European Union Safety Risk Management Plan

Hyrimoz
Hefiya
GPN017(Adalimumab)

Risk Management Plan (RMP) version to be assessed as part of this application	
Active substance (International Non-Proprietary Name (INN) or common name)	Adalimumab
Document status	Draft
RMP version number	6.0
Data lock point for this RMP	30 Jun 2025
Date of final sign off	01 Oct 2025
Rationale for submitting an updated RMP	The RMP has been updated to align the safety concerns with the originator product (Humira) RMP v.16.2. Dated Sep 2024.

Summary of significant changes in this RMP version:

RMP part/module	High level description of major changes
Part I Product overview	Updated "Dosage in EEA" and "Pharmaceutical forms and strengths", Information was placed into 'Current' from 'Proposed' and aligned with effective SmPC. Updated "Is/will the product be subject to additional monitoring in the EU?" from 'yes' to 'no', to be aligned with current Product Information. The removal of additional monitoring from the EU Product Information was requested during the renewal procedure EMEA/H/C/004320/R/0037. Therefore, RMP is updated to be line with the current safety information.
Part II - Module SI	None

RMP part/module	High level description of major changes
Epidemiology of the indication(s) and target populations	
Part II - Module SII Non-clinical part of the safety specification	None
Part II - Module SIII Clinical trial exposure	None
Part II - Module SIV Populations not studied in clinical trials	None
Part II - Module SV Post-authorization experience	Updated data for 'Estimated post-marketing exposure'
Part II - Module SVI Additional EU requirements for the safety specification	None
Part II - Module SVII Identified and potential risks	Updated reference details for originator product (Humira) RMP v.16.2. Updated details for the removed and reworded safety concerns post alignment with originator product (Humira) RMP v.16.2.
Part II - Module SVIII Summary of the safety concerns	Updated details for the removed and reworded safety concerns post alignment with originator product (Humira) RMP v.16.2.
Part III Pharmacovigilance plan (including post-authorisation safety studies)	None
Part IV Plans for post-authorisation efficacy studies	None
Part V Risk minimisation measures (including evaluation of the	Updated information for additional risk minimization measures in alignment with originator product (Humira) RMP v.16.2.

RMP part/module	High level description of major changes
effectiveness of risk minimisation activities)	Updated details for the removed and reworded safety concerns.
Part VI Summary of the risk management plan	Updated 'List of important risks and missing information' in alignment with Part II: SVIII. Updated details for the removed and reworded safety concerns.
Part VII Annexes	Updated 'Annex 6 - Details of proposed additional risk minimization activities'. Updated 'Annex 7 – Reference details' Updated 'Annex 8 - Summary of changes to the risk management plan over time'.
Others	The template has been updated from Novartis to Sandoz following the completion of Sandoz's spinoff from Novartis. Qualified Person for Pharmacovigilance (QPPV) details have been updated.

Other RMP versions under evaluation: None

Details of the currently approved RMP	
Version number	5.0
Approved with procedure	EMEA/H/C/004320/X/0036/G EMEA/H/C/004865/X/0036/G
Date of approval (opinion date)	26 Jan 2023

Qualified Person for Pharmacovigilance (QPPV) Details	
QPPV name:	Dr. Mohamed Ali Kotal
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV/deputy.

QPPV/deputy signature:	I am approving this document as Deputy QPPV on behalf of the EU QPPV.

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List of abbreviations

6-MP	6-mercaptopurine
AE	Adverse Event
AI	Autoinjector
ALS	Amyotrophic Lateral Sclerosis
ALT	Alanine Transaminase
AML	Acute myeloid leucaemia
AS	Ankylosing Spondylitis
ATC	Anatomical Therapeutic Chemical (Classification System)
axSpA	Axial Spondyloarthritis
AZA	Azathioprine
BCC	Basal cell carcinoma
BSA	Body surface area
CD	Crohn's Disease
CI	Confidence interval
CLL	Chronic lymphocytic leucemia
CML	Chronic myeloid leucemia
CNS	Central nervous system
CRP	C-Reactive Protein
DDD	Defined Daily Dose
DMARDs	Disease-Modifying Anti-Rheumatic Drugs
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Enthesitis-Related Arthritis
EU	European Union
EU-Humira	EU-authorized Humira®; the registered trademark sign "®" was omitted in the remainder of this document for better readability.
FDA	Food and Drug Administration
GBS	Guillain-Barre Syndrome
GPN017/GP2017	Sandoz product code for the adalimumab containing biosimilar; this code was used in the initial Marketing Authorization Application, corresponding study documentation, and other documents. This code is still in use, e.g. in the RMP or PSUR.
HBV	Hepatitis B virus
HCF	High-concentration formulation
HLGT	High level group term
HLT	High level term
Hyrimoz-HCF	Hyrimoz high-concentration formulation (development code: GPN017B1)
Hyrimoz-LCF	Hyrimoz low-concentration formulation (development code: GP2017)
HS	Hidradenetis Suppurativa

HSTCL	Hepatosplenic T-Cell Lymphoma
IBD	Inflammatory bowel disease
IL	Interleukin
JC	Jacob Creutzfeldt
JIA	Juvenile Idiopathic Arthritis
LCF	Low-concentration formulation
MAH	Marketing authorization holder
MS	Multiple Sclerosis
N/A	Not Applicable
NMSC	Non Melanoma Skin Cancer
pedCD	Pediatric Crohn's Disease
PFS	Pre-filled syringe(s)
PK	Pharmacokinetic
PL	Package Leaflet
PML	Progressive Multifocal Leukoencephalopathy
Ps	Chronic plaque psoriasis
PsA	Psoriatric arthritis
PT	Preferred term
PV	Pharmacovigilance
PTY	Patient year
RA	Rheumatoid Arthritis
RCT(s)	Randomized controlled trial
RMP	Risk Management Plan
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SOC	System organ class
SpA	Spondyloarthritis
TB	Tuberculosis
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis
US(A)	United States (of America)
US-Humira	US-licensed Humira®; the registered trademaks sign "®" was omitted in the remainder of this document for better readability.
WHO	World Health Organization

Part I: Product(s) Overview

Table 0-1Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Adalimumab
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, Tumor Necrosis Factor alpha (TNF-α) inhibitors (L04AB04)
Marketing Authorization Holder	Sandoz GmbH, Kundl, Austria
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Hyrimoz Hefiya
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Immunosuppressants, Tumor Necrosis Factor alpha (TNF-α) inhibitors (L04AB04)
	Summary of mode of action: Adalimumab binds specifically to Tumor Necrosis Factor (TNF) and neutralizes 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 produced by recombinant deoxyribonucleic acid technology in a Chinese hamster ovary mammalian expression system
Hyperlink to the Product Information	Module 1.3.1-Annex I SmPC and Module 1.3.1-Annex III Labelling and Package Leaflet
Indication(s) in the EEA	Current: **Rheumatoid arthritis (RA)** Hyrimoz / Hefiya 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 including methotrexate has been inadequate. • the treatment of severe, active and progressive RA in adults not previously treated with methotrexate. Hyrimoz / Hefiya can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Adalimumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate. **Juvenile idiopathic arthritis (JIA)** *Polyarticular JIA*

	Hyrimoz / Hefiya 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 disease-modifying anti-rheumatic drugs (DMARDs). Hyrimoz / Hefiya 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 (ERA)* Hyrimoz / Hefiya is indicated for the treatment of active ERA in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy. **Axial spondyloarthritis (axSpA)** *Ankylosing spondylitis (AS)* Hyrimoz / Hefiya is indicated for the treatment of adults with severe active AS who have had an inadequate response to conventional therapy. *axSpA without radiographic evidence of AS (nr-axSpA)* Hyrimoz / Hefiya is indicated for the treatment of adults with severe *axSpA* without radiographic evidence of AS 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 (PsA)** Hyrimoz / Hefiya is indicated for the treatment of active and progressive PsA in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Adalimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function. **Psoriasis (Ps)** Hyrimoz / Hefiya is indicated for the treatment of moderate to severe chronic plaque Ps in adult patients who are candidates for systemic therapy. **Pediatric plaque Ps** Hyrimoz / Hefiya 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 (HS)** Hyrimoz / Hefiya 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 HS therapy.

	Crohn's disease (CD) Hyrimoz / Hefiya 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. **Pediatric CD (pedCD)** Hyrimoz / Hefiya is indicated for the treatment of moderately to severely active CD in pediatric 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)** Hyrimoz / Hefiya 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. **Pediatric ulcerative colitis (pedUC)** Hyrimoz / Hefiya is indicated for the treatment of moderately to severely active ulcerative colitis in pediatric 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** Hyrimoz / Hefiya 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. **Pediatric Uveitis (pedUveitis)** Hyrimoz / Hefiya is indicated for the treatment of paediatric chronic non-infectious anterior uveits in patients from 2 years of age who have had an inadequate response to or are intolerant to the conventional therapy, or in whom conventional therapy is inappropriate.
	Proposed: Not applicable
Dosage in the EEA	Current: Hyrimoz / Hefiya treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which Hyrimoz / Hefiya is indicated. Ophthalmologists are advised to consult with an appropriate specialist before initiation of treatment with Hyrimoz / Hefiya. Patients treated with Hyrimoz / Hefiya should be given the Patient Reminder Card. After proper training in injection technique, patients may self-inject with Hyrimoz / Hefiya if their physician determines that it is appropriate and with

	medical follow-up as necessary. During treatment with Hyrimoz / Hefiya, other concomitant therapies (e.g., corticosteroids and/or immunomodulatory agents) should be optimized. ***Posology*** **Rheumatoid arthritis** The recommended dose of Hyrimoz / Hefiya 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 Hyrimoz / Hefiya. Glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, or analgesics can be continued during treatment with Hyrimoz / Hefiya. Regarding combination with disease-modifying anti-rheumatic drugs other than methotrexate see Section 4.4 and Section 5.1 in the SmPC.In monotherapy, some patients who experience a decrease in their response to Hyrimoz/Hefiya 40 mg every other week may benefit from an increase in dosage 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. Dose interruption: There may be a need for dose interruption, for instance before surgery or if a serious infection occurs. Re-introduction of adalimumab after discontinuation for 70 days or longer resulted in the same magnitudes of clinical response and similar safety profile as before dose interruption. **Ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis and psoriatic arthritis** The recommended dose of Hyrimoz / Hefiya for patients with AS, axSpA without radiographic evidence of AS and for patients with PsA is 40 mg Hyrimoz / Hefiya administered every other week as a single dose via subcutaneous injection. 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. **Psoriasis** The recommended dose of Hyrimoz / Hefiya 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. Hyrimoz 40 mg solution for injection in pre-filled syringe and/or pre-filled pen is available for the maintenance 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 may benefit from an increase in dosage 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 dosing frequency. If adequate response is achieved with an increased dosing frequency, the dose may subsequently be reduced to 40 mg every other week.

	Hidradenitis suppurativa The recommended Hyrimoz / Hefiya dose regimen for adult patients with HS is 160 mg initially at Day 1 (given as two 80 mg injections or four 40 mg injections in one day or as one 80 mg injection or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later at Day 15 (given as one 80 mg injection or 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 one 80 mg injection or two 40 mg injections in one day). Antibiotics may be continued during treatment with Hyrimoz / Hefiya if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with Hyrimoz / Hefiya. Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period. Should treatment be interrupted, Hyrimoz / Hefiya 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. **Crohn's disease** The recommended Hyrimoz / Hefiya 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 two 80 mg injections or four 40 mg injections in one day or as one 80 mg injection or as two 40 mg injections per day for two consecutive days), followed by 80 mg at week 2 (given as one 80 mg injection or two 40 mg injections in one day), can be used with the awareness that the risk for 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 Hyrimoz / Hefiya and signs and symptoms of disease recur, Hyrimoz / Hefiya 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 Hyrimoz/ Hefiya 40 mg every other week may benefit from an increase in in dosage to 40 mg Hyrimoz/Hefiya 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. **Ulcerative colitis** The recommended Hyrimoz / Hefiya induction dose regimen for adult patients with moderate to severe UC is 160 mg at week 0 (given as two 80 mg injections or four 40 mg injections in one day or as one 80 mg injection or as two 40 mg injections per day for two consecutive days) and 80 mg at week 2 (given as one 80 mg injection or 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 Hyrimoz/ Hefiya 40 mg every other week may benefit from an increase in dosage to 40 mg Hyrimoz every week or 80 mg every other week. The clinical response is usually achieved within 2-8 weeks of treatment. Hyrimoz / Hefiya

therapy should not be continued in patients failing to respond within this time period.

Uveitis

The recommended dose of Hyrimoz / Hefiya 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. Hyrimoz / Hefiya 40 mg solution for injection in pre-filled syringe and/or pre-filled pen is available for the maintenance dose. There is limited experience in the initiation of treatment with adalimumab alone. Treatment with Hyrimoz / Hefiya 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 Hyrimoz / Hefiya. It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis.

Special populations

Elderly

No dose adjustment is required.

Renal and/or hepatic impairment

Adalimumab has not been studied in these patient populations. No dose recommendations can be made.

Juvenile idiopathic arthritis

Polyarticular JIA from 2 years of age

The recommended dose of Hyrimoz / Hefiya for patients with polyarticular JIA, from 2 years of age is based on body weight (Table 1). Hyrimoz / Hefiya is administered every other week via subcutaneous injection.

Table 1. Hyrimoz/Hefiya dose for patients with polyarticular juvenile idiopathic arthritis

Patient weight	Dosing regimen
10 kg to < 30 kg	20 mg every other week
≥ 30 kg	40 mg every other week

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.

There is no relevant use of adalimumab in patients aged less than 2 years for this indication.

ERA

The recommended dose of Hyrimoz / Hefiya for patients with ERA from 6 years of age is based on body weight (Table 2). Hyrimoz is administered every other

week via subcutaneous injection. Adalimumab has not been studied in patients with enthesitis-related arthritis aged less than 6 years.

Table 2. Hyrimoz/Hefiya dose for patients with ERA

Patient weight	Dosing regimen
15 kg to < 30 kg	20 mg every other week
≥ 30 kg	40 mg every other week

Pediatric plaque psoriasis

The recommended Hyrimoz / Hefiya dose for patients with plaque psoriasis from 4 to 17 years of age is based on body weight (Table 3). Hyrimoz / Hefiya is administered via subcutaneous injection.

Table 3. Hyrimoz/Hefiya dose for paediatric patients with plaque psoriasis

Patient weight	Dosing regimen
15 kg to < 30 kg	Initial dose of 20 mg, followed by 20 mg every other week starting one week after the initial dose
≥ 30 kg	Initial dose of 40 mg, followed by 40 mg given every other week starting one week after the initial dose

Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this time period. If re-treatment 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. There is no relevant use of adalimumab in children aged less than 4 years for this indication.

Adolescent hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)

There are no clinical trials with adalimumab in adolescent patients with HS. The posology of adalimumab in these patients has been determined from pharmacokinetic modelling and simulation. The recommended Hyrimoz / Hefiya 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 Hyrimoz / Hefiya 40 mg every other week, an increase in dosage to 40 mg every week or 80 mg every other week may be considered. Antibiotics may be continued during treatment with Hyrimoz / Hefiya if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with Hyrimoz / Hefiya. Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period. Should treatment be interrupted, Hyrimoz / Hefiya may be re-introduced as appropriate. The benefit and risk of continued long-term treatment should be periodically evaluated. There is no relevant use of adalimumab in children aged less than 12 years in this indication.

Pediatric Crohn's disease

The recommended dose of Hyrimoz/Hefiya for patients with Crohn's disease from 6 to 17 years of age is based on body weight (Table 4). Hyrimoz/Hefiya is administered via subcutaneous injection.

Table 4. Hyrimoz/Hefiya dose for paediatric patients with Crohn's disease

Patient weight	Induction dose	Maintenance dose starting at week 4
< 40 kg	40 mg at week 0 and 20 mg at week 2 In case there is a need for a more rapid response to therapy with the awareness that the risk for adverse events may be higher with use of the higher induction dose, the following dose may be used: 80 mg at week 0 and 40 mg at week 2	20 mg every other week
≥ 40 kg	80 mg at week 0 and 40 mg at week 2 In case there is a need for a more rapid response to therapy with the awareness that the risk for adverse events may be higher with use of the higher induction dose, the following dose may be used: 160 mg at week 0 and 80 mg at week 2	40 mg every other week

Patients who experience insufficient response may benefit from an increase in dosage.

- < 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.

Pediatric ulcerative colitis

The recommended dose of Hyrimoz/Hefiya for patients from 6 to 17 years of age with ulcerative colitis is based on body weight (Table 5). Hyrimoz/Hefiya is administered via subcutaneous injection.

Table 5. Hyrimoz/Hefiya dose for paediatric patients with Ulcerative Colitis

Patient weight	Induction Dose	Maintenance Dose Starting at Week 4*

< 40 kg	• 80 mg at Week 0 (given as one 80 mg injection or 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 two 80 mg injections or four 40 mg injections in one day or one 80 mg injection or two 40 mg injections per day for two consecutive days) and • 80 mg at Week 2 (given as one 80 mg injection or two 40 mg injections in one day)	• 80 mg every other week (given as one 80 mg injection or two 40 mg injections in one day)

* Paediatric patients who turn 18 years of age while on Hyrimoz/Hefiya should continue their prescribed maintenance dose.

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 Hyrimoz/Hefiya in children aged less than 6 years in this indication.

Hyrimoz/Hefiya may be available in different strengths and/or presentations depending on the individual treatment needs.

Pediatric uveitis

The recommended dose of Hyrimoz/Hefiya for paediatric patients with uveitis from 2 years of age is based on body weight (Table 4). Hyrimoz/Hefiya is administered via subcutaneous injection. In paediatric uveitis, there is no experience in the treatment with adalimumab without concomitant treatment with methotrexate.

Table 6. Hyrimoz/Hefiya dose for paediatric patients with uveitis

Patient weight	Dosing regimen
< 30 kg	20 mg every other week in combination with methotrexate
≥ 30 kg	40 mg every other week in combination with methotrexate

When Hyrimoz/Hefiya 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. There is no relevant use of Hyrimoz in children aged less than 2 years in this indication. It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis.

	Psoriatic arthritis and axial spondyloarthritis including ankylosing spondylitis There is no relevant use of adalimumab in the pediatric population for the indications of ankylosing spondylitis and psoriatic arthritis. **Method of administration** Hyrimoz / Hefiya is administered by subcutaneous injection. Full instructions for use are provided in the package leaflet.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: 20 mg solution for injection in pre-filled syringe Each 0.4 ml single-dose pre-filled syringe contains 20 mg of adalimumab. 40 mg solution for injection in pre-filled syringe Each 0.8 ml single-dose pre-filled syringe contains 40 mg of adalimumab. 40 mg solution for injection in pre-filled SensoReady® pen Each 0.8 ml single-dose pre-filled pen contains 40 mg of adalimumab. 20 mg solution for injection in pre-filled syringe Each 0.2 ml single-dose pre-filled syringe contains 20 mg of adalimumab. 40 mg solution for injection in pre-filled syringe Each 0.4 ml single-dose pre-filled syringe contains 40 mg of adalimumab. 40 mg solution for injection in pre-filled SensoReady® pen Each 0.4 ml single-dose pre-filled pen contains 40 mg of adalimumab. 80 mg solution for injection in pre-filled syringe Each 0.8 ml single-dose pre-filled syringe contains 80 mg of adalimumab. 80 mg solution for injection in pre-filled SensoReady® pen Each 0.8 ml single-dose pre-filled pen contains 80 mg of adalimumab.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

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

Hyrimoz / Hefiya is a biosimilar to Humira (adalimumab), which is its reference medicinal product. The active ingredient of Hyrimoz / Hefiya is a mAb with the identical primary amino acid sequence as adalimumab. Both products are also considered as similar in all other relevant quality attributes. In such a case, several safety assessments relevant for new drugs are not warranted, including developmental and reproductive toxicity, genotoxicity, carcinogenicity, as well as safety pharmacology and drug interaction studies. In line with the analytical evidence, preclinical and clinical data support the conclusion on biosimilarity of Hyrimoz / Hefiya. The extensive clinical and postmarketing experience as well as preclinical data on Humira is therefore considered relevant for Hyrimoz / Hefiya.

Two comparative toxicity studies were performed with Hyrimoz / Hefiya. Neither the 4-week repeat-dose general toxicity study in male and female cynomolgus monkeys, exceeding the clinical treatment regimen regarding dose level as well as frequency, nor the local tolerance study, assessing tolerability upon intended as well as unintended routes of exposure, showed any meaningful toxicological difference between Hyrimoz / Hefiya and Humira. The difference in formulation between the 2 products did not have an impact on the toxicity profile. The non-clinical studies performed with GP2017 did not reveal any new safety concerns which are not already known for Humira.

A high level summary on significant non-clinical safety findings from the development of Humira are summarized in Table 2-1.

Table 0-1 Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity: A 4 week repeat dose toxicity study (study number GP17-002, 100 mg/kg once every week s.c.) revealed that Hyrimoz/Hefiya had a similar toxicity profile and a similar exposure to Humira. Effects seen with historical studies of Humira in repeat-dose toxicity studies in cynomolgus monkeys involved organs of the immune system, including thymus (decreased weight, involution, reduced lymphocytes, cystic transformation) and spleen (reduced activation and cellularity of the follicular centre). In the 4-week comparative study 1 animal administered Hyrimoz / Hefiya had a mycobacterial infection which was judged as not being drug-related because it was part of an outbreak which affected four animals at the test facility.	Hyrimoz / Hefiya is a biosimilar product to Humira, which is marketed for more than 10 years. Both products show similar target binding, similar pharmacological effects and bioavailability. In line with this, the toxicity profile for both products is comparable as well.
Developmental and reproductive toxicity, genotoxicity, carcinogenicity, safety pharmacology and drug interaction studies were not performed with Hyrimoz / Hefiya in accordance with Directive	The same safety profile is expected for Humira and Hyrimoz / Hefiya, due to their high similarity.

Key Safety findings (from non-clinical studies)	Relevance to human usage
2001/83/EC and EMEA/CHMP/BMWP/42832/2005 Rev. 1.	
In rabbits, no local intolerance was observed after administration of Hyrimoz / Hefiya in the formulation proposed for marketing, neither for the intended (s.c.) route of exposure nor unintended, incidental routes of exposure (i.a., i.v., p.v. and i.m.) in study GP17-008.	Based on the data of study GP17-008 no local intolerability is expected for Hyrimoz / Hefiya in humans.

Part II Safety specification Module SIII Clinical trial exposure

Part II Module SIII Clinical trial exposure

GP2017 was developed as a biosimilar to Humira (INN: adalimumab). The active ingredient of GP2017 is adalimumab.

Hyrimoz / Hefiya is available as LCF and as HCF. The LCF is presented as single dose PFS containing 20 mg adalimumab in 0.4 mL and as single dose PFS and as single dose pre-filled pen containing 40 mg adalimumab in 0.8 mL solution for s.c. use. The HCF is presented as single dose PFS containing 20 mg adalimumab in 0.2 mL and as single dose PFS and single dose pre-filled pen containing 40 mg adalimumab in 0.4 mL or 80 mg adalimumab in 0.8 mL solution for s.c. use.

The HCF of Hyrimoz / Hefiya was developed based on the approved LCF. Both HCF and LCF contain the same active ingredient, adalimumab. In contrast to the LCF, the HCF does not contain citric acid and sodium chloride. The remainder of the excipients of the HCF are the same as those of the LCF, albeit at different concentrations. No new excipients were added to the HCF.

The LCF was used during clinical development of GP2017 as a biosimilar to Humira. The clinical development program consisted of 4 single dose PK studies in healthy subjects and 1 confirmatory efficacy and safety study in patients with moderate to severe Ps.

The 4 single dose PK studies in healthy subjects were as follows: 2 studies comparing GP2017 with Humira, 1 study comparing GP2017 administered by PFS with GP2017 administered by pre-filled pen (AI), and 1 study comparing GP2017 containing drug substance manufactured at Sandoz Biopharmaceuticals, Schaftenau, Austria, with GP2017 containing drug substance manufactured at Cook Pharmica, USA.

The pivotal 3-arm PK study GP17-104 compared GP2017 with EU-Humira and EU-Humira with US-Humira; PK similarity between these treatment groups was demonstrated. Supportive data from the 3-arm bioequivalence PK study GP17-101 are included. In this study, PK similarity between GP2017 and EU-Humira and between EU-Humira and US-Humira could not be shown, while PK similarity between GP2017 and US-Humira was demonstrated.

The 2-arm PK study GP17-102 was a randomized, open-label, single-dose parallel-group study to determine the PK and safety of GP2017 following a single s.c. injection by AI or by PFS in healthy male subjects.

A further 2-arm PK study, GP17-103, was as a randomized, double-blind, single-dose, 2-arm parallel study to determine the PK, safety, and immunogenicity of GP2017 from 2 drug substance production facilities following a single subcutaneous injection in healthy male subjects (Module 2.5 Clinical Overview).

A confirmatory efficacy and safety study (GP17-301) demonstrated equivalent efficacy and similar safety and immunogenicity of GP2017 and Humira in patients with moderate to severe Ps exposed up to 51 weeks (Module 2.5 Clinical Overview).

To support registrations in other legislations, Study GP17-302 was conducted to demonstrate equivalent efficacy and similar safety and immunogenicity between GP2017 and Humira in patients with moderate to severe RA.

The clinical development program of the HCF consisted of a single comparative PK study CGPN017B12101. Study CGPN017B12101 was a randomized, double-blind, single dose, 2-arm parallel study in healthy male subjects to demonstrate PK comparability between Hyrimoz-HCF (100 mg/mL) and Hyrimoz-LCF (50 mg/mL).

In the 4 clinical studies GP17-104, GP17-101, GP17-102, and GP17-103 in healthy subjects aged 18 to 55 years, 466 subjects received a single dose of GP2017, and 357 subjects received a single dose of Humira. In terms of gender, 442 subjects (94.8%) in the GP2017 and 306 subjects (85.7%) in the Humira treatment group were male. In terms of race, 439 subjects (94.2%) in the GP2017 and 329 subjects (92.2%) in the Humira treatment group were White (Table 3-1).

Table 0-1 Pooled demogaphic data from Studies GP17-101, GP17-102, GP17-103 and GP17-104 in healthy subjects

	GP2017 N=466	**Humira N=357**	**Total N=823**
Gender - n (%)			
Female	24 (5.2)	51 (14.3)	75 (9.1)
Male	442 (94.8)	306 (85.7)	748 (90.9)
Race - n (%)			
American Indian or Alaska Native	1 (0.2)	3 (0.8)	4 (0.5)
Asian	2 (0.4)	2 (0.6)	4 (0.5)
Black of African American	13 (2.8)	10 (2.8)	23 (2.8)
Multiple	7 (1.5)	5 (1.4)	12 (1.5)
Other	4 (0.9)	8 (2.2)	12 (1.5)
White	439 (94.2)	329 (92.2)	768 (93.3)
Ethnicity - n (%)			
Hispanic of Latino	7 (1.5)	8 (2.2)	15 (1.8)
Not Hispanic or Latino	459 (98.5)	349 (97.8)	808 (98.2)
Body weight group - n (%)			
Low (< 65 kg)	50 (10.7)	41 (11.5)	91 (11.1)
Middle (65-80 kg)	193 (41.4)	171 (47.9)	364 (44.2)
High (≥ 80 kg)	223 (47.9)	145 (40.6)	368 (44.7)
Age (years)			
n	466	357	823
Mean (SD)	35.3 (11.31)	33.4 (10.9)	34.5 (11.17)
Median (Min-Max)	33 (18-55)	30 (18-55)	32 (18-55)
Height (cm)			
n	466	357	823

	GP2017 N=466	Humira N=357	Total N=823
Mean (SD)	179.6 (7.38)	178.3 (7.88)	179 (7.63)
Median (Min-Max)	180 (159-203)	178 (151-199)	179 (151-203)
Weight (kg)			
n	466	357	823
Mean (SD)	79.7 (12.22)	76.9 (9.56)	78.5 (11.23)
Median (Min-Max)	79 (53-133)	77 (51-95)	79 (51-133)
Body Mass Index (kg/m^2)			
n	466	357	823
Mean (SD)	24.7 (3.09)	24.2 (2.41)	24.4 (2.82)
Median (Min-Max)	25 (18-40)	24 (19-29)	24 (18-40)

Exposure to GP2017 in clinical studies GP17-301 and GP17-302 in patients with Ps or RA, respectively, is summarized in the following tables.

Table 0-2 Duration of exposure during Treatment Period 1 (patients with psoriasis or rheumatoid arthritis)

Duration (days)	GP2017 N=408	Humira N=410
Mean (SD)	121.0 (33.12)	120.4 (35.24)
Median (min, max)	107.0 (1, 171)	107.0 (1, 175)
Patient exposure (years)	135.1	135.1

Exposure is defined in terms of last dose of study drug.
Patient exposure years = summation of duration of exposure for all patients in years.

Table 0-3 Duration of exposure during Treatment Period 2 (and Extension Period) (patients with psoriasis or rheumatoid arthritis)

Duration (days)	Humira to GP2017 N=229	Continued Humira N=127	GP2017 to Humira N=63	Continued GP2017 N=285
Mean (SD)	161.2 (42.54)	198.0 (59.27)	203.2 (48.69)	167.1 (54.99)
Median (min, max)	155.0 (1, 238)	225.0 (1, 235)	225.0 (16, 233)	155.0 (1, 239)
Patient exposure (years)	101.1	68.8	35.1	130.4

Exposure is defined in terms of last dose of study drug.
Patient exposure years = summation of duration of exposure for all patients in years.

Table 0-4 Duration of exposure by age group and gender during Treatment Period 1 (patients with psoriasis or rheumatoid arthritis)

Gender Age (years)	Duration (days)	GP2017 N=408	Patient exposure (years)	Humira N=410	Patient exposure (years)
Female					
Overall	n	242	85.8	234	82.2
	Mean (SD)	129.5 (35.24)		128.4 (36.66)	
	Median (min, max)	154.0 (1, 171)		154.0 (1, 175)	
18-64	n	202	71.8	196	68.6
	Mean (SD)	129.9 (34.93)		127.9 (36.02)	
	Median (min, max)	154.0 (1, 164)		153.0 (1, 175)	
65-74	n	29	9.9	30	10.8
	Mean (SD)	124.7 (39.37)		131.8 (40.21)	
	Median (min, max)	153.0 (1, 155)		154.5 (1, 156)	
75-84	n	11	4.1	7	2.4
	Mean (SD)	135.9 (30.90)		123.7 (45.12)	
	Median (min, max)	153.0 (77, 171)		154.0 (36, 156)	
≥ 85	n	0	N/A	1	0.4
	Mean (SD)	N/A		153.0 (N/A)	
	Median (min, max)	N/A		153.0 (153, 153)	
Male					
Overall	n	166	49.3	176	52.9
	Mean (SD)	108.5 (25.07)		109.8 (30.23)	
	Median (min, max)	106.0 (1, 158)		106.0 (8, 170)	
18-64	n	148	43.6	152	45.0
	Mean (SD)	107.5 (23.17)		108.0 (30.35)	
	Median (min, max)	106.0 (8, 158)		106.0 (8, 157)	
65-74	n	17	5.5	22	7.2
	Mean (SD)	117.3 (38.14)		120.0 (27.61)	
	Median (min, max)	107.0 (1, 156)		106.0 (63, 170)	
75-84	n	1	0.3	2	0.7
	Mean (SD)	105.0 (N/A)		130.0 (35.36)	
	Median (min, max)	105.0 (105, 105)		130.0 (105, 155)	
≥ 85	n	0	N/A	0	N/A
	Mean (SD)	N/A		N/A	
	Median (min, max)	N/A		N/A	

Exposure is defined in terms of last dose of study drug.
Patient exposure years = summation of duration of exposure for all patients in years.

Table 0-5 Duration of exposure by age group and gender during Treatment Period 2 (and Extension Period) (patients with psoriasis or rheumatoid arthritis)

Gender Age (years)	Duration (days)	Humira to GP2017 N=229	Continued Humira N=127	GP2017 to Humira N=63	Continued GP2017 N=285
Female					
Overall	n	161	46	27	181
	Mean (SD)	153.9 (41.97)	193.3 (65.64)	206.8 (50.8)	158.9 (48.32)
	Median (min, max)	155.0 (1, 229)	224.5 (1, 235)	225.0 (16, 230)	155.0 (1, 239)
	Patient exposure (years)	67.9	24.4	15.3	78.8
18-64	n	132	42	22	151
	Mean (SD)	154.2 (43.03)	190.8 (68.17)	203.3 (55.9)	159.4 (47.34)
	Median (min, max)	155.0 (1, 229)	225.0 (1, 235)	225.0 (16, 230)	155.0 (1, 239)
	Patient exposure (years)	55.7	21.9	12.2	65.9
65-74	n	22	4	4	22
	Mean (SD)	149.0 (31.99)	220.3 (8.18)	221.3 (6.24)	158.2 (54.51)
	Median (min, max)	155.0 (57, 225)	221.0 (210, 229)	224.0 (212, 225)	155.0 (1, 232)
	Patient exposure (years)	9.0	2.4	2.4	9.5
75-84	n	6	0	1	8
	Mean (SD)	179.5 (35.68)	N/A	226.0 (N/A)	152.4 (55.21)
	Median (min, max)	158.0 (155, 226)	N/A	226.0 (226, 226)	156.0 (29, 223)
	Patient exposure (years)	2.9	N/A	0.6	3.3
≥ 85	n	1	0	0	0
	Mean (SD)	71.0 (N/A)	N/A	N/A	N/A
	Median (min, max)	71.0 (71, 71)	N/A	N/A	N/A
	Patient exposure (years)	0.2	N/A	N/A	N/A
Male					
Overall	n	68	81	36	104
	Mean (SD)	178.5 (39.00)	200.6 (55.59)	200.5 (47.52)	181.4 (62.72)
	Median (min, max)	156.0 (90, 238)	225.0 (1, 234)	225.0 (71, 233)	223.0 (1, 232)
	Patient exposure (years)	33.2	44.5	19.8	51.7
18-64	n	59	67	32	92

Gender Age (years)	Duration (days)	Humira to GP2017 N=229	Continued Humira N=127	GP2017 to Humira N=63	Continued GP2017 N=285
	Mean (SD)	183.8 (38.22)	205.9 (45.78)	202.7 (46.59)	182.6 (62.16)
	Median (min, max)	159.0 (112, 238)	225.0 (44, 232)	225.0 (71, 233)	223.0 (1, 232)
	Patient exposure (years)	29.7	37.8	17.8	46.0
65-74	n	8	13	3	12
	Mean (SD)	142.9 (26.38)	171.4 (89.09)	211.3 (21.94)	172.8 (69.10)
	Median (min, max)	155.0 (90, 162)	224.0 (1, 234)	224.0 (186, 224)	188.5 (1, 228)
	Patient exposure (years)	3.1	6.1	1.7	5.7
75-84	n	1	1	1	0
	Mean (SD)	156.0 (N/A)	226.0 (N/A)	99.0 (N/A)	N/A
	Median (min, max)	156.0 (156, 156)	226.0 (226, 226)	99.0 (99, 99)	N/A
	Patient exposure (years)	0.4	0.6	0.3	N/A
≥ 85	n	0	0	0	0
	Mean (SD)	N/A	N/A	N/A	N/A
	Median (min, max)	N/A	N/A	N/A	N/A
	Patient exposure (years)	N/A	N/A	N/A	N/A

Exposure is defined in terms of last dose of study drug.
Patient exposure years = summation of duration of exposure for all patients in years.

In Study CGPN017B12101, a total of 330 subjects were exposed to 1 dose of study treatment, 162 subjects to 40 mg s.c. Hyrimoz-HCF and 168 subjects to 40 mg s.c. Hyrimoz-LCF.

Demographics and baseline characteristics, including body weight and BMI were well balanced between the 2 treatment groups (Table 3-6).

Table 0-6 Demographic summary of Study CGPN017B12101

Characteristic Categories/Statistics	Hyrimoz-HCF N=162	Hyrimoz-LCF N=168
Age (years)		
n	162	168
Mean (SD)	36.8 (9.04)	37.8 (9.52)
Median	36.0	37.5
Min-Max	18-55	19-55
Sex – n (%)		
Male	162 (100)	168 (100)

Characteristic Categories/Statistics	Hyrimoz-HCF N=162	Hyrimoz-LCF N=168
Race – n (%)		
American Indian or Alaska Native	0	1 (0.6)
Asian	1 (0.6)	1 (0.6)
Black or African American	38 (23.5)	26 (15.5)
Multiple	1 (0.6)	0
White	122 (75.3)	140 (83.3)
Ethnicity – n (%)		
Hispanic or Latino	134 (82.7)	140 (83.3)
Not Hispanic or Latino	28 (17.3)	28 (16.7)
Height (cm)		
n	162	168
Mean (SD)	173.7 (6.47)	174.4 (6.65)
Median	173.0	173.0
Min-Max	159-197	159-193
Weight (kg)		
n	162	168
Mean (SD)	81.21 (9.101)	81.24 (8.792)
Median	81.90	80.05
Min-Max	65.1-109.8	65.0-107.0
Weight stratification factor – n (%)[1]		
65.0 - <76.0 kg	50 (30.9)	50 (29.8)
76.0 - <92.0 kg	94 (58.0)	100 (59.5)
92.0 - 110.0 kg	18 (11.1)	18 (10.7)
BMI (kg/m^2)		
n	162	168
Mean (SD)	26.90 (2.242)	26.70 (2.343)
Median	27.41	26.92
Min-Max	20.7-29.9	20.5-29.9

[1] For 8 subjects that were placed into incorrect weight strata at randomization, weight stratification factors were based on subject's body weight at baseline instead of the assigned weight stratum in IRT.

Part II Safety specification Module SIV: Populations not studied in clinical trials

Since this MAA has been submitted for a similar biological medicinal product under Article 10 (4) of Directive 2001/83/EC, as amended, a tailored clinical program was justified. Ps is considered an appropriate sensitive indication that can be used to detect differences between treatments, if any exist. Therefore, the confirmatory efficacy and safety study GP17-301 was conducted in patients with moderate to severe chronic plaque Ps. The design, conduct, and within group response rates of study GP17-301 were generally similar to those characteristics in historical clinical trials that demonstrated relatively large and consistent treatment effects of adalimumab over placebo.

Part II Module SIV.1. Exclusion criteria in pivotal clinical studies within the development program

Table 0-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Forms of psoriasis other than chronic plaque-type (e.g. pustular, erythrodermic and guttate psoriasis) and drug-induced psoriasis (i.e. new onset or current exacerbation from e.g. beta-blockers, or lithium)	Different psoriasis entity with unknown efficacy and safety profile for adalimumab	No	Not an approved indication
Systemic manifestation of rheumatoid arthritis, except for rheumatoid nodules and Sjogren syndrome	Different rheumatoid arthritis entity with unknown efficacy and safety profile for adalimumab	No	Not an approved indication
Ongoing use of prohibited psoriasis treatments (e.g. topical or systemic corticosteroids, UV-therapy)	Possible interference with efficacy assessment	Yes	
Previous exposure to adalimumab	Possible interference with efficacy assessment and possible impact on safety and immunogenicity	Yes	

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Any known exposure to any TNFα inhibitor in the past	Possible interference with efficacy assessment and possible impact on safety and immunogenicity	Yes	
Use of other investigational drugs at the time of signing the informed consent form, or within 3 months, or 5 half-lives at the time of signing the informed consent form, whichever was longer	Possible interference with efficacy assessment and possible unknown impact on safety and immunogenicity	No	Use of unapproved medications
Active ongoing inflammatory diseases other than psoriasis or rheumatoid arthritis that might have confounded the evaluation of the benefit of treatment with adalimumab	Possible interference with study efficacy assessments	Yes	
Underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal) which in the opinion of the investigator significantly immunocompromised the patient and/or placed the patient at unacceptable risk for receiving an immunomodulatory therapy	possible interference with study assessments and impact on safety	Yes	
History of an ongoing, chronic or recurrent infectious disease history of active tuberculosis or presence of latent (inactive) tuberculosis	Possible impact on safety, listed in Section Warning and Precautions of Humira SmPC	Yes	
Had received live vaccination within 6 weeks prior to randomization or planned to receive one during the study	Possible impact on safety	Yes	

Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

Clinical study experience with GP2017 comprises 639 patients with chronic plaque-type psoriasis or moderate to severe RA. This experience is unsuitable to detect rare adverse reactions, reactions with a long latency or due to cumulative effects, or reactions that are specific to other target populations than patients with Ps or RA. The study program for GP2017 is also not suitable to recognize rare differences between the originator product and the biosimilar.

However, since GP2017 exhibited physical, chemical and functional similarity to Humira, had a similar PK, PD and safety profile to that of Humira in non-clinical studies and a similar PK and safety profile in the clinical studies, it is justified to build also on the extensive clinical trial experience that has accumulated for the originator product Humira. As of 31-Dec-2015, a total of 41872 subjects have been enrolled in adalimumab trials and registry studies (33200 treated with adalimumab with > 45,000 PTYs of exposure) in RA, JIA, pediatric enthesitis-related arthritis, PsA, CD, pediatric CD, Ps, pediatric Ps, UC, AS, SpA, non-radiographic axial SpA, HS, uveitis, or intestinal Behçet's disease. The estimated cumulative postmarketing patient exposure since the international birth date (31-Dec-2002) through 31-Dec-2015 is almost 4.3 million PTYs (EMEA/H/C/000481/II/0158). This vast clinical experience is sufficient to detect reliably rare adverse reactions (≤1 in 10,000) and even those as infrequent as 1:100000, which is considered as very rare. These adverse reactions are reflected in the current Humira SmPC and the Hyrimoz / Hefiya SmPC.

Children

There is no clinical study experience with GP2017 in children. There is, however, quite extensive clinical study experience with Humira in the treatment of children with:

- Polyarticular juvenile idiopathic arthritis in children from 2 years of age and older
- Enthesitis-related arthritis in children from 6 years of age and older
- Crohn's disease in children from 6 years of age
- Plaque psoriasis in children from 4 years of age
- HS adolescents from 12 years of age with an inadequate response to conventional systemic HS therapy

Humira is approved in these indications (Humira SmPC) and GP2017 is proposed for pediatric indications and respective age groups that are eligible to be administered a full dose of 40 mg as single subcutaneous injection.

In addition, the EMA Paediatric Committee has agreed to grant waivers based on the extremely low incidence for the following patient populations: Children aged less than 12 years for HS, children aged less than 6 years for CD, children aged less than 4 years for UC and Ps, children aged less than 2 years for polyarticular juvenile idiopathic arthritis, PsA, and noninfectious uveitis, and children aged less than 6 years for pediatric enthesis-related arthritis.

Long term Humira safety information in the treatment of children aged from 6 to less than 18 years with CD is missing.

Elderly

Clinical study experience with GP2017 in the elderly is limited and no pharmacokinetic data are available from this population. However, based on the PK of Humira in older patients it has been concluded that no dose adjustment is required for older subjects (Humira SmPC). As the pharmacokinetic properties of GP2017 and Humira are similar, the same should apply to GP2017.

With the originator product Humira, however, there is significant clinical trial and postmarketing experience in the elderly age group. The frequency of serious infections among Humira treated subjects over 65 years of age (3.7%) was higher than for those under 65 years of age (1.5%). Some of those had a fatal outcome. The increased risk of infections in elderly is added to the SmPC. Particular attention should be paid when treating the elderly (Hyrimoz / Hefiya SmPC).

Pregnant or breast feeding women

Pregnant women have not been directly studied in Humira clinical trials. However, limited AE data derived from 28 global adalimumab RA trials in 15,132 patients suggest – using in addition the information from the Adalimumab Pregnancy Registry – that pregnancy outcomes in healthy women without RA and not exposed to adalimumab (N=219), women with RA exposed to adalimumab (N=74) and women with RA exposed to Placebo (N=80) are similar (Burmester et al 2016).

A large number (approximately 2100) of prospectively collected pregnancies exposed to adalimumab resulting in live birth with known outcomes, including more than 1500 exposed during the first trimester, does not indicate an increase in the rate of malformation in the newborn.

In a prospective cohort registry, 257 women with rheumatoid arthritis (RA) or Crohn's disease (CD) treated with adalimumab at least during the first trimester and 120 women with RA or CD not treated with adalimumab were enrolled. The primary endpoint was the birth prevalence of major birth defects. The rate of pregnancies ending with at least one live born infant with a major birth defect was 6/69 (8.7 %) in the adalimumab-treated women with RA and 5/74 (6.8 %) in the untreated women with RA (unadjusted OR 1.31, 95 % CI 0.38–4.52) and 16/152 (10.5 %) in the adalimumab-treated women with CD and 3/32 (9.4 %) in the untreated women with CD (unadjusted OR 1.14, 95 % CI 0.31–4.16). The adjusted OR (accounting for baseline differences) was 1.10 (95% CI 0.45–2.73) with RA and CD combined. There were no distinct differences between adalimumab-treated and untreated women for the secondary endpoints spontaneous abortions, minor birth defects, preterm delivery, birth size and serious or opportunistic infections and no stillbirths or malignancies were reported. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomized design.

In a developmental adalimumab (Humira) toxicity study conducted in monkeys, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. Preclinical data on postnatal toxicity or fertility of adalimumab are not available. Due to its inhibition of TNF, adalimumab administered during pregnancy could affect normal immune responses in the newborn. Adalimumab should only be used during pregnancy if clearly needed (Hyrimoz / Hefiya SmPC).

Limited information from the published literature indicates that adalimumab is excreted in breast milk at very low concentrations with the presence of adalimumab in human milk at concentrations of 0.1 % to 1 % of the maternal serum level. Given orally, immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability. No effects on the breastfed newborns / infants are anticipated. Consequently, Hyrimoz can be used during breastfeeding (Hyrimoz / Hefiya SmPC).

Two pregnancies were observed in study GP17-301. One was an extra-uterine pregnancy and was treated by surgery; the other pregnancy resulted in a delivery of a healthy baby.

Patients with hepatic or renal impairment

Patients with hepatic or renal impairment have not been directly studied in Humira clinical trials. Since adalimumab is a protein, it is likely to be metabolized in a similar fashion as other human antibodies, which is not significantly impaired even in patients with end-stage liver or kidney disease.

Adalimumab has not been studied in this patient population. No dose recommendations can be made (Hyrimoz / Hefiya SmPC).

Patients with other relevant co-morbidity

Hepatitis B reactivation

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including Humira, who are chronic carriers of this virus (i.e. surface antigen positive). Some cases have had a fatal outcome. Patients should be tested for HBV infection before initiating treatment with Humira. For patients who test positive for hepatitis B infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Carriers of HBV who require treatment with Humira should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data from treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, Humira should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Tuberculosis

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

Before initiation of therapy with Humira, all patients must be evaluated for both active or inactive ("latent") tuberculosis infection. This evaluation should include a detailed medical assessment of patient history of tuberculosis or possible previous exposure to people with active tuberculosis 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). It is recommended that the conduct and results of these tests are recorded in the patient reminder card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, Humira therapy must not be initiated.

In all situations described below, the benefit/risk balance of therapy should be very carefully considered.

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted.

If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylaxis treatment before the initiation of Humira, and in accordance with local recommendations.

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

Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with Humira. Some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with Humira.

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

Congestive heart failure

In a clinical trial with another TNF inhibitor worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Cases of worsening congestive heart failure have also been reported in patients receiving Humira. Adalimumab should be used with caution in patients with mild heart failure (New York Heart Association class I/II). Adalimumab is contraindicated in moderate to severe heart failure (New York Heart Association class III/IV). Treatment with adalimumab must be discontinued in patients who develop new or worsening symptoms of congestive heart failure. This is reflected in the Hyrimoz / Hefiya SmPC.

Surgery

The clinical experience of surgical procedures in patients treated with Humira is limited. A patient who requires surgery while on adalimumab should be closely monitored for infections, and appropriate actions should be taken. This is reflected in the Hyrimoz / Hefiya SmPC.

Immunocompromised patients

The concomitant use of some immunosuppressants, which are mentioned in the SmPC, is not recommended due to the increased risk of infection (Hyrimoz / Hefiya SmPC).

Concurrent administration of biologic DMARDs or TNF-antagonists (Immune suppression)

Serious infections were seen in clinical studies with concurrent use of anakinra and the TNF inhibitor etanercept with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNF inhibitors. Therefore, the combination of adalimumab and anakinra is not recommended. Concomitant administration of adalimumab with other biologic DMARDS (e.g. anakinra and abatacept) or other TNF-antagonists is not recommended based upon the possible increased risk for infections, including serious infections (Hyrimoz / Hefiya SmPC).

Patients with a disease severity different from the inclusion criteria in the clinical trial population

Chronic plaque psoriasis

Humira has been studied in patients of a defined disease severity for the approved indications and is not approved for other forms of severity of the disease. For instance, adalimumab has been studied in patients with moderate to severe chronic plaque psoriasis but not in patients with “mild” psoriasis. Less severe forms of psoriasis as well as unapproved severities of other indications should be amenable to standard of care treatment. However, according to a current European S3-Guideline on the systemic treatment of psoriasis patient with mild psoriasis (‘PASI ≤10 and BSA ≤10 and DLQI ≤10’) may be upgraded to moderate severity when taking into account the patient’s perspective (e.g. major involvement of visible areas) (Nast et al 2015).

Sub-populations carrying known and relevant polymorphisms

There are no known relevant genetic polymorphisms that affect metabolism, degradation or pharmacological effects of TNF inhibitors including adalimumab.

The clinical trials with Humira and GP2017 enrolled mostly Caucasians but also subjects of other ethnic/racial origin. There are no known obvious safety or tolerability differences with regard to racial groups reported.

Part II Module SIV.3. Limitations in respect to populations typically under represented in clinical trial development programs

Table 0-2 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	not included in the clinical development program
Breastfeeding women	not included in the clinical development program
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	not included in the clinical development program
Subpopulations carrying relevant genetic polymorphisms	not included in the clinical development program
Other:	
• Children	not included in the clinical development program
• Elderly	120 patients ≥ 65 years old included into the clinical development program

Part II Safety specification Module SV: Post-authorization experience

Part II Module SV.1. Post-authorization exposure

Part II Module SV.1.1 Method used to calculate exposure

An estimate of patient exposure is calculated based on worldwide sales volume in mg of active substance sold cumulatively and the DDD.

The DDD is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose. Therapeutic doses for individual patients and patient groups will often differ from the DDD, as they will be based on individual characteristics (such as age, weight, type and severity of disease) and pharmacokinetic considerations. Drug utilization data presented in DDDs only give a rough estimate of consumption.

As per WHO/ATC, the DDD of Hyrimoz is 2.9 mg.

Post-authorization estimate exposure is calculated using the following formula:

Estimated exposure in PTYs = Total number of mg sold/recommended daily dose×365 days⁄year.

Part II Module SV.1.2 Exposure

The estimated cumulative post-approval exposure to the LCF of Hyrimoz is approximately 179,471 PTY, based on a DDD of 2.9 mg (Table 5-1).

Table 0-1 Estimated post-marketing exposure (DDD of 2.9 mg)

Formulation	Cumulative Until 30-Jun-2025	
	Amount sold (mg)	Estimated exposure (PTY)
Pre-filled pen	761,375,904	719,297
Pre-fill syringe	225,034,968	212,598
Total	**986,410,873**	**931,895**

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

Potential for misuse for illegal purposes

Not applicable, as a potential for abuse and dependence is not anticipated based on the mechanism of action of adalimumab.

Part II Safety specification Module SVII: Identified and potential risks

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

This section is not applicable, the RMP was already approved.

Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

The safety concerns are updated in line with the RMP public summary for the reference product Humira v.16.2 dated Sep 2024. Below changes were implemented:

'Patients with immune-compromised conditions' and 'Long-term safety information in the treatment of children with uveitis' previously classified as missing information is now removed from the list of safety concerns.

'Episodic treatment in Ps, UC, and JIA' reworded to 'Episodic treatment in UC' in missing information.

Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Serious infections

Incidence, severity and outcome of treatment-emergent AEs of serious infections are summarized in Table 7-1 for all healthy subjects and patients exposed to at least 1 dose of GP2017. Treatment-emergent AEs of serious infections were not observed in Study CGPN017B12101 in healthy male subjects comparing Hyrimoz-HCF with the Hyrimoz-LCF.

Other details are presented in Table 7-2.

Table 0-1 GP2017 clinical trial data of serious infections (healthy subjects and patients with Ps or RA)

	Healthy subjects exposed to 1 dose of GP2017 in Studies GP17-101, GP17-102, GP17-103 and GP17-104 N=466 n (%) 95% CI	Healthy subjects exposed to 1 dose of Hyrimoz HCF or Hyrimoz-LCF in Study CGPN017B12101 N=330 n (%) 95% CI	Patients exposed to at least 1 dose of GP2017 in Studies GP17-301, GP17-302 N=639 n (%) 95% CI
Number of subjects or patients with at least 1 event	1 (0.2) (0.01 - 1.19)	0	8 (1.3) (0.54 - 2.45)
Maximum severity			
Mild	1 (0.2)	0	0
Moderate	0	0	4 (0.6)
Severe	0	0	4 (0.6)
SAEs	1 (0.2)	0	8 (1.3)
AE outcome			
Recovered/resolved	1 (0.2)	0	6 (0.9)
Recovering/resolving	0	0	2 (0.3)
Not recovered/not resolved	0	0	0
Recovered/resolved with sequelae	0	0	0
Fatal	0	0	0
Unknown	0	0	0
Leading to death	0	0	0

Numbers (n) represent counts of subjects or patients.
MedDRA versions 22.1 (Studies GP17-101, GP17-102, GP17-103, GP17-104, GP17-301, and GP17-302) and 24.1 (Study CGPN017B12101)

Table 0-2 Important identified risk serious infections: Other details

Serious infections	Details
MedDRA Search terms for spontaneous post-marketing data	SOC Infections and infestations, (excluding Tuberculosis and PML related preferred terms)
Potential mechanisms	TNF plays a complex role in innate immunity and host defence (Tracey et al 2008); an inhibition of TNF by TNF inhibitors affect the defence against pathogens (Sozzani et al 2014) and usually create an immunosuppressant status (Sedger and McDermott 2014).
Evidence source(s) and strength of evidence	Serious infections are listed in section 4.4 Special warnings and precautions and section 4.8 Undesirable effects of the Humira SmPC and are considered to be an important identified risk of the reference product Humira. Serious infections are therefore considered as an important identified risk of Hyrimoz / Hefiya, a biosimilar to Humira.

Serious infections	Details
Characterization of the risk	Studies in healthy subjects: 1 subject (0.2%) reported acute appendicitis categorized as serious and not related to study drug in Study GP17-102 (Table 0-1). GP2017 studies in patients (GP17-301 and GP17-302): Serious infections were reported for 8 patients (pneumonia (3 patients) and pneumonia bacterial), pyelonephritis, staphylococcal infection, diverticulitis, and bronchitis (each in 1 patient)) (Table 0-1). Humira SmPC: In Humira clinical trials the incidence of serious infections was 0.04 per PTY in adalimumab treated patients and 0.03 per PTY in placebo and active control treated patients. In controlled and open label adult and pediatric studies with adalimumab, serious infections (including fatal infections, which occurred rarely) have been reported, which invasive opportunistic infections (e.g. disseminated or extrapulmonary histoplasmosis, blastomycosis, coccidioidomycosis, pneumocystis candidiasis, aspergillosis and listeriosis). In the pivotal Humira controlled trials in adults and children, the rate of non-serious and serious infections was 1.51 per PTY in the adalimzumab treated patients and 1.46 per PTY in the placebo and active control-treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, and sinusitis. Most patients continued on adalimumab after the infection resolved.
Risk factors and risk groups	Serious infections were reported in both adult and pediatric subjects treated with TNF inhibitors and across all indications. Patients concomitantly treated with other immunosuppressant medicines are at increased risk as well as a past medical history of serious infections, glucocorticoid dose, and older age (> 65 years). These are important independent predictors of serious infection risks in patients treated with TNF inhibitors. Patients with RA had a 2-fold increased adjusted risk of hospitalized infections compared to those without RA concluded from a retrospective cohort. Current prednisone use > 7.5 mg/day, previous infections and previous hospitalized infections increased the risk of hospitalized infections as well as probably RA disease activity (Galloway et al 2011, Singh 2016).
Preventability	Carefully evaluate patients for active (and hidden) infections and treat them promptly. Reduce concomitant immune suppressive treatments to a minimum to maintain or achieve envisaged treatment goal.
Impact on the benefit-risk balance of the product	The totality of the evidence established similarity of GP2017 to the reference product EU-Humira in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise as required by CHMP/437/04 Rev. 1. Overall, the results of the global development program confirm that GP2017 is biosimilar to the reference product EU-Humira and has a similar and positive benefit-risk ratio.
Public health impact	Serious infections are not likely to be transmitted by casual contact with an infected individual and therefore public health impact is expected to be low.

Important identified risk: Tuberculosis (TB)

TB was not reported in healthy subjects treated with a single dose of GP2017 or Hyrimoz-HCF and in patients treated with at least 1 dose of GP2017. One patient with Ps treated with US-

Humira was reported with TB in study GP17-301; this patient was laboratory and imaging negative for TB at screening.

Other details are presented in Table 7-3.

Table 0-3 Important identified risk tuberculosis (TB): Other details

Tuberculosis	Details
MedDRA Search terms for spontaneous post-marketing data	HLT Mycobacteria identification and serology and HLT Tuberculous infections
Potential mechanisms	TNF plays a complex role in innate immunity and host defence (Tracey et al 2008); an inhibition of TNF by TNF inhibitors affect the defence against pathogens (Sozzani et al 2014) and usually create an immunosuppressant status (Sedger and McDermott 2014).
Evidence source(s) and strength of evidence	TB is listed in section 4.4 Special warnings and precautions and section 4.8 Undesirable effects of the Humira SmPC and is considered to be an important identified risk of the reference product Humira. TB is therefore considered as an important identified risk of Hyrimoz / Hefiya, a biosimilar to Humira.
Characterization of the risk	Subjects with a positive laboratory result and imaging for active or latent tuberculosis at screening were excluded from study participation in the GP2017 development program. Studies in healthy subjects: No case of TB was reported in 796 healthy subjects. GP2017 studies in patients (GP17-301 and GP17-302): TB was not reported for patients treated with at least 1 dose of GP2017. TB was reported for 1 patient treated with US-Humira in study GP17-301; this patient was laboratory and imaging negative for TB at screening. In the Humira SmPC, TB is described as an uncommon undesirable effect. The incidence of serious infections (including TB) was 0.04 per PTY in Humira treated patients and 0.03 per PTY in placebo and active control treated patients. Comprehensive long-term safety data of Humira from 18 clinical trials in adult Ps patients showed an incidence rate for TB of 0.3 events/100 PTYs (Leonardi et al 2019).
Risk factors and risk groups	Tuberculosis has been reported in adult and pediatric subjects treated with TNF inhibitors and across all indications. Patients concomitantly treated with other immunosuppressant medicines are at increased risk as well as a past medical history of serious infections, glucocorticoid dose, and older age (> 65 years). These are important independent predictors of serious infection risks in patients treated with TNF inhibitors (Dixon 2010, Galloway et al 2011, Singh 2016).
Preventability	All patients must be screened for latent TB before initiating adalimumab. Carefully evaluate patients for active (and hidden) infections and treat them promptly. Reduce concomitant immune suppressive treatments to a minimum to maintain or achieve envisaged treatment goal.
Impact on the benefit-risk balance of the product	The totality of the evidence established similarity of GP2017 to the reference product EU-Humira in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise as required by CHMP/437/04 Rev. 1. Overall, the results of the global development program

Tuberculosis	Details
	confirm that GP2017 is biosimilar to the reference product EU-Humira and has a similar and positive benefit-risk ratio.
Public health impact	TB in individuals exposed to adalimumab may lead to a public health burden due to the fact that the TB bacillus is spread from person to person by airborne transmission (LoBue et al 2010).

Important Identified Risk: Malignancies

Malignancies were not reported in healthy subjects treated with a single dose of GP2017 or Hyrimoz-HCF. Incidence, severity and outcome of treatment-emergent AEs of malignancies are summarized in Table 7-4 for all patients exposed to at least 1 dose of GP2017. Other details are presented in Table 7-5.

Table 0-4 Clinical trial data of malignancies (patients with Ps or RA)

	Patients exposed to at least 1 dose of GP2017 N=639 n (%) 95% CI
Number of patients with at least 1 event	3 (0.5) (0.10 - 1.37)
Maximum severity	
Mild	0
Moderate	3 (0.5)
Severe	0
SAEs	2 (0.3)
AE outcome	
Recovered/resolved	3 (0.5)
Recovering/resolving	0
Not recovered/not resolved	1 (0.2)
Recovered/resolved with sequelae	0
Fatal	0
Unknown	0
Leading to death	0

Numbers (n) represent counts of patients.
MedDRA version 22.1

Table 0-5 Important identified risk malignancies: Other details

Malignancies	Details
MedDRA Search terms for spontaneous post-marketing data	SMQ Malignancies
Potential mechanisms	The immune system can recognize and destroy nascent transformed cells and as this function maybe impacted in immune compromised patients, it may be the

Malignancies	Details
	mechanism of action for increased malignancy risk. Data clearly show the existence of cancer immunosurveillance and also indicate that it may function as a component of a more general process of cancer immunoediting. This process is responsible for both eliminating tumors and sculpting the immunogenic phenotypes of tumors that eventually form in immunocompetent hosts (Dunn 2002, Mohme 2017).
Evidence source(s) and strength of evidence	Malignancies (including lymphoma, HSTCL, leukemia, NMSC, melanoma, Merkel cell carcinoma, and other malignancies) are listed in section 4.4 Special warnings and precautions and section 4.8 Undesirable effects of the Humira SmPC and are considered to be an important identified risk of the reference product Humira. Malignancies are therefore considered as an important identified risk of Hyrimoz / Hefiya, a biosimilar to Humira.
Characterization of the risk	Studies in healthy subjects: There were no such events reported in 796 healthy subjects. GP2017 studies in patients (GP17-301 and GP17-302): There were no events of lymphoma, HSTCL, leukemia, melanoma, or Merkel cell carcinoma reported in the 639 patients exposed to at least 1 dose of GP2017. Four events of malignancy were reported for 3 of 639 (0.5%) patients exposed to at least 1 dose of GP2017. These were 3 events of basal cell carcinoma (2 reported as SAE), and for 1 of these patients, additionally an SAE of prostate cancer was reported. All events of basal cell carcinoma resolved. The prostate cancer was considered not resolved at the time of last reporting and was not suspected to be related to study drug. **Lymphoma** Humira SmPC: During the controlled portions of pivotal Humira trials in adults of at least 12 weeks duration across indications the rate of lymphomas was 0.7 (95% CI 0.2, 2.7) per 1000 PTYs among adalimumab-treated patients and 0.6 (95% CI 0.1, 4.5) per 1000 PTYs among control patients. The frequency of lymphoma – based on Humira RCT and open extension trial data – is declared as uncommon. **HSTCL** Humira SmPC: Rare post marketing cases of hepatosplenic T-cell lymphoma have been identified in patients treated with adalimumab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Some of these hepatosplenic T-cell lymphomas with Humira have occurred in young adult patients on concomitant treatment with azathioprine or 6-mercaptopurine used for inflammatory bowel disease. The potential risk with the combination of azathioprine or 6-mercaptopurine and GP2017 should be carefully considered. A risk for the development of hepatosplenic T-cell lymphoma in patients treated with adalimumab cannot be excluded; the frequency of this event is not known. In Humira SmPC, the frequency – based on Humira RCT and spontaneous reporting data – is declared as not known. **Leukemia** Rare cases of leukemia have been reported – including post-marketing data – with use of adalimumab (Humira). In Humira SmPC the frequency – based on Humira RCT and spontaneous reporting data – is declared as rare. **NMSC** Humira SmPC: During the controlled portions of pivotal Humira trials in adults of at least 12 weeks in duration the rate (95% CI) of non-melanoma skin cancers was 8.8 (6.0, 13.0) per 1000 PTYs among adalimumab-treated patients and 3.2 (1.3,

Malignancies	Details
	7.6) per 1000 PTYs among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates of 2.7 (1.4, 5.4) per 1000 PTYs among active and 0.6 (0.1, 4.5) per 1000 PTYs among control patients. When combining controlled portions of these trials and ongoing and completed open label extension studies with a median duration of approximately 3.3 years including 6,427 patients and over 26,439 PTYs of therapy the observed rate of non-melanoma skin cancers is approximately 9.6 per 1000 PTYs. The reported rate for non-melanoma skin cancers in the Humira post-marketing setting is approximately 0.2 per 1,000 PTYs. In Humira SmPC the frequency for skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma) is declared as common. **Melanoma** Humira SmPC: Melanoma has been reported in patients treated with TNF inhibitors including adalimumab. The frequency – based on Humira RCT, open extension trial and spontaneous reporting data – is declared as uncommon. **Merkel cell carcinoma** Humira SmPC: Merkel cell carcinoma has been reported in patients treated with TNF inhibitors including adalimumab. The frequency – based on Humira RCT, open extension trial data and spontaneous reporting data – is declared as unknown. **Other malignancies** Humira SmPC: In an exploratory clinical trial evaluating the use of another TNF blocker, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Therefore, caution should be exercised when using any TNF inhibitor in COPD patients, as well as in patients with increased risk for malignancy due to heavy smoking. With current data it is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer. 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. Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy ≤ 18 years of age), including adalimumab in the post marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded (Humira SmPC).
Risk factors and risk groups	**Lymphoma** For Hodgkin lymphoma age at diagnosis is a strong risk factor for survival, for non-Hodgkin lymphoma gender with a higher survival rate in males (De Angelis et al 2015). The most commonly used prognostic system for Hodgkin lymphoma is the International Prognostic System, which uses the following factors: serum albumin

Malignancies	Details
	less than 4 g/dL, hemoglobin less than 10.5 g/dL, male sex, age ≥45, stage IV disease, WBC count >15,000/µL, absolute lymphocyte count <600/µL or <8% of the total WBC count or both (Lash 2016). **HSTCL** A moderate risk factor is immune-mediated disease, concomitant azathioprine, and possibly TNF inhibitor treatment (Montgomery et al 2015). **Leukemia** General risk factors are gender and age. Men are more likely to develop CML, CLL and AML than women. The risk of most leukemias, with the exception of ALL, typically increases with age. Genetics: For most leukemias there is no clear link. First degree relatives of CLL patients or identical twins of AML or ALL patients are at increased risk. Lifestyle: Smoking cigarettes increase risks for AML. Exposures: High-energy radiation, long term exposure to chemicals such as pesticides or industrial chemicals like benzene are considered a risk. Previous treatment: Certain types of chemotherapy and radiation therapy for other cancers are considered leukemia risk factors (Cancer Treatment Centers of America 2016). **NMSC** BCC: white skin type, male sex, sunlight exposure - patient geographic location affects the risk of developing skin cancer. A latency period of 20-50 years is typical between the time of ultraviolet damage and clinical onset of cancer, gene mutations, X-ray, immunosuppressed patients, previous non-melanoma skin cancer (Bader 2016). Squamous cell carcinoma: Patient related risk factors are organ transplantation, hematologic malignancy, long-term immunosuppressive therapy, HIV infection or AIDS (Najjar 2016). **Merkel cell carcinoma** The following factors are associated with increased risks: Whites / fair skin, UV radiation, age, long-term immunosuppression (risk 15 times increased compared to general population), RA, autoimmune disorders, organ transplantation, HIV, arsenic exposure, Merkel cell polyomavirus (Lowe et al 2013). **Melanoma** Important tumor specific risk factors are depth of invasion, the presence or absence of ulceration, and the nodal status at diagnosis. Patient factors are white skin, age, sun exposure (Leiter et al 2014, Tan 2016). TNF seems to be a negative prognostic factor in melanoma surgery and correlates with chemotherapy resistance. However, high intra-tumor levels of TNF might be beneficial for immunotherapy (Nenu et al 2015). **Other malignancies** No specific risk groups or risk factors are known within the population of patients treated with adalimumab.
Preventability	The Hyrimoz / Hefiya SmPC section Warnings and precautions includes the texts on malignancies, the patient leaflets also includes the recommendation to inform physician when signs of cancer are observed. In addition, additional risk minimization measures contain relevant safety messages for patients.

Malignancies	Details
	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. Melanoma and Merkel cell carcinoma have also been reported in patients treated with TNF-antagonists including adalimumab. 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. All patients with UC who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis 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 benefit-risk balance of the product	The totality of the evidence established similarity of GP2017 to the reference product EU-Humira in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise as required by CHMP/437/04 Rev. 1. Overall, the results of the global development program confirm that GP2017 is biosimilar to the reference product EU-Humira and has a similar and positive benefit-risk ratio.
Public health impact	Public health impact is expected to be low. Regarding squamous cell carcinoma a mild increased usage of required healthy system resources (mainly surgical excision) is possible.

Important Identified Risk: Demyelinating disorders (including multiple sclerosis (MS), Guillain-Barre syndrome (GBS), and optic neuritis (ON))

Demyelinating disorders were not observed in clinical studies with GP2017 or Hyrimoz-HCF.

Table 0-6 Important identified risk demyelinating disorders (including multiple sclerosis (MS), Guillain-Barre syndrome (GBS), and optic neuritis (ON)): Other details

Demyelinating disorders	Details
MedDRA Search terms for spontaneous post-marketing data	SMQ Demyelination (broad)
Potential mechanisms	Unknown. TNF inhibitors may upregulate the autoimmune response by activation and survival of peripheral autoreactive myelin specific T cells which then could enter the CNS causing demyelination (Kaltsonoudis et al 2014).
Evidence source(s) and strength of evidence	Demyelinating disorders are listed in section 4.4 Special warnings and precautions and section 4.8 Undesirable effects of the Humira SmPC and considered to be an important identified risk of the reference product Humira. Demyelinating disorders are therefore considered as an important identified risk of Hyrimoz / Hefiya, a biosimilar to Humira.
Characterization of the risk:	Studies in healthy subjects: There were no such events reported in 796 healthy subjects. GP2017 studies in patients (GP17-301 and GP17-302): There were no such events reported in the 639 patients exposed to at least one dose of GP2017.

Demyelinating disorders	Details
	Humira SmPC: TNF inhibitors including Humira have been associated in rare instances (≥1/10,000 to <1/1000) with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease including MS, ON and peripheral demyelinating disease including GBS. The frequency – based on Humira RCT, open extension trial and spontaneous reporting data – is declared as rare.
Risk factors and risk groups	Potential risk factors may include subjects with pre-existing or recent onset central demyelinating disorders (Kaltsonoudis et al 2014). MS: Genetic susceptibility and presumed non-genetic trigger such as viral infection or low vitamin D levels (Luzzio 2016). GBS: Preceding gastrointestinal infection, older age, and upper extremity muscle strengths (Andary 2016). ON: Young adults, female, Caucasian (Ergene 2016).
Preventability	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.
Impact on the benefit-risk balance of the product	The totality of the evidence established similarity of GP2017 to the reference product EU-Humira in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise as required by CHMP/437/04 Rev. 1. Overall, the results of the global development program confirm that GP2017 is biosimilar to the reference product EU-Humira and has a similar and positive benefit-risk ratio.
Public health impact	Public health impact is expected to be low to moderate.

Important Identified Risk: BCG disease following live BCG vaccination in infants with in utero exposure to Hyrimoz / Hefiya

BCG disease following live BCG vaccination in infants with in utero exposure to Hyrimoz / Hefiya was not observed in clinical studies with GP2017 or Hyrimoz-HCF.

Table 0-7 Important identified risk BCG disease following live BCG vaccination in infants with in utero exposure to Hyrimoz / Hefiya: Other details

BCG disease following live BCG vaccination in infants with in utero exposure to Hyrimoz / Hefiya	Details
MedDRA Search terms for spontaneous post-marketing data	SMQ Agranulocytosis, HLT Narrow Tuberculous infections, PT Vaccine breakthrough infection
Potential mechanisms	BCG vaccine, made from an attenuated strain of Mycobacterium bovis, is administered routinely in the neonatal period in TB endemic countries. While in immunocompetent individuals the BCG vaccine is only associated with local skin inflammation, in those with significant immunodeficiency a severe disseminated disease may develop.

BCG disease following live BCG vaccination in infants with in utero exposure to Hyrimoz / Hefiya	Details
	As TNF regulates and enhances inflammatory, innate and adaptive immune responses to pathogenic organisms (Hehlgans and Pfeffer 2005), TNF inhibition in utero by adalimumab may thus increase the potential for the development of BCG disease in children receiving the BCG vaccine in early infancy.
Evidence source(s) and strength of evidence	BCG disease following live BCG vaccination in infants with in utero exposure to Humira is considered to be an important identified risk of the reference product Humira and is therefore considered as an important identified risk of Hyrimoz / Hefiya, a biosimilar to Humira.
Characterization of the risk:	There were no such events reported in the studies in healthy subjects and the GP2017 studies in patients (GP17-301 and GP17-302). European and North American guidelines recommend postponing the use of live vaccines until 6 months post pregnancy (van der Woude et al 2015, Nguyen et al 2016). Case reports of fatal disseminated BCG infection in an infant who received BCG vaccination at 3 months whose mother received infliximab for Crohn's disease during pregnancy (Cheent et al 2010). However, a retrospective assessment in a French regional health insurance database (Luu et al 2019) assessed a cohort of 670 babies exposed to anti-TNF agents in utero, with 315 (47%) exposed up to the time of delivery. Of these 670 babies, 88 received BCG vaccination, with 64 receiving it before 6 months of age. No BCG-related severe AEs were observed during the first year of life.
Risk factors and risk groups	Adalimumab treatment may be required to maintain disease stability for women during pregnancy. Adalimumab may cross the placenta, leading to in-utero exposure, impairing the development of the immune system. A prolonged half-life of adalimumab in infants may prolong this exposure, and hence lead to a compromised immunosystem after childbirth. Therefore, the risk is potentially related to the maternal dose of adalimumab and how late into the pregnancy adalimumab treatment continued. The practice for BCG vaccine of neonates also differs across countries depending on national guidelines and the risk of TB exposure for the infant.
Preventability	As per Hyrimoz / Hefiya SmPC and Humira SmPC, patients on adalimumab may receive concurrent vaccinations, except for live vaccines. Administration of live vaccines (e.g. BCG vaccine) to infants exposed to adalimumab is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.
Impact on the benefit-risk balance of the product	The totality of the evidence established similarity of GP2017 to the reference product EU-Humira in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise as required by CHMP/437/04 Rev. 1. Overall, the results of the global development program confirm that GP2017 is biosimilar to the reference product EU-Humira and has a similar and positive benefit-risk ratio.
Public health impact	Impact is low if labelled recommendations are followed.

Important Potential Risk: Progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy has not been observed in clinical studies with GP2017 or Hyrimoz-HCF.

Table 0-8 Important potential risk progressive multifocal leukoencephalopathy (PML): Other details

Progressive multifocal leukoencephalopathy	Details
MedDRA Search terms for spontaneous post-marketing data	PTs Progressive multifocal leukoencephalopathy, Human polyomavirus infection, JC polyomavirus test positive, JC virus CSF test positive, JC virus granule cell neuronopathy, JC virus infection, Leukoencephalomyelitis, Leukoencephalopathy, Polyomavirus test positive
Potential mechanisms	Reactivation of polyomavirus JC (often called JC virus) (Palazzo and Yahia 2012) due to TNF inhibitor immune modulation.
Evidence source(s) and strength of evidence	PML mainly occurs in immunocompromised individuals, and isolated cases were described in association with biologic therapy. PML is considered to be an important potential risk of the reference product Humira and is therefore considered as an important potential risk of Hyrimoz / Hefiya, a biosimilar to Humira.
Characterization of the risk:	Studies in healthy subjects: There were no such events reported in 796 healthy subjects. GP2017 studies in patients (GP17-301 and GP17-302): There were no such events reported in the 639 patients exposed to at least one dose of GP2017. In the Humira SmPC, no information on PML is provided. Case reports have been published for patients treated with adalimumab developing PML (Boggs and Barnes 2018).
Risk factors and risk groups	The development of PML has been most extensively studied with natalizumab (1.78 per 1000 for patients treated more than 2 years). Contributors to the risk to develop PML under natalizumab, rituximab or efalizumab and possibly also infliximab are the combined application and sequential application of immunomodulatory/ immunosuppressive compounds and the duration and exposure of treatment (Weissert 2011).
Preventability	Correction of the immune deficiency (Palazzo and Yahia 2012).
Impact on the benefit-risk balance of the product	The totality of the evidence established similarity of GP2017 to the reference product EU-Humira in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise as required by CHMP/437/04 Rev. 1. Overall, the results of the global development program confirm that GP2017 is biosimilar to the reference product EU-Humira and has a similar and positive benefit-risk ratio.
Public health impact	This potential event is very rare in the context of adalimumab exposure; a low impact on the public health is foreseen.

Important Potential Risk: Reversible posterior leukoencephalopathy syndrome (RPLS)

Reversible posterior leukoencephalopathy syndrome has not been observed in clinical studies with GP2017 or Hyrimoz-HCF.

Table 0-9 Important potential risk reversible posterior leukoencephalopathy syndrome (RPLS): Other details

Reversible posterior leukoencephalopathy syndrome (RPLS)	Details
MedDRA Search terms for spontaneous post-marketing data	PT Posterior reversible encephalopathy syndrome
Potential mechanisms	Acute change of blood pressure may lead to an endothelial dysfunction and breakdown of the blood-brain barrier (Fugate and Rabinstein 2015); TNF inhibitors may potentially have an impact on acute blood pressure changes.
Evidence source(s) and strength of evidence	RPLS mainly occurs in immunocompromised individuals, and isolated cases were described in association with biologic therapy. RPLS considered to be an important potential risk of the reference product Humira and is therefore considered as an important potential risk of Hyrimoz / Hefiya, a biosimilar to Humira.
Characterization of the risk:	Studies in healthy subjects: There were no such events reported in 796 healthy subjects. GP2017 studies in patients (GP17-301 and GP17-302): There were no such events reported in the 639 patients exposed to at least one dose of GP2017. In the Hyrimoz / Hefiya SmPC, no information on RPLS is provided. Case reports have been published of patients treated with adalimumab developing RPLS/PRES (Mahévas et al 2016).
Risk factors and risk groups	Risk factors are probably comorbid conditions (e.g. autoimmune disorders).
Preventability	Unknown
Impact on the benefit-risk balance of the product	The totality of the evidence established similarity of GP2017 to the reference product EU-Humira in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise as required by CHMP/437/04 Rev. 1. Overall, the results of the global development program confirm that GP2017 is biosimilar to the reference product EU-Humira and has a similar and positive benefit-risk ratio.
Public health impact	This potential event is very rare; a low impact in the context of adalimumab exposure on the public health is foreseen.

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

Patients with UC were not studied in GP2017 and Hyrimoz-HCF clinical studies. Adenocarcinoma of colon in UC patients has not been observed in these clinical studies.

Table 0-10 Important potential risk adenocarcinoma of colon in ulcerative colitis (UC) patients: Other details

Adenocarcinoma of colon in UC patients	Details
MedDRA Search terms for spontaneous post-marketing data	HLTs Colorectal and anal neoplasms malignancy unspecified, Colorectal neoplasms malignant, PTs Gastrointestinal adenocarcinoma, Intestinal adenocarcinoma
Potential mechanisms	Continuing inflammation is a plausible mechanism causing malignant transformation (Yashiro 2014) – here, a paradoxical potential effect of TNF may play a role. Also, the immune system can recognize and destroy nascent transformed cells and may be the mechanism of action for increased malignancy risk in immune compromised patients. Data clearly show the existence of cancer immunosurveillance and also indicate that it may function as a component of a more general process of cancer immunoediting. This process is responsible for both eliminating tumors and sculpting the immunogenic phenotypes of tumors that eventually form in immunocompetent hosts (Dunn 2002, Mohme 2017). It is attenuated in immunocompromised hosts.
Evidence source(s) and strength of evidence	It is not known if adalimumab treatment influences the risk for adenocarcinoma of the colon. Adenocarcinoma of colon in UC patients is considered to be an important potential risk of the reference product Humira and is therefore considered to be an important potential risk of Hyrimoz / Hefiya, a biosimilar to Humira.
Characterization of the risk:	Studies in healthy subjects: There were no such events reported in 796 healthy subjects. GP2017 studies in patients (GP17-301 and GP17-302): There were no such events reported in the 639 patients exposed to at least 1 dose of GP2017. Humira SmPC: With current data it is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer. 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.
Risk factors and risk groups	Risk factors for colorectal cancer in UC patients include young age at diagnosis, longer duration, greater anatomical extent of colonic involvement, the degree of inflammation, family history of colorectal cancer, and presence of primary sclerosing cholangitis (Yashiro 2014).
Preventability	Early detection can limit morbidity. Routine screening of UC patients for dysplasia (pre-cancerous lesions) prior to and during therapy with adalimumab is recommended for early detection and intervention Hyrimoz / Hefiya SmPC.
Impact on the benefit-risk balance of the product	The totality of the evidence established similarity of GP2017 to the reference product EU-Humira in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise as required by

Adenocarcinoma of colon in UC patients	Details
	CHMP/437/04 Rev. 1. Overall, the results of the global development program confirm that GP2017 is biosimilar to the reference product EU-Humira and has a similar and positive benefit-risk ratio.
Public health impact	Public health impact is expected to be low to moderate.

SVII.3.2. Presentation of the missing information

Table 0-11 Missing information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD

Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD	Details
MedDRA Search terms for spontaneous post-marketing data	PT Crohn's disease
Evidence source	Hyrimoz / Hefiya was not studied in this population. Hyrimoz / Hefiya and Humira are indicated for the treatment of moderately to severely active Crohn's disease in pediatric 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. The Hyrimoz / Hefiya SmPC and Humira SmPC contain the following information on the treatment of pediatric CD in children from 6 to 17 years of age: Section 4.2 Posology and method of administration: Pediatric CD Continued therapy should be carefully considered in a subject not responding by week 12. There is no relevant use of adalimumab in children aged below 6 years for this indication. Evidence of the use of Humira in pediatric CD is of low quality (1 RCT, 13 case series, including 664 patients, age: 1.9 to 21 years) (Dziechciarz et al 2016). Patients' age in the one RCT (the IMAginE trial) was 6 to 17 years (Humira SmPC, Ruemmele et al 2014, Ruemmele et al 2018).
Anticipated risk/ consequence of the missing information:	No difference in safety profile and warning and precautions is anticipated.

Table 0-12 Missing information: Episodic treatment in UC

Episodic treatment in UC	Details
MedDRA Search terms for spontaneous post-marketing data	HLT Psoriatic conditions, PTs Colitis ulcerative, Condition aggravated, Drug withdrawal syndrome, Juvenile idiopathic arthritis, Psoriatic arthropathy, Rebound eczema, Rebound effect, Rebound psoriasis, Withdrawal syndrome
Evidence source	Humira SmPC: in a Humira study, a total of 347 stable Ps responders participated in a withdrawal and retreatment evaluation in an open-label extension study. During the withdrawal period, symptoms of psoriasis returned over time with a median time to relapse (decline to PGA "moderate" or worse) of approximately 5 months. None of these patients experienced rebound during the withdrawal period. A total of 76.5% (218/285) of patients who entered the retreatment period had a response of PGA "clear" or "minimal" after 16 weeks of retreatment, irrespective of whether they relapsed during withdrawal: (69.1% (123/178) and 88.8% (95/107) for patients who relapsed and who did not relapse during the withdrawal period, respectively). A similar safety profile was observed during retreatment as before withdrawal. No data on episodic treatment in UC is available.
Anticipated risk/ consequence of the missing information:	No difference in safety profile and warning and precautions is anticipated

Table 0-13 Missing information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis

Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis	Details
MedDRA Search terms for spontaneous post-marketing data	PT Ulcerative colitis
Evidence source	Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a chronic, progressive, and incurable inflammatory disorder of the gastrointestinal tract, with approximately 25% of patients presenting before 18 years of age. Compared to adult IBD, pediatric IBD presents with a more severe, aggressive phenotype and unique complications, notably growth impairment (Breton et al 2020). Pediatric evidence for the use of adalimumab in UC is currently limited to small retrospective studies in patients with IBD/UC experiencing secondary loss of response to infliximab. In 2 of these studies, response to anti-TNFα therapy was recaptured in 55% and 83% of patients (Volonaki et al 2015 and Vahabnezhad et al 2014, respectively), with clinical remission maintained for up to 28 months (Volonaki et al 2015). Another retrospective study from a national registry, including 32 children with UC, with the rate of corticosteroid-free remission at Week 52 as the primary endpoint

Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis	Details
	revealed corticosteroid-free remission in 13 patients (41%) treated with adalimumab. During a 52-week follow-up, 19 patients (59%) maintained the treatment with adalimumab. 7 patients (22%) experienced an AE, but no serious side effects were observed and none of the events resulted in the discontinuation of adalimumab treatment (Aloi et al 2018).
Anticipated risk/ consequence of the missing information:	No difference in safety profile and warning and precautions is anticipated.

Part II Safety specification Module SVIII: Summary of the safety concerns

Table 0-1 Table Part II SVIII.1: Summary of safety concerns

Important identified risks	• Serious infections • Tuberculosis (TB) • Malignancies • Demyelinating disorders (including multiple sclerosis (MS), Guillain-Barre syndrome (GBS), and optic neuritis (ON)) • BCG disease following live BCG vaccination in infants with in utero exposure to Hyrimoz / Hefiya
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 UC • Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis (UC)

Part III: Pharmacovigilance plan (including post-authorization safety studies)

Part III.1. Routine pharmacovigilance activities

The global pharmacovigilance system ensures the services of a Qualified Person responsible for Pharmacovigilance and the necessary means for the notification of any adverse reaction suspected of occurring either in the community or in a third country.

Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Other forms of routine pharmacovigilance activities

Follow up of case reports: The minimum desired case information for adalimumab includes the brand name and batch number of the suspect product. Additional efforts must be made to collect this information in accordance with GVP VI.

Part III.2. Additional pharmacovigilance activities

Routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and to detect new safety signals. Additional pharmacovigilance activities are therefore not considered necessary.

Part III.3. Summary Table of additional pharmacovigilance activities

Table 0-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

Part IV: Plans for post-authorization efficacy studies

No studies are planned.

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

Risk Minimization Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

Part V.1. Routine risk minimization measures

Table 0-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Serious infections	Routine risk communication SmPC sections: Section 4.2 Posology and method of administration Section 4.3 Contraindications Section 4.4 Special warnings and precautions for use Section 4.6 Fertility, pregnancy and lactation Section 4.8 Undesirable effects PL sections: 2. What you need to know before you use Hyrimoz / Hefiya 4. Possible side effects Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4: Patients who develop a new infection while undergoing treatment with Hyrimoz/Hefiya, should be monitored closely and undergo a complete diagnostic evaluation. Administration of Hyrimoz/Hefiya 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 Hyrimoz 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. Other routine risk minimization measures beyond the Product Information: Legal status: Prescription-only medicine
Tuberculosis (TB)	Routine risk communication SmPC sections: Section 4.2 Posology and method of administration Section 4.3 Contraindications Section 4.4 Special warnings and precautions for use Section 4.6 Fertility, pregnancy and lactation Section 4.8 Undesirable effects

Safety concern	Routine risk minimization activities
	PL sections: 2. What you need to know before you use Hyrimoz / Hefiya 4. Possible side effects Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4: Before initiation of therapy with Hyrimoz/Hefiya, all patients must be evaluated for both active and inactive ("latent") tuberculosis infection. This evaluation should include a detailed medical assessment of patient history of tuberculosis or possible previous exposure to people with active tuberculosis 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). It is recommended that the conduct and results of these tests are recorded in the Patient Reminder Card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised. If active tuberculosis is diagnosed, Hyrimoz therapy must not be initiated. In all situations described below, the benefit / risk balance of therapy should be very carefully considered. If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted. If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylaxis treatment before the initiation of Hyrimoz, and in accordance with local recommendations. Use of anti-tuberculosis prophylaxis treatment should also be considered before the initiation of Hyrimoz in patients with several or significant risk factors for tuberculosis despite a negative test for tuberculosis and in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with adalimumab. Some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with adalimumab. Patients should be instructed to seek medical advice if signs / symptoms suggestive of a tuberculosis infection (e.g., persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with Hyrimoz. Other routine risk minimization measures beyond the Product Information: Legal status: Prescription-only medicine
Malignancies	Routine risk communication SmPC sections: Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects Section 5.3 Preclinical safety data PL sections: 2. What you need to know before you use Hyrimoz / Hefiya 4. Possible side effects Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4: All patients, and in particular patients with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of

Safety concern	Routine risk minimization activities
	PUVA treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with Hyrimoz/Hefiya. Other routine risk minimization measures beyond the Product Information: Legal status: Prescription-only medicine
Demyelinating disorders (including MS, GBS, and ON)	Routine risk communication SmPC sections: Section 4.4 Special warnings and precautions for use Section 4.8 Undesirable effects PL sections: 2. What you need to know before you use Hyrimoz / Hefiya 4. Possible side effects Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4: Prescribers should exercise caution in considering the use of Hyrimoz in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of Hyrimoz should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders. Neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of Hyrimoz therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders. Other routine risk minimization measures beyond the Product Information: Legal status: Prescription-only medicine
BCG disease following live BCG vaccination in infants with in utero exposure to Hyrimoz / Hefiya	Routine risk communication SmPC sections: Section 4.4 Special warnings and precautions for use Section 4.6 Fertility, pregnancy and lactation PL sections: 2. What you need to know before you use Hyrimoz / Hefiya Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4: Patients on Hyrimoz/Hefiya may receive concurrent vaccinations, except for live vaccines. 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. SmPC Section 4.6: Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection. 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. PL Section 2: Vaccinations

Safety concern	Routine risk minimization activities
	Certain vaccines contain living but weakened forms of disease-causing bacteria or viruses and should not be given during treatment with Hyrimoz/Hefiya in case they cause infections. Check with your doctor before you receive any vaccines. It is recommended that, if possible, children be given all the scheduled vaccinations for their age before they start treatment with Hyrimoz. If you receive Hyrimoz while you are pregnant, your baby may be at higher risk for getting an infection for up to about five months after the last dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals about your Hyrimoz use during your pregnancy so they can decide when your baby should receive any vaccine. Other routine risk minimization measures beyond the Product Information: Legal status: Prescription-only medicine
Progressive multifocal leukoencephalopathy (PML)	Routine risk communication None Other routine risk minimization measures beyond the Product Information: Legal status: Prescription-only medicine
Reversible posterior leukoencephalopathy syndrome (RPLS)	Routine risk communication None Other routine risk minimization measures beyond the Product Information: Legal status: Prescription-only medicine
Adenocarcinoma of colon in UC patients	Routine risk communication SmPC section: Section 4.4 Special warnings and precautions for use PL section: 4. Possible side effects Routine risk minimization activities recommending specific clinical measures to address the risk: SmPC Section 4.4: With current data it is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis 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. Other routine risk minimization measures beyond the Product Information: Legal status: Prescription-only medicine
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD	Routine risk communication SmPC section: Section 4.2 Posology and method of administration PL section: 2. What you need to know before you use Hyrimoz / Hefiya

Safety concern	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information: Legal status: Prescription-only medicine
Episodic treatment in UC	Routine risk communication None Other routine risk minimization measures beyond the Product Information: Legal status: Prescription-only medicine
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis	Routine risk communication None Other routine risk minimization measures beyond the Product Information: Legal status: Prescription-only medicine

Part V.2. Additional risk minimization measures

Additional risk minimization measures taken for Hyrimoz / Hefiya include those listed below:

Patient Reminder Cards (adult and paediatric)

Objectives:

The objective of the measure is to remind patients (or caregivers) on the key risks for adalimumab. These include serious infections, Tuberculosis (TB), demyelinating disorders, malignancies, and the risk of BCG disease following live BCG vaccination in infants with in utero exposure to Hyrimoz / Hefiya. In addition, the patient reminder card can also serve as information that a patient can provide to any HCPs that may treat the patient (i.e., non Hyrimoz / Hefiya 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 minimization 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 recognize when they should seek medical advice.

Target audience and planned distribution path:

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

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

Routine PV; AE reports will be reviewed on an on-going basis and appropriate action taken as needed.

Outcome indicator: Frequency and severity of AEs related to serious infections, TB, malignancies, demyelinating disorders (including MS, GBS, and ON), and BCG disease following live BCG vaccination in infants with in utero exposure to Hyrimoz/Hefiya.

Part V.3. Summary of risk minimization measures

Table 0-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Serious infections	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.2 Posology and method of administration, 4.3 Contraindications, 4.4 Special warnings and precautions for use, 4.6 Fertility, pregnancy and lactation, 4.8 Undesirable effects. PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** Patient reminder card – adult and pediatric	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none
Tuberculosis (TB)	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.2 Posology and method of administration, 4.3 Contraindications, 4.4 Special warnings and precautions for use, 4.6 Fertility, pregnancy and lactation, 4.8 Undesirable effects. PL sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Before initiation of therapy with Hyrimoz / Hefiya, all patients must be evaluated for both active and inactive (“latent”) TB infection. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: Patient reminder card – adult and pediatric	
Malignancies	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use (for NMSC: recommendations are done to all patients, and in particular patients with a medical history of extensive immunosuppressant therapy or psoriasis 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), 4.8 Undesirable effects and 5.3 Preclinical safety data PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** Patient reminder card – adult and pediatric	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none
Demyelinating disorders (including MS, GBS, and ON)	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects. PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** Patient reminder card – adult and pediatric	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none

Safety concern	Risk minimization measures	Pharmacovigilance activities
BCG disease following live BCG vaccination in infants with in utero exposure to Hyrimoz / Hefiya	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use; and 4.6 Fertility, pregnancy and lactation PL sections 2 Legal status: Prescription only **Additional risk minimization measures:** Patient reminder card – adult and pediatric	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none
Progressive multifocal leukoencephalopathy	**Routine risk minimization measures:** None Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none
Reversible posterior leukoencephalopathy syndrome	**Routine risk minimization measures:** None Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none
Adenocarcinoma of colon in UC patients	**Routine risk minimization measures:** Guidance is provided in the section 4.4 Special warnings and precautions for use of the SmPC. PL section 4. Routine risk minimization activities recommending specific clinical measures to address the risk: 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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none

Safety concern	Risk minimization measures	Pharmacovigilance activities
	throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations (SmPC section 4.4). Legal status: Prescription only	
Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.2 Posology and method of administration. PL section 2. Legal status: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none
Episodic treatment in UC	**Routine risk minimization measures:** Legal status: Prescription only	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: Prescription only	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: none Additional pharmacovigilance activities: none

Part VI: Summary of the risk management plan Hyrimoz / Hefiya (adalimumab)

This is a summary of the risk management plan (RMP) for Hyrimoz / Hefiya, a biosimilar to Humira. The RMP details important risks of Hyrimoz / Hefiya, how these risks can be minimized, and how more information will be obtained about these risks and uncertainties (missing information).

Hyrimoz / Hefiya SmPC and Hyrimoz / Hefiya Labelling and Package Leaflet give essential information to healthcare professionals and patients on how Hyrimoz / Hefiya should be used.

This summary of the RMP for Hyrimoz / Hefiya 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 the RMP for Hyrimoz / Hefiya.

Part VI: I. The medicine and what it is used for

Hyrimoz / Hefiya is authorized for use in rheumatoid arthritis (RA), juvenile idiopathic arthritis (Polyarticular juvenile idiopathic arthritis and Enthesitis-related arthritis), axial spondyloarthritis (Ankylosing spondylitis and Axial spondyloarthritis without radiographic evidence of AS), Psoriatic arthritis, Psoriasis, Paediatric plaque psoriasis, Hidradenitis suppurativa (HS), Crohn's disease (CD), Paediatric Crohn's disease , Ulcerative colitis (UC), Uveitis, Paediatric uveitis, and Paediatric ulcerative colitis (see SmPC for the full indication). It contains adalimumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of the benefits of Hyrimoz / Hefiya can be found in the respective EPARs, including its plain-language summary, available on the EMA website, under the medicines' webpages:
https://www.ema.europa.eu/en/medicines/human/EPAR/hyrimoz
https://www.ema.europa.eu/en/medicines/human/EPAR/hefiya

Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Hyrimoz / Hefiya together with measures to minimize such risks and the proposed studies for learning more about these risks, are outlined below.

Measures to minimize 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 authorized 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 minimize its risks.

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

These measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and analyzed regularly, 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 Hyrimoz / Hefiya is not yet available, it is listed under 'missing information' below.

Part VI – II.A: List of important risks and missing information

Important risks of Hyrimoz / Hefiya are risks that need special risk management activities to further investigate or minimize 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 Hyrimoz / Hefiya. 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).

Table 0-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	Serious infections Tuberculosis (TB) Malignancies Demyelinating disorders (including multiple sclerosis (MS), Guillain-Barre syndrome (GBS), and optic neuritis (ON)) BCG disease following live BCG vaccination in infants with in utero exposure to Hyrimoz / Hefiya
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 crohn's disease (CD) Episodic treatment in UC Long-term safety information in the treatment of children aged from 6 years to less than 18 years with UC

Part VI – II.B: Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Table 0-2 Important identified risk: Serious infections

Evidence for linking the risk to the medicine	Serious infections are listed in section 4.4 Special warnings and precautions and section 4.8 Undesirable effects of the Humira SmPC and considered to be an important identified risk of the reference product Humira. Serious infections are therefore considered as an important identified risk of Hyrimoz / Hefiya, a biosimilar to Humira.
Risk factors and risk groups	Serious infections were reported in both adult and pediatric subjects treated with TNF inhibitors and across all indications. Patients concomitantly treated with other immunosuppressant medicines are at increased risk as well as a past medical history of serious infections, glucocorticoid dose, and older age (> 65 years). These are important independent predictors of serious infection risks in patients treated with TNF inhibitors. Patients with RA had a 2-fold increased adjusted risk of hospitalized infections compared to those without RA concluded from a retrospective cohort. Current prednisone use > 7.5 mg/day, previous infections and previous hospitalized infections increased the risk of hospitalized infections as well as probably RA disease activity.

Risk minimization measures	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.2 Posology and method of administration, 4.3 Contraindications, 4.4 Special warnings and precautions for use, 4.6 Fertility, pregnancy and lactation, 4.8 Undesirable effects. PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** Patient reminder card – adult and pediatric

Table 0-3 Important identified risk: Tuberculosis (TB)

Evidence for linking the risk to the medicine	TB is listed in section 4.4 Special warnings and precautions and section 4.8 Undesirable effects of the Humira SmPC and is considered to be an important identified risk of the reference product Humira. TB is therefore considered as an important identified risk of Hyrimoz / Hefiya, a biosimilar to Humira.
Risk factors and risk groups	Tuberculosis has been reported in both adult and pediatric subjects treated with TNF inhibitors and across all indications. Patients concomitantly treated with other immunosuppressant medicines are at increased risk as well as a past medical history of serious infections, glucocorticoid dose, and older age (> 65 years). These are important independent predictors of serious infection risks in patients treated with TNF inhibitors.
Risk minimization measures	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.2 Posology and method of administration, 4.3 Contraindications, 4.4 Special warnings and precautions for use, 4.6 Fertility, pregnancy and lactation, 4.8 Undesirable effects. Routine risk minimization activities recommending specific clinical measures to address the risk: Before initiation of therapy with Hyrimoz / Hefiya, all patients must be evaluated for both active and inactive (“latent”) TB infection. PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** Patient reminder card – adult and pediatric

Table 0-4 Important identified risk: Malignancies

Evidence for linking the risk to the medicine	Malignancies (including lymphoma, HSTCL, leukemia, NMSC, melanoma, Merkel cell carcinoma, and other malignancies) are listed in section 4.4 Special warnings and precautions and section 4.8 Undesirable effects of the Humira SmPC and are considered to be an important identified risk of the reference product Humira. Malignancies are therefore considered as an important identified risk of Hyrimoz / Hefiya, a biosimilar to Humira.
Risk factors and risk groups	**Lymphoma** For Hodgkin lymphoma age at diagnosis is a strong risk factor for survival, for non-Hodgkin lymphoma gender with a higher survival rate in males. The most commonly used prognostic system for Hodgkin lymphoma is the International Prognostic System, which uses the following factors: serum

	albumin less than 4 g/dL, hemoglobin less than 10.5 g/dL, male sex, age ≥45, stage IV disease, WBC count >15,000/µL, absolute lymphocyte count <600/µL or <8% of the total WBC count or both. **HSTCL** A moderate risk factor is immune-mediated disease, concomitant azathioprine, and possibly TNF inhibitor treatment. **Leukemia** General risk factors are gender and age. Men are more likely to develop CML, CLL and AML than women. The risk of most leukemias, with the exception of ALL, typically increases with age. Genetics: For most leukemias there is no clear link. First degree relatives of CLL patients or identical twins of AML or ALL patients are at increased risk. Lifestyle: Smoking cigarettes increase risks for AML. Exposures: High-energy radiation, long term exposure to chemicals such as pesticides or industrial chemicals like benzene are considered a risk. Previous treatment: Certain types of chemotherapy and radiation therapy for other cancers are considered leukemia risk factors. **NMSC** BCC: white skin type, male sex, sunlight exposure - patient geographic location affects the risk of developing skin cancer. A latency period of 20-50 years is typical between the time of ultraviolet damage and clinical onset of cancer, gene mutations, X-ray, immunosuppressed patients, previous non-melanoma skin cancer. Squamous cell carcinoma: Patient related risk factors are organ transplantation, hematologic malignancy, long-term immunosuppressive therapy, HIV infection or AIDS. **Merkel cell carcinoma** The following factors are associated with increased risks: Whites / fair skin, UV radiation, age, long-term immunosuppression (risk 15 times increased compared to general population), RA, autoimmune disorders, organ transplantation, HIV, arsenic exposure, Merkel cell polyomavirus. **Melanoma** Important tumor specific risk factors are depth of invasion, the presence or absence of ulceration, and the nodal status at diagnosis. Patient factors are white skin, age, sun exposure. TNF seems to be a negative prognostic factor in melanoma surgery and correlates with chemotherapy resistance. However, high intra-tumor levels of TNF might be beneficial for immunotherapy. **Other malignancies** No specific risk groups or risk factors are known within the population of patients treated with adalimumab.
Risk minimization measures	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, 4.8 Undesirable effects and 5.3 Preclinical safety data PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:**

	Patient reminder card – adult and pediatric

Table 0-5 Important identified risk: Demyelinating disorders (including multiple sclerosis (MS), Guillain-Barre syndrome (GBS), and optic neuritis (ON))

Evidence for linking the risk to the medicine	Demyelinating disorders are listed in section 4.4 Special warnings and precautions and section 4.8 Undesirable effects of the Humira SmPC and considered to be an important identified risk of the reference product Humira. Demyelinating disorders are therefore considered as an important identified risk of Hyrimoz / Hefiya, a biosimilar to Humira.
Risk factors and risk groups	Potential risk factors may include subjects with pre-existing or recent onset central demyelinating disorders. MS: Genetic susceptibility and presumed non-genetic trigger such as viral infection or low vitamin D levels. GBS: Preceding gastrointestinal infection, older age, and upper extremity muscle strengths. ON: Young adults, female, Caucasian.
Risk minimization measures	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use, where recommendations are done to perform a neurologic evaluation in patients with non-infectious intermediate uveitis prior to the initiation, and 4.8 Undesirable effects. PL sections 2 and 4 Legal status: Prescription only **Additional risk minimization measures:** Patient reminder card – adult and pediatric

Table 0-6 Important identified risk: BCG disease following live BCG vaccination in infants with in utero exposure to Hyrimoz / Hefiya

Evidence for linking the risk to the medicine	BCG disease following live BCG vaccination in infants with in utero exposure to Humira is considered to be an important identified risk of the reference product Humira and is therefore considered as an important identified risk of Hyrimoz / Hefiya, a biosimilar to Humira.
Risk factors and risk groups	Adalimumab treatment may be required to maintain disease stability for women during pregnancy. Adalimumab may cross the placenta, leading to in-utero exposure, impairing the development of the immune system. A prolonged half-life of adalimumab in infants may prolong this exposure, and hence lead to a compromised immunosystem. Therefore, the risk is potentially related to the maternal dose of adalimumab and how late into the pregnancy adalimumab treatment continued. The practice for BCG vaccine of neonates also differs across countries depending on national guidelines and the risk of TB exposure for the infant.
Risk minimization measures	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: 4.4 Special warnings and precautions for use; and 4.6 Fertility, pregnancy and lactation PL sections 2 Legal status: Prescription only

	Routine risk minimization activities recommending specific clinical measures to address the risk: 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. **Additional risk minimization measures:** Patient Reminder Card – adult and pediatric

Table 0-7 Important potential risk: Progressive multifocal leukoencephalopathy (PML)

Evidence for linking the risk to the medicine	PML mainly occurs in immunocompromised individuals, and isolated cases were described in association with biologic therapy. PML is considered to be an important potential risk of the reference product Humira and is therefore considered as an important potential risk of Hyrimoz / Hefiya, a biosimilar to Humira.
Risk factors and risk groups	The development of PML has been most extensively studied with natalizumab (1.78 per 1000 for patients treated more than 2 years). Contributors to the risk to develop PML under natalizumab, rituximab or efalizumab and possibly also infliximab are the combined application and sequential application of immunomodulatory/ immunosuppressive compounds and the duration and exposure of treatment.
Risk minimization measures	**Routine risk minimization measures:** Legal status: Prescription only

Table 0-8 Important potential risk: Reversible posterior leukoencephalopathy syndrome (RPLS)

Evidence for linking the risk to the medicine	RPLS mainly occurs in immunocompromised individuals, and isolated cases were described in association with biologic therapy. RPLS considered to be an important potential risk of the reference product Humira and is therefore considered as an important potential risk of Hyrimoz / Hefiya, a biosimilar to Humira.
Risk factors and risk groups	Risk factors are probably comorbid conditions (e.g. autoimmune disorders).
Risk minimization measures	**Routine risk minimization measures:** Legal status: Prescription only.

Table 0-9 Important potential risk: Adenocarcinoma of colon in ulcerative colitis (UC) patients

Evidence for linking the risk to the medicine	It is not known if adalimumab treatment influences the risk for adenocarcinoma of the colon. Adenocarcinoma of colon in UC patients is considered to be an important potential risk of the reference product Humira and is therefore considered to be an important potential risk of Hyrimoz / Hefiya, a biosimilar to Humira.
Risk factors and risk groups	Risk factors for colorectal cancer in UC patients include young age at diagnosis, longer duration, greater anatomical extent of colonic involvement, the degree of inflammation, family history of colorectal cancer, and presence of primary sclerosing cholangitis.
Risk minimization measures	**Routine risk minimization measures:**

	Guidance is provided in the section 4.4 Special warnings and precautions for use of the SmPC, where it is recommended 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. PL section 4. Legal status: Prescription only.

Table 0-10 Missing information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with CD

Risk minimization measures	**Routine risk minimization measures:** Guidance is provided in the following sections of the SmPC: Section 4.2 Posology and method of administration PL section 2. Legal status: Prescription only

Table 0-11 Missing information: Episodic treatment in UC

Risk minimization measures	**Routine risk minimization measures:** Legal status: Prescription only

Table 0-12 Missing information: Long-term safety information in the treatment of children aged from 6 years to less than 18 years with ulcerative colitis

Risk minimization measures	**Routine risk minimization measures:** Legal status: Prescription only

Part VI: II.C: Post-authorization development plan

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

There are no studies which are conditions of the marketing authorization or specific obligation of Hyrimoz / Hefiya.

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

There are no studies required for Hyrimoz / Hefiya.

Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable

Annex 6 - Details of proposed additional risk minimization activities (if applicable)

Key messages of the additional risk minimization measures

Patient Material:

- Patient Reminder Card

Patient Reminder Card:

- Contact details of the Hyrimoz/ Hefiya 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 TB before taking Hyrimoz/ Hefiya and reminder that they should record the TB screening results on the card.
- Inform the patient concerning key risks (i.e., serious infections, Tuberculosis (TB), demyelinating disorders, malignancies, and BCG disease following live BCG vaccination in infants with in utero exposure to Hyrimoz/ Hefiya) and the need to be vigilant for symptoms associated with them.
- A message for the patient to not receive live vaccinations while using Hyrimoz/ Hefiya and to warn of BCG disease following live BCG vaccination in infants with in utero exposure to Hyrimoz/ Hefiya, so if they took Hyrimoz/ Hefiya while pregnant, their baby should not receive a 'live vaccine,' such as BCG (used to prevent tuberculosis) 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