancer diagnosis equalled 1.03 (95% CI: 0.78-1.34) among 27,606 patients between 1964 and 2004 [Hemminki, 2008a].

For Humira-indicated populations, the background mortality from NMSC is not well described.

Melanoma:

RA

The incidence rate of melanoma per 10,000 Pys as shown in a cohort of 789 Spanish RA patients was 4.0 (95% CI: 1.0-31.0) [Abasolo, 2008].

Compared to the general Danish population, the relative risk for melanoma was 1.1 (95% CI: 0.8-1.5) among 20,699 Denmark RA patients with inpatient records between 1977 and 1991 and followed 1-15 years after initial hospitalisation. The first year of follow-up for cancer was excluded from the analysis [Mellemkjaer, 1996].

The SIR for melanoma was 0.34 (95% CI: 0.04-1.22) for males and 1.21 (95% CI: 0.79-1.77) for females among 26,673 Scottish RA patients with inpatient hospital records between 1981 and 1996, excluding events occurring ≤3 months after initial hospitalisation [Thomas, 2000b].

In Sweden, the SIR for melanoma was 0.93 (95% CI: 0.5-1.6) among 11,683 RA patients with inpatient hospital records between 1965 and 1983 and followed-up through 1984. Patients with less than 60-days of follow up prior to death or cancer were excluded [Gridley, 1993].

The SIR of melanoma developing 1-4 years after initial RA hospitalisation in a study of Danish RA patients with inpatient hospital records between 2000 and 2004 was 1.83 (95% CI: 1.00-3.07) [Hemminki, 2008b].

A study using inpatient records from California hospitals linked to the California Cancer Registry reported the SIR for melanoma was 0.80 (95% CI: 0.63-1.00) for males and 0.63 (95% CI: 0.51-0.76) for females among 84,475 patients with inpatient records between 1991 and 2002, excluding events occurring ≤6 months after initial hospitalisation [Parikh-Patel, 2009].

Among 459 RA patients treated with methotrexate and receiving care at rheumatology clinics in Melbourne, Australia, the SIR for melanoma was 3.0 (95% CI: 1.2-6.2). Methotrexate treatment began prior to June 1986 for all patients and follow-up spanned 1983-1998 [Buchbinder, 2008].

The period prevalence (March 1999 through June 2005) of melanoma as shown in a cohort of 568 female Spanish RA patients was 0.17% (95% CI: 0.004-0.98) [Abasolo, 2008].

CD

The age-adjusted incidence rate of melanoma per 100,000 Pys as shown in a population-based cohort of 2,857 CD patients in Manitoba, Canada was 16.4 (95% CI not reported) for the years 1984-1997 [Bernstein, 2001b]. In this study, the IRR comparing the population-based cohort of CD patients with non-CD residents of Manitoba by age, sex, and postal area of residence for melanoma was 1.06 (95% CI: 0.32-3.50) [Bernstein, 2001b].

The SIR of melanoma among 21,788 Swedish CD patients with inpatient hospital records between 1964 and 2004 was 1.41 (95% CI: 0.75-2.43 1-4 years subsequent to initial CD hospitalisation [Hemminki, 2009].

A study of 5,127 hospitalised English CD patients reported the adjusted RR of malignant melanoma that occurred at least one year subsequent to initial hospitalisation as 0.57 (95% CI: 0.07-2.07) for the period 01 January 1963 to 31 March 1999 [Goldacre, 2008].

A follow-up study of 2,645 Danish patients starting 1 year subsequent to hospitalisation with CD between 1977 and 1989 reported the SIR of melanoma as 0.8 (95% CI: 0.2-2.4) [Mellemkjaer, 2000].

The standard morbidity ratio for melanoma was 1.21 (95% CI: 0.25-3.53) in a population of 1251 CD patients in Stockholm with inpatient hospital records from 1955-1984 and followed until 1989 [Persson, 1994].

Ps

The SIR for melanoma among 15,858 Swedish Ps patients with inpatient hospital records between 1965 and 2004 was 0.95 (95% CI: 0.66-1.32) ≥1 year after initial Ps hospitalisation [Ji, 2009].

The SIR for melanoma among 5,687 Finnish Ps patients with inpatient hospital records between 1973 and 1984 and followed up through 1995 was 0.8 (95% CI: 0.3-1.6) ≥6 months following initial Ps hospitalisation [Hannuksela-Svahn, 2000].

The SIR for melanoma among 6,905 Danish Ps patients with inpatient hospital records between 1977 and 1987 and followed-up through 1993 was 1.3 (95% CI: 0.8-2.1) [Frentz, 1999].

The incidence of melanoma among 33,760 Ps patients in the UK equalled 0.18 per 1,000 person-years (0.13-0.26). The incidence of melanoma among 34,001 patients without Ps equalled 0.22 per 1,000 person-years (95% CI: 0.16-0.31) [Brauchli, 2009b].

UC

The age-adjusted incidence rate of melanoma per 100,000 Pys as shown in a population-based cohort of 2,672 UC patients in Manitoba, Canada was 16.7 (95% CI not reported) [Bernstein, 2001b]. In this study, the IRR comparing the population-based cohort of UC patients with non-UC

residents of Manitoba by age, sex, and postal area of residence for melanoma was 1.11 (95% CI: 0.40-3.13) [Bernstein, 2001b].

When compared to non-IBD, the adjusted RR of melanoma among 6,990 English UC patients with inpatient hospital records between 01 January 1963 to 31 March 1999 was 0.81 (95% CI: 0.22-2.11) at least 1 year subsequent to the initial UC hospitalisation [Goldacre, 2008].

In Sweden, the SIR for melanoma was 1.01 (95% CI: 0.78-1.29) at least 1 year subsequent to initial UC hospitalisation among 27,606 UC patients with inpatient hospital records between 1964 and 2004 [Hemminki, 2008a].

For Humira-indicated populations, the background mortality from melanoma is not well described.

MCC:

Studies estimate the incidence of MCC in the general population is in the range of 1.3 to 4.4 case per 1,000,000, [Hodgson, 2005; Kaae, 2010; Gatta, 2011; Reichgelt, 2011] and increases dramatically with age (18.3 to 56.2 per 1,000,000 for those aged 65-69 years and 85+ years, respectively) [Hodgson, 2005]. RA and other autoimmune diseases may increase the risk of MCC in elderly patients [Lanoy, 2010]. In a case-control study using Surveillance, Epidemiology, and Ends Results (SEER) Medicare-linked data, RA was associated with an increased risk of MCC [OR= 1.39 (1.10-1.75)] [Lanoy, 2010]. Ps may increase the risk of MCC [Ps OR = 1.29] while autoimmune gastrointestinal conditions may decrease the risk of MCC [Crohn's disease OR = 0.46; UC OR = 0.83], but these results failed to meet statistical significance [Lanoy, 2010]. The study findings are limited to elderly patients (≥65 years) and did not adjust for immunosuppressive therapy [Lanoy, 2010].

In Europe, the prevalence of MCC is estimated to be 0.86 per 100,000 [Gatta, 2011].

In Europe, the 5-year survival of MCC is estimated to be 39.1% [Gatta, 2011].

Risk factors and risk groups:

Lymphoma:

Factors associated with an increased risk of NHL include weakened immune system (e.g. heritable disease, certain drugs used after an organ transplant), infection (e.g. HIV, Epstein-Barr virus, *H. pylori*, human T-cell lymphoma/leukaemia virus type I (HTLV-I), and hepatitis C), and age (over 60 years) [National Cancer Institute, 2008b].

Factors associated with an increased risk of HL include weakened immune system (e.g. heritable disease, certain drugs used after an organ transplant), viral infection (e.g. HIV, Epstein-Barr virus), and age (among teens and adults aged 15 to 35 years and adults aged 55 years or older) [National Cancer Institute, 2008b].

A prospective observational cohort study of 19,486 patients with IBD, including 7,727 patients with UC or unclassified IBD, found an increased risk for developing lymphoproliferative disorders among patients receiving thiopurines compared to patients who had never received these drugs (hazard ratio: 5.28; 95% CI: 2.01-13.9) [Beaugerie, 2009].

HSTCL:

Past and concomitant thiopurine therapy appears to contribute to the risk in patients with IBD. Other risks in Section SVII.3 may or may not be applicable to HSTCL which is rare [Kotlyar, 2011, Parakkal, 2011].

Leukaemia:

Risk factors for leukaemia depend on the type of leukaemia. In general, factors associated with an increased risk of leukaemia include smoking, exposure to certain chemicals such as benzene, exposure to radiation, past treatment with chemotherapy or radiation therapy, having certain inherited or genetic disorders, having certain blood disorders, and having a family history of leukaemia [National Cancer Institute, 2014].

NMSC:

Factors associated with an increased risk of skin cancer include radiation (e.g. sunlight, tanning, therapy), personal or family history of melanoma, fair skin, certain drugs (e.g. antibiotics, hormones, antidepressants, thiopurines [Peyrin-Biroulet, 2011]), medical conditions or drugs that suppress the immune system, damaged skin (old scars, burns, ulcers, or areas of inflammation), and exposure to arsenic [National Cancer Institute, 2011b]. Additional risk factors that increase squamous cell cancer risk are human papilloma virus infection and actinic keratosis [National Cancer Institute, 2011b].

Melanoma:

Factors associated with an increased risk of melanoma include ultraviolet radiation (e.g. sunlight, tanning), personal history of melanoma, family history of melanoma, fair skin, certain drugs (e.g. antibiotics, hormones, antidepressants), medical conditions that suppress the immune system or are treated with drugs that suppress the immune system, dysplastic nevus, and having many common moles [National Cancer Institute, 2011b].

MCC:

Factors associated with an increased risk of MCC include advanced age, immunosuppression (e.g. organ transplant, HIV), other cancers (e.g. squamous cell carcinoma, basal cell carcinoma, Bowen disease, internal malignancies and haematological neoplasias) and ultraviolet light exposure [Becker, 2010a].

Preventability:

According to the SmPC, the potential risk with the combination of AZA or 6-MP should be considered. All patients, and in particular patients with a medical history of extensive immunosuppressant therapy or Ps patients with a history of psoralen + ultraviolet A (PUVA) treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with adalimumab. In addition, there is a warning in the SmPC stating that caution should be exercised when using any TNF-antagonist in chronic obstructive pulmonary disease (COPD) patients, as well as in patients with increased risk for malignancy due to heavy smoking.

The SmPC also states that all patients with UC who are at increased risk for dysplasia or colon carcinoma (e.g. patients with long-standing UC or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations.

In addition, in order to minimise the risk, a patient reminder card will be distributed (see Part V.2 and Annex 6 for further information).

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC and the patient reminder card, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

There is no potential public health risk or impact.

Important Identified Risk 4: Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis)

Potential mechanisms:

Adalimumab may alter T-cell mediated immunity that may in turn influence the appearance of demyelinating disorders, but the mechanism is unknown.

Evidence source(s) and strength of evidence:

Data from adalimumab trials as described below.

Characterisation of the risk:

- Frequency by incidence

In controlled trials, the rate of demyelinating disorders in subjects treated with adalimumab was between 0/100 Pys in the JIA, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, Ps, paediatric Ps, UC, hidradenitis suppurativa, nr-axSpA, and peripheral spondylarthritis indications and 0.6/100 Pys in the uveitis indication.

- Seriousness/Outcomes

In all clinical trials with adalimumab (non-registry and registry trials), 335 deaths with associated fatal Aes occurred among 46,537 (0.7%) subjects. Of the 335 deaths with associated fatal Aes, none were due at least in part to demyelinating disorders.

- Severity and nature of risk

The risk includes serious disability and death.

- Background incidence/prevalence/mortality

RA

A cohort study conducted using the GPRD found that the incidence of MS, the most common demyelinating disease, was not increased in RA patients compared to the general population (SIR = 0.73 [95% CI: 0.39-1.25]). Additionally MS patients were not at increased risk of developing RA (SIR= 0.80 [95% CI: 0.54-1.14]) [Somers, 2009].

CD

A cohort study conducted using the GPRD found the risk of MS/demyelinating disease/optic neuritis was increased among CD patients compared to those without IBD (RR= 2.12 [95% CI: 0.94-4.50]) [Gupta, 2005].

A cross-sectional study of health records in Manitoba Canada found the prevalence of MS among CD patients equalled 0.41%. Risk of MS was not significantly elevated compared to non-IBD controls (OR= 1.11 [95% CI: 0.67-1.84) [Bernstein, 2006].

A cross-sectional analysis of two large administrative medical claim databases (IMS Health and MarketScan) found MS prevalence was increased among patients with CD compared to those without IBD (OR= 1.48 [95% CI: 1.00-2.18] in MarketScan and OR= 1.59 [95% CI: 1.17-2.16] in IMS Health) [Cohen, 2008b].

A cross-sectional study of administrative medical claims (Kaiser Permanente Medical Care Program) found MS prevalence was greater among patients with CD than patients without IBD (OR = 2.4 [95% CI: 1.2-4.8 [Weng, 2007].

A cross-sectional analysis of the GPRD found MS and optic neuritis prevalence was similar between patients with CD and without IBD (OR= 1.35 [95% CI: 0.83-2.22] and OR= 0.96 [95% CI: 0.39-2.34], respectively). However, the combined prevalence of MS, optic neuritis and demyelination was greater in CD patients compared to controls (OR= 1.54 [95% CI: 1.03-2.32]) [Gupta, 2005].

UC

A cohort study conducted using the GPRD found the incidence of MS/demyelinating disease/optic neuritis was increased among UC patients compared to patients without IBD (RR= 2.63 [95% CI: 1.29-5.15]) [Gupta, 2005].

A cross-sectional study of health records in Manitoba Canada found the prevalence of MS among UC patients equalled 0.54%. This prevalence was higher than the prevalence observed in non-IBD controls

(OR= 1.90 [95% CI: 1.19-3.03]) [Bernstein, 2006].

A cross-sectional analysis was conducted in two large administrative medical claim databases (IMS Health and MarketScan). Among IMS Health enrolees, MS prevalence was increased among patients with UC compared to those without IBD (OR= 1.47 [95% CI: 1.11-1.95]). Among MarketScan enrolees, MS prevalence was similar among patients with UC and those without IBD (OR= 1.17 [95% CI: 0.81-1.68]) [Cohen, 2008b].

A cross-sectional study of administrative medical claims (Kaiser Permanente Medical Care Program) found MS prevalence was greater among patients with UC than patients without IBD (OR = 2.3 [95% CI: 1.6-3.3]) [Weng, 2007].

A cross-sectional analysis of the GPRD found MS and optic neuritis prevalence was increased in patients with UC compared to those without IBD (OR= 1.49 [95% CI: 1.03-2.16] and OR= 2.72 [95% CI: 1.47-5.04], respectively). The combined prevalence of MS, optic neuritis and demyelination was greater in UC patients compared to controls (OR 1.75 [95% CI: 1.28-2.39]) [Gupta, 2005].

Uveitis

A retrospective analysis of a large administrative claims database (MarketScan) found the incidence of demyelinating disease was highest in patients with intermediate uveitis (1.00/100 Pys compared to 0.24/100 Pys for anterior uveitis, 0.44/100 Pys for posterior uveitis, and 0.75/100 Pys for panuveitis uveitis) and MS (0.81/100 Pys compared to 0.12/100 Pys for anterior uveitis, 0.21/100 Pys for posterior uveitis, and 0.34/100 Pys for panuveitis) (data on file).

In a small study, Zein et al. reported that the prevalence of MS in patients with uveitis was 1.3% and that 44% of the 16 MS cases had optic neuritis [Zein, 2004].

Among 2,617 uveitis patients treated at a single centre in Vienna, Austria between 1995 and 2009, the prevalence of MS equalled 1.0%. MS was one of the most common comorbidities associated with intermediate uveitis with a prevalence rate of 4.9% among this group [Barisani-Asenbauer, 2012].

The prevalence of MS among 1,686 uveitis patients treated at a single centre in Germany was reported between 2001 and 2006. MS was diagnosed in 10.3% of patients with intermediate uveitis [Jakob, 2009].

A single-centre Spanish study including 1,022 uveitis patients treated between 2009 and 2012 reported that the overall prevalence of MS equalled 0.8%. MS had the highest prevalence among patients with intermediate uveitis (7%), while the prevalence among patients with panuveitis equalled 0.6% [Llorenc, 2015].

A retrospective cohort study including 1,450 uveitis patients treated between 1985 and 2000 at a single centre in the US reported that the prevalence of MS and optic neuritis equalled 1.0% and 0.5%, respectively [Smith, 2004].

No studies/analyses with incidence or prevalence data for demyelinating disorders in paediatric uveitis patients are available.

For Humira-indicated populations, the background mortality from demyelinating disorders is not well described.

Risk factors and risk groups:

Factors associated with an increased risk of MS include genetic predisposition (e.g. HLA-DR2 [HLADRB1 *15], ethnic origin (being white), female sex, Epstein-Barr infection, smoking, latitude/vitamin D, and early exposure to environmental risk factors) [Ramagopalan, 2010].

Factors associated with an increased risk of GBS include male sex, *Campylobacter jejuni* infection, some vaccines, and increased age [Sejvar, 2011].

Subjects with intermediate uveitis have a high prevalence of demyelination [Zein, 2004; Burkholder, 2012; Llorenc, 2012; Messenger, 2015].

Preventability:

According to the SmPC, prescribers should exercise caution in considering the use of adalimumab in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of adalimumab should be considered if any of these disorders develop. In addition, neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of adalimumab therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.

In addition, in order to minimise the risk, a patient reminder card will be distributed (see Part V.2 and Annex 6 for further information).

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC and the patient reminder card, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

There is no potential public health risk or impact.

Important Identified Risk 5: BCG disease following live BCG vaccination in infants with *in utero* exposure to adalimumab

Potential mechanisms:

Adalimumab may alter T-cell mediated immunity through modulation of TNF-α.

Evidence source(s) and strength of evidence:

Data from adalimumab trials and registries as described below and from Humira's post-marketing safety database.

Characterisation of the risk:

Patients treated with adalimumab may receive concurrent vaccinations, except those using live viruses.

It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating adalimumab therapy. Administration of live vaccines (e.g. BCG vaccine) to infants exposed to adalimumab *in utero* is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

Risk factors and risk groups:

lnfants exposed to adalimumab *in utero*.

Preventability:

According to the SmPC, administration of live vaccines (e.g. BCG vaccine) to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

In addition, in order to minimise the risk, a patient reminder card will be distributed (see Part V.2 and Annex 6 for further information).

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC and the patient reminder card, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

There is no potential public health risk or impact.

Important Potential Risk 1: Progressive Multifocal Leukoencephalopathy (PML)

Potential mechanisms:

Reactivation of Polyomavirus JC (often called JC virus).

Evidence source(s) and strength of evidence:

Potential source data from adalimumab trials as described below and from Humira's post-marketing safety database.

Characterisation of the risk:

- Frequency by incidence

There were no reports of PML in all controlled, non-registry, and registry clinical trials.

- Seriousness/Outcomes

In all clinical trials with adalimumab (non-registry and registry trials), 335 deaths with associated fatal Aes occurred among 46,537 (0.7%) subjects. Of the 335 deaths with associated fatal Aes, none were due at least in part to PML.

- Severity and nature of risk

Severe neurological disabilities and death.

- Background incidence/prevalence/mortality

Estimates from ARTIS equal 0.3 per 100,000 (0.1-0.6) person-years in the general population, 1.0 per 100,000 person-years (0.3-2.5) among RA patients overall, 0.8 (0.2-2.5) per 100,000 person-years among RA biologic naïve patients, and 2.3 (0.1-71) per 100,000 person-years among RA biologic-treated patients [Arkema, 2012].

The mortality of PML in USA (estimated from analysis of national mortality and acquired immune deficiency syndrome (AIDS) surveillance data) rose from 0.15 cases per million before the AIDS pandemic to 0.61 cases per million during the HIV/AIDS era [Holman, 1991; Weber, 2008].

Risk factors and risk groups:

PML occurs predominantly among severely immunosuppressed patients. Currently, over 80% of PML cases are diagnosed in patients with HIV/AIDS [Weber, 2008]. Prior to the era of HIV and AIDS, more than 60% of PML cases were seen in patients with lymphoproliferative disorders, with the highest incidence reported in patients with chronic lymphocytic leukaemia [Carson, 2009]. Other immunosuppressive conditions that put patients at risk of developing PML include malignancies, organ transplants, systemic lupus erythematosus (SLE) and other rheumatic diseases [Bartt, 2006; Eng, 2006; Calabrese, 2007; Govindappa, 2007; Carson, 2009].

The potential mechanism for PML is reactivation of polyomavirus JC in the brain that is believed to be started by severe immunosuppression as in HIV infection. There is no known association of PML with the use of adalimumab or other TNF inhibitors, however, because PML is rare and often fatal its appearance in patients on biologic medications including adalimumab is under observation.

Preventability:

Reversal of immune deficient state.

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

There is no potential public health risk or impact.

Important Potential Risk 2: Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Potential mechanisms:

Unknown.

Evidence source(s) and strength of evidence:

Potential source data from adalimumab trials as described below and from Humira's post-marketing safety database.

Characterisation of the risk:

- Frequency by Incidence

There were no reports of RPLS in all controlled, non-registry, and registry clinical trials.

- Seriousness/Outcomes

In all clinical trials with adalimumab (non-registry and registry trials), 335 deaths with associated fatal Aes occurred among 46,537 (0.7%) subjects. Of the 335 deaths with associated fatal Aes, none were due at least in part to RPLS.

- Severity and nature of risk

Neurological disabilities, multisystem organ involvement, and sequelae, blindness, death.

- Severity and nature of risk

The background incidence and prevalence of and the mortality from RPLS are not well described.

Risk factors and risk groups:

Suspected aetiologies in a published case series included hypertension (68%), eclampsia (11%), calcineurin inhibitor use (11%), and other (11%). Comorbid conditions were common and included hypertension (53%), kidney disease (45%), dialysis dependency (21%), organ/marrow transplantation (24%), and various malignancies (32%) [Lee, 2008].

RPLS is a syndrome characterised by headache, confusion, seizures and visual loss. This syndrome appears in patients who become severely immunosuppressed by drugs like those used for antirejection.

Stopping the drug(s) makes the condition reverse. There is no known association of this event with adalimumab use; however, rare RPLS reports in patients using adalimumab have been received and although most have other causes, the reports are under observation for a possible association.

Preventability:

Unknown.

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

There is no potential public health risk or impact.

Important Potential Risk 3: Adenocarcinoma of colon in UC patients

Potential mechanisms:

Unknown.

Evidence source(s) and strength of evidence:

Potential source data from adalimumab trials as described below.

Characterisation of the risk:

- Frequency by Incidence

In controlled trials, 10 (<0.1 %) instances of adenocarcinoma of colon were observed in the adalimumab and control groups.

- Seriousness/Outcomes

In all clinical trials with adalimumab (non-registry and registry trials), 335 deaths with associated fatal Aes occurred among 46,537 (0.7%) subjects. Of the 335 deaths with associated fatal Aes, 2 (<0.1%) were due at least in part to adenocarcinoma of colon in UC.

- Severity and nature of risk

The risk includes death.

- Severity and nature of risk

The age-adjusted incidence rate of colon cancer in a population-based cohort of 2,672 UC patients in Manitoba, Canada from 1984 to 1997 was 161.1 per 100,000 Pys (95% CI not reported) [Bernstein, 2001b]. In this study, the IRR comparing the population-based cohort of 2,672 UC patients in Manitoba, Canada with a non-UC cohort matched on age, sex, and postal area of residence for colon cancer was 2.75 (95% CI: 1.91-3.97) [Bernstein, 2001b].

Excluding the first year after initial UC hospitalisation, the adjusted RR of colon cancer among 6,990 English patients with an inpatient diagnosis of UC between 01 January 1963 through 31 March 1999 and followed through 31 March 1999 was 2.22 (95% CI: 1.71-2.83) when compared to hospitalised patients without IBD [Goldacre, 2008].

The age-adjusted incidence rate of rectal cancer as shown in a population-based cohort of 2,672 UC patients in Manitoba, Canada from 1984 to 1997 was 56.7 per 100,000 Pys (95% CI not reported) [Bernstein, 2001b]. In this study, the IRR comparing the population-based cohort of 2,673 UC patients in Manitoba, Canada with a non-UC cohort matched on age, sex, and postal area of residence for rectal cancer was 1.90 (95% CI: 1.05-3.43) [Bernstein, 2001b].

Excluding the first year after initial UC hospitalisation, the adjusted RR of rectal cancer among 6,990 English patients with an inpatient diagnosis of UC between 01 Jan 1963 through 31 Mar 1999 and followed through 31 Mar 1999 was 1.00 (95% CI: 0.50-1.81) when compared to hospitalised patients without IBD [Goldacre, 2008].

For Humira-indicated populations, the background prevalence of colorectal cancer in the UC population is not well described.

The SMR for colon cancer was 0.75 (95% CI: 0.01-4.2) in a population-based cohort of 689 UC patients in Florence, Italy diagnosed between 1978 and 1992 and followed through 1996 [Palli, 1998].

The SMR for colorectal cancer was 4.4 (95% CI: 3.2-0.9) in a study of 2,509 patients diagnosed with UC between 1965 and 1983 in Sweden and followed through 1986 [Ekbom, 1992].

The SMR for rectal cancer was 4.35 (95% CI: 0.9-12.7) in a population-based cohort of 689 UC patients in Florence, Italy diagnosed between 1978 and 1992 and followed through 1996 [Palli, 1998].

Risk factors and risk groups:

Factors associated with an increased risk of colorectal cancer include age greater than 50 years, presence of colorectal polyps, genetic predisposition, personal or family history of some cancers, duration of UC, extent and severity of UC, comorbid primary sclerosing cholangitis [Van Assche, 2013], diet, and cigarette smoking [National Cancer Institute, 2006].

There is a known increased risk of adenocarcinoma of colon in UC patients that increases with degree of bowel inflammation as well as the duration of disease. Since early detection can limit morbidity from adenocarcinoma of colon, patients with UC, regardless of the therapy used, should receive routine screening (colonoscopy) more frequently than that recommended for the general population according to current practice guidelines. Since there may be an increased risk of cancer in patients receiving adalimumab, it is not known if this therapy further increases the risk of adenocarcinoma of colon in UC patients, thus, reports of this cancer are under observation in this patient group.

Preventability:

Not preventable, however early detection can limit morbidity.

There is a warning in the SmPC stating that all patients with UC who are at increased risk for dysplasia or colon carcinoma (e.g. patients with long-standing UC or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations.

Impact on the risk-benefit balance of the product:

Considering the safety measures described in the SmPC, it is expected that the risk-benefit balance of the product will be favourable.

Public health impact:

There is no potential public health risk or impact.

SVII.3.2. Presentation of the missing information

Missing information 2: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD:

Evidence source:

Insufficient data on long-term safety are available for this population group.

Anticipated risk/consequence of the missing information:

Since there is scarce experience with the use of adalimumab in long-term use in the treatment of children aged from 6 years to less than 18 years with CD, this use needs to be further studied.

Missing information 3: Episodic treatment in Ps, UC, and JIA:

Evidence source:

Insufficient data on efficacy and safety are available for this population group.

Anticipated risk/consequence of the missing information:

Since there is scarce experience with the use of adalimumab in Episodic treatment in Ps, UC and JIA, this use needs to be further studied.

Missing information 4: Long-term safety information in the treatment of children with uveitis:

Evidence source:

Insufficient data on long-term safety are available for this population group.

Anticipated risk/consequence of the missing information:

Since there is scarce experience with the use of adalimumab in long-term use in the treatment of children with uveitis, this use needs to be further studied.

Missing information 5: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis:

Insufficient data on long-term safety are available for this population group.

Anticipated risk/consequence of the missing information:

Since there is scarce experience with the use of adalimumab in long-term use in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis, this use needs to be further studied.

Part II: Module SVIII — Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Serious infections • Tuberculosis (TB) • Malignancies • Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis) • BCG disease following live BCG vaccination in infants with *in utero* exposure to adalimumab
Important potential risks	• Progressive multifocal leukoencephalopathy (PML) • Reversible posterior leukoencephalopathy syndrome (RPLS) • Adenocarcinoma of colon in ulcerative colitis (UC) patients
Missing information	• Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD • Episodic treatment in psoriasis (Ps), ulcerative colitis (UC) and juvenile idiopathic arthritis (JIA) • Long-term safety information in the treatment of children with uveitis • Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis.

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will be conducted.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities will be conducted.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable as no post-authorisation efficacy studies are planned.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Serious infections	Routine risk communication: SmPC sections 4.3, 4.4 and 4.8. In order to inform patients of this risk, corresponding text is also present in the package leaflet. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4 of the SmPC states that patients taking TNF-antagonists are more susceptible to serious infections. Impaired lung function may increase the risk for developing infections. Patients must therefore be monitored closely for infections, before, during and after treatment with adalimumab. Because the elimination of adalimumab may take up to four months, monitoring should be continued throughout this period. It also warns that treatment with adalimumab should not be initiated in patients with active infections including chronic or localised infections until infections are controlled. Patients who develop a new infection while undergoing treatment with adalimumab should be monitored closely and undergo a complete diagnostic evaluation. Administration of adalimumab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled. Physicians should exercise caution when considering the use of adalimumab in patients with a history of recurring infection or with underlying conditions which may predispose patients to infections, including the use of concomitant immunosuppressive medications. Section 4.4 of the SmPC also states that, for patients who develop the signs and symptoms such as fever, malaise, weight loss, sweats, cough, dyspnoea, and/or pulmonary infiltrates or other serious systemic illness with or without concomitant shock an invasive fungal infection should be suspected and administration of adalimumab should be promptly discontinued. Diagnosis and administration of empiric antifungal therapy in these patients

Safety concern	Routine risk minimisation activities
	should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription.
Tuberculosis (TB)	Routine risk communication: SmPC sections 4.3, 4.4 and 4.8. In order to inform patients of this risk, corresponding text is also present in the package leaflet. Routine risk minimisation activities recommending specific clinical measures to address the risk: According to section 4.4 of the SmPC, before initiation of therapy with adalimumab, all patients must be evaluated for both active or inactive ("latent") TB infection. This evaluation should include a detailed medical assessment of patient history of TB or possible previous exposure to people with active TB and previous and/or current immunosuppressive therapy. Appropriate screening tests (i.e. tuberculin skin test and chest X-ray) should be performed in all patients (local recommendations may apply). Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised. If active TB is diagnosed, adalimumab therapy must not be initiated. If latent TB is suspected, a physician with expertise in the treatment of TB should be consulted. In addition, appropriate treatment must be started with anti-TB prophylaxis treatment before the initiation of adalimumab, and in accordance with local recommendations. Use of anti-TB prophylaxis treatment should also be considered before the initiation of adalimumab in patients with several or significant risk factors for TB despite a negative test for TB and in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients should be instructed to seek medical advice if signs/symptoms suggestive of a TB infection (e.g. persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with adalimumab. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription.

Safety concern	Routine risk minimisation activities
Malignancies	Routine risk communication: SmPC sections 4.4 and 4.8. In order to inform patients of this risk, corresponding text is also present in the package leaflet. Routine risk minimisation activities recommending specific clinical measures to address the risk: There is a warning in section 4.4 of the SmPC stating that all patients, and in particular patients with a medical history of extensive immunosuppressant therapy or Ps patients with a history of PUVA treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with adalimumab. In addition, there is a warning in section 4.4 of the SmPC stating that caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with increased risk for malignancy due to heavy smoking. Section 4.4 of the SmPC also states that all patients with UC who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing UC or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription.
Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis)	Routine risk communication: SmPC sections 4.4 and 4.8. In order to inform patients of this risk, corresponding text is also present in the package leaflet. Routine risk minimisation activities recommending specific clinical measures to address the risk: According to section 4.4 of the SmPC, prescribers should exercise caution in considering the use of adalimumab in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of adalimumab should be considered if any of these disorders develop. In addition, neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of

Safety concern	Routine risk minimisation activities
	adalimumab therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription.
BCG disease following live BCG vaccination in infants with *in utero* exposure to adalimumab	Routine risk communication: SmPC sections 4.4 and 4.6. In order to inform patients of this risk, corresponding text is also present in the package leaflet. Routine risk minimisation activities recommending specific clinical measures to address the risk: According to section 4.4 of the SmPC, administration of live vaccines (e.g. BCG vaccine) to infants exposed to adalimumab *in utero* is not recommended for 5 months following the mother's last adalimumab injection during pregnancy. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription.
Progressive Multifocal Leukoencephalopathy (PML)	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription.
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription.
Adenocarcinoma of colon in UC patients	Routine risk communication: SmPC section 4.4.

Safety concern	Routine risk minimisation activities
	In order to inform patients of this risk, corresponding text is also present in the package leaflet. Routine risk minimisation activities recommending specific clinical measures to address the risk: There is a warning in section 4.4 of the SmPC stating that all patients with UC who are at increased risk for dysplasia or colon carcinoma (e.g. patients with long-standing UC or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription.
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription.
Episodic treatment in psoriasis (Ps), ulcerative colitis (UC) and juvenile idiopathic arthritis (JIA)	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription.
Long-term safety information in the treatment of children with uveitis	Routine risk communication: Section 4.2. In order to inform patients of this risk, corresponding text is also present in the package leaflet.

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.2 of the SmPC states that it is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription.
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis.	Routine risk communication: Section 4.2. In order to inform patients of this risk, corresponding text is also present in the package leaflet. Routine risk minimisation activities recommending specific clinical measures to address the risk: None. Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription.

V.2. Additional Risk Minimisation Measures

The following additional risk minimisation measures are in place for the following safety concerns: serious infections; TB; malignancies; demyelinating disorders (including MS, GBS and optic neuritis); or BCG disease following live BCG vaccination in infants within *in utero* exposure to adalimumab.

Patient reminder card

Objectives:

The objective of the measure is to remind patients (or caregivers) on the key risks for adalimumab. These include serious infections, TB (information about tests and treatment), demyelinating disorders, malignancies, and the risk of BCG disease following live BCG vaccination in infants with *in utero* exposure to Hukyndra. In addition, the patient reminder card can also serve as information that a patient can provide to any healthcare professionals (HCP)s that may treat the patient (i.e. non Hukyndra prescribing HCP), so that the HCP is aware that the patient is being treated with adalimumab and are aware of these risks.

Rationale for the additional risk minimisation activity:

The targeted risks are believed to be those which patients need to be aware of and in which signs/symptoms may be used to help patients recognise when they should seek medical advice.

Target audience and planned distribution path:

The patient reminder card is distributed to prescribers (HCPs) of Hukyndra (regardless of indication of use) who then distributes it to their patients.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Success of the measures will be achieved if a low number of adverse event reports (serious infections; TB; malignancies; demyelinating disorders (including MS, GBS and optic neuritis); or BCG disease following live BCG vaccination in infants within in utero exposure to adalimumab) is observed, after 1 year of marketing of the product. Effectiveness of aRMMs will be achieved if no disproportionate reporting rates are identified.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious infections	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.8. In order to inform patients of this risk, corresponding text is also present in the package leaflet. Section 4.4 of the SmPC states that patients taking TNF-antagonists are more susceptible to serious infections. Impaired lung function may increase the risk for developing infections. Patients must therefore be monitored closely for infections, before, during and after treatment with adalimumab. Because the elimination of adalimumab may take up to four months, monitoring should be continued throughout this period. It also warns that treatment with adalimumab should not be initiated in patients with active infections including chronic or localised infections until infections are controlled. Patients who develop a new infection while undergoing treatment with adalimumab should be monitored closely and undergo a complete diagnostic evaluation. Administration of adalimumab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled. Physicians should exercise caution when considering the use of adalimumab in patients with a history of	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	recurring infection or with underlying conditions which may predispose patients to infections, including the use of concomitant immunosuppressive medications. Section 4.4 of the SmPC also states that, for patients who develop the signs and symptoms such as fever, malaise, weight loss, sweats, cough, dyspnoea, and/or pulmonary infiltrates or other serious systemic illness with or without concomitant shock an invasive fungal infection should be suspected and administration of adalimumab should be promptly discontinued. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Legal status: restricted medical prescription. Additional risk minimisation measures: Patient reminder card.	
Tuberculosis (TB)	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.8. In order to inform patients of this risk, corresponding text is also present in the package leaflet. According to section 4.4 of the SmPC, before initiation of therapy with adalimumab, all patients must be evaluated for both active or inactive ("latent") TB infection. This evaluation should include a detailed medical assessment of patient history of TB or possible previous exposure to people with active TB and previous and/or current immunosuppressive therapy. Appropriate screening tests (i.e. tuberculin skin test and chest X-ray) should be performed in all patients	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	(local recommendations may apply). Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised. If active TB is diagnosed, adalimumab therapy must not be initiated. If latent TB is suspected, a physician with expertise in the treatment of TB should be consulted. In addition, appropriate treatment must be started with anti-TB prophylaxis treatment before the initiation of adalimumab, and in accordance with local recommendations. Use of anti-TB prophylaxis treatment should also be considered before the initiation of adalimumab in patients with several or significant risk factors for TB despite a negative test for TB and in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients should be instructed to seek medical advice if signs/symptoms suggestive of a TB infection (e.g. persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with adalimumab. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Legal status: restricted medical prescription. Additional risk minimisation measures: Patient reminder card.	
Malignancies	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC sections 4.4 and 4.8. In order to inform patients of this risk, corresponding text is also present in the package leaflet. There is a warning in section 4.4 of the SmPC stating that all patients, and in particular patients with a medical history of extensive immunosuppressant therapy or Ps patients with a history of PUVA treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with adalimumab. In addition, there is a warning in section 4.4 of the SmPC stating that caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with increased risk for malignancy due to heavy smoking. Section 4.4 of the SmPC also states that all patients with UC who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing UC or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Legal status: restricted medical prescription. Additional risk minimisation measures: Patient reminder card.	Additional pharmacovigilance activities: None.
Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis)	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. In order to inform patients of this risk, corresponding text is also present in the package leaflet.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	According to section 4.4 of the SmPC, prescribers should exercise caution in considering the use of adalimumab in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of adalimumab should be considered if any of these disorders develop. In addition, neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of adalimumab therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Legal status: restricted medical prescription. Additional risk minimisation measures: Patient reminder card.	None. Additional pharmacovigilance activities: None.
BCG disease following live BCG vaccination in infants with *in utero* exposure to adalimumab	Routine risk minimisation measures: SmPC sections 4.4 and 4.6. In order to inform patients of this risk, corresponding text is also present in the package leaflet. According to section 4.4 of the SmPC, administration of live vaccines (e.g. BCG vaccine) to infants exposed to adalimumab *in utero* is not recommended for 5 months following the mother's last adalimumab injection during pregnancy. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Legal status: restricted medical prescription. Additional risk minimisation measures: Patient reminder card.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Progressive Multifocal Leukoencephalopathy (PML)	Routine risk minimisation measures: Legal status: restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	Routine risk minimisation measures: Legal status: restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Adenocarcinoma of colon in UC patients	Routine risk minimisation measures: SmPC section 4.4. In order to inform patients of this risk, corresponding text is also present in the package leaflet. There is a warning in section 4.4 of the SmPC stating that all patients with UC who are at increased risk for dysplasia or colon carcinoma (e.g. patients with long-standing UC or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Legal status: restricted medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None.	
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD	Routine risk minimisation measures: Legal status: restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Episodic treatment in psoriasis (Ps), ulcerative colitis (UC) and juvenile idiopathic arthritis (JIA)	Routine risk minimisation measures: Legal status: restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term safety information in the treatment of children with uveitis	Routine risk minimisation measures: Section 4.2. In order to inform patients of this risk, corresponding text is also present in the package leaflet. Section 4.2 of the SmPC states that it is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Legal status: restricted medical prescription. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis	Routine risk minimization measures: Legal status: restricted medical prescription. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Part VI: Summary of the risk management plan

Summary of risk management plan for Hukyndra (adalimumab)

This is a summary of the risk management plan (RMP) for Hukyndra. The RMP details important risks of Hukyndra, how these risks can be minimised, and how more information will be obtained about Hukyndra's risks and uncertainties (missing information).

Hukyndra's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Hukyndra should be used.

This summary of the RMP for Hukyndra should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Hukyndra's RMP.

I. The medicine and what it is used for

Hukyndra is authorised for rheumatoid arthritis (RA), psoriasis (Ps), hidradenitis suppurativa, Crohn's disease (CD), paediatric CD, ulcerative colitis (UC), paediatric UC, uveitis and paediatric uveitis. Hukyndra 40 mg solution is also indicated in juvenile idiopathic arthritis (JIA), axial spondylarthritis, psoriatic arthritis, paediatric plaque Ps (see SmPC for the full indication). It contains adalimumab as the active substance, and it is given by subcutaneous route of administration.

Further information about the evaluation of Hukyndra's benefits can be found in Hukyndra's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage (link to the EPAR summary landing page).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Hukyndra, together with measures to minimise such risks and the proposed studies for learning more about Hukyndra's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Hukyndra, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Hukyndra is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Hukyndra are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Hukyndra. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Serious infections • Tuberculosis (TB) • Malignancies • Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis) • Bacillus Calmette–Guérin (BCG) disease following live BCG vaccination in infants with *in utero* exposure to adalimumab
Important potential risks	• Progressive multifocal leukoencephalopathy (PML) • Reversible posterior leukoencephalopathy syndrome (RPLS) • Adenocarcinoma of colon in ulcerative colitis (UC) patients
Missing information	• Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD • Episodic treatment in Ps, UC, and JIA • Long-term safety information in the treatment of children with uveitis • Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis

II.B Summary of important risks

Important identified risk: Serious infections	
Evidence for linking the risk to the medicine	Data from adalimumab trials and registries and from the Humira's post-marketing safety database.
Risk factors and risk groups	Risk factors for infection, in general, may include increased age, impaired immune function, presence of comorbidities, and duration of exposure to and the number of concomitant immunosuppressive therapies. Infections that present a serious risk to those with advanced age include respiratory infections (e.g. pneumonia, influenza, and tuberculosis), bacteraemia,

Important identified risk: Serious infections	
	urinary tract infections, salmonellosis, hepatitis, and nosocomial infections [Institute of Medicine, 1992].
Risk minimisation measures	Routine risk minimisation measures: Text in SmPC: Section 4.3: Contraindications for severe infections such as sepsis and opportunistic infections. Section 4.4: Warnings regarding serious infections such as sepsis due to bacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis. Warning regarding a higher risk of infections in the elderly population ≥ 65 years. Section 4.8: Diverticulitis is listed as an adverse reaction. In order to inform patients of these risks, corresponding text is also present in the package leaflet. **Prescription only medicine.** Additional risk minimisation measures: Patient reminder card.

Important identified risk: Tuberculosis (TB)	
Evidence for linking the risk to the medicine	Data from adalimumab trials and registries and from the Humira's post-marketing safety database.
Risk factors and risk groups	Risk factors for infection, in general, may include increased age, impaired immune function, presence of comorbidities, and duration of exposure to and the number of concomitant immunosuppressive therapies. Infections that present a serious risk to those at advanced age include respiratory infections (e.g. pneumonia, influenza, and tuberculosis), bacteraemia, urinary tract infections, salmonellosis, hepatitis, and nosocomial infections [Institute of Medicine, 1992].
Risk minimisation measures	Routine risk minimisation measures: Text in SmPC: Section 4.3: Contraindications for active TB Section 4.4: Warnings regarding active TB In order to inform patients of these risks, corresponding text is also present in the package leaflet. **Prescription only medicine.** Additional risk minimisation measures: Patient reminder card.

Important identified risk: Malignancies	
Evidence for linking the risk to the medicine	Data from adalimumab trials. No reports of hepatosplenic T-cell lymphoma (HSTCL) were received from any clinical trial, open-label or controlled. Information from the Humira's post-marketing safety database.
Risk factors and risk groups	A prospective observational cohort study of 19,486 patients with inflammatory bowel disease (IBD), including 7,727 patients with UC or unclassified IBD, found an increased risk for developing lymphoproliferative disorders among patients receiving thiopurines compared to patients who had never received these drugs (hazard ratio: 5.28; 95% CI: 2.01-13.9) [Beaugerie, 2009]. Past and concomitant thiopurine therapy appears to contribute to the risk in patients with IBD. Other risks in Section SVII.3 may or may not be applicable to HSTCL which is rare [Kotlyar, 2011, Parakkal, 2011]. Risk factors for leukaemia depend on the type of leukaemia. In general, factors associated with an increased risk of leukaemia include smoking, exposure to certain chemicals such as benzene, exposure to radiation, past treatment with chemotherapy or radiation therapy, having certain inherited or genetic disorders, having certain blood disorders, and having a family history of leukaemia [National Cancer Institute, 2014]. Factors associated with an increased risk of skin cancer include radiation (e.g. sunlight, tanning, therapy), personal or family history of melanoma, fair skin, certain drugs (e.g. antibiotics, hormones, antidepressants, thiopurines [Peyrin-Biroulet, 2011]), medical conditions or drugs that suppress the immune system, damaged skin (old scars, burns, ulcers, or areas of inflammation), and exposure to arsenic [National Cancer Institute, 2011b]. Additional risk factors that increase squamous cell cancer risk are human papilloma virus infection and actinic keratosis [National Cancer Institute, 2011b]. Factors associated with an increased risk of melanoma include ultraviolet radiation (e.g. sunlight, tanning), personal history of melanoma, family history of melanoma, fair skin, certain drugs (e.g. antibiotics, hormones, antidepressants), medical conditions that suppress the immune system or are treated with drugs that suppress the immune system, dysplastic nevus, and having many common moles [National Cancer Institute, 2011b]. Factors associated with an increased risk of MCC include advanced age, immunosuppression (e.g. organ transplant, HIV),

Important identified risk: Malignancies	
	other cancers (e.g. squamous cell carcinoma, basal cell carcinoma, Bowen disease, internal malignancies and haematological neoplasias) and ultraviolet light exposure [Becker, 2010a].
Risk minimisation measures	Routine risk minimisation measures: Text in SmPC: Sections 4.4: warning regarding patients with a medical history of extensive immunosuppressant therapy or Ps patients with a history of PUVA treatment; warning regarding the use of any TNF-antagonist in chronic obstructive pulmonary disease (COPD) patients, as well as in patients with increased risk for malignancy due to heavy smoking; warning regarding patients with UC who are at increased risk for dysplasia or colon carcinoma, or who had a prior history of dysplasia or colon carcinoma Section 4.8: Malignancies listed as adverse reactions. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Prescription only medicine. Additional risk minimisation measures: Patient reminder card.

Important identified risk: Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis)	
Evidence for linking the risk to the medicine	Data from adalimumab trials.
Risk factors and risk groups	Factors associated with an increased risk of MS include genetic predisposition (e.g. HLA-DR2 [HLADRB1 *15], ethnic origin (being white), female sex, Epstein-Barr infection, smoking, latitude/vitamin D, and early exposure to environmental risk factors) [Ramagopalan, 2010]. Factors associated with an increased risk of GBS include male sex, *Campylobacter jejuni* infection, some vaccines, and increased age [Sejvar, 2011]. Subjects with intermediate uveitis have a high prevalence of demyelination [Zein, 2004; Burkholder, 2012; Llorenc, 2012; Messenger, 2015].
Risk minimisation measures	Routine risk minimisation measures:

Important identified risk: Demyelinating disorders (including multiple sclerosis [MS], Guillain Barré syndrome [GBS] and optic neuritis)	
	Text in SmPC: Section 4.4: Warning on demyelinating disorders included Section 4.8: Demyelinating disorders are also listed as adverse reaction In order to warn patients about this risk, corresponding text is also present in the package leaflet. Prescription only medicine Additional risk minimisation measures: Patient reminder card.

Important identified risk: BCG disease following live BCG vaccination in infants with *in utero* exposure to adalimumab	
Evidence for linking the risk to the medicine	Data from adalimumab trials and registries and from the Humira's post-marketing safety database.
Risk factors and risk groups	lnfants exposed to adalimumab *in utero*.
Risk minimisation measures	Routine risk minimisation measures: Text in SmPC: Section 4.4 has a section on vaccinations Section 4.6: warning on live vaccines In order to warn patients about this risk, corresponding text is also present in the package leaflet. Prescription only medicine Additional risk minimisation measures: Patient reminder card.

Important potential risk: Progressive Multifocal Leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	Potential source data from adalimumab trials and from the Humira's post-marketing safety database.
Risk factors and risk groups	PML occurs predominantly among severely immunosuppressed patients. Currently, over 80% of PML cases are diagnosed in patients with HIV/acquired immune deficiency syndrome (AIDS) [Weber, 2008]. Prior to the era of HIV and AIDS, more than 60% of PML cases were seen in patients with lymphoproliferative disorders, with the highest incidence reported in patients with chronic lymphocytic leukaemia [Carson, 2009]. Other immunosuppressive conditions that put patients at risk of developing PML include malignancies, organ transplants, systemic lupus erythematosus (SLE) and other

	rheumatic diseases [Bartt, 2006; Eng, 2006; Calabrese, 2007; Govindappa, 2007; Carson, 2009].
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: None.

Important potential risk: Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	
Evidence for linking the risk to the medicine	Potential source data from adalimumab trials and from the Humira's post-marketing safety database.
Risk factors and risk groups	Suspected aetiologies in a published case series included hypertension (68%), eclampsia (11%), calcineurin inhibitor use (11%), and other (11%). Comorbid conditions were common and included hypertension (53%), kidney disease (45%), dialysis dependency (21%), organ/marrow transplantation (24%), and various malignancies (32%) [Lee, 2008].
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: None.

Important potential risk: Adenocarcinoma of colon in UC patients	
Evidence for linking the risk to the medicine	Potential source data from adalimumab trials.
Risk factors and risk groups	Factors associated with an increased risk of colorectal cancer include age greater than 50 years, presence of colorectal polyps, genetic predisposition, personal or family history of some cancers, duration of UC, extent and severity of UC, comorbid primary sclerosing cholangitis [Van Assche, 2013], diet, and cigarette smoking [National Cancer Institute, 2006].
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4: There is a warning in section 4.4 of the SmPC stating that all patients with UC who are at increased risk for dysplasia or colon carcinoma (e.g. patients with long-standing UC or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for

Important potential risk: Adenocarcinoma of colon in UC patients	
	dysplasia at regular intervals before therapy and throughout their disease course. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Prescription only medicine Additional risk minimisation measures: None.

Missing information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD	
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: None.

Missing information: Episodic treatment in psoriasis (Ps), ulcerative colitis (UC) and juvenile idiopathic arthritis (JIA)	
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: None.

Missing information: Long-term safety information in the treatment of children with uveitis	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2: Section 4.2 of the SmPC states that it is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis. In order to warn patients about this risk, corresponding text is also present in the package leaflet. Prescription only medicine Additional risk minimisation measures: None.

Missing information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis	
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine Additional risk minimisation measures: None.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Hukyndra.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Hukyndra.

Part VII: Annexes

Table of contents

Annex 4 — Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 — Details of proposed additional risk minimisation activities (if applicable)

Draft key messages of the additional risk minimisation measures

- **Patient material:**

  Prior to launch of Hukyndra in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the patient material, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

  The MAH shall ensure that, in each Member State where Hukyndra is marketed, all patients/carers who are expected to use Hukyndra have access to the following patient material:

  - Patient Reminder Card

  The **Patient Reminder Card** hall contain the following key elements:

  - Contact details of the Hukyndra prescriber.
  - That the Patient Reminder Card can be carried by the patient and shared with healthcare professionals involved in their treatment.
  - A message for the patient that they should undergo screening for Tuberculosis (TB) before taking Hukyndra and reminder that they should record the TB screening results on the card.
  - Inform the patient concerning key risks (i.e. serious infections, TB, demyelinating disorders, malignancies, and BCG disease following live BCG vaccination in infants with *in utero* exposure to Hukyndra) and the need to be vigilant for symptoms associated with them.
  - A message for the patient to not receive live vaccinations while using Hukyndra and to warn of BCG disease following live BCG vaccination in infants with *in utero* exposure to Hukyndra, so if they took Hukyndra while pregnant, their baby should not receive a “live vaccine”, such as BCG (used to prevent TB) within 5 months following your last adalimumab injection during pregnancy.
  - Signs or symptoms of the safety concern and when to seek attention from a healthcare professional.