1.0 Title Page

AbbVie

STUDY PROTOCOL Amendment
HUMIRA P13-562

Assessment of Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Plaque Psoriasis, Crohn's Disease and Ulcerative Colitis patients`
adherence attitudes to maintenance therapy with a scheduled Adalimumab treatment in routine clinical practice

Product Name:	HUMIRA®
Type of Study:	Non Interventional - Post-Marketing Observational Study
Original Protocol Date:	26 July 2011
Protocol Amendment Date:	27. October 2016
Biometrics/Datamanagement:	[redacted]
Sponsor:	
Primary AbbVie Contact Person / Affiliated Scientific Lead	

This study will be conducted in compliance with this protocol including country specific amendment(s)

2.0 Table of Contents

1.0 Title Page 1
2.0 Table of Contents 2
3.0 Introduction 3
4.0 Rationale 4
5.0 Study Objectives 7
5.1 Main objectives 7
5.2 Secondary objectives 7
6.0 Investigational Plan 7
6.1 Selection of Study Population 8
6.1.1 Inclusion Criteria 8
6.1.2 Exclusion Criteria 9
6.2 Number of patients to be enrolled 9
6.3 Investigator Selection Criteria 9
6.4 Study Duration 9
6.5 Study Conduct and Schedule of Activities: 10
6.5.1 Description of Activities 12
6.5.2 Description of the Visits 18
6.5.2.1 Inclusion visit 18
6.5.2.2 Follow-up visits 19
6.6 Product Supply 20
7.0 Management and Reporting of Complaints 21
7.1 Medical Complaints 22
7.1.1 Adverse event and serious adverse event definition, serious adverse event categories 22
7.1.2 Severity 24
7.1.3 Relationship to Pharmaceutical Product 24
7.1.4 Spontaneously Serious Adverse Event - collection period 25
7.1.5 Spontaneously reported Serious Adverse Event - reporting 25
7.1.6 Pregnancy Reporting 26
8.0 Product Complaint 27
8.1 Definition 27
8.2 Reporting 27
9.0 Ethics and Quality 28
10.0 Data Report Forms 29
11.0 Data Analysis Plans 29
11.1 End points 29
11.1.1 Primary end point 29
11.1.2. Secondary end points 29
11.2 Plan of Analysis 30
12.0 Final Reports and Publications 30
13.0 Conduct of the PMOS 31
14.0 References 31
15. Appendix 32
16. Research Plan Signature Page 110

3.0 Introduction

The Adherence to biological medication in Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), plaque psoriasis (PsO), Crohn's disease (CD) and ulcerative colitis (UC):

As there exist a lot of variations in the definitions and methodologies of measurement used to characterize adherence - compliance and persistence - first of all it is important to provide a definition for these terms. Compliance or more precisely medication compliance refers to the extent a patient is passively following the physician`s orders as acting in accordance with the prescribed timing, frequency and dosage. It is typically measured as a percentage of total number of doses taken in relation to the time period of observation, during which medication compliance is measured [1,2]. In the literature an arbitrary cut-off value of 80% is used to distinguish between compliance and non-compliance although it is not clear what the clinically relevant cut-off point is. It is also understandable that the required drugs which are necessary to achieve an optimal treatment goal may be different for each patient and each drug. Therefore some patients may be well controlled with a standard dosage scheme while other patients may require a more frequent administration. Persistence or more precisely medication persistence is the duration of time from the beginning to the discontinuation of the prescribed therapy and is measured in units of time [1,2]. Adherence can be considered as an umbrella term for medication compliance and medication persistence as this term involves both perceptions of taking a medication, namely regularity and consistency [1,2]. Poor or non-adherence to a drug is a very important aspect in contributing to inadequate response to or failure of treatment and worsening of the disease. In consequence of an insufficient adherence clinical outcomes will deteriorate and may prompt a physician to further diagnostic procedures and eventually to an unnecessary change in medication [3]. Clearly this may lead to a longer patient recovery period and increased healthcare costs. This raises the question: how can we improve adherence in those patients who are afflicted with chronic inflammatory diseases like RA, AS, PsA, PsO, CD or UC? The answer is not easy because adherence is a complex phenomenon and it can both be difficult to identify factors associated with non-adherence and applying help in an effective manner. In clinical studies about tight control such factors can be easier identified and patients can therefore be more intensively motivated to be

compliant and continue their treatment (persistence). Although on the contrary in routine clinical practice such a tight control is hardly possible, medical aid for the optimization of treatment adherence should as far as possible be tailored to individual´s primary reasons and concerns (e.g. worries of potential adverse events of biological treatment) for not taking a drug. In this context, patients' attitudes to treatment play an important role for adherence – mainly due to the fact that attitudes are varying.

4.0 Rationale

The aim of this non-interventional post-marketing observational study (PMOS) is to assess RA, PsA, AS, PsO, CD and UC patients` adherence attitudes (beliefs), currently being managed in a specialist rheumatology, dermatology or gastroenterology practice or respective hospital department, to maintenance therapy with a scheduled Adalimumab monotherapy or a combination therapy with methotrexate and to investigate whether there are correlations between such beliefs and adherence to maintenance treatment. For the assessment of RA, PsA, AS, PsO, CD or UC patients attitudes/beliefs to their scheduled maintenance treatment and medicine in general we are going to use the **Beliefs about Medicines Questionnaire (BMQ)** [4] at the beginning of this study. In order to identify RA, PsA, AS, PsO, CD or UC patients at risk for non-adherence in due time in the course of this study the **Morisky Medication Adherence Scale (MMAS)** [5] shall be used. In this context it is also of interest to evaluate patients` treatment satisfaction during Adalimumab monotherapy or combination therapy with methotrexate for which reason the **Treatment Satisfaction Questionaire for Medication (TSQM)** [6,7] is used. As part of clinical practice the laboratory parameters ESR and/or CRP will be measured as an indication for disease activity. Furthermore the degree of disease activity has certainly a significant impact of treatment adherence for which reason the **Rheumatoid Arthritis Disease Acitivity Index** (**RADAI**) for RA and if reasonable for PsA patients,the **Bath Ankylosing Activity Index** (**BASDAI**) for AS patients, the **Psoriasis Area and Severity Index (PASI)**[10,11] for plaque psoriasis, **Harvey-Bradshaw Index (HBI)**[12] for CD patients and the **Partial Mayo score (PMS)**[13] for UC patients shall be used.

Remark: A patient support program is not offered or scheduled by the sponsor. As this is a non-interventional study all decisions are up to a participating physician. A physician may offer a patient support program to a patient anyhow. As this might affect study results a respective question is incorporated in the eCRF.

- **Adalimumab**

The fully human (100% human peptide sequences) recombinant monoclonal IgG1 antibody adalimumab has been approved in combination with methotrexate for the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate and for the treatment of severe active and progressive rheumatoid arthritis in adults not previously treated with methotrexate [8]. In case of incompatibility against methotrexate or continuing treatment with methotrexate is considered as not appropriate, adalimumab can also be administered as a monotherapy. Adalimumab in combination with methotrexate is also indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in children and adolescents aged 13 to 17 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Adalimumab can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Adalimumab is also indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy and for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Moreover, adaliumumab is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA[8].

In gastroenterology, adalimumab is indicated for treatment of moderately to severely active Crohn's disease, 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, as well as for treatment of moderately to severely active ulcerative colitis 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[8].

The recommended dose for adults in patients with rheumatoid arthritis is 40 mg Adalimumab administered every two weeks as single dose via subcutaneous injection. Methotrexate should be continued during treatment with adalimumab. The recommended dose of Adalimumab for patients with ankylosing spondylitis and for patients with psoriatic arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection.

The recommended dose of Adalimumab for adult patients with plaque psoriasis 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.

For adult patients with moderately to severely active Crohn's disease an induction dose regimen 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, 80 mg at Week 2, can be used. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Some patients who experience decrease in their response may benefit from an increase in dosing frequency to 40 mg Adalimumab every week. The recommended Adalimumab induction dose regimen for adult patients with moderate to severe ulcerative colitis is 160 mg at Week 0 and 80 mg at Week 2. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Some patients who experience decrease in their response may benefit from an increase in dosing frequency to 40 mg Adalimumab every week[8]. Indistinguishable in structure and function from naturally occurring human immunoglobulin G1 (IgG1) Adalimumab has been estimated to have a terminal half-life of 10 –14 days [9]. Because of the linear pharmacokinetic of Adalimumab it allows to be self-administered by either a pre-filled syringe or an autoinjection pen.

5.0 Study Objectives

5.1 Main objectives

The main purpose of this study is to assess patients` adherence attitudes (beliefs) to the maintenance therapy with a scheduled Adalimumab monotherapy or a combination therapy with methotrexate and to investigate whether there are correlations between such beliefs and adherence to maintenance treatment. In order to measure such beliefs the following questionnaire is used:

- Changes in the Beliefs about Medicines Questionnaire (**BMQ**) at 12 months compared to baseline. In addition, the correlations between beliefs and adherence to treatment will be done at baseline and at 12 months

5.2 Secondary objectives

- Changes in the Morisky Medication Adherence Scale (**MMAS**) at 12 months compared to month 3,
- Changes of the Treatment Satisfaction Questionaire for Medication (**TSQM**) over time,
- Changes in Rheumatoid Arthritis Disease Activity Index (**RADAI**) in patients with RA and if reasonable in patients with PsA,
- Changes in Bath Ankylosing Spondylitis Disease Activity Index (**BASDAI**) in patients with AS,
- Changes in Psoriasis Area and Severity Index (**PASI**) in patients with plaque psoriasis,
- Changes in Harvey-Bradshaw Index (**HBI**) for patients with CD,
- Changes in Partial Mayo Score (**PMS**) for patients with UC,
- Changes of the C-reactive protein (**CRP**) over time
- Changes of the Erythrocyte sedimentation rate (**ESR**) over time

6.0 Investigational Plan

6.1 Selection of Study Population

The study P13-562 is a non-interventional, observational study in which HUMIRA® is prescribed in the usual manner in accordance with the terms of the local marketing authorization with regards to dose, population and indication. The assignment of the patient to a HUMIRA® - containing regimen has to be decided in advance and has to be current practice. The prescription of HUMIRA® is clearly separated from the decision to include the patient in this study! No additional procedures (other than standard of care) shall be applied to the patients.

It is planned to enroll approximately 140 patients in total. All patient data entered in the patient's data report form (CRF) will be forwarded - without naming the patient - for evaluation to AbbVie. In order to maintain patient confidentiality, the patient's age in year, gender and race will be documented in the CRF. The patients must provide written authorization to the investigator to use and/or disclose personal and/or health data before entry into study P13-562. .

6.1.1 Inclusion Criteria

- Patients aged ≥ 18 years with **RA, PsA, AS, PsO, CD, or UC** that have been prescribed adalimumab in accordance to physician's clinical decision and according to local guidelines, up to 30 days prior to screening.

- Patients must fulfil international and national guidelines for the use of a BDMARD in **RA**, **PsA, AS, PsO, CD, or UC** (Chest X-ray and IGRA* interferon gamma release assay or PPD-skin test negative for tuberculosis). *Please see also APPENDIX-C!

  In addition one of the following criteria must be fulfilled:

  - Unsatisfactory DMARD response defined as failure to treatment with at least two DMARDs including Methotrexate in patients with **RA** or **PsA**
  - Unsatisfactory NSAID response in patients with **AS** or unsatisfactory response to prior BDMARDs in patients with **RA** or **PsA** or **AS**.
  - Unsatisfactory response to or contraindication to, or intolerance to other systemic therapy including cyclosporine, methotrexate or PUVA in patients with PsO.Unsatisfactory response

despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or intolerance or medical contraindications for such therapies in CD.

- Unsatisfactory response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or intolerance to or medical contraindications for such therapies in UC.

6.1.2 Exclusion Criteria

The following patients will not be included in this observational study:

- Patients who are not covered in the latest version of the HUMIRA syringe® SPC and HUMIRA Pen® SPC;
- Patients participating in another study program or clinical trial.
- Patients who have been treated with Adalimumab before.-

6.2 Number of patients to be enrolled

It is planned to enroll approximately 140 patients in total (80 RA, PsA and AS / 30 PsO /30 MCeor UC). The study will be conducted at 28 sites in Austria. Each site shall enroll approximately 5 patients.

6.3 Investigator Selection Criteria

The investigational sites will be centers with experience in the treatment of RA, PsA, AS, PsO, CD and UC patients. For the investigators it is not mandatory to have any clinical research (i.e. PMOS) experience but it may be beneficial.

6.4 Study Duration

This PMOS has started In RA, PsA and AS in Feb 2013. The study start for PsO, CD and UC was in November 2014. The estimated end of the patient inclusion is September 2016. Each patient will be observed for a period of max.12 months. Follow-up of patients should enable approximately 5 patient visits (including screening = visit 1) during 12 months. For these reasons, the most likely visits are defined as “V1”,“V2”,“V3”,“V4” and “V5” although numbers

and dates will depend only on the decision of the physician. A schedule of activities can be found in the next section. According to the standard of care the approximate frequency of the visits will be 3 months. As a result, failure to meet these suggested dates will not constitute a breach of the protocol.

6.5 Study Conduct and Schedule of Activities:

The study will be conducted in a prospective, single-country, multicenter format. The participating investigator will provide the patient with a prescription for HUMIRA®40mg syringe or HUMIRA®40mg pen, as the patient can select between two available application devices. Depending on a patient´s selection, the investigator will also provide him/her the instructions for appropriate use of the HUMIRA®40mg pen (please see Appendix-A) or HUMIRA®40mg syringe (please see Appendix-B). Patient safety data and information about co-medications other medications or supplements taken for RA, PsA, AS, PsO, CD or UC will be recorded on electronic data report forms (eCRFs) at study enrollment and during their regularly scheduled visits. If treatment with Adalimumab is interrupted, standard practice is to review the patient after a period of 3 months. If the physician decides to permanently discontinue Adalimumabbefore the end of the planned observational period of 12 months, the reason for discontinuation and the new RA, PsA,AS, PsO, CD or UC treatment regimen prescribed, if applicable, will be documented. The next routine follow-up visit will be the termination visit for this patient in the post-marketing observational study.

There is no recommendation regarding an appropriate amount of time for wash out of previous BDMARDs prior to initiating Adalimumab therapy. The determination of an appropriate time to initiate Adalimumab following discontinuation of another BDMARD is at the discretion of the physician. While individual patient variability can affect drug elimination, it is generally felt that a majority of a drug is eliminated after 4 to 5 drug half-lives. The health care professional may wish to consider this in determining the appropriate time to initiate Adalimumab therapy. Health care providers should use their knowledge of TNFα biology and best clinical judgment when determining an appropriate washout period of previous BDMARD therapy. AbbVie Austria's recommended wash out periods are: Etanercept received > 3 weeks (21 days) before 1st

Adalimumab application Infliximab received > 8 weeks (56 days) before 1st Adalimumab application

Schedule of Activities

ACTIVITIES	VISIT 1 SREENING	VISIT 2	VISIT 3	VISIT 4	VISIT 5	EARLY TERMI-NATION
TIME	Month 0	Month 3	Month 6	Month 9	Month 12	
Inclusion /Exclusion Criteria	x					
Written authorization to use data	x					
Patient demographics [a]	x					
TB: Chest X-ray [i]	x					
TB: IGRA test [i]	x					
TB: PPD skin test [i]	x					
ESR	x	x	x	x	x	x
CRP	x	x	x	x	x	x
RADAI [c]	x	x	x	x	x	x
BASDAI[d]	x	x	x	x	x	x
PASI[e]	x	x	x	x	x	x
Harvey-Bradshaw Index (HBI)[f]	x	x	x	x	x	x
Partial Mayo Score[g]	x	x	x	x	x	x
Beliefs about Medicines Questionnaire *(BMQ)*	x				x	x
Morisky Medication Adherence Scale *(MMAS)*		x	x	x	x	x
Treatment Satisfaction Questionnaire for Medication *(TSQM)*		x	x	x	x	x
Concomitant treatment	x	x	x	x	x	x
Adalimumabapplication [b]	x	x	x	x	x	x
Final Statement [h]					x	x

a. Patient demographics: year of birth, gender, race, disease, duration of RA,PsA,AS and previous as well as concomitant treatment
b. Adalimumabadministration: at screening information about dosing frequency and date of first as well as any further applications.
c. for RA and if reasonable for PsA, only
d. for patients with AS only
e. for patients with PsO only
f. for patients with CD only
g. for patients with UC only

h. Final statement shall also include a statement about pain-management with respect to a potential influence of adalimumab
i. According to the recommendations of the German central committee for the fight against tuberculosis all patients who are about to be treated with a TNF-inhibitor should be screened for a latent tuberculosis infection by the use of a highly specific interferon-γ-test (IGRA interferon gamma release assay) in addition to chest X-ray and an accurate careful anamnesis.
Please see also APPENDIX C !
AUSTRIAN CONSENSUS STATEMENT ABOUT TUBERCULOSIS & BIOLOGICALS

RECOMMENDATIONS FOR TUBERCULOSIS SCREENING BEFORE INITIATION OF TNFα-INHIBITOR TREATMENT IN RHEUMATIC DISEASES

As by the use of the PPD skin test (Mendel Mantoux) false positive or false negative test results are expected in patients with latent tuberculosis, the PPD skin test shall be used in exceptional cases only.

The PPD-skin test as a supplementary test is useful only in the following cases, if:

- in spite of a negative IGRA test an earlier tight exposure to a patient with infectious lung TB is anamnestic plausible
- a BCG (Bacille Calmette-Guérin) vaccination in due consideration of the immunisation policy of the respective country of origin of a patient is implausible and/or
- a IGRA-test is indeterminable in the repetition

In such cases a positive PPD test defines the further course of action.

If a patient has had a PPD test placed within 3 months prior to the first Adalimumab-application, a repetition of the PPD test
will not be required provided the following conditions are met:

1. There is documentation signed by a licensed health care professional that the PPD test was read within 48-72 hours of placement and a precise assessment of induration in millimetres is included.
2. The chest x-ray before first Adalimumab-application does not indicate any evidence of TB (no evidence of calcified granulomas, no evidence of pleural scarring and no evidence of latent TB)
3. Nothing in the patient's history has changed since the time of the PPD tests to warrant a repeat test.

Please see also APPENDIX C! CDC Treatment Recommendations for Positive PPD; CDC CENTERS FOR DISEASE CONTROL AND PREVENTION

6.5.1 Description of Activities

Beliefs about Medicines Questionnaire (BMQ)

The BMQ is a method for assessing cognitive representations of medication. The questionnaire comprises two sections: the BMQ-Specific which assesses representations of medication prescribed for personal use and the BMQ-General which assesses beliefs about medicines in general. The BMQ-Specific comprises two 5-item factors assessing beliefs about the necessity of prescribed medication (Specific-Necessity) and concerns about prescribed medication based on beliefs about the danger of dependence and long-term toxicity and the disruptive effects of medication (Specific-Concern). The BMQ-General comprises two 4-item factors assessing beliefs that medicines are harmful, addictive, poisons which should not be taken continuously (General-Harm) and that medicines are overused by doctors (General-Overcure). The total

score, the sum of all the points from the Specific AND General questions range from 17 (lowest score) to 85 (highest score). Patients who have positive beliefs about medicine have a score < 47 and patients who have negative beliefs have a score > 47.

Morisky Medication Adherence Scale (MMAS)

The MMAS is a 4-item Self-Report Measure of Medication-Taking Behavior. It measures both intentional and non-intentional non-adherence (based on forgetting, carelessness, stopping medication when feeling better, or stopping medication when feeling worse). The 4-item MMAS-4-item consists of 4 questions which can be answered with yes (=0 point) and no (=1 point). The MMAS score is the sum of all four question and range from 0 (=non-adherent) to 4 (=adherent).

Treatment Satisfaction Questionaire for Medication (TSQM)

The 11-item Treatment Satisfaction Questionnaire for Medication (TSQM) Version II is an instrument to assess patients' satisfaction with medication, providing scores on four scales – *side effects*, *effectiveness*, *convenience* and *global satisfaction*. The 11 questions can be answered either with yes/no or by means of a five or seven stage scale (e.g. ranging from very unsatisfied to satisfied). SCALE SCORING ALGORITHM: TSQM Scale scores range from 0 to 100 and no computed score should be lower or higher than these limits. Higher scores represent higher satisfaction. EFFECTIVENESS: ([(Item 1 + Item 2) − 2] divided by (12) × 100 SIDE EFFECTS: ([Sum of Item 4 to Item 6) − 3] divided by 12) × 100 If one item is missing: ([(Sum of the two completed items) − 2] divided by (8) × 100 CONVENIENCE: ([Sum of Item 7 to Item 9) − 3] divided by 18) × 100 If one item is missing: ([(Sum of the two completed items) − 2] divided by (12) × 100 GLOBAL SATISFACTION: ([Sum of Item 10 to Item 11) − 2] divided by 12) × 100.

Rheumatoid Arthritis Disease Activity Index (RADAI):

The RADAI is a questionnaire for patients used for measuring disease activity. The index consists of 6 questions. The items ask the patient about (1) global disease activity in the last 6 months , (2) disease activity in terms of current swollen and tender joints, (3) arthritis pain, (4) the current status of health, (5) duration of morning stiffness and (6) tender joints to be rated in a

joint list. The joint list asks about pain in the left and right shoulders, elbows, wrists, fingers, hips, knees, ankles and toes. The first four items are all rated on a numeric rating scale from 0 to 10, where higher scores indicate more disease activity. The scores on the last two items range from 0 to 6 and 0 to 48, respectively, but are transformed on the same scale of 0 to 10.

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI):
The BASDAI is used for measuring and evaluating disease activity in Ankylosing Spondylitis. This index consists of 6 questions pertaining to the 5 major symptoms of AS: fatigue, spinal pain, joint pain/swelling, areas of localized tenderness (=enthesitis – inflammation of tendons and ligaments), duration of morning stiffness, severity of morning stiffness. A visual analogue scale ranging from 0 to 10 is used to answer the questions (zero being no problem and 10 being the worst problem).

Psorasis Area and Severity Index (PASI):
The PASI has been developed to provide quantitative assessment of psoriasis lesional burden based on the amount of BSA involved and degree of severity of erythema, induration, and scale, weighted by body part. The head, upper extremities, lower extremities, and trunk are assessed separately and then combined using weighting based on the surface area represented by each area (head 0.1, upper extremities 0.2, trunk 0.3, and lower extremities 0.4). The degree of erythema, induration, and scale in each area is judged on a 0–4 scale, the sum of which represents disease severity. The area of involvement of each area is graded from 0–6, depending on the estimated percentage of lesion area (0: 0 %, 1: 0-10%, 2: 10-29%, 3: 30-49%, 4: 50-69%, 5: 70-89%, and 6: 90-100%). These body scores are multiplied by the disease severity score and the weighting for each body area, yielding a score between 0 and 72[10].

Harvey-Bradshaw Index (HBI):
The Harvey-Bradshaw index is a score for quantification of symptoms in patients with CD. It consists of only clinical parameters:
general well-being (0 = very well, 1 = slightly below average, 2 = poor, 3 = very poor, 4 = terrible)

abdominal pain (0 = none, 1 = mild, 2 = moderate, 3 = severe)

number of liquid stools per day

abdominal mass (0 = none, 1 = dubious, 2 = definite, 3 = tender)

complications, as above, with one point for each.

The values can range from 0 (in healthy subjects) to 30 points, whereas moderate to severe patients have Harvey-Bradshaw index ≥ 7. A score of less than 5 is generally considered to represent clinical remission[12].

Partial Mayo score (PMS)

For the evaluation of the patient's disease activity the partial Mayo score will be documented at each visit. In this study, an average score of five measurements (see subscore sections) shall be used for analysis. The partial Mayo Score has been proven to be a valid and reliable noninvasive measure to evaluate disease activity in adults with UC[13]. If endoscopy is routinely performed during the visit the full mayo score can be documented[14]. (Please see definition of Mayo Score below)

The Mayo Score is a composite of the following subscores: Stool Frequency subscore, Rectal Bleeding subscore, Endoscopy subscore, and Physician's Global Assessment subscore[13].

The Partial Mayo Score is a composite of the following subscores: Stool Frequency subscore, Rectal Bleeding subscore, and Physician's Global Assessment subscore[14].

Stool Frequency Subscore

The stool frequency subscore is calculated by comparing the stool frequency to a reference number. The reference number is the number of stools per day (24 hours) that is typical for the subject when having active UC but not experiencing a flare and needs to be designated once prior to enrollment. The reference number should represent a full number of at least 1.

Subjects will record the daily number of stools throughout the trial. Using these numbers, the Stool Frequency subscore will be assessed for each study day as follows:

> A number of bowel movements lower than or equal to the reference number of bowel movements should be scored as 0 = Normal.

One or 2 bowel movements more than the reference number of bowel movements should be scored as 1.

Three or 4 bowel movements more than the reference number of bowel movements should be scored as 2.

Five or more bowel movements more than the reference number of bowel movements should be scored as 3.

The Stool Frequency subscores from the 5 days prior to each study visit will be averaged and used for the Stool Frequency subscore for each study visit.

The Stool Frequency subscore during days which the subject received anti-diarrheal medication will be scored as a 3.

Diary entries for stool frequency should not be included in the 5 days prior to the visit that are evaluated for the Stool Frequency subscore for the following days: (1) the day the subject received medication for bowel preparation prior to endoscopy, (2) the day the subject underwent an endoscopy, and (3) 2 days following the endoscopy. Earlier diary entries will be used accordingly in order to provide the most recent data for 5 days prior to the respective study visit.

Rectal Bleeding Subscore

Subjects should record a daily rectal bleeding subscore value as follows:

No visible blood with stool during the respective day should be scored as 0.

Visible blood with stool less than half the time during the respective day should be scored as 1.

Visible blood with stool at least half the time during the respective day should be scored as 2.

A score of 3 for bleeding requires subjects to have at least 50% of bowel movements accompanied by visible blood and at least one bowel movement with blood alone.

The score entries into subject's diary from the 5 days prior to each study visit will be averaged and used for the Rectal Bleeding subscore for each study visit.

Diary entries for rectal bleeding should not be included in the 5 days prior to the visit that are evaluated for the Rectal Bleeding subscore for the following days: (1) the day the subject received medication for bowel preparation prior to endoscopy, (2) the day the subject underwent an endoscopy, and (3) 2 days following the endoscopy . Earlier diary entries will be used accordingly in order to provide the most recent data for 5 days prior to the respective study visit.

Physician's Global Assessment Subscore

The physician's global assessment acknowledges the 2 subject-reported subscores, the endoscopy subscore as applicable, the subject's daily record of abdominal discomfort (pain/cramps) and general well-being during the 5 days prior to the visit, and other observations such as physical findings, and the subject's performance status in order to assess disease activity as follows:

0 = Normal

1 = Mild disease

2 = Moderate disease

3 = Severe disease

Endoscopy Subscore

The endoscopist should evaluate each observed segment of the colon (rectum, sigmoid, descending colon, transverse colon, ascending colon/cecum) by using the classification as follows:

0 = Normal or inactive disease

1 = Mild disease (erythema, decreased vascular pattern, mild friability)

2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)

3 = Severe disease (spontaneous bleeding, ulceration)

The endoscopic subscore for the subject will be the worst score of the observed segments.

The local endoscopist should also separately assess presence or absence of friability (yes/no).

The endoscopy will be recorded on a videotape and will undergo a central review process for endoscopy subscore assessment.

C-reactive protein CRP:

The CRP is an acute phase reactant plasma protein, normally produced by the liver, which is commonly used as an indirect measure of the extent and activity of an inflammation. Synthesis of this protein increases rapidly in response to inflammatory stimuli in both acute and chronic settings. After the inflammation is over the CRP level is rapidly decreased again. The normal reference range in the blood is as a rule from 0 to 1,0 mg/dl CRP. The CRP is increased in a variety of disorders like rheumatic diseases.

Erythrocyte sedimentation rate (ESR):

The ESR is based on the sedimentation and aggregation of erythrocytes. It is influenced due to the large and asymmetric plasmaproteins as immunoglobulins, fibrinogen and α2-macro-globulin. These plasmaproteins favour the production of erythrocyte aggregates which sediment faster than every single erythrocyte. The ESR is a practicable and sensitive but not specific parameter for measuring disease progression. By means of the ESR it can be generally distinguished between an active and non-active rheumatic disease. The normal reference range is as a rule for men 0 – 10 mm/h and for women 0-15 mm/h.

6.5.2 Description of the Visits

6.5.2.1 Inclusion visit

Patients will be documented according to the following procedure: demographics (year of birth, gender, disease and disease duration, results of Chest X-ray and a highly specific interferon-γ-release assay [IGRA] or PPD-test for Tb-screening and RA, PsA, AS, PsO, CD or UC treatment in the past), ESR, CRP; Beliefs about Medicines Questionnaire (BMQ), concomitant treatment other medication or supplement, start of Adalimumab application will be documented in the appropriate eCRF.

6.5.2.2 Follow-up visits

The total treatment period is max. 12 months for each patient.

Approximately 4 follow-up visits are expected over the 12 months period. These visits should occur at an interval of 3 months - "**V2**","**V3**","**V4**","**V5**".

The visit schedule is to be decided by the investigator according to the routine clinical practice.

Intercurrent visits will be documented using the CRF module with the next following visit number, **Visits V2,V3,V4,V5.**

Follow up visits shall comprise the following:

V2: ESR,CRP, MMAS, TSQM, RADAI, BASDAI, PASI, HBI, PMS concomitant treatment, Adalimumab-application

V3: ESR,CRP, MMAS, TSQM, RADAI, BASDAI, PASI, HBI, PMS concomitant treatment, Adalimumab application

V4: ESR,CRP, MMAS, TSQM, RADAI, BASDAI, PASI, HBI, PMS concomitant treatment, Adalimumab application

V5: ESR,CRP, BMQ, MMAS, TSQM, RADAI, BASDAI, PASI, HBI, PMS concomitant treatment, Adalimumab-application, final statement

Evaluation of the tolerability of the Adalimumab treatment

Any serious adverse events (**SAEs**) of the Adalimumab regimen will be collected throughout this study and 70-days following the last dose of Adalimumab.

Evaluation of the durability of the Adalimumab treatment

Any changes to RA, PsA, AS, PsO, CD or UC treatment and the type of change (dose modification or discontinuation) will be recorded in the data report form, whether the modifications relate to the use of Adalimumab or to the use of concomitant RA, PsA, AS, PsO, CD or UC treatments. If Adalimumab is temporarily interrupted or permanently discontinued before the end of the planned observational period of 12 months, the reason for interruption/discontinuation and the details on the subsequent RA, PsA, AS, PsO, CD or UC treatment, if applicable, will be recorded.

The next routine follow-up visit will be the post interruption/discontinuation visit (see 6.5.1.3).

6.5.2.3 Follow-up visit after temporary interruption or early permanent discontinuation of the Adalimumab treatment (Post interruption / discontinuation visit)

Follow-up visits after temporary interruption or early permanent discontinuation shall comprise the following:

ESR,CRP, Beliefs about Medicines Questionnaire (BMQ), Morisky Medication Adherence Scale (MMAS), Treatment Satisfaction Questionnaire for Medication (TSQM), concomitant treatment, Adalimumab application, final statement.

Evaluation of the tolerability since the interruption/discontinuation of the Adalimumab treatment

All serious adverse events (SAEs) will be reported to AbbVie until 70 days following intake of the last dose of physician-prescribed Adalimumab treatment.

If the physician decides to permanently discontinue Adalimumab this visit will be the termination visit for the patient in the post-marketing observational study.

6.6 Product Supply

Since this is a post-marketing observational study, Adalimumab is not supplied by AbbVie. All treatments must be prescribed in accordance with the authorization and local reimbursement guidelines.

Study treatment:

All regimens will be prescribed according to international and national guidelines for treating RA, PsA, AS, PsO, CD or UC. Adalimumab will be prescribed according to the standard dosing regimen as detailed in the released SPC.

Permitted treatments:

In the context of an observational non-interventional study, the physician is free to initiate any co-prescriptions according to his or her own judgment, although he or she will pay attention to treatments interacting with Adalimumab.

Prohibited treatments:

In the context of an observational study the physician may prescribe according to his or her own judgment although he or she is reminded that Adalimumab must be associated with neither IL-1-antagonists (Anakinra) nor abatacept.

7.0 Management and Reporting of Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The investigational product in this trial contains both:

- Biologic compound(s) and
- Device component(s) (pre-filled syringe, pen).

Complaints associated with any component of this investigational product must be reported to the Sponsor. For adverse events, please refer to Sections 7.1.1 through 7.1.6. For product complaints, please refer to Section 8.

7.1 Medical Complaints

7.1.1 Adverse event and serious adverse event definition, serious adverse event categories

An "**adverse event" (AE)** is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been documented as pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done, will be considered an adverse event.

A "**serious adverse event**" **(SAE)** is an adverse event, which results in death, is life-threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, leads to persistent or significant disability or invalidity, or is a congenital anomaly/birth defect.

If an adverse event meets any of the following criteria, it is considered a serious adverse event (SAE) and has to be reported within 24 hours of the site being made aware of the SAE:

Death of Subject An event that results in the death of a subject.

Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the study subject is hospitalized and prolongs the subject's hospital stay.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Invalidity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (*e.g.*, sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical reaction that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (*i.e.,* death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/invalidity). Examples of such reaction include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Spontaneous Abortion	Miscarriage experienced by study subject.

Elective Abortion Elective abortion performed on study subject.

7.1.2 Severity

The physician will use the following definitions to rate the severity of any adverse reaction being collected as an endpoint/datapoint in the study and for all serious adverse reactions:

Mild The adverse event is transient and easily tolerated by the subject.

Moderate The adverse event causes the subject discomfort and interrupts the subject's usual activities.

Severe The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

7.1.3 Relationship to Pharmaceutical Product

This is any report of an adverse event or the absence of an effect or the contamination of an AbbVie product, which may jeopardize the patient, as well as frequently observed inappropriate use or serious abuse. A SAE, that occurs after the therapy has been terminated, has to be reported if it occurs within 5 half-lives of the AbbVie product.

An SAE must meet the following criteria for consideration:

- An identifiable patient
- An e suspected product
- An AE, in utero exposure to AbbVie pharmaceutical or fatal outcome
- An identifiable reporter

The physician will use the following definitions for all serious adverse events, to assess the relationship of the serious adverse event to the use of the pharmaceutical product:

Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (*e.g.*, has no temporal relationship to study drug or has a much more likely alternative etiology). This is per definition not a serious adverse reaction.
Probably Not Related	An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
Possibly Related	An adverse event has a strong temporal relationship to the study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug.
Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and another etiology is unlikely or significantly less likely.
Definitely Related	An adverse event has a strong temporal relationship to study drug, is known AR, another etiology is unlikely, it disappears respectively reappears with dechallenge respectively rechallenge.

If an investigator's opinion of possibly, probably not, or not related to pharmaceutical product is given, an alternate etiology must be provided by the investigator for the serious adverse event.

7.1.4 Spontaneously Serious Adverse Event - collection period

All serious adverse events (SAEs) related or not related to Adalimumab will be reported to AbbVie from the time the physician obtains the patient's authorization to use and disclose information (or the patient's informed consent) until 70 days following the intake of the last dose of physician-prescribed treatment.

7.1.5 Spontaneously reported Serious Adverse Event - reporting

In the event of a serious adverse event (SAE), and additionally, any non-serious event of malignancy in patients 30 years of age and younger, related or not related to Adalimumab, the

physician will notify the AbbVie contact person identified below within 24 hours of the physician becoming aware of the even. The physician has to complete the SAE section of the electronic Data Report Form (eCRF). The designated AbbVie pharmacovigilance contact person identified below, will be automatically informed via e-mail in case a SAE occurred, including an attachment containing the entire SAE-form. The local project manager will - in case a SAE occurred - receive this e-mail including the SAE -form for his / her information only.

Aggregate safety data will be integrated into the final study report as well as into periodic safety update reports for the marketed product. Local AbbVie pharmacovigilance contact persons are:

[redacted]

7.1.6 Pregnancy Reporting

Pregnancies in patients will be collected from the date of the first dose through 150 days following the last dose of adalimumab taken during the study. In the event of pregnancy, the physician will notify the AbbVie contact person identified in Section 7.1.5 within 24 hours of the physician becoming aware of the pregnancy.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

Pregnancy in a study subject is not considered an adverse event. However the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a **serious adverse event** and must be reported to AbbVie within 24 hours of the site becoming aware of the event!

8.0 Product Complaint

8.1 Definition

A Product Complaint is any Complaint (see Section 0 for the definition) related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

8.2 Reporting

The relevant AbbVie Product Complaint contact details are specified below:

[redacted]

In the event of a product complaint related to concerning the investigational product and/or device, the physician has to retrieve the form for product complaints from the InterTrial page (see miscellaneous documents), complete the form and will notify AbbVie, by faxing (fax-no.: [redacted]) this form within 24 hours of the physician becoming aware of the event. In instances where a return is requested, every effort should be made by the investigator to return

the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

Please return the concerned product to the pharmacy where the patient did purchase it along with the specified description of the complaint. The pharmacy will return it via wholesaler to AbbVie for investigation.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

9.0 Ethics and Quality

All patient data entered in the patient's electronic data report form (eCRF) will be forwarded - without naming the patient - for evaluation to AbbVie. In order to maintain patient confidentiality, instead of date of birth, the patient's age will be documented in the eCRF.

The patients must provide written authorization to the investigator to use and/or disclose personal and/or health data before entry into this PMOS. The investigator will document this authorization in the patient's chart. There are no local law requirements for monitoring, notification /submission of a post-marketing observational study to an ethics committee and/or regulatory body. However, a written confirmation from one of the Lead–ECs will be obtained. In this the following statement should be documented: "According to §2 paragraph 3 of the Austrian Pharmaceutical Act it is an observational study and therefore an evaluation by the ethics committee (EC) is not required". The protocol and the IC/ADU should be provided to the EC for review. It will be submitted to a regulatory body. The study will not be monitored. However in order to assure professional site data-management a qualified Clinical Research Organisation (CRO) as well as a statistician is assigned. Concretely this means that data entered in the eCRFs by the sites will be checked for consistency of data. Inconsistent data will be queried.

10.0 Data Report Forms

Examinations, diagnostic measures, findings and observations routinely performed in patients included in this postmarketing observational study will be entered by the investigator or staff according to the protocol in the data report forms provided by AbbVie. AbbVie Austria will document data in electronic data report forms (eCRF). Completed eCRF visit modules will be sent electronically immediately after completion to the contracted statistician and CRO.

11.0 Data Analysis Plans

11.1 End points

11.1.1 Primary end point

Patients` adherence attitudes (beliefs) to maintenance therapy with a scheduled Adalimumab monotherapy or a combination therapy with methotrexate will be assessed at baseline (visit 1 =screening) and at the end of the study at visit 5. Furthermore it shall be investigated whether there are correlations between such beliefs and adherence to maintenance treatment.

11.1.2. Secondary end points

As secondary endpoints the following parameters will be evaluated: changes in the Morisky Medication Adherence Scale (**MMAS**) at visit 2, 3, 4 and 5, changes in the Treatment Satisfaction Questionnaire for Medication (**TSQM**) at visit 2, 3, 4 and 5, changes at the laboratory parameters such as C-reactive protein (**CRP)** and Erythrocyte sedimentation rate (**ESR**).

Changes in the Rheumatoid Arthritis Disease Activity Index (**RADAI**), Bath Ankylosing Activity Index (**BASDAI**), Psoriasis Area and Severity Index (PASI), Harvey-Bradshaw Index (HBI) and the Partial Mayo score (PMS) at visit 2, 3, 4 and 5. The quality of the analyses will depend on the fact that laboratory measurements are not stringent in the context of a non-interventional observational study. Tolerability and safety will be assessed by collection and classification of serious adverse events. Serious adverse reactions observed on treatment with Adalimumab will be described. The duration on treatment with Adalimumab until development

of a serious adverse reaction leading to Adalimumab discontinuation or until escape from treatment will be measured.

11.2 Plan of Analysis

The statistical analysis shall describe the characteristics of patients included in the survey together with outcomes and clinical tolerability of Adalimumab.

Subject to the level of measurement of the respective variables appropriate descriptive statistics is used: e.g. frequency absolute and/or percental; nonmissing, missing data respectively; mean, standard deviation, where applicable: median, 25th percentile (first quartile) and 75th percentile (third quartile), minimum and maximum, range, calculation of confidence intervals (if applicable). Appropriate graphs are used (e.g. scatterplot, boxplot, histogram, etc.). **As the study is an open label non-interventional post marketing observational study there is no working hypothesis allowed!**

Compliance with treatments, outcomes and clinical tolerability of treatments will be compared as a function of patient characteristics.

A data analysis plan will be available prior to the conduct of the statistical analysis for the study.

12.0 Final Reports and Publications

At the end of the data collection of Plaque Psoriasis patients the final report for all indications will be written at the end of the study. A publication (e.g. an abstract and/or poster) based on the final report will be published. The report will contain a description of the objectives of the survey, the methodology of the survey, its results, conclusions and a list of all involved physicians/hospitals. The information contained in the data report forms, the statistical analysis report and the clinical report must be treated as the confidential property of AbbVie. It may not be released to unauthorized people in any form (publications or presentations) without explicit written approval from AbbVie. The results of this survey may be published or presented by the sponsor and author of the present protocol alone or under participation by one of the investigators after agreement with the sponsor or by one of the investigators alone after agreement with the sponsor.

13.0 Conduct of the PMOS

This PMOS will be supervised by AbbVie [redacted] If there is any question regarding the conduct of this PMOS, please call [redacted]

14.0 References

1. Osterberg L, Blaschke T, Adherence to Medication. N Engl J Med 2005;353:487-97
2. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, Wong PK, Medication Compliance and Persistence: Terminology and Definitions. Value In Health 2008;11(1), pp.:44-47
3. Koncz T, Pentek M, Brodszky V, Ersek K, Orlewska E, Gulacsi L, Adherence to biologic DMARD therapies in rheumatoid arthritis. Expert Opin. Biol. Ther. 2010;10(9):1367-1378
4. Horne R, Weinman J, Hankins M, The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. Psychology and Health. 1999;14,pp.:1-24
5. Morisky DE, Green LW, Levine DM, Concurrent and Predictive Validity of a Self-reported Measure of Medication Adherence. Medical Care, 1986,24(1),pp.:67-74
6. Atkinson MJ, Sinha A, Hass SL, Colman SS, Kumar RN, Brod M, Rowland CR, Validation of a general measure of treatment stisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease
7. Hierachical Construct Validity of the Treatment Satisfaction Questionnaire for Medication (TSQM Version II) among Outpatient Pharmacy Consumers. Value In Health 2005,8(Suppl I) S9-S24
8. HUMIRA EPAR/SPC as downloaded from EMEA homepage on 22 October 2013. Link: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000481/WC500050870.pdf
9. Scallon B, Cai A, Solowski N, Rosenberg A, Song XY, Shealy D, Wagner C. Binding and Functional Comparisons of Tumor Necrosis Factor Antagonists. J Pharmacol Exp Ther 2002; 301; pp.:418-2610.

10. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica. 1978;157(4):238-44.

11. Mease, P. J. Measures of Psoriatic Arthritis. Arthritis Care Res, 2011,63(Suppl 11): S64–S85.

12. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet. 1980; 1(8167):514.

13. Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. Inflamm Bowel Dis 200814(12):1660-6.

14. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderatly active ulcerative colitis. A randomized study. N Engl J Med 1987; 317(26):1625-9.

15. Appendix

Appendix A: HUMIRA® PEN-Instruction (EMA)

Humira 40 mg solution for injection in pre-filled pen
Adalimumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
Keep this leaflet. You may need to read it again.
Your doctor will also give you a Patient Alert Card, which contains important safety information that you need to be aware of before you are given Humira and during treatment with Humira. Keep this Patient Alert Card with you.
If you have any further questions, ask your doctor or pharmacist.
This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet (see section 4).

What is in this leaflet:
1. What Humira is and what it is used for
2. What you need to know before you use Humira
3. How to use Humira
4. Possible side effects

5 How to store Humira
6. Contents of the pack and other information

1. WHAT HUMIRA IS AND WHAT IT IS USED FOR

Humira contains the active substance adalimumab, a selective immunosuppressive agent.Humira is intended for treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease and ulcerative colitis. It is a medicine that decreases the inflammation process of these diseases. The active ingredient, adalimumab, is a human monoclonal antibody produced by cultured cells. Monoclonal antibodies are proteins that recognise and bind to other unique proteins. Adalimumab binds to a specific protein (tumour necrosis factor or TNFα), which is present at increased levels in inflammatory diseases such as rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease and ulcerative colitis.

Rheumatoid arthritis

Humira is used to treat rheumatoid arthritis in adults. Rheumatoid arthritis is an inflammatory disease of the joints. If you have moderate to severe active rheumatoid arthritis, you may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira to treat your rheumatoid arthritis.

Humira can also be used to treat severe, active and progressive rheumatoid arthritis without previous methotrexate treatment.

Humira has been shown to slow down the damage to the cartilage and bone of the joints caused by the disease and to improve physical function.

Usually, Humira is used with methotrexate. If your doctor determines that methotrexate is inappropriate, Humira can be given alone.

Polyarticular juvenile idiopathic arthritis

Humira is used to treat polyarticular juvenile idiopathic arthritis in children and adolescents aged 2 to 17 years. Polyarticular juvenile idiopathic arthritis is an inflammatory disease, affecting one or more joints, with diagnosis typically occurring in children under the age of 16 years. You may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira to treat your polyarticular juvenile idiopathic arthritis.

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Humira is used to treat ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis in adults. Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, are inflammatory diseases of the spine. If you have ankylosing spondylitis or axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira to reduce the signs and symptoms of your disease.

Psoriatic arthritis

Humira is used to treat psoriatic arthritis in adults. Psoriatic arthritis is an inflammation of the joints associated with psoriasis. Humira has been shown to slow down the damage to the cartilage and bone of the joints caused by the disease and to improve physical function.

Psoriasis

Humira is used to treat psoriasis in adults. Psoriasis is an inflammatory disease of the skin. If you have moderate to severe plaque psoriasis, you will first be given other medicines or e.g. phototherapy. If you do not respond well enough to these treatments, you will be given Humira to reduce the signs and symptoms of your psoriasis.

Crohn’s disease in Aults and Children

Humira is used to treat Crohn’s disease in adults and children aged 6 to 17 years of of age. Crohn’s disease is an inflammatory disease of the digestive tract. Humira is indicated for the treatment of Crohn's disease in adults and in children aged 6 to 17 years. If you have Crohn’s disease you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira to reduce the signs and symptoms of your Crohn’s disease.

Ulcerative Colitis

Humira is used to treat ulcerative colitis in adults. Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira to reduce the signs and symptoms of your disease.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE HUMIRA

Do not use Humira

If you are allergic to adalimumab or any of the other ingredients ofthis medicine (listed in section 6).

If you have a severe infection, including active tuberculosis (see "Warnings and precautions"). It is important that you tell your doctor if you have symptoms of infections, e.g. fever, wounds, feeling tired, dental problems.

If you have moderate or severe heart failure. It is important to tell your doctor if you have had or have a serious heart condition (see "Warnings and precautions").

Warnings and precautions

Talk to your doctor or pharmacist before using Humira

If you experience allergic reactions with symptoms such as chest tightness, wheezing, dizziness, swelling or rash do not inject more Humira and contact your doctor immediately.

If you have an infection, including long-term or localized infection (for example, leg ulcer) consult your doctor before starting Humira. If you are unsure, please contact your doctor.

You might get infections more easily while you are receiving Humira treatment. This risk may increase if your lung function is impaired. These infections may be serious and include tuberculosis, infections caused by viruses, fungi, parasites or bacteria, or other opportunistic infections and sepsis that may, in rare cases, be life-threatening. It is important to tell your doctor if you get symptoms such as fever, wounds, feeling tired or dental problems. Your doctor may recommend temporary discontinuation of Humira.

As cases of tuberculosis have been reported in patients treated with Humira, your doctor will check you for signs and symptoms of tuberculosis before starting Humira. This will include a thorough medical evaluation including your medical history and appropriate screening tests (for example chest X-ray and a tuberculin test). The conduct and results of these tests should be recorded on your Patient Alert Card. It is very important that you tell your doctor if you have ever had tuberculosis, or if you have been in close contact with someone who has had tuberculosis. Tuberculosis can develop during therapy even if you have received preventative treatment for tuberculosis. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy tell your doctor immediately.

Advise your doctor if you reside or travel in regions where fungal infections such as histoplasmosis coccidioidomycosis or blastomycosis are endemic.

Advise your doctor if you have a history of recurrent infections or other conditions that increase the risk of infections.

Advise your doctor if you are a carrier of the hepatitis B virus (HBV), if you have active HBV or if you think you might be at risk of contracting HBV. Your doctor should test you for

HBV. Humira can cause reactivation of HBV in people who carry this virus. In some rare cases, especially if you are taking other medicines that suppress the immune system, reactivation of HBV can be life-threatening.

If you are over 65 years you may be more susceptible to infections while taking Humira. You and your doctor should pay special attention to signs of infection while you are being treated with Humira. It is important to tell your doctor if you get symptoms of infections, such as fever, wounds, feeling tired or dental problems.

If you are about to undergo surgery or dental procedures please inform your doctor that you are taking Humira. Your doctor may recommend temporary discontinuation of Humira.

If you have demyelinating disease such as multiple sclerosis, your doctor will decide if you should receive Humira.

Certain vaccines may cause infections and should not be given while receiving Humira. Please check with your doctor before you receive any vaccines. It is recommended that children, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Humira therapy. If you received Humira while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately 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 Humira use during your pregnancy so they can decide when your baby should receive any vaccine.

- If you have mild heart failure and you are being treated with Humira, your heart failure status must be closely monitored by your doctor. It is important to tell your doctor if you have had or have a serious heart condition. If you develop new or worsening symptoms of heart failure (e.g. shortness of breath, or swelling of your feet), you must contact your doctor immediately. Your doctor will decide if you should receive Humira.

In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. If you develop a fever that does not go away, bruise or bleed very easily or look very pale, call your doctor right away. Your doctor may decide to stop treatment.

There have been very rare cases of certain kinds of cancer in children and adult patients taking Humira or other TNF blockers. People with more serious rheumatoid arthritis that have had the disease for a long time may have a higher than average risk of getting lymphoma (a kind of cancer that affects the lymph system), and leukemia (a kind of cancer that affects the blood and bone marrow). If you take Humira the risk of getting lymphoma, leukemia, or other cancers may increase. On rare occasions, a specific and severe type of lymphoma, has been observed in patients taking Humira. Some of those patients were also treated with azathioprine or 6- mercaptopurine. Tell your doctor if you are taking azathioprine or 6-

mercaptopurine with Humira. In addition cases of non-melanoma skin cancer have been observed in patients taking Humira. If new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.

There have been cases of cancers, other than lymphoma in patients with a specific type of lung disease called Chronic Obstructive Pulmonary Disease (COPD) treated with another TNF blocker. If you have COPD, or are a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for you.

Children and adolescents

- Vaccinations: if possible children should be up to date with all vaccinations before using Humira.
- Do not give Humira to children with polyarticular juvenile idiopathic arthritis below the age of 2 years.

Other medicines and Humira

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Humira can be taken together with methotrexate or certain disease-modifying anti-rheumatic agents (sulfasalazine, hydroxychloroquine, leflunomide and injectable gold preparations), steroids or pain medications including non-steroidal anti-inflammatory drugs (NSAIDs).

You should not take Humira with medicines containing the active substance, anakinra or abatacept. If you have questions, please ask your doctor.

Humira with food and drink

Since Humira is injected under the skin (subcutaneously), food and drink should not affect Humira.

Pregnancy and breast-feeding

The effects of Humira in pregnant women are not known and so the use of Humira in pregnant women is not recommended. You are advised to avoid becoming pregnant and must use adequate contraception while using Humira and for at least 5 months after the last Humira treatment. If you become pregnant, you should consult your doctor.

It is not known whether adalimumab passes into breast milk.

If you are a breast-feeding mother, you should stop breast-feeding during Humira treatment and for at least 5 months after the last Humira treatment. If you received Humira during your

pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy before the baby receives any vaccine (for more information see section on vaccination).

If you think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Humira may have a minor influence on your ability to drive, cycle or use machines. Room spinning sensation and vision disturbances may occur after taking Humira.

3. HOW TO USE HUMIRA

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Adults with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Humira is injected under the skin (subcutaneous use). The usual dose for adults with rheumatoid arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, and for patients with psoriatic arthritis is 40 mg adalimumab given every other week as a single dose.

In rheumatoid arthritis, methotrexate is continued while using Humira. If your doctor determines that methotrexate is inappropriate, Humira can be given alone.

If you have rheumatoid arthritis and you do not receive methotrexate with your Humira therapy, your doctor may decide to give 40 mg adalimumab every week.

Children with polyarticular juvenile idiopathic arthritis

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis, aged 2 to 12 years depends on the height and weight of the child. .

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis, aged 13 to 17 years, is 40mg every other week.

Adults with Psoriasis

The usual dose for adults with psoriasis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. You should continue to inject Humira for as long as your doctor has told you.

Adults with Crohn's disease

The usual dose regimen for Crohn's disease is 80 mg initially followed by 40 mg every other week two weeks later. If a faster response is required your doctor may prescribe an initial dose of 160 mg (as 4 injections in one day or 2 injections per day for two consecutive days), followed by 80 mg two weeks later, and thereafter as 40 mg every other week. Depending on your response, your doctor may increase the dose frequency to 40 mg every week.

Children or adolescents with Crohn's Disease

Children or adolescents weighing less than 40 kg:

The usual dose regimen is 40 mg initially followed by 20 mg two weeks later. If a faster response is required, your doctor may prescribe an initial dose of 80 mg (as 2 injections in 1 day) followed by 40 mg two weeks later.

Thereafter, the usual dose is 20 mg every other week. Depending on your response, your doctor may increase the dose frequency to 20 mg every week.

Children or adolescents weighing 40 kg or more:

The usual dose regimen is 80 mg initially followed by 40 mg two weeks later. If a faster response is required, your doctor may prescribe an initial dose of 160 mg (as 4 injections in 1 day or as 2 injections per day for 2 consecutive days) followed by 80 mg two weeks later.

Thereafter, the usual dose is 40mg every other week. Depending on your response, your doctor may increase the dose frequency to 40 mg every week.

For patients who do not require a full 40 mg dose of Humira, a 40mg vial is also available.

Adults with ulcerative colitis

The usual Humira dose for adults with ulcerative colitis is 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days) and 80 mg at Week 2, and thereafter 40 mg every other week. Depending on your response, your doctor may increase the dose to 40 mg every week.

Method and route of administration

Humira is administered by injection under the skin (by subcutaneous injection).

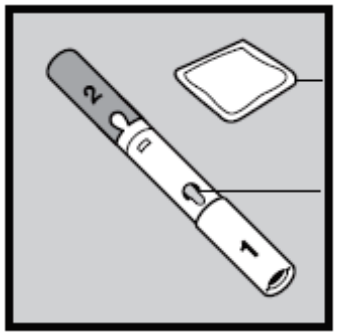
Injecting Humira yourself

The following instructions explain how to give yourself an injection of Humira using the pre-filled pen. Please read the instructions carefully and follow them step by step. You will be instructed by your doctor or his/her assistant on the technique of self-injection. Do not attempt to self-inject until you are sure that you understand how to prepare and give the injection. After proper training, the injection can be self-administered or given by another person, for example a family member or friend.

What should I do before I give myself a subcutaneous injection of Humira?

1. Wash your hands thoroughly.
2. Take one dose tray containing a pre-filled pen of Humira from the refrigerator.
3. Do not shake or drop the pre-filled pen.
4. Set up the following items on a clean surface.

   One pre-filled pen of Humira
   One alcohol pad

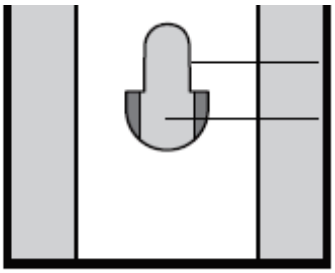


Pad

Window

5. Check the expiry date on the pre-filled pen label (EXP:) Do not use the product if the date has passed the month and year shown.

6. Hold the pre-filled pen with the grey cap (labelled ‘1’) pointing up. Check the appearance of the Humira solution through the windows on the sides of the pre-filled pen. It must be clear and colourless. If it is cloudy or discoloured or has flakes or particles in it, you must not use it. Do not use a pre-filled pen that is frozen or if it has been left in direct sunlight. Only remove both the grey cap and the plum cap **immediately** before injection



Window

Clear Liquid in Syringe

Where should I give my injection?

1. **Choose a site on the top of your thigh or stomach (except the area around the navel).**

2. Change the place that you inject each time so that you do not become sore in one area. Each new injection should be given at least 3 cm from the last injection site.

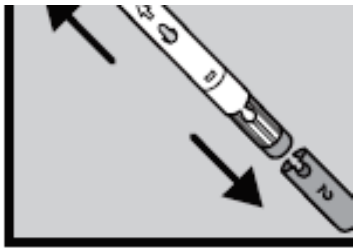
3. Do not inject in an area where the skin is reddened, bruised, or hard. This may mean there is an infection.

How do I give my injection?

1. Wipe your skin by using the enclosed alcohol pad, using a circular motion. Do not touch the area again before injecting.

2. Only remove both the grey cap and the plum cap **immediately** before injection. Hold the grey body of the pre-filled pen with one hand. Place hand on the middle of the pen so that neither the grey cap (1) nor the plum cap (2) is covered. Hold the pre-filled pen with the grey cap (1) pointing up. With your other hand, pull the grey cap (1) straight off and discard cap. Check that the small grey needle cover of the syringe has been removed with

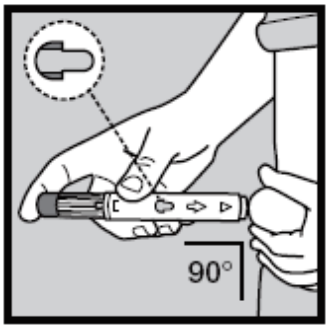
the cap. . If a few small drops of liquid come out of the needle, that is okay. The white needle sleeve will now be exposed. Do not try to touch the needle housed in the barrel. **DO NOT RECAP** as you may damage the needle inside.

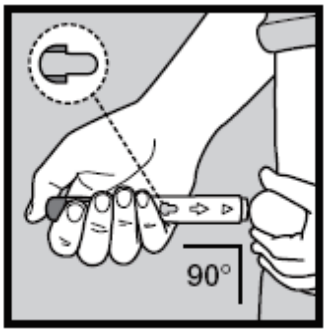


3. Pull the plum safety cap (labelled '2') straight off to expose the plum coloured activation button. The pre-filled pen is now ready to use. Do not press the plum activation button until properly positioned as this will result in discharge of medication. **DO NOT RECAP as this could cause the unit to discharge.**

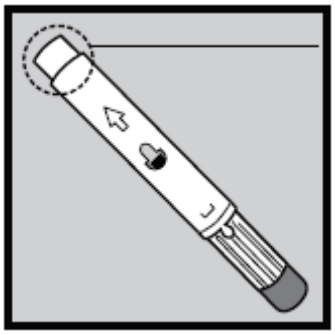
Giving the injection

1. With your free hand, gently grasp a sizable area of the cleaned skin at the injection site and hold firmly (see below).
2. Place the white end of the pre-filled pen at a right angle (90 degrees) to the skin, so that you can see the window. The presence of one or more bubbles in the window is normal.
3. Holding the barrel of the pre-filled pen, press down slightly onto the injection site (holding in place without moving).
4. With your index finger or your thumb, press the plum coloured button on top once you are ready to begin the injection (see below). You will then hear a loud 'click' as the needle is released, and you will feel a small prick as the needle advances.
5. Keep pressing and continue to hold the pre-filled pen with steady pressure in place for about **10 seconds to ensure a complete injection.** Do not remove the pre-filled pen while the injection is being given.

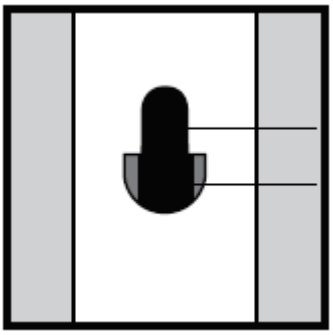




6. You will see a yellow indicator move into the windows during the injection. The injection is complete when the yellow indicator stops moving.
7. Lift the pre-filled pen straight up from the injection site. The white needle sleeve will move down over the needle and lock into place over the needle tip. Do not try to touch the needle. The white needle sleeve is there to protect you from touching the needle.



White Needle Sleeve



Window

Yellow Indicator Visible

8. You may notice a spot of blood at the injection site. You can press a cotton ball or a piece of gauze over the injection site for 10 seconds. Do not rub the injection site. Use a plaster if you want to.

Throwing away supplies

Only use each pre-filled pen for one injection. Do not put either of the caps back on the pre-filled pen
After injecting Humira, immediately throw away the used pre-filled pen in a special container as instructed by your doctor, nurse or pharmacist
Keep this container out of the reach and sight of children

If you use more **Humira** than you should:

If you accidentally inject Humira more frequently than told to by your doctor or pharmacist, you should call your doctor or pharmacist and tell him/her that you have taken more. Always take the outer carton of medicine with you, even if it is empty.

If you forget to use Humira:

If you forget to give yourself an injection, you should inject the next dose of Humira as soon as you remember. Then take your next dose as you would have on your originally scheduled day, had you not forgotten a dose.

If you stop using Humira:

The decision to stop using Humira should be discussed with your doctor. Your symptoms may return upon discontinuation.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However, some may be serious and require treatment. Side effects may occur at least up to 4 months after the last Humira injection.

Tell your doctor immediately if you notice any of the following:
Severe rash, hives or other signs of allergic reaction;
Swollen face, hands, feet;
Trouble breathing, swallowing;
Shortness of breath with exertion or upon lying down or swelling of the feet;

Tell your doctor as soon as possible if you notice any of the following:
Signs of infection such as fever, feeling sick, wounds, dental problems, burning on urination;
Feeling weak or tired;
Coughing;
Tingling;
Numbness;
Double vision;
Arm or leg weakness
A bump or open sore that doesn't heal

- e

The symptoms described above can be signs of the below listed side effects, which have been observed with Humira:

Very common (may affect more than 1 in 10 people):

- injection site reactions (including pain, swelling, redness or itching;
- respiratory tract infections (including cold, runny nose, sinus infection, pneumonia);
- headache;
- abdominal pain;
- nausea and vomiting;
- rash;
- musculoskeletal pain.

Common (may affect up to 1 in 10 people):

- serious infections (including blood poisoning and influenza);
- skin infections (including cellulitis and shingles);
- ear infections;
- oral infections (including tooth infections and cold sores);
- reproductive tract infections;
- urinary tract infection);
- fungal infections;
- joint infections;
- benign tumours;
- skin cancer;
- allergic reactions (including seasonal allergy);
- dehydration;
- mood swings (including depression);
- anxiety;
- difficulty sleeping;
- sensation disorders such as tingling, prickling or numbness;
- migraine;
- nerve root compression (including low back pain and leg pain);
- vision disturbances;
- eye inflammation;
- inflammation of the eye lid and eye swelling;
- vertigo;
- sensation of heart beating rapidly;
- high blood pressure;
- flushing;
- haematoma;
- cough;
- asthma;
- shortness of breath;
- gastrointestinal bleeding;

- dyspepsia (indigestion, bloating, heart burn);
- acid reflux disease;
- sicca syndrome (including dry eyes and dry mouth);
- itching;
- itchy rash;
- bruising;
- inflammation of the skin (such as eczema);
- breaking of finger nails and toe nails;
- increased sweating;
- hair loss;
- new onset or worsening of psoriasis;
- muscle spasms;
- blood in urine;
- kidney problems;
- chest pain;
- oedema;
- fever;
- reduction in blood platelets which increases risk of bleeding or bruising;
- impaired healing.

Uncommon (may affect up to 1 in 100 people):

- opportunistic infections (which include tuberculosis and other infections that occur when resistance to disease is lowered);
- neurological infections (including viral meningitis);
- eye infections;
- bacterial infections;
- diverticulitis (inflammation and infection of the large intestine);
- cancer;
- cancer that affects the lymph system;
- melanoma;
- immune disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis);
- tremor;
- neuropathy;
- stroke;
- double vision;
- hearing loss, buzzing;
- sensation of heart beating irregularly such as skipped beats;
- heart problems that can cause shortness of breath or ankle swelling;

- heart attack;
- a sac in the wall of a major artery, inflammation and clot of a vein, blockage of a blood vessel;
- lung diseases causing shortness of breath (including inflammation);
- pulmonary embolism (blockage in an artery of the lung);
- pleural effusion (abnormal collection of fluid in the pleural space);
- inflammation of the pancreas which causes severe pain in the abdomen and back;
- difficulty in swallowing;
- facial oedema;
- gallbladder inflammation, gallbladder stones;
- fatty liver;
- night sweats;
- scar;
- abnormal muscle breakdown;
- systemic lupus erythematosus (including inflammation of skin, heart, lung, joints and other organ systems);
- sleep interruptions;
- impotence;
- inflammations.

Rare (may affect up to 1 in 1000 people)

- leukemia (cancer affecting the blood and bone marrow);
- severe allergic reaction with shock;
- multiple sclerosis;
- nerve disorders (such as eye nerve inflammation and Guillain-Barré syndrome that may cause muscle weakness, abnormal sensations, tingling in the arms and upper body);

heart stops pumping;
pulmonary fibrosis (scarring of the lung);
intestinal perforation;
hepatitis;
reactivation of hepatitis B;
autoimmune hepatitis (inflammation of the liver caused by the body's own immune system)
cutaneous vasculitis (inflammation of blood vessels in the skin);
Stevens-Johnson syndrome (early symptoms include malaise, fever, headache and rash);
facial oedema associated with allergic reactions;
erythema multiforme (inflammatory skin rash);
lupus-like syndrome.

Not known (frequency cannot be estimated from available data):

- hepatosplenic T-cell lymphoma (a rare blood cancer that is often fatal);
- Merkel cell carcinoma (a type of skin cancer);
- liver failure;
- worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness).

Some adverse experiences observed with Humira may not have symptoms and may only be discovered through blood tests. These include:

Very common (may affect more than 1 in 10 people)

- low blood measurements for white blood cells;
- low blood measurements for red blood cells;
- increased lipids in the blood;
- elevated liver enzymes.

Common (may affect up to 1 in 10 people):

- high blood measurements for white blood cells;
- low blood measurements for platelets;
- increased uric acid in the blood;
- abnormal blood measurements for sodium;
- low blood measurements for calcium;
- low blood measurements for phosphate;
- high blood sugar;
- high blood measurements for lactate dehydrogenase;
- autoantibodies present in the blood.

Rare (may affect up to in 1 in 1,000 people):

- low blood measurements for white blood cells, red blood cells and platelet count.

Not known (frequency cannot be estimated from the available data):

- liver failure.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist . This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. HOW TO STORE HUMIRA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the label/blister/carton after EXP:. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

Alternative Storage:

When needed (for example when you are travelling), a single Humira pre-filled pen may be stored at room temperature (up to 25°C) for a maximum period of 14 days – be sure to protect it from light. Once removed from the refrigerator for room temperature storage, the pen **must be used within 14 days or discarded**, even if it is returned to the refrigerator.

You should record the date when the pen is first removed from refrigerator, and the date after which it should be discarded.

DO NOT THROW AWAY ANY MEDICINES VIA WASTEWATER OR HOUSEHOLD WASTE. ASK YOUR DOCTOR OR PHARMACIST HOW TO THROW AWAY MEDICINES YOU NO LONGER USE. THESE MEASURES WILL HELP PROTECT THE ENVIRONMENT. ANY UNUSED PRODUCT OR WASTE MATERIAL SHOULD BE DISPOSED OF IN ACCORDANCE WITH LOCAL REQUIREMENTS.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Humira contains

The active substance is adalimumab.
The other ingredients are mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections.

This medicinal product contains less than 1 mmol of sodium (23 mg) per 0.8 ml dose, i.e. essentially 'sodium-free' and does not contain preservatives.

What the Humira pre-filled pen looks like and contents of the pack

Humira 40 mg solution for injection in pre-filled pen is supplied as a sterile solution of 40 mg adalimumab dissolved in 0.8 ml solution.

The Humira pre-filled pen is a single-use grey- and plum-coloured pen which contains a glass syringe with Humira. There are two caps – one is grey and labelled '1' and the other is plum and labelled '2'. There is a window on each side of the pen through which you can see the Humira solution inside the syringe.

The Humira pre-filled pen is available in packs containing 1, 2, 4, and 6 pre-filled pens. Each pre-filled pen comes with 1 alcohol pad. Not all pack sizes may be marketed.

Humira is available as a vial, a pre-filled syringe and a pre-filled pen.

Marketing Authorisation Holder

AbbVie Ltd
Maidenhead
SL6 4XE
United Kingdom

Manufacturer

[redacted]

For any information about thismedicine, please contact the local representative of the Marketing Authorisation Holder.

[redacted]

[redacted]

This leaflet was last revised in 09/2013.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Appendix B: HUMIRA® -Pre-Filled Syringe-Instruction (EMA)

Humira 40 mg solution for injection in pre-filled syringe
Adalimumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a Patient Alert Card, which contains important safety information that you need to be aware of before you are given Humira and during treatment with Humira. Keep this Patient Alert Card with you.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet (see section 4).

What is in this leaflet:
1. What Humira is and what it is used for
2. What you need to know before you use Humira
3. How to use Humira
4. Possible side effects
5 How to store Humira
6. Contents of the pack and other information

1. WHAT HUMIRA IS AND WHAT IT IS USED FOR

Humira contains the active substance adalimumab, a selective immuno suppressive agent. Humira is intended for treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease and ulcerative colitis. It is a medicine that decreases the inflammation process of these diseases. The active ingredient, adalimumab, is a human monoclonal antibody produced by cultured cells. Monoclonal antibodies are proteins that recognise and bind to other unique proteins. Adalimumab binds to a specific protein (tumour necrosis factor or TNFα), which is present at increased levels in inflammatory diseases such as rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease and ulcerative colitis.

Rheumatoid arthritis

Humira is used to treat rheumatoid arthritis in adults. Rheumatoid arthritis is an inflammatory disease of the joints. If you have moderate to severe active rheumatoid arthritis, you may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira to treat your rheumatoid arthritis.

Humira can also be used to treat severe, active and progressive rheumatoid arthritis without previous methotrexate treatment.

Humira has been shown to slow down the damage to the cartilage and bone of the joints caused by the disease and to improve physical function.

Usually, Humira is used with methotrexate. If your doctor determines that methotrexate is inappropriate, Humira can be given alone.

Polyarticular juvenile idiopathic arthritis

Humira is used to treat polyarticular juvenile idiopathic arthritis in children and adolescents aged 2 to 17 years. Polyarticular juvenile idiopathic arthritis is an inflammatory disease, affecting one or more joints, with diagnosis typically occurring in children under the age of 16 years. You may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira to treat your polyarticular juvenile idiopathic arthritis.

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Humira is used to treat ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis in adults. Ankylosing spondylitis and axial spondyloarthritis

without radiographic evidence of ankylosing spondylitis, are inflammatory diseases of the spine. If you have ankylosing spondylitis or axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira to reduce the signs and symptoms of your disease.

Psoriatic arthritis

Humira is used to treat psoriatic arthritis in adults. Psoriatic arthritis is an inflammation of the joints associated with psoriasis. Humira has been shown to slow down the damage to the cartilage and bone of the joints caused by the disease and to improve physical function.

Psoriasis

Humira is used to treat psoriasis in adults. Psoriasis is an inflammatory disease of the skin. If you have moderate to severe plaque psoriasis, you will first be given other medicines or e.g. phototherapy. If you do not respond well enough to these treatments, you will be given Humira to reduce the signs and symptoms of your psoriasis.

Crohn's disease in Adults and Children

Humira is used to treat Crohn's disease in adults and children aged 6 to 17 years of age. Crohn's disease is an inflammatory disease of the digestive tract. Humira is indicated for the treatment of Crohn's disease in adults and in children aged 6 to 17 years. If you have Crohn's disease you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira to reduce the signs and symptoms of your Crohn's disease.

Ulcerative Colitis

Humira is used to treat ulcerative colitis in adults. Ulcerative colitis is an inflammatory disease of the bowel. If you have ulcerative colitis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira to reduce the signs and symptoms of your disease.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE HUMIRA

Do not use Humira

- If you are allergic to adalimumab or any of the other ingredients ofthis medicine (listed in section 6).

- If you have a severe infection, including active tuberculosis (seeWarnings and precautions"). It is important that you tell your doctor if you have symptoms of infections, e.g. fever, wounds, feeling tired, dental problems.

- If you have moderate or severe heart failure. It is important to tell your doctor if you have had or have a serious heart condition (see "Warnings and precautions").

Warnings and precautions

Talk to your doctor or pharmacist before using Humira

- If you experience allergic reactions with symptoms such as chest tightness, wheezing, dizziness, swelling or rash do not inject more Humira and contact your doctor immediately.

- If you have an infection, including long-term or localized infection (for example, leg ulcer) consult your doctor before starting Humira. If you are unsure, please contact your doctor.

- You might get infections more easily while you are receiving Humira treatment. This risk may increase if your lung function is impaired. These infections may be serious and include tuberculosis, infections caused by viruses, fungi, parasites or bacteria, or other opportunistic infections and sepsis that may, in rare cases, be life-threatening. It is important to tell your doctor if you get symptoms such as fever, wounds, feeling tired or dental problems. Your doctor may recommend temporary discontinuation of Humira.

- As cases of tuberculosis have been reported in patients treated with Humira, your doctor will check you for signs and symptoms of tuberculosis before starting Humira. This will include a thorough medical evaluation including your medical history and appropriate screening tests (for example chest X-ray and a tuberculin test). The conduct and results of these tests should be recorded on your Patient Alert Card. It is very important that you tell your doctor if you have ever had tuberculosis, or if you have been in close contact with someone who has had tuberculosis. Tuberculosis can develop during therapy even if you have received preventative treatment for tuberculosis. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy tell your doctor immediately.

- Advise your doctor if you reside or travel in regions where fungal infections such as histoplasmosis coccidioidomycosis or blastomycosis are endemic.

- Advise your doctor if you have a history of recurrent infections or other conditions that increase the risk of infections.

- Advise your doctor if you are a carrier of the hepatitis B virus (HBV), if you have active HBV or if you think you might be at risk of contracting HBV. Your doctor should test you for HBV. Humira can cause reactivation of HBV in people who carry this virus. In some rare cases, especially if you are taking other medicines that suppress the immune system, reactivation of HBV can be life-threatening.

- If you are over 65 years you may be more susceptible to infections while taking Humira. You and your doctor should pay special attention to signs of infection while you are being treated with Humira. It is important to tell your doctor if you get symptoms of infections, such as fever, wounds, feeling tired or dental problems.

- If you are about to undergo surgery or dental procedures please inform your doctor that you are taking Humira. Your doctor may recommend temporary discontinuation of Humira.

- If you have demyelinating disease such as multiple sclerosis, your doctor will decide if you should receive Humira.

- Certain vaccines may cause infections and should not be given while receiving Humira. Please check with your doctor before you receive any vaccines. It is recommended that children, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Humira therapy. If you received Humira while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately 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 Humira use during your pregnancy so they can decide when your baby should receive any vaccine.

- If you have mild heart failure and you are being treated with Humira, your heart failure status must be closely monitored by your doctor. It is important to tell your doctor if you have had or have a serious heart condition. If you develop new or worsening symptoms of heart failure (e.g. shortness of breath, or swelling of your feet), you must contact your doctor immediately. Your doctor will decide if you should receive Humira.

- In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. If you develop a fever that does not go away, bruise or bleed very easily or look very pale, call your doctor right away. Your doctor may decide to stop treatment.

- There have been very rare cases of certain kinds of cancer in children and adult patients taking Humira or other TNF blockers. People with more serious rheumatoid arthritis that have had the disease for a long time may have a higher than average risk of getting lymphoma (a kind of cancer that affects the lymph system), and leukemia (a kind of cancer that affects the blood and bone marrow). If you take Humira the risk of getting lymphoma,

leukemia, or other cancers may increase. On rare occasions, a specific and severe type of lymphoma has been observed in patients taking Humira. Some of those patients were also treated with azathioprine or 6- mercaptopurine. Tell your doctor if you are taking azathioprine or 6-mercaptopurine with Humira. In addition cases of non-melanoma skin cancer have been observed in patients taking Humira. If new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.

- There have been cases of cancers other than lymphoma in patients with a specific type of lung disease called Chronic Obstructive Pulmonary Disease (COPD) treated with another TNF blocker. If you have COPD, or are a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for you.

Children and adolescents

- Vaccinations: if possible children should be up to date with all vaccinations before using Humira.
- Do not give Humira to children with polyarticular juvenile idiopathic arthritis below the age of 2 years.

Other medicines and Humira

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Humira can be taken together with methotrexate or certain disease-modifying anti-rheumatic agents (sulfasalazine, hydroxychloroquine, leflunomide and injectable gold preparations), steroids or pain medications including non-steroidal anti-inflammatory drugs (NSAIDs).

You should not take Humira with medicines containing the active substance, anakinra or abatacept. If you have questions, please ask your doctor.

Humira with food and drink

Since Humira is injected under the skin (subcutaneously), food and drink should not affect Humira.

Pregnancy and breast-feeding

The effects of Humira in pregnant women are not known and so the use of Humira in pregnant women is not recommended. You are advised to avoid becoming pregnant and must use adequate contraception while using Humira and for at least 5 months after the last Humira treatment. If you become pregnant, you should consult your doctor.

It is not known whether adalimumab passes into breast milk.

If you are a breast-feeding mother, you should stop breast-feeding during Humira treatment and for at least 5 months after the last Humira treatment. If you received Humira during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy before the baby receives any vaccine (for more information see section on vaccination).

If you think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Humira may have a minor influence on your ability to drive, cycle or use machines. Room spinning sensation and vision disturbances may occur after taking Humira.

3. HOW TO USE HUMIRA

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Adults with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Humira is injected under the skin (subcutaneous use). The usual dose for adults with rheumatoid arthritis, ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, and for patients with psoriatic arthritis is 40 mg adalimumab given every other week as a single dose.

In rheumatoid arthritis, methotrexate is continued while using Humira. If your doctor determines that methotrexate is inappropriate, Humira can be given alone.

If you have rheumatoid arthritis and you do not receive methotrexate with your Humira therapy, your doctor may decide to give 40 mg adalimumab every week.

Children with polyarticular juvenile idiopathic arthritis

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis, aged 2 to 12 years depends on the height and weight of the child.

The recommended dose of Humira for patients with polyarticular juvenile idiopathic arthritis, aged 13 to 17 years, is 40 mg every other week.

Adults with Psoriasis

The usual dose for adults with psoriasis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. You should continue to inject Humira for as long as your doctor has told you.

Adults with Crohn's disease

The usual dose regimen for Crohn's disease is 80 mg initially followed by 40 mg every other week two weeks later. If a faster response is required your doctor may prescribe an initial dose of 160 mg (as 4 injections in one day or 2 injections per day for two consecutive days), followed by 80 mg two weeks later, and thereafter as 40 mg every other week. Depending on your response, your doctor may increase the dose frequency to 40 mg every week.

Children or adolescents with Crohn's Disease

Children or adolescents weighing less than 40 kg:

The usual dose regimen is 40 mg initially followed by 20 mg two weeks later. If a faster response is required, your doctor may prescribe an initial dose of 80 mg (as 2 injections in 1 day) followed by 40 mg two weeks later.

Thereafter, the usual dose is 20 mg every other week. Depending on your response, your doctor may increase the dose frequency to 20 mg every week.

Children or adolescents weighing 40 kg or more:

The usual dose regimen is 80 mg initially followed by 40 mg two weeks later. If a faster response is required, your doctor may prescribe an initial dose of 160 mg (as 4 injections in 1 day or as 2 injections per day for 2 consecutive days) followed by 80 mg two weeks later.

Thereafter, the usual dose is 40mg every other week. Depending on your response, your doctor may increase the dose frequency to 40 mg every week.

For patients who do not require a full 40 mg dose of Humira, a 40mg vial is also available.

Adults with ulcerative colitis

The usual Humira dose for adults with ulcerative colitis is 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days) and 80 mg at Week 2, and thereafter 40 mg every other week. Depending on your response, your doctor may increase the dose to 40 mg every week.

Method and route of administration

Humira is administered by injection under the skin (by subcutaneous injection).

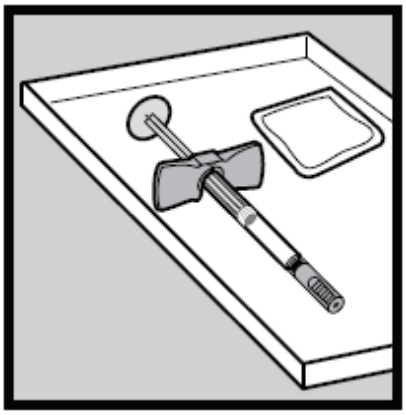
Instructions for preparing and giving an injection of Humira:

The following instructions explain how to inject Humira. Please read the instructions carefully and follow them step by step. You will be instructed by your doctor or his/her assistant on the technique of self-injection. Do not attempt to self-inject until you are sure that you understand how to prepare and give the injection. After proper training, the injection can be self-administered or given by another person, for example a family member or friend.

This injection should not be mixed in the same syringe or vial with any other medicine.

1) Setting up

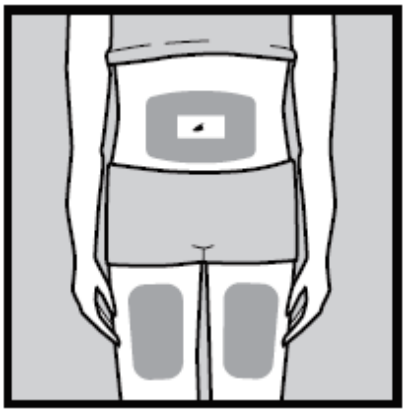
- Wash your hands thoroughly
- Set up the following items on a clean surface
    - One pre-filled syringe of Humira for injection
    - One alcohol pad



- Look at the expiry date on the syringe. Do not use the product after the month and year shown.

2) Choosing and preparing an injection site

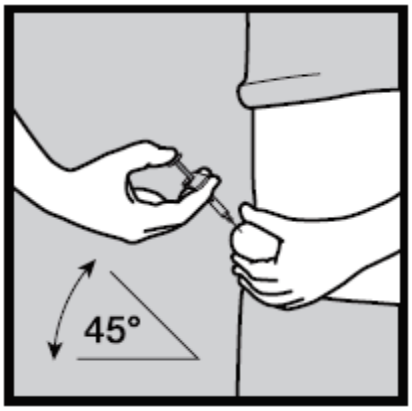
- Choose a site on your thigh or stomach



- Each new injection should be given at least 3 cm from the last injection site.
  - Do not inject in an area where the skin is reddened, bruised, or hard. This may mean there is an infection.
  - Wipe the injection site with the enclosed alcohol pad, using a circular motion.
  - Do not touch the area again before injecting.

3) Injecting Humira

- Do NOT shake the syringe.
- Remove cap from needle syringe, being careful not to touch the needle or let it touch any surface.
- With one hand, gently grasp the cleaned areas of skin and hold firmly



- With the other hand, hold syringe at 45-degree angle to skin, with the grooved side up.
- With one quick, short motion, push needle all the way into skin
- Release the skin with the first hand
- Push plunger to inject solution – it can take from 2 to 5 seconds to empty the syringe
- When the syringe is empty, remove the needle from skin, being careful to keep it at the same angle as when it was inserted

- Using your thumb or a piece of gauze, apply pressure over the injection site for 10 seconds. A little bleeding may occur. Do not rub the injection site. Use a plaster if you want to.

4) Throwing away supplies

- The Humira syringe should **NEVER** be reused. **NEVER** recap a needle.
- After injecting Humira, immediately throw away the used syringe in a special container as instructed by your doctor, nurse or pharmacist.
- Keep this container out of the reach and sight of children

If you use more Humira than you should:

If you accidentally inject Humira more frequently than told to by your doctor or pharmacist, you should call your doctor or pharmacist and tell him/her that you have taken more. Always take the outer carton of medicine with you, even if it is empty.

If you forget touse Humira:

If you forget to give yourself an injection, you should inject the next dose of Humira as soon as you remember. Then take your next dose as you would have on your originally scheduled day, had you not forgotten a dose.

If you stop using Humira:

The decision to stop using Humira should be discussed with your doctor. Your symptoms may return upon discontinuation

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However, some may be serious and require treatment. Side effects may occur at least up to 4 months after the last Humira injection.

Tell your doctor immediately if you notice any of the following:
- Severe rash, hives or other signs of allergic reaction;
- Swollen face, hands, feet;
- Trouble breathing, swallowing;
- Shortness of breath with exertion or upon lying down or swelling of the feet;

Tell your doctor as soon as possible if you notice any of the following:

- Signs of infection such as fever, feeling sick, wounds, dental problems, burning on urination;
- Feeling weak or tired;
- Coughing;
- Tingling;
- Numbness;
- Double vision;
- Arm or leg weakness;
- A bump or open sore that doesn't heal.
- Signs and symptoms suggestive of blood disorders such as persistant fever, bruising, bleeding, paleness

The symptoms described above can be signs of the below listed side effects, which have been observed with Humira:

Very common (may affect more than 1 in 10 people):

- injection site reactions (including pain, swelling, redness or itching);
- respiratory tract infections (including cold, runny nose, sinus infection, pneumonia);
- headache;
- abdominal pain;
- nausea and vomiting;
- rash;
- musculoskeletal pain.

Common (may affect up to 1 in 10people):

- serious infections (including blood poisoning and influenza);
- skin infections (including cellulitis and shingles);
- ear infections;
- oral infections (including tooth infections and cold sores);
- reproductive tract infections;
- urinary tract infection;
- fungal infections;
- joint infections;
- benign tumours;
- skin cancer;
- allergic reactions (including seasonal allergy);
- dehydration;
- mood swings (including depression);
- anxiety;
- difficulty sleeping;

- sensation disorders such as tingling, prickling or numbness;
- migraine;
- nerve root compression(including low back pain and leg pain);
- vision disturbances;
- eye inflammation;
- inflammation of the eye lid and eye swelling;
- vertigo;
- sensation of heart beating rapidly;
- high blood pressure;
- flushing;
- haematoma;
- cough;
- asthma;
- shortness of breath;
- gastrointestinal bleeding;
- dyspepsia (indigestion, bloating, heart burn);
- acid reflux disease;
- sicca syndrome (including dry eyes and dry mouth);
- itching;
- itchy rash;
- bruising;
- inflammation of the skin (such as eczema);
- breaking of finger nails and toe nails;
- increased sweating;
- hair loss;
- new onset or worsening of psoriasis;
- muscle spasms;
- blood in urine;
- kidney problems;
- chest pain;
- oedema;
- fever;
- reduction in blood platelets which increases risk of bleeding or bruising;
- impaired healing.

Uncommon (may affect up to 1 in 100 people):

- opportunistic infections (which include tuberculosis and other infections that occur when resistance to disease is lowered);
- neurological infections (including viral meningitis);
- eye infections;

- bacterial infections;
- diverticulitis (inflammation and infection of the large intestine);
- cancer;
- cancer that affects the lymph system;
- melanoma;
- immune disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis);
- tremor;
- neuropathy;
- stroke;
- double vision;
- hearing loss, buzzing;
- sensation of heart beating irregularly such as skipped beats;
- heart problems that can cause shortness of breath or ankle swelling;
- heart attack;
- a sac in the wall of a major artery, inflammation and clot of a vein; blockage of a blood vessel;
- lung diseases causing shortness of breath (including inflammation);
- pulmonary embolism (blockage in an artery of the lung);
- pleural effusion (abnormal collection of fluid in the pleural space);
- inflammation of the pancreas which causes severe pain in the abdomen and back;
- difficulty in swallowing;
- facial oedema;
- gallbladder inflammation, gallbladder stones;
- fatty liver;
- night sweats;
- scar;
- abnormal muscle breakdown;
- systemic lupus erythematosus (including inflammation of skin, heart, lung, joints and other organ systems);
- sleep interruptions;
- impotence;
- inflammations.

Rare (may affect up to 1 in 1,000 people):

- leukaemia (cancer affecting the blood and bone marrow);
- Severe allergic reaction with shock;
- multiple sclerosis;
- nerve disorders (such as eye nerve inflammation and Guillain-Barré syndrome that may cause muscle weakness, abnormal sensations, tingling in the arms and upper body);

- heart stops pumping;
- pulmonary fibrosis (scarring of the lung);
- intestinal perforation;
- hepatitis;
- reactivation of hepatitis B;
- autoimmune hepatitis (inflammation of the liver caused by the body's own immune system)
- cutaneous vasculitis (inflammation of blood vessels in the skin);
- Stevens-Johnson syndrome (early symptoms include malaise, fever, headache and rash);
- facial oedema associated with allergic reactions;
- erythema multiforme (inflammatory skin rash);
- lupus-like syndrome.

Not known (frequency cannot be estimated from available data):

- hepatosplenic T-cell lymphoma (a rare blood cancer that is often fatal);
- Merkel cell carcinoma (a type of skin cancer);
- liver failure;
- worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness).

Some adverse experiences observed with Humira may not have symptoms and may only be discovered through blood tests. These include:

Very common (may affect more than 1 in 10people):

- low blood measurements for white blood cells;
- low blood measurements for red blood cells;
- increased lipids in the blood;
- elevated liver enzymes.

Common (may affect up to 1 in 10 people):

- high blood measurements for white blood cells;
- low blood measurements for platelets;
- increased uric acid in the blood;
- abnormal blood measurements for sodium;
- low blood measurements for calcium;
- low blood measurements for phosphate;
- high blood sugar;
- high blood measurements for lactate dehydrogenase;
- autoantibodies present in the blood.

Rare (may affect up to 1 in 1,000 people):

- low blood measurements for white blood cells, red blood cells and platelet count.

Not known (frequency cannot be estimated from available data):

- liver failure.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist . This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. HOW TO STORE HUMIRA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the label/blister/carton after EXP:. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

Alternative Storage:

When needed (for example when you are travelling), a single Humira pre-filled syringe may be stored at room temperature (up to 25°C) for a maximum period of 14 days – be sure to protect it from light. Once removed from the refrigerator for room temperature storage, the syringe **must be used within 14 days or discarded**, even if it is returned to the refrigerator.

You should record the date when the syringe is first removed from refrigerator, and the date after which it should be discarded.

Do not throw any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.
Any unused product or waste material should be disposed of in accordance with local requirements.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Humira contains

The active substance is adalimumab.
The other ingredients are mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections.

This medicinal product contains less than 1 mmol of sodium (23 mg) per 0.8 ml dose, i.e. essentially 'sodium-free' and does not contain preservatives.

What the Humira pre-filled syringe looks like and contents of the pack

Humira 40 mg solution for injection in pre-filled syringe is supplied as a sterile solution of 40 mg adalimumab dissolved in 0.8 ml solution.

The Humira pre-filled syringe is a glass syringe containing a solution of adalimumab.Each pack contains 1, 2, 4 or 6 pre-filled syringes for patient use with 1, 2, 4 or 6 alcohol pads, respectively. Not all pack sizes may be marketed.

Humira is available as a vial, , a pre-filled syringeand a pre-filled pen.

Marketing Authorisation Holder:

AbbVie Ltd
Maidenhead
SL6 4XE
United Kingdom

Manufacturer:

[redacted]

For any information about thismedicine, please contact the local representative of the Marketing Authorisation Holder.

[redacted]

[redacted]

This leaflet was last revised in 09/2013.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Appendix C:

AUSTRIAN CONSENSUS STATEMENT TUBERCULOSIS & BIOLOGICALS

Leeb B, Thalhammer F, Brezinschek H.P., Bröll H., Erlacher L., Gaugg M., Herold M., Indra A., Kneussl M., Knoflach P., Krause R., Novacek G., Papay P., Reinisch W., Rumetshofer R. Trautinger F., Weiss G., Wenisch C., Winkler S.

(Österreichische Ärztezeitung, Supplementum, März 2011:1-12)

Recommendations for the Tbc-Screening and performance of a preventive therapy by a scheduled therapy with biologicals are currently available for TNF-blocking agents only, but not for other biologicals [1,2]. As basis for the recommendations of TB-Screening and preventive therapy with other biologicals there are the respective latest SPCs available. If due to medical history, medical status, X-ray (or CT), TB-tests, as well as sputum, bacterial culture results in the diagnosis in an active TB TNF-blocking agents are at first contraindicated. Following a TB therapy must be initiated according to the usual scheme. Regarding the question when, after having started with a TB-treatment a therapy with TNF-blocking agents shall be started there exists no consensus. Even in case of high emergency of a TNF-blocking therapy it has to be await the intensive phase of the TB therapy (at least a combination of three drugs for at least 2 months). If a TB is diagnosed based on medical history and treated *lege artis* as well as documented appropriately, a therapy with TNF blocking agents is possible without preventive therapy. Clinical monitoring on a regular basis are required. In case of afflictions further radiological examinations (thorax-X-ray and thorax-CT), at pulmonal abnormality sputum examinations respectively. Bronchial are recommended (ZN, PCR and Tbc-culture).Has a pulmonal or extrapulmonal TB existed without having performed a respective therapy, both a thorax-CT and a ZN-sputum examination including bacterial culture (alternative ZN and bacterial culture from bronchial lavage) shall be performed. If an active TB appears the course of action is as explained above (active therapy, TNF-alpha-blocking agents after two months at the earliest). Is in such a case an active TB ruled out a preventive therapy is indicated. However is

there a normal thorax-X-ray without any anamnestic indication of TB the further course of action depends on the results of the IGRA (resp.MMT). In case of the IGRA-test yields a positive result a preventive therapy shall be started. Should the result of the IGRA-test render inconclusive and a subsequent performed MMT positive, a preventive therapy is indicated too. The preventive therapy should be administered as monotherapy. Mainly lsoniazid (INH; 1x daily 300mg over a period of 9 months see Tab below) is used.. It is recommended that even at a preventive treatment a therapy with TNF-alpha-blocking agents should not be started at once but rather at the end of at least 4 weeks medicinally preventive TB therapy. This has especially pragmatic reasons such as a better assignability to a potential hepatotoxicity or other side effects. If a patient suffer from an increased risk for the occurrence of a polyneuropathy (diabetes, alcohole abuse, macrocytic anaemia, specific medicinal therapy), he/she should be treated with daily 50mg Pyridoxin (possibly by use of a Vitamin-B-combination therapy) in addition to INH. A potential alternative to INH represents Rifampicin (RIF; 1x daily .600mg over a period of 4 months. see Tab.). As a matter of course a patient must be enlightened about potential side effects of a preventive therapy. Controls of liver laboratory findings should be performed, before start of a preventive therapy and at the beginning in a one week or two week basis, afterwards every 4 to 8 weeks – at medical conditions however at once– in order to identify a hepatopathy in due time. In case of a medicinal preventive therapy must be interrupted after a biological therapy has already been commenced a tight control is recommended.

Drug	Dosage	Maximal daily dose
Isoniazid (INH)	5mg/kg; >50kg: 300mg	300mg
Rifampicin (RIF)	10mg/kg; at >50kg: 600mg; at < 50kg: 450mg	600mg

Reference:
1. *Diel Ret al.: [Recommendations for tuberculosis screening before initiation of TNF-alpha-inhibitor treatment in rheumatic diseases]. Pneumologie 2009;63(6):329-334*
2. *British Thoracic Society Standards ofCare Committee: BTS recommendations for assessing risk and for managing Mycobacterium tubercul05is infection and disease in patients due to start anti-TNF-alpha treatment. Thorax2005;60(10):800-805*

TUBERCULOSIS INFORMATION

Diel R., Hauer B., Loddenkemer R., Manger B., Krüger K.

RECOMMENDATIONS FOR TUBERCULOSIS SCREENING BEFORE INITIATION OF TNFα-INHIBITOR TREATMENT IN RHEUMATIC DISEASES

German Central Committee for the fight against tuberculosis (Deutsches Zentralkomitee zur Bekämpfung der Tuberkulose DZK) Zeitschrift für Rheumatologie 2009, 68:411–416

Due to the increased risk of tuberculosis (TB) under treatment with TNF-α inhibitors for rheumatoid arthritis and other autoimmune diseases, precautionary measures are required before initiating TNF-α-inhibitor therapy. Patients should have active TB ruled out and screening for latent TB infection should be performed. The screening should include chest X-ray, complete medical history, and the administration of a highly specific interferon-γ-release assay (IGRA). (In the future, the reimbursement of IGRA tests under an analogue procedure code is expected to be formalized by the application of a code specific to the TB-IGRA procedure.) As tuberculin skin test (TST) results can be expected to be either false-positive or false-negative in these patients, the TST, as commonly performed in the past, is recommended only in exceptional situations. For chemopreventive treatment of latent TB infection (LTBI), Isoniazid (INH) is usually given for 9 months.

CDC Treatment Recommendations for Positive PPD

CDC CENTERS FOR DISEASE CONTROL AND PREVENTION

Treatment of Tuberculosis Infection (Preventive Therapy)

When taken as prescribed, isoniazide therapy is highly effective in preventing latent tuberculosis (TB) infection from progressing to TB disease.

Who should receive preventive therapy?

The following persons should be given high priority for preventive therapy if they have positive skin test results, regardless of their age:

- Persons known to have or suspected of having HIV infection (5 mm or greater of induration);
- Persons who have been in close contact with someone who has infectious TB disease (5 mm or greater);
- Persons whose skin test results converted from negative to positive within the past 2 years (10 mm or greater increase for persons < 35 years old; 15 mm increase for persons 35 years of age or older) including children < 4 years old who have a positive skin test result (10 mm or greater);
- Persons with abnormal chest radiographs who have never been treated for TB or who have been inadequately treated for TB (5 mm or greater);
- Persons who have injected drugs and who are HIV seronegative (10 mm or greater), and
- Persons who have medical conditions that increase the risk for TB (10 mm or greater). These conditions include diabetes mellitus, prolonged corticosteroid therapy, immunosuppressive therapy, gastrectomy, some hematologic and reticuloendothelial diseases, and end-stage renal disease, silicosis, and body weight that is 10% or more below ideal.

In addition, in the absence of any of the above risk factors, persons younger than 35 years old in the following groups should be evaluated for preventive therapy if their reaction to the tuberculin skin test is 10 mm or greater:

- Foreign-born persons from countries where TB is common;
- Medically underserved, low-income populations; and
- Residents of long-term care facilities.

Preventive therapy should also be considered for persons who are younger than 35 years old, who have positive skin test results, and who have no risk factors for TB.

In addition, staff of facilities in which a person with infectious TB disease would pose a risk to large numbers of susceptible persons (e.g., health care facilities, correctional facilities, and nursing homes) should be evaluated for preventive therapy if they have a positive skin test result.

Persons who have a positive reaction to the tuberculin skin test should not be given preventive therapy until the possibility of TB disease has been ruled out. In addition, persons who are being considered for preventive therapy should be evaluated for medical contraindications, such as:

- Previous isoniazide-associated hepatic injury;
- History of severe adverse reactions to isoniazide, and;
- Acute or active liver disease.

Also, special precautions should be taken for some persons who are receiving preventive therapy.

Precautions are indicated for:

- Persons who are older than 35;
- Persons who abuse alcohol;
- Pregnant women;
- Persons with chronic liver disease;
- Persons with peripheral neuropathy; and
- Persons who in the past have stopped using isoniazide because of adverse effects.

Regimens for Preventive Therapy

The usual preventive therapy regimen is 9 months of daily isoniazide, in a dosage of 5 milligrams per kilogram of body weight. The maximum daily dose is 300 milligrams. HIV-infected persons should receive 12 months of preventive therapy. For persons with a strain of M. tuberculosis that is resistant to isoniazide but susceptible to rifampin, CDC recommends the use of rifampin alone at a dose of 10 mg/kg with a max of 600 mg daily for preventive therapy.

Appendix D: eCRF including Questionnaires

HUMIRA®
(Adalimumab)

1.0 INVESTIGATOR

PMOS Investigator name:_____

Unique IMPACT investigator number:_____

2.0 PATIENT DEMOGRAPHICS

1. **Patient meets all applicable inclusion criteria as outlined in the protocol:** ☐ y ☐ n

2. **Patient gave written authorization to use data:**

   Date of consent: _____

3. **Year of birth:** |___|___|___|___| **(YYYY)**

4. **Gender:** ☐ m ☐ f

5. **Race:** ☐ **caucasian** ☐ **black** ☐ **asian** ☐ **other**

6. **RA** ☐ **or PsA** ☐ **or AS** ☐**or Ps** ☐**or CD**
7. **Duration of disease:** _____ years

8. **Results of TB – Screening:**

   - ***Chest X-ray:*** Date performed: _____

   Findings: normal ☐ abnormal ☐ Calcified granulomas: absent: ☐ present:☐ Pleural scarring absent: ☐ present: ☐

   Comments, if abnormal:_____

   - **Interferon gamma test:** (IGRA interferon gamma release assay,)

Date performed: _____

Please tick which test was used. ☐ Quantiferon –TB Gold In Tube ☐ T-SPOT-TB
If another type of IGRA assay is used please specify:_____

Findings: ☐ negative ☐ positiv ☐ indecisive

Comments: _____

- ***PPD Skin Test:*** Date performed: _____
  Date assessed: _____

  Result: Induration _____ mm

  ☐ pos. ☐ neg.

- ***PPD Skin Re – test:*** Date: _____

  Result: Induration _____ mm

  ☐ pos. ☐ neg.

10. Normal lab value (reference values): ESR_____ (mm /1 hr)

CRP_____ (mg/dl)

11. Pre-treatment of disease:

(Please answer the following questions where applicable)

11.1. Biological –naïve - pre-treatment with DMARDs (please specify):

_____

_____

11.2 Pre-treatment with BDMARDs

11.2.1 Which BDMARD was used ?

_____

_____

In the following table please fill in the start date, end date, dosage, units and frequency of the latest BDMARD which was used before the switch to Adalimumab.

Start date:	**End date:**
|__|__| |__|__| |__|__| DD MON YY	|__|__| |__|__| |__|__| DD MON YY

Doasge	**Units**	**Frequency**

11.2.2 Reason for switch to HUMIRA®

Never achieved satisfactory response: ☐ y ☐ n

Achieved satisfactory response initially, but lost it over time: ☐ y ☐ n

Discontinued treatment due to intolerance/side effect(s) : ☐ y ☐ n

Others_____

HUMIRA®
(Adalimumab)
For each visit

ESR (mm / 1 hr)
(Erythrocyte Sedimentation Rate)

|__|__|__|

CRP (mg/l)
(C-Reactive Protein)

|__|__|__|.|__|

Adalimumab

For Visit 1, Visit 5, and as appropriate for Early Termination

10-item Beliefs about Medicines Questionnaire (BMQ)

We would like to ask you about your personal views about your medicine and medicine in general. Please circle how you feel about each of the statements. There is no right or wrong answer, we are interested in your personal views.

Score:1-5

1. My health, at present, depends on my medicines

a. Strongly disagree **b.** disagree **c.** uncertain **d.** agree **e**. strongly agree

2. My life would be impossible without my medicines
a. Strongly disagree **b.** disagree **c.** uncertain **d.** agree **e.** strongly agree

3. Without my medicines I would become very sick
a. Strongly disagree **b.** disagree **c.** uncertain **d.** agree **e.** strongly agree

4. My health in the future will depend on my medicines
a. Strongly disagree **b.** disagree **c.** uncertain **d.** agree **e.** strongly agree

5. My medicines protect me from becoming worse
a. Strongly disagree **b.** disagree **c.** uncertain **d.** agree **e.** strongly agree

6. Having to take medicines worries me
a. Strongly disagree **b.** disagree **c.** uncertain **d.** agree **e.** strongly agree

7. I sometimes worry about the long term effects of my medicines
a. Strongly disagree **b.** disagree **c.** uncertain **d.** agree **e.** strongly agree

8. My medicines are a mystery to me
a. Strongly disagree **b.** disagree **c.** uncertain **d.** agree **e.** strongly agree

9. My medicines disrupt my life
a. Strongly disagree **b.** disagree **c.** uncertain **d.** agree **e.** strongly agree

10. I sometimes worry about becoming too dependent on my medicines
a. Strongly disagree **b.** disagree **c.** uncertain **d.** agree **e.** strongly agree

Scoring	
YES	**NO**

Total 10-item BMQ Specific Score:

Adalimumab
For Visit 2, Visit 3, Visit 4, Visit 5, and as appropriate for Early Termination
Morisky Medication Adherence Scale (MMAS)

Patient self-reported Medication-taking-Scale: Scoring: high-low;

YES = 0; No = 1

Range: 0- 4

1. Do you ever forget to take your medicine ?

2. Are you careless at times about taking your medicines ?

3. When you feel better do you sometimes stop taking your medicine ?

4. Sometimes if you feel worse when you take the medicine, do you stop taking it ?

Total Score (sum of points) =

Adalimumab
For Visit 3, Visit 5, and as appropriate for Early Termination
Treatment Satisfaction Questionnaire for Medication (TSQM)

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

3. As a result of taking this medication, do you currently experience any side effects at all?

☐1 Yes
☐0 No

Remark for the physician.: If YES please document on the SAE-Form !

4. How dissatisfied are you by side effects that interfere with your physical health and ability to function (e.g., strength, energy levels)?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Somewhat Dissatisfied
☐4 Slightly Dissatisfied
☐5 Not at all Dissatisfied

5. How dissatisfied are you by side effects that interfere with your mental function (e.g., ability to think clearly, stay awake)?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Somewhat Dissatisfied
☐4 Slightly Dissatisfied
☐5 Not at all Dissatisfied

6. How dissatisfied are you by side effects that interfere with your mood or emotions (e.g., anxiety/fear, sadness, irritation/anger)?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Somewhat Dissatisfied
☐4 Slightly Dissatisfied
☐5 Not at all Dissatisfied

7. How satisfied or dissatisfied are you with how easy the medication is to use?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

8. How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

9. How satisfied or dissatisfied are you by how often you are expected to use/take the medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

10. How satisfied are you that the good things about this medication outweigh the bad things?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

11. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

SCALE SCORING ALGORITHM: TSQM Scale scores range from 0 to 100 and no computed score should be lower or higher than these limits.

EFFECTIVENESS: ([(Item 1 + Item 2) − 2] divided by (12) × 100

SIDE EFFECTS: ([Sum of Item 4 to Item 6) - 3] divided by 12) × 100
If one item is missing: ([(Sum of the two completed items) - 2] divided by (8) × 100

CONVENIENCE: ([Sum of Item 7 to Item 9) - 3] divided by 18) × 100
If one item is missing: ([(Sum of the two completed items) - 2] divided by (12) × 100

GLOBAL SATISFACTION: ([Sum of Item 10 to Item 11) − 2] divided by 12) × 100

Adalimumab
Each Visit - for RA and if reasonable for PsA patients only !
Rheumatoid Arthritis Disease Activity Index (RADAI)

Please choose only one appropriate number, by ticking one box, between 0 and 10 for each of the following 4 numeric rating scales.

1.) How active has **generally** your arthritis (inflammatory joint disease) been **over the past 6 month** ?

Calculation:

Not active at all	0	1	2	3	4	5	6	7	8	9	10	**Extremely active**

1.) ☐

+

2.)

+

2.) How active is your arthritis **today** in terms of **joint tenderness and swelling** ?

Not active at all | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

3.) How much **arthritis pain** do you feel **today** ?

No pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | **Unbearable pain**

4.) How would you describe your **current** state of health ?

Very well | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | **Very poorly**

5.) Did your joints (hands) feel stiff when you awake **this morning**?

☐ NO **(0)**

☐ YES – If yes, how long were your joints stiff today ?

☐ less than 30 min **(1)** ☐ 2 – 4 hours **(4)**

☐ 30 min – 1 hour **(2)** ☐ more than 4 hours **(5)**

☐ 1 – 2 hours **(3)** ☐ all day **(6)**

6.) Please choose in the following table the **intensity of pain** in each joint (left side and right side) you feel today? (give only 1 answer – by making a tick – per row)

Sum Points page1:

+

5.) ☐ **x10/6**

+

6.)

+

+

Left Side:	none	mild	moderate	severe	
	(0)	**(1)**	**(2)**	**(3)**	
shoulder	☐	☐	☐	☐	☐
elbow	☐	☐	☐	☐	☐
wrist	☐	☐	☐	☐	☐
finger	☐	☐	☐	☐	☐
hip	☐	☐	☐	☐	☐
knee	☐	☐	☐	☐	☐
ankle	☐	☐	☐	☐	☐
toes	☐	☐	☐	☐	☐

Right Side:	none	mild	moderate	severe	
	(0)	**(1)**	**(2)**	**(3)**	
shoulder	☐	☐	☐	☐	☐ +
elbow	☐	☐	☐	☐	☐ +
wrist	☐	☐	☐	☐	☐ +
finger	☐	☐	☐	☐	☐ +
hip	☐	☐	☐	☐	☐ +
knee	☐	☐	☐	☐	☐ +
ankle	☐	☐	☐	☐	☐ +
	___	___	___	___	☐

Sum points question 6 (left + right side)

x 10/48

toes ☐ ☐ ☐ ☐

☐

☐

RADAI =

Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

Please let the patient place a vertical mark on each line below to show how he/she was doing in the past week. Even though the medical condition (pain, fatigue) fluctuated please decide on one number as indicator for the average severity of the medical condition.

1. How would you describe the overall level of **fatigue/tiredness** you have experienced?

None |——————————————————| Very severe
0 10

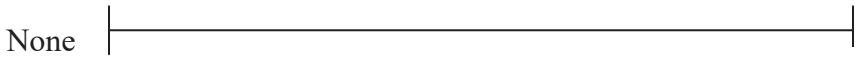
|__|__|.|__|cm

2. How would you describe the overall level of AS **neck, back or hip** pain you have had?

None |——————————————————| Very severe
0 10

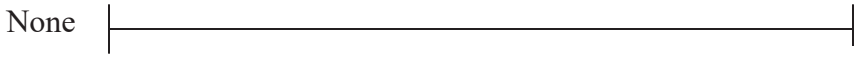
|__|__|.|__|cm

3. How would you describe the overall level of pain/swelling in joints, **other** than neck, back or hips you have had?



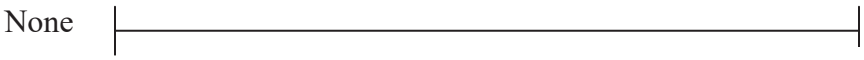
|__|__|.|__|cm

4. How would you describe the overall level of discomfort you have had from **any areas tender to touch or pressure**?



|__|__|.|__|cm

5. How would you describe the overall level of **morning stiffness** you have had from the time you wake up?



|__|__|.|__|cm

6. How long does your morning stiffness generally last from the time you wake up?

|__|__|.|__|cm

Scoring of the BASDAI: The BASDAI Score has a range from 0 to10.

- Measure each item of the BASDAI in centimeters (out of a total of 10)
- **Calculation:**

$$\textbf{BASDAI Score} = 0.2 \times \left(\text{Item 1} + \text{Item 2} + \text{Item 3} + \text{Item 4} + \frac{\text{Item 5}}{2} + \frac{\text{Item 6}}{2}\right)$$

Psoriasis Area and Severity Index

PASI Scoring and Calculation

Assessor Requirements

The assessor should be a dermatologist or experienced physician.

PASI Scoring

Four anatomic sites - head, upper extremities, trunk, and lower extremities - are assessed for erythema, induration (plaque thickness), and desquamation (scaling) as seen on the day of the examination. The severity of each sign is assessed using a 5-point scale:

- 0 = No symptoms
- 1 = Slight
- 2 = Moderate
- 3 = Marked
- 4 = Very marked

The table outlines the characteristics of each category

	Erythema	Desquamation	Induration
0 = none	No redness	No scaling	No elevation over normal skin
1 = slight	Faint redness	Fine scale partially covering lesions	Slight but definite elevation, typically edges indistinct or sloped
2 = moderate	Red coloration	Fine to coarse scale covering most of all of the lesions	Moderate elevation with rough or sloped edges
3 = marked	Very or bright red coloration	Coarse, non tenacious scale predominates covering most or all of the lesions	Marked elevation typically with hard or sharp edges
4 = very marked	Extreme red coloration; dusky to deep red coloration	Coarse, thick, tenacious scale over most or all lesions; rough surface	Very marked elevation typically with hard sharp edges

a. Do not include residual hyperpigmentation or hypopigmentation as erythema.

The area affected by psoriasis within a given anatomic site is estimated as a percentage of the total area of that anatomic site and assigned a numerical value according to the degree of psoriatic involvement as follows:

- 0 = no involvement
- 1 = <10%

- 2 = 10 to <30%
- 3 = 30 to <50%
- 4 = 50 to <70%
- 5 = 70 to <90%
- 6 = 90 to 100%

The Rule of Nines to determine the Affected Area Score

This method uses the assumption that when recording the % affected Area Involvement for each body region (See Table below), the number recorded represents that % of psoriasis in this region as a fraction of the Total BSA. Thus, the sum of the regions equals the Total BSA for that subject. The assessor must convert to determine the Affected Area Score for the region.

REFERENCE CHART 3: Body Region (Rule of 9s)	Head & Neck	Upper Extremities	Trunk Axillae & Genitals	Lower Extremities & Buttocks	Total BSA
% of Total Body Surface when using the rule of 9s	9%	18%	37%	36%	100%

In order to calculate the Affected Area Score, the % Area Involvement noted on physical examination, must be divided by the % Total Body Surface.

Example: Upper Extremity involvement = 10% of total BSA (using palm method). Affected Area Score = 10/18 = 55%. Affected Area Score = 4 (See Below).
Assignments for the following body regions are as follows:

- Neck: include with the head
- Buttocks: include with the lower extremities
- Axilla: include with the trunk
- Genitals: include with the trunk
- The inguinal canal separates the trunk and legs

PASI Score Calculation:

The PASI score for each body region is obtained by multiplying the sum of the severity scores by the area score, then multiplying the result by the constant weighted value assigned to that body region. Since the head, upper extremities, trunk, and lower extremities correspond to approximately 10, 20, 30, and 40% of body surface area, respectively; the PASI score is calculated using the formula

$$\mathbf{PASI = 0.1(E_h + I_h + D_h)A_h + 0.2(E_u + I_u + D_u)A_u + 0.3(E_t + I_t + D_t)A_t + 0.4(E_l + I_l + D_l)A_l}$$

where *E*, *I*, *D*, and A denote erythema, induration, desquamation, and area, respectively, and *h, u, t*, and *l* denote head, upper extremities, trunk, and lower extremities, respectively. PASI scores range from 0.0 to 72.0 with the highest score representing complete erythroderma of the severest degree.

Based on articles: Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica. 1978;157(4):238-44, and Mease, P. J. Measures of Psoriatic Arthritis. Arthritis Care Res, 2011,63(Suppl 11): S64–S85.

Harvey-Bradshaw Index (HBI)

HBI BASED ON PATIENT'S SYMPTOMS IN PREVIOUS 24 HOURS
General Well-Being 0 = very well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible
Abdominal Pain 0 = none, 1 = mild, 2 = moderate, 3 = severe
Number of Liquid Stools per Day
Abdominal Mass 0 = none, 1 = dubious, 2 = definite, 3 = definite and tender

Complications: (Score 1 Per Item) Arthralgia Uveitis Erythema Nodosum Aphthous Ulcers Pyoderma Gangrenosum Anal Fissure New Fistula Abscess
TOTAL HARVEY–BRADSHAW SCORE =

Harvey-Bradshaw Index Score:

<5	remission
5 – 7	mild
8 – 16	moderate
> 16	severe

Based on the article Harvey RF, Bradshaw JM. A simple Index of Crohn's disease activity. Lancet 1980; 1:514.

Partial Mayo score (PMS)

Based on Patients symptoms in previous 24 hours	Score
Stool Frequency 0 = normal, 1 = 1 to 2 stools per day more than normal 2 = 3 to 4 stools per day more than normal 3 = ≥ 5 stools per day more than normal	___
Rectal Bleeding 0 = No Blood seen 1 = Streaks of blood with stool less than half the time 2 = Obvious blood with stool most of the time 3 = Blood alone passes	___

Physician's Global Assessment 0 = Normal 1 = mild disease 2 = moderate disease 3 = severe disease	___
≤ 2 no activity; 3-4 mild; 5-6 moderate; ≥ 7 severe TOTAL	___

Was Endoscopy performed in this Visit? ☐yes ☐no

If Yes:

Endoscopic findings 0 = Normal 1 = mild disease 2 = moderate disease 3 = severe disease	___
≤ 2 no activity; 3-5 mild; ≥ 6 moderate to severe TOTAL (incl. partial Mayo Score)	___

Based on the article Schroeder KW, et al. N Engl J Med 1987;317:1625–9[14]

Full Mayo Score (FMS) is obtained when the endoscopy has been performed and the score of the endoscopic finding has been added to the partial Mayo score.

HUMIRA®
(Adalimumab)
complete at visit 1 and entry changes as appropriate at each visit

Concomitant Medication, Other Medication And Supplements:

Visit 1 (=screening)

1. Name (Trade name preferred)	**2. Start date**	**3. End date**
	|__|__| |__|__|__| |__|__| DD MON YY	|__|__| |__|__|__| |__|__| DD MON YY
4. Dose and Units and Route of Administration	**5. Frequency**	**6. Reason for use**
	☐ 1qd ☐ 2bid ☐ 3tid ☐ 4qid Other:	
1. Name (Trade name preferred)	**2. Start date**	**3. End date**
	|__|__| |__|__|__| |__|__| DD MON YY	|__|__| |__|__|__| |__|__| DD MON YY
4. Dose and Units and Route of Administration	**5. Frequency**	**6. Reason for use**
	☐ 1qd ☐ 2bid ☐ 3tid ☐ 4qid Other:	

1. Name (Trade name preferred)	**2. Start date**	**3. End date**
	|__|__| |__|__|__| |__|__| DD MON YY	|__|__| |__|__|__| |__|__| DD MON YY
4. Dose and Units and Route of Administration	**5. Frequency**	**6. Reason for use**
	☐ 1qd ☐ 2bid ☐ 3tid ☐ 4qid Other:	
1. Name (Trade name preferred)	**2. Start date**	**3. End date**
	|__|__| |__|__|__| |__|__| DD MON YY	|__|__| |__|__|__| |__|__| DD MON YY
4. Dose and Units and Route of Administration	**5. Frequency**	**6. Reason for use**
	☐ 1qd ☐ 2bid ☐ 3tid ☐ 4qid Other:_____	

HUMIRA®
(Adalimumab)
complete at visit 1 and entry changes as appropriate at each visit

Concomitant Medication, Other Medication And Supplements:

If there is a change in medication fromVisit 1 please specify below.
The change has been carried out on :_____(DD/MM/YY)

1. Name (Trade name preferred)	2. Start date	3. End date
	|__|__| |__|__|__| |__|__| DD MON YY	|__|__| |__|__|__| |__|__| DD MON YY
4. Dose and Units and Route of Administration	**5. Frequency**	**6. Reason for use**
	☐ 1qd ☐ 2bid ☐ 3tid ☐ 4qid Other:	
1. Name (Trade name preferred)	**2. Start date**	**3. End date**
	|__|__| |__|__|__| |__|__| DD MON YY	|__|__| |__|__|__| |__|__| DD MON YY
4. Dose and Units and Route of Administration	**5. Frequency**	**6. Reason for use**
	☐ 1qd ☐ 2bid ☐ 3tid ☐ 4qid Other:	
1. Name (Trade name preferred)	**2. Start date**	**3. End date**
	|__|__| |__|__|__| |__|__| DD MON YY	|__|__| |__|__|__| |__|__| DD MON YY

4. Dose and Units and Route of Administration	5. Frequency	6. Reason for use
	☐ 1qd ☐ 2bid ☐ 3tid ☐ 4qid Other:_____	

1. Name (Trade name preferred)	2. Start date	3. End date
	|__|__| |__|__|__| |__|__| DD MON YY	|__|__| |__|__|__| |__|__| DD MON YY
4. Dose and Units and Route of Administration	**5. Frequency**	**6. Reason for use**
	☐ 1qd ☐ 2bid ☐ 3tid ☐ 4qid Other:	

(Adalimumab)
for each visit

HUMIRA ADMINISTRATION

Dosage Frequency:

☐ Every other week ☐ Other (please specify): _____

- **Patient first visit** (PFV): |__|__| |__|__| |__|__| **(DD/MM/YY)**
- **Patient first dose** (PFD): |__|__| |__|__| |__|__ | **(DD/MM/YY)**
- **Patient last visit** (PLV): |__|__| |__|__| |__|__| **(DD/MM/YY)**
- **Patient last dose** (PLD): |__|__| |__|__| |__|__| **(DD/MM/YY)**

Further applications (date):

1.
2.
3.
4.
5.
6.
7.
8.
9.
10.
11.
12.
etc.

HUMIRA®

(Adalimumab)
final visit

FINAL STATEMENT:

Final remarks about compliance and adherence:

Please provide a final statement about compliance and adherence (non-adherent, adherent) of the patient in general.

_____

_____

Tolerability:

Serious Adverse Events : ☐ NO ☐ YES (If yes, please complete Serious Adverse Event Form)

Therapy with Humira: ☐ ongoing after PMOS

☐ stopped after _____

Reasons for treatment change:

☐ Serious adverse events

☐ treatment failure

☐ other reasons (please specify): _____

HUMIRA®
(Adalimumab)
early termination

Discontinuation:

Date of discontinuation: |__|__| |__|__| |__|__| **(DD/MM/YY)**

Reason for Discontinuation:

☐ 1 Serious Adverse Event (please record on Serious Adverse Avent Form)

☐ 2 Lost to follow-up

☐ 3 Lack of Efficacy

☐ 4 Death (please specify below; please record on Serious Adverse Avent Form)

☐ 5 Other (please specify below)

Specification Comments:

_____

_____

NON SERIOUS *AND* SERIOUS ADVERSE EVENT FORM

Adverse Event Description **In case of further questions please contact :**		SDV: not done
[redacted]		

[redacted]		
Does this event represent a pregnancy exposure	[ ] No [ ] Yes (If yes, please fill in the pregnancy exposure form)	SDV: not done
Event onset date	___/___/20___ [day/month/year]	SDV: not done
Event end date	___/___/20___ [day/month/year]	SDV: not done
HUMIRA start date	___/___/20___ [day/month/year]	SDV: not done
HUMIRA end date	___/___/20___ [day/month/year]	SDV: not done
HUMIRA Unit Dose and Frequency	_____ _____	SDV: not done
Severity	( ) mild ( ) moderate ( ) severe **Mild**: A suspected adverse event is considered as mild if it is transient and easily tolerated by the patient. **Moderate**: A suspected adverse event is considered as moderate if it causes the patient discomfort and interrupts the patient`s usual activities. **Severe**: A suspected adverse event is considered as severe if it causes considerable interference with the patient´s usual activities and may be incapacitating or life-threatening.	SDV: not done

Serious adverse event criteria	Please check all that apply:
	[ ] death
	[ ] life-threatening
	[ ] hospitalization or prolonged hospitalization
	[ ] congenital anomaly/birth defect
	[ ] persistent or significant disability/incapacity
	[ ] medically important event
	[ ] elective abortion/miscarriage
	[ ] Humira discontinued due to Serious Adverse Event
	
	if death:
	date of death: ___/___/20___ [day/month/year]
	death cause:
	_____
	_____
	_____
	
	if hospitalization or prolonged hospitalization:
	onset date: ___/___/20___ [day/month/year]
	end date: ___/___/20___ [day/month/year] or [ ] still ongoing
		SDV: not done

Medical History Narrative	(Record any relevant, concurrent, or past medical history, family history, pregnancy history, pertinent negatives, risk factors occupation, and HIV status. Please provide dates when possible.) _____ _____ _____ _____ _____	SDV: not done
Concomitant Medication		
Duration	( ) nonrecurring	SDV:

	( ) intermittent ( ) ongoing	not done
Resolution	( ) recovered/resolved ( ) recovering/resolving ( ) not recovered ( ) recovered/resolved with sequelae ( ) unknown ( ) fatal	SDV: not done
Investigator's opinion of causal relationship to HUMIRA	( ) not related ( ) probably not related ( ) possibly related ( ) probably related ( ) definitely related if not "probably" or not "definitely" - altern. etiology: _____ _____ _____ Not related: SAE is due to underlying or concurrent illness or effect of another drug and is not related to HUMIRA (per definition no AR) Probably not: SAE has little or no temp. relationship to HUMIRA and/or more likely altern. etiology exists Possible: SAE has strong temp. relationship to HUMIRA and altern. etiology is equally or less likely compared to the potenial relationship to HUMIRA Probably: SAE has strong temp. relationship to HUMIRA or recurs on rechallenge, and another etiology is unlikely or significant less likely Definitely: SAE has strong temp. relationship to HUMIRA, is known AR, another etiology is unlikely, it disappears resp. reappears with dechallenge resp. rechallenge	SDV: not done

Treatment of SAE	[ ] no [ ] HUMIRA doses reduced [ ] HUMIRA discontinued due to Adverse Reaction [ ] HUMIRA temporarily discontinued [ ] treatment medication or surgery intervention [ ] others if HUMIRA doses reduced: ____.__ mg if "treatment medication or surgery intervention" or "others" - please specify: _____ _____ _____	SDV: not done
Seriousness Criteria	please - check all that apply: [ ] death [ ] life-threatening [ ] hospitalization or prolonged hospitalization [ ] congenital anomaly/birth defect [ ] persistent or significant disability/incapacity [ ] medically important event [ ] elective abortion/miscarriage [ ] Humira discontinued due to Serious Adverse Event if death: date of death: __/__/20__ [day/month/year] death cause: _____ _____ _____	SDV: not done

	if hospitalization or prolonged hospitalization: onset date: ___/___/20___ [day/month/year] end date: ___/___/20___ [day/month/year] or [ ] still ongoing	

Global Medical Services, Pharmacovigilance Global Pharmaceutical Research and Development

Q-15-01-009-F16
Version 2.0

In Utero Exposure Initial Report

AER # _____ **Abbott Awareness Date** ___/___/___

INITIAL REPORT SOURCE INFORMATION

Patient ☐ Primary Reporter

Name: _____

Address: _____

Phone _____ Fax _____

☐ M ☐ F DOB ___/___/___ Age _____

Race _____ Occupation _____

Health Care Provider ☐ Primary Reporter

Name: _____

Address: _____

Phone _____ Fax _____

Specialty _____

ABBOTT PRODUCT INFORMATION

Product Name	Total Daily Dose	Unit Dose & Frequency	Route	Start Date/ Duration	End Date	Indication(s)

CURRENT PREGNANCY

Is pregnancy ongoing? ☐ Yes ☐ No *If no, was the termination:* ☐ Spontaneous abortion ___/___ (date/EGA)

☐ Elective abortion ___/___ (date/EGA) Were any fetal abnormalities diagnosed? ☐ Yes ☐ No

If yes, please provide further details including dates and pathology results (if available): _____

Date of last menstrual period (LMP): ___/___/___ Estimated date of delivery (EDC): ___/___/___

Date of pregnancy confirmation: ___/___/___ Confirmed by: ☐ Serum ☐ Dipstick ☐ Ultrasound

Confirmed by: ☐ Consumer ☐ Healthcare Provider Any medical problems or complications during this pregnancy? ☐ Yes ☐ No

If yes, please provide further details: _____

Diagnostic tests performed during pregnancy? ☐ Yes ☐ No

If yes, provide further details including dates and results: _____

PREGNANCY HISTORY

Total:

Pregnancies _____ Full term deliveries _____ Premature deliveries _____ Ectopic pregnancies _____

Stillbirths _____ Spontaneous abortions _____ Elective abortions _____

Any family history of birth defects, genetic disorders, multiple births, fetal abnormalities, or pregnancy complications?

If yes, circle and provide further details: _____

MATERNAL PAST MEDICAL HISTORY

☐ Hypertension ☐ Seizures ☐ Thyroid disorder ☐ Allergies ☐ Heart disease ☐ Rheumatologic disease

☐ Autoimmune disease ☐ Diabetes ☐ Infectious disease (hepatitis, rubella, Epstein-Barr virus, cytomegalovirus, HIV, etc.) ☐ Recreational drug use

☐ Environmental/ occupational exposure ☐ Hospitalization ☐ Surgery ☐ Tobacco ☐ Alcohol ☐ Other _____

Please provide further details and onset dates for checked items: _____

CONCOMITANT MEDICATION INFORMATION

List prescribed drugs and over-the-counter drugs, including dietary/herbal supplements, vaccines, inhalers and insertable or implantable medical devices.

Product Name	Total Daily Dose	Unit Dose & Frequency	Route	Start/ Duration	End	Indication(s)

Name: _____ Date: _____ Signature and Date: _____

Note: A signature/date is not required on the form, if it is documented in an electronic system.

Page 1 of 1

[redacted]

Non-medical C
labelling, dura

Patient Information and Declaration of Consent concerning authorization to use data

Title of the this study:

Assessment of Rheumatoid Arthritis, Psoriatic Arthritis and Ankylosing Spondylitis, Psoriasis, Crohns Disease, Colitis Ulcerosa, patients`adherence attitudes to maintenance therapy with a scheduled Adalimumab treatment in routine clinical practice

Dear patient,

Introduction and Purpose

Your physician has decided your treatment in accordance with usual medical practice and you are treated as recommended in the product label. This treatment was decided after diligent clarifications and the decision of your physician, that this treatment will be advantageous for you.

The aim of this post-marketing observational study (PMOS) is the assessment of Rheumatoid Arthritis, Psoriatic Arthritis,Ankylosing Spondylitis, Psoriasis, Crohns Disease and Colitis Ulcerosa patients` adherence attitudes/beliefs to maintenance therapy with a scheduled Adalimumab treatment in routine clinical practice.

Therefore data about your attitudes/beliefs to an intented therapy and your medication adherence according to a physicians specification as well as your treatment satisfaction will be collected during the course of your treatment with Adalimumab. Independently of the treatment duration, this data collection period will be for a maximum of 1 year.

In this context, some important points concerning the protection of data privacy have to be adhered to. If you agree, you will be asked to sign and date this consent form and you will be given a copy of the signed form.

Details

This study is an observational study according to §2a paragraph 3 of the Austrian Pharmaceutical Act. The observational study will involve approximately140 individuals in 28 centers. Individuals will be observed for a maximum period of 1 year. Your participation in this observational study makes it necessary that you allow your doctor to disclose some of your medical data to the sponsor (Abbott Gesellschaft m.b.H., A-1230 Wien). The observational study does not ask or require that a particular treatment should be used, your treatment should be altered or additional testing should be performed.

- **Release of Medical Information, and Confidentiality and Authorization**

People from Abbott, its related companies or independent companies auditing the results on behalf of Abbott, or employees of regulatory authorities will have access to your medical records

for the purpose of collecting data, verifying that the data is correct and checking that the procedure is properly done. Your data will be anonymized with the purpose, that you cannot be identified. By signing this form you are allowing these people to see your medical records. If the results of the observational study are published, the published report will not identify you.

If you cancel your authorization, your personal and anonymized data may not be used or provided anymore from the time of your withdrawal. Cancelling authorization does not affect information that has already been disclosed or information gathered as a result of your participation in the trial.
Records identifying you will be kept confidential and, to the extent permitted by the data protection act, will not be made publicly available.
You understand that you have the right to access your medical records as allowed by national law.

- **Contact Information**

If you have any questions about this study, please ask your physician.

- **Declaration of Consent**

- ✓ I agree to take part in this Post-Marketing Observational Study. I understand that I do not have to participate in this observational study and that I can withdraw my participation and my consent at any time without any loss of advantages or benefits that I am otherwise entitled to.
- ✓ I hereby declare my consent with the use, the storage, the processing and the transfer of my medical data disclosed during the observational study to Abbott Laboratories, its related companies and independent companies auditing the results of the observational study on behalf of Abbott, the supervisory authorities, and the Ethics Committee, as necessary.
- ✓ I declare my consent with the use, the storage, the processing and the transfer of my personal data disclosed during the study to Abbott Laboratories and its related companies and other companies hired by Abbott. I understand and declare my consent with the transfer of my personal and medical data to Abbott Laboratories and its related companies and other companies hired by Abbott which may be located in other countries, including the United States. This includes but is not limited to the use of these data by licensees or franchisees of Abbott. I agree that these data may be used for scientific presentations, research and development operations of Abbott.
- ✓ I understand that I will receive a copy of this signed and dated consent form.
- ✓ By signing this form I have not given up any of the legal rights that I would have as a participant in this study.
- ✓ I understand that by my signature I am authorizing access to my personal data as described above under the heading Release of Medical Information and Confidentiality and Authorization. I understand that I may revoke my authorization to the use or disclosure of my personal or medical data at any time.

_____
Patient Name (print)

_____ _____
Patient Signature Date

_____ _____
Signature and stamp of the responsible physician Date

16. Research Plan Signature Page

AbbVie Inc. (AbbVie)

Post Marketing Observational Study

Protocol (P13-562)

**Assessment of Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Plaque Psoriasis, Crohn's Disease and Ulcerative Colitis patients`
adherence attitudes to maintenance therapy with a scheduled adalimumab treatment in routine clinical practice**

Administrative Change, 27 October 2016

Approved by:

[redacted]

_____ _____
Date

_____ _____
Date

_____ _____
Date