ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

Humira 40 mg solution for injection

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each 0.8 ml single dose vial contains 40 mg of adalimumab. Adalimumab is a recombinant human monoclonal antibody expressed in Chinese Hamster Ovary cells.

For excipients, see 6.1.

3. **PHARMACEUTICAL FORM**

Solution for injection

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Humira is indicated 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.

To ensure maximum efficacy, Humira is given in combination with methotrexate. Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

4.2 **Posology and method of administration**

Humira treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis. Patients treated with Humira should be given the special alert card.

After proper training in injection technique, patients may self-inject with Humira if their physician determines that it is appropriate and with medical follow-up as necessary.

**Adults**

The recommended dose of Humira for adult patients with rheumatoid arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection. Methotrexate should be continued during treatment with Humira.

Glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, or analgesics can be continued during treatment with Humira. Regarding combination with disease modifying anti-rheumatic drugs other than methotrexate see 4.4 and 5.1.

In monotherapy, some patients who experience decrease in their response may benefit from an increase in dose intensity to 40 mg adalimumab every week.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

**Elderly patients**
No dose adjustment is required.

**Children and adolescents**

Humira has not been studied in this patient population. Therefore, use of Humira cannot be recommended in patients aged below 18 years until further data become available.

**Impaired renal and/or hepatic function**

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

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Active tuberculosis or other severe infections such as sepsis, and opportunistic infections (see 4.4).

Moderate to severe heart failure (NYHA class III/IV) (see 4.4).

### 4.4 Special warnings and special precautions for use

**Infections**

Patients must be monitored closely for infections, including tuberculosis, before, during and after treatment with Humira. Because the elimination of adalimumab may take up to five months, monitoring should be continued throughout this period.

Treatment with Humira should not be initiated in patients with active infections including chronic or localized infections until infections are controlled.

Patients who develop a new infection while undergoing treatment with Humira should be monitored closely. Administration of Humira should be discontinued if a patient develops a new serious infection until infections are controlled. Physicians should exercise caution when considering the use of Humira in patients with a history of recurring infection or with underlying conditions which may predispose patients to infections.

Serious infections, sepsis, and opportunistic infections, including fatalities, have been reported with Humira. Tuberculosis has been observed in patients treated with Humira. All patients recovered after standard antimicrobial therapy. No deaths due to tuberculosis occurred during the clinical trials.

Before initiation of therapy with Humira, all patients must be evaluated for both active or inactive (latent) tuberculosis infection. This evaluation should include a detailed medical history with a personal history of tuberculosis or possible previous exposure to patients with active tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e. tuberculin skin test and chest x-ray, should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the patient’s alert card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, Humira therapy must not be initiated (see 4.3).

If latent tuberculosis is diagnosed, appropriate anti-tuberculosis prophylaxis in accordance with local recommendations must be initiated before starting treatment with Humira. In this situation, the benefit/risk balance of therapy with Humira should be very carefully considered.
Patients should be instructed to seek medical advice if signs/symptoms (eg, persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur during or after therapy with Humira.

**Neurological events**

TNF-antagonists including Humira have been associated in rare cases with exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease. Prescribers should exercise caution in considering the use of Humira in patients with pre-existing or recent-onset central nervous system demyelinating disorders.

**Allergic reactions**

Serious allergic adverse reactions have not been reported with subcutaneous administration of Humira during clinical trials. Non-serious allergic reactions associated with Humira were uncommon during clinical trials. If an anaphylactic reaction or other serious allergic reaction occurs, administration of Humira should be discontinued immediately and appropriate therapy initiated.

**Immunosuppression**

In a study of 64 patients with rheumatoid arthritis that were treated with Humira, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T-and B cells and NK-cells, monocyte/macrophages, and neutrophils. It is not known whether exposure to adalimumab can increase the risk of developing malignancies and lymphoproliferative disorders.

**Vaccinations**

Sixty-one patients with rheumatoid arthritis were given pneumococcal vaccinations against a background of Humira and methotrexate therapy. Most patients receiving Humira were able to mount effective B-cell immune responses to pneumococcal polysaccharide vaccine. Since no data are available, concurrent administration of live vaccines and Humira is not recommended.

**Congestive heart failure**

In a clinical trial with another TNF antagonist worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Humira should be used with caution in patients with mild heart failure (NYHA class I/II). Humira is contraindicated in moderate to severe heart failure (see 4.3). Treatment with Humira must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

**Autoimmune processes**

Treatment with Humira may result in the formation of autoimmune antibodies. The impact of long-term treatment with Humira on the development of autoimmune diseases is unknown.

**Concurrent administration of TNF-alpha inhibitor and anakinra**

Concurrent administration of etanercept (another agent that inhibits TNFα) and anakinra (a recombinant, non-glycosylated form of the human interleukin-1 receptor antagonist) has been associated with an increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared to these medicinal products alone. The safety and efficacy of anakinra used in combination with adalimumab has not been established. Therefore, combination of adalimumab and anakinra is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction
Humira has been studied both in rheumatoid arthritis patients taking Humira as monotherapy and those taking concomitant methotrexate. Antibody formation was low (< 1%) when Humira was given together with methotrexate in comparison with use as monotherapy. Administration of Humira without methotrexate resulted in increased formation of antibodies and increased clearance of adalimumab (see 5.1).

There is no experience with the efficacy and safety in patients previously treated with other TNF-antagonists.

4.6 Pregnancy and lactation

For adalimumab, there is no experience in pregnant women.

In a developmental toxicity study conducted in monkeys, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. Preclinical data on postnatal toxicity and fertility effects of adalimumab are not available (see 5.3).

Due to its inhibition of TNFα, adalimumab administered during pregnancy could affect normal immune responses in the newborn. Administration of adalimumab is not recommended during pregnancy. Women of childbearing potential are strongly recommended to use adequate contraception to prevent pregnancy and continue its use for at least five months after the last Humira treatment.

Use during lactation

It is not known whether adalimumab is excreted in human milk or absorbed systemically after ingestion.

However, because human immunoglobulins are excreted in milk, women must not breast-feed for at least five months after the last Humira treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Humira was studied in 2334 patients in placebo-controlled trials and in long term follow-up studies, including 2073 patients exposed for six months and 1497 patients exposed for greater than one year. The data in the table is based on the adequate and well-controlled studies I, II, III and IV (see 5.1) involving 1380 patients receiving adalimumab during the placebo-controlled period by randomised treatment. The population had a mean age of 54.5 years, 77% were female, 91% were Caucasian and had moderate to severely active rheumatoid arthritis. Most patients received 40 mg Humira every other week.

The proportion of patients who discontinued treatment due to adverse events during the double-blind, placebo controlled portion of Studies I, II, III and IV was 6.6% for patients taking Humira and 4.2% for placebo-treated patients.

Adverse events at least possibly causally-related to adalimumab, both clinical and laboratory, are displayed by system organ class and frequency (very common > 1/10; common > 1/100 ≤ 1/10; uncommon > 1/1000 ≤ 1/100) in Table 1 below.

<table>
<thead>
<tr>
<th>Body system</th>
<th>Frequency</th>
<th>Adverse event</th>
</tr>
</thead>
</table>

Table 1
Undesirable Effects in Clinical Studies
<table>
<thead>
<tr>
<th>System</th>
<th>Commonality</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasia</td>
<td>Uncommon</td>
<td>Skin benign neoplasm</td>
</tr>
<tr>
<td>Haemic and Lymphatic system</td>
<td>Common</td>
<td>Decreased haemoglobin, Granulocytopenia, coagulation time increased, antinuclear antibody present, leukopenia, lymphadenopathy, lymphocytosis, platelet count decreased, purpura</td>
</tr>
<tr>
<td>Metabolic and Nutritional Disorders</td>
<td>Uncommon</td>
<td>Hyperlipidaemia, Hypercholesterolaemia, alkaline phosphatase increased, BUN increased, hyperuricaemia, peripheral oedema, weight gain, creatinine phosphokinase increased, healing abnormal, hypokalaemia, lactic dehydrogenase increased</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Uncommon</td>
<td>Depression, somnolence, insomnia, agitation</td>
</tr>
<tr>
<td>Nervous System</td>
<td>Common</td>
<td>Headache, dizziness, Paresthaesia, vertigo, hypeaesthesia, neuralgia, tremor</td>
</tr>
<tr>
<td>Special senses</td>
<td>Uncommon</td>
<td>Conjunctivitis, eye disorder*, otitis media, taste perversion, abnormal vision, blurred vision, dry eye, ear disorder*, eye pain</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td>Uncommon</td>
<td>Hypertension, vasodilatation, chest pain, migraine</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>Uncommon</td>
<td>Ecchymosis</td>
</tr>
<tr>
<td>Respiratory System</td>
<td>Common</td>
<td>Upper respiratory infection, rhinitis, sinusitis, bronchitis, cough increased, pneumonia, Pharyngitis, dyspnoea, lung disorder*, asthma</td>
</tr>
<tr>
<td>Digestive System</td>
<td>Common</td>
<td>Nausea, diarrhoea, sore throat</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td>Uncommon</td>
<td>Rash, pruritus, herpes simplex</td>
</tr>
<tr>
<td>Musculo-skeletal System</td>
<td>Uncommon</td>
<td>Arthralgia, muscle cramps, myalgia, joint disorder, synovitis, tendon disorder*</td>
</tr>
<tr>
<td>Urogenital System</td>
<td>Common</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Vaginal moniliasis, haematuria, cystitis, menorrhagia, proteinuria, increased urinary frequency</td>
</tr>
<tr>
<td>Body as a whole</td>
<td>Common</td>
<td>Laboratory test abnormal, asthenia, clinical flare reaction, flu syndrome, abdominal pain,</td>
</tr>
</tbody>
</table>
**Infections**

In placebo-controlled trials, the rate of infection was 1 per patient year in the Humira treated patients and 0.9 per patient year in the placebo-treated patients. The incidence of serious infections was 0.04 per patient year in Humira treated patients and 0.02 per patient year in placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, bronchitis and urinary tract infections. Most patients continued on Humira after the infection resolved.

**Malignancies**

Twenty-four (24) non-melanoma skin cancers and 30 other malignancies of various types were observed in 2334 rheumatoid arthritis patients treated in clinical trials with Humira for up to 53 months. The observed rates and incidences were similar to those expected for the population studied.

**Autoantibodies**

Patients had serum samples tested for autoantibodies at multiple time points. In the adequate and well-controlled trials, 12.6% of patients treated with Humira and 7.3% of placebo-treated patients that had negative baseline anti-nuclear antibody titres reported positive titres at week 24. One patient out of 2334 treated with Humira developed clinical signs suggestive of new-onset lupus-like syndrome. The patient improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms.

### 4.9 Overdose

No dose-limiting toxicity was observed during clinical trials of rheumatoid arthritis patients. The highest dose level evaluated has been multiple intravenous doses of 10 mg/kg.

5. **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Pharmacotherapeutic group: Selective immunosuppressive agents. ATC code: L04AA17

**Mechanism of action**
Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC$_{50}$ of 1-2 X $10^{-10}$ M).

**Pharmacodynamic effects**

After treatment with Humira, a rapid decrease in levels of acute phase reactants of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) and serum cytokines (IL-6) was observed compared to baseline in patients with rheumatoid arthritis. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodelling responsible for cartilage destruction were also decreased after Humira administration. Patients treated with Humira usually experienced improvement in haematological signs of chronic inflammation.

**Clinical trials**

Humira was evaluated in over 2330 patients in all clinical trials. Some patients were treated for greater than 36 months duration. The efficacy and safety of Humira were assessed in four randomised, double-blind and well-controlled studies.

Study I evaluated 271 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, had failed therapy with at least one disease-modifying, anti-rheumatic drug and had insufficient efficacy with methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate dose remained constant at 10 to 25 mg every week. Doses of 20, 40 or 80 mg of Humira or placebo were given every other week for 24 weeks.

Study II evaluated 544 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old and had failed therapy with at least one disease-modifying, anti-rheumatic drug. Doses of 20 or 40 mg of Humira were given by subcutaneous injection every other week with placebo on alternative weeks or every week for 26 weeks; placebo was given every week for the same duration. No other disease-modifying anti-rheumatic drugs were allowed.

Study III evaluated 619 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, had insufficient efficacy to methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate dose remained constant at 12.5 to 25 mg every week. There were three groups in this study. The first received placebo injections every week for 52 weeks. The second received 20 mg of Humira every week for 52 weeks. The third group received 40 mg of Humira every other week with placebo injections on alternate weeks.

Study IV primarily assessed safety in 636 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old. Patients were permitted to be either disease-modifying, anti-rheumatic drug-naïve or to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. These therapies include methotrexate, leflunomide, hydroxychloroquine, sulfasalazine and/or gold salts. Patients were randomised to 40 mg of Humira or placebo every other week for 24 weeks.

The primary end point in Studies I, II and III and the secondary endpoint in Study IV was the percent of patients who achieved an ACR 20 response at Week 24 or 26. Study III had additional primary endpoints at 52 weeks of retardation of disease progression (as detected by x-ray results) and changes in quality of life.

**ACR response**

The percent of Humira-treated patients achieving ACR 20, 50 and 70 responses was consistent across trials I, II and III. The results for the 40 mg every other week dose are summarised in Table 2.
<table>
<thead>
<tr>
<th>Response</th>
<th>Study I*</th>
<th></th>
<th>Study II*</th>
<th></th>
<th>Study III**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo/MTXc n=60</td>
<td>Humira®/MTXc n=63</td>
<td>Placebo n=110</td>
<td>Humira® n=113</td>
<td>Placebo/MTXc n=200</td>
</tr>
<tr>
<td>ACR 20</td>
<td>6 months</td>
<td>13.3%</td>
<td>65.1%</td>
<td>19.1%</td>
<td>46.0%</td>
</tr>
<tr>
<td></td>
<td>12 months</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ACR 50</td>
<td>6 months</td>
<td>6.7%</td>
<td>52.4%</td>
<td>8.2%</td>
<td>22.1%</td>
</tr>
<tr>
<td></td>
<td>12 months</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ACR 70</td>
<td>6 months</td>
<td>3.3%</td>
<td>23.8%</td>
<td>1.8%</td>
<td>12.4%</td>
</tr>
<tr>
<td></td>
<td>12 months</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Study I at 24 weeks, Study II at 26 weeks, and Study III at 24 and 52 weeks

** Study III: Placebo n=110, Humira® n=113

b 40 mg Humira administered every other week
c MTX = methotrexate

*p<0.01, Humira versus placebo

In Studies I-IV, all individual components of the ACR response criteria (number of tender and swollen joints, physician and patient assessment of disease activity and pain, disability index (HAQ) scores and CRP (mg/dl) values) improved at 24 or 26 weeks compared to placebo. In Study III, these improvements were maintained throughout 52 weeks.

In Study IV, the ACR 20 response of patients treated with Humira plus standard of care was statistically significantly better than patients treated with placebo plus standard of care (p<0.001).

In all four studies, Humira-treated patients achieved statistically significant ACR 20 and 50 responses compared to placebo as early as one to two weeks after initiation of treatment.

Quality of life and physical function

Health-related quality of life and physical function was assessed using the disability index of the Health Assessment Questionnaire (HAQ) in all four adequate and well-controlled trials, which was a pre-specified primary endpoint at Week 52 in Study III. All doses/schedules of Humira in all four studies showed statistically significantly greater improvement in the disability index of the HAQ from baseline to Month 6 compared to placebo and in Study III the same was seen at Week 52. Results from the Short Form Health Survey (SF 36) for all doses/schedules of Humira in all four studies support these findings, with statistically significant physical component summary (PCS) scores, as well as statistically significant pain and vitality domain scores for the 40 mg every other week dose. A statistically significant decrease in fatigue as measured by functional assessment of chronic illness therapy (FACIT) scores was seen in all three studies in which it was assessed (Studies I, III, IV).

Immunogenicity

Patients in Studies I, II and III were tested at multiple timepoints for antibodies to adalimumab during the 6 to 12 month period. In the pivotal trials, anti-adalimumab antibodies were identified in 58/1053 (5.5%) patients treated with adalimumab, compared to 2/370 (0.5%) on placebo. In patients not given concomitant methotrexate, the incidence was 12.4%, compared to 0.6% when adalimumab was used as add-on to methotrexate.

Because immunogenicity analyses are product-specific, comparison of antibody rates with those from other products is not appropriate.

5.2 Pharmacokinetic properties
After subcutaneous administration of a single 40 mg dose, absorption and distribution of adalimumab was slow, with peak serum concentrations being reached about 5 days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. After single intravenous doses ranging from 0.25 to 10 mg/kg, concentrations were dose proportional. After doses of 0.5 mg/kg (~40 mg), clearances ranged from 11 to 15 ml/hour, the distribution volume (Vss) ranged from 5 to 6 litres and the mean terminal phase half-life was approximately two weeks. Adalimumab concentrations in the synovial fluid from several rheumatoid arthritis patients ranged from 31-96% of those in serum.

Following subcutaneous administration of 40 mg of Humira every other week the mean steady-state trough concentrations were approximately 5 μg/ml (without concomitant methotrexate) and 8 to 9 μg/ml (with concomitant methotrexate), respectively. The serum adalimumab trough levels at steady-state increased roughly proportionally with dose following 20, 40 and 80 mg every other week and every week subcutaneous dosing.

Population pharmacokinetic analyses with data from over 1300 patients revealed a trend toward higher apparent clearance of adalimumab with increasing body weight. After adjustment for weight differences, gender and age appeared to have a minimal effect on adalimumab clearance. The serum levels of free adalimumab (not bound to anti-adalimumab antibodies, AAA) were observed to be lower in patients with measurable AAA. Humira has not been studied in children or in patients with hepatic or renal impairment.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on studies of single dose toxicity, repeated dose toxicity, and genotoxicity.

An embryo-foetal developmental toxicity/perinatal developmental study has been performed in cynomologous monkeys at 0, 30 and 100 mg/kg (9-17 monkeys/group) and has revealed no evidence of harm to the foetuses due to adalimumab. Carcinogenicity studies, and standard assessment of fertility and postnatal toxicity, were not performed with adalimumab due to the lack of appropriate models for an antibody with limited cross-reactivity to rodent TNF and the development of neutralizing antibodies in rodents.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Citric acid monohydrate
Sodium citrate
Sodium dihydrogen phosphate dihydrate
Disodium phosphate dihydrate
Sodium chloride
Polysorbate 80
Sodium hydroxide
Water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
18 months

6.4 Special precautions for storage

Store at 2°C – 8°C (in a refrigerator). Keep the container in the outer carton. Do not freeze.

6.5 Nature and contents of container

Humira 40 mg solution for injection in single-use vial (type I glass), fitted with rubber stops, 
aluminium crimps and flip-off seals.

Packs of:
1 vial (0.8 ml sterile solution), 1 empty sterile injection syringe in pouch and 2 alcohol pads, all in a 
blister.

6.6 Instructions for use and handling and disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Abbott Laboratories Ltd.
Queenborough
Kent ME11 5EL
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.8 ml single dose pre-filled syringe contains 40 mg of adalimumab.

Adalimumab is a recombinant human monoclonal antibody expressed in Chinese Hamster Ovary cells.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

4. CLINICAL PARTICULARS

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Humira is indicated 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.

To ensure maximum efficacy, Humira is given in combination with methotrexate. Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

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Humira treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis. Patients treated with Humira should be given the special alert card.

After proper training in injection technique, patients may self-inject with Humira if their physician determines that it is appropriate and with medical follow-up as necessary.

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Elderly patients
No dose adjustment is required.

**Children and adolescents**

Humira has not been studied in this patient population. Therefore, use of Humira cannot be recommended in patients aged below 18 years until further data become available.

**Impaired renal and/or hepatic function**

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### 4.3 Contraindications

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If active tuberculosis is diagnosed, Humira therapy must not be initiated (see 4.3). If latent tuberculosis is diagnosed, appropriate anti-tuberculosis prophylaxis in accordance with local recommendations must be initiated before starting treatment with Humira. In this situation, the benefit/risk balance of therapy with Humira should be very carefully considered.
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Neurological events

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Treatment with Humira may result in the formation of autoimmune antibodies. The impact of long-term treatment with Humira on the development of autoimmune diseases is unknown.

Concurrent administration of TNF-alpha inhibitor and anakinra

Concurrent administration of etanercept (another agent that inhibits TNFα) and anakinra (a recombinant, non-glycosylated form of the human interleukin-1 receptor antagonist) has been associated with an increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared to these medicinal products alone. The safety and efficacy of anakinra used in combination with adalimumab has not been established. Therefore combination of adalimumab and anakinra is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction
Humira has been studied both in rheumatoid arthritis patients taking Humira as monotherapy and those
taking concomitant methotrexate. Antibody formation was low (<1%) when Humira was given
together with methotrexate in comparison with use as monotherapy. Administration of Humira
without methotrexate resulted in increased formation of antibodies and increased clearance of
adalimumab (see 5.1).

There is no experience with the efficacy and safety in patients previously treated with other TNF-
agonists.

4.6 Pregnancy and lactation

For adalimumab, there is no experience in pregnant women.

In a developmental toxicity study conducted in monkeys, there was no indication of maternal toxicity,
embryotoxicity or teratogenicity. Preclinical data on postnatal toxicity and fertility effects of
adalimumab are not available (see 5.3).

Due to its inhibition of TNFα, adalimumab administered during pregnancy could affect normal
immune responses in the newborn. Administration of adalimumab is not recommended during
pregnancy. Women of childbearing potential are strongly recommended to use adequate contraception
to prevent pregnancy and continue its use for at least five months after the last Humira treatment.

Use during lactation

It is not known whether adalimumab is excreted in human milk or absorbed systemically after
ingestion.

However, because human immunoglobulins are excreted in milk, women must not breast-feed for at
least five months after the last Humira treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Humira was studied in 2334 patients in placebo-controlled trials and in long term follow-up studies,
including 2073 patients exposed for six months and 1497 patients exposed for greater than one year.
The data in the table is based on the adequate and well-controlled studies I, II, III and IV (see 5.1)
involving 1380 patients receiving adalimumab during the placebo-controlled period by randomised
treatment. The population had a mean age of 54.5 years, 77% were female, 91% were Caucasian and
had moderate to severely active rheumatoid arthritis. Most patients received 40 mg Humira every
other week.

The proportion of patients who discontinued treatment due to adverse events during the double-blind,
placebo controlled portion of Studies I, II, III and IV was 6.6% for patients taking Humira and 4.2%
for placebo-treated patients.

Adverse events at least possibly causally-related to adalimumab, both clinical and laboratory, are
displayed by system organ class and frequency (very common > 1/10; common > 1/100 ≤ 1/10;
uncommon > 1/1000 ≤ 1/100) in Table 1 below.

<table>
<thead>
<tr>
<th>Body system</th>
<th>Frequency</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasia</td>
<td>Uncommon</td>
<td>Skin benign neoplasm</td>
</tr>
<tr>
<td>System</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>--------</td>
<td>----------</td>
</tr>
<tr>
<td>Haemic and Lymphatic system</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased haemoglobin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Granulocytopenia, coagulation time increased, antinuclear antibody present, leukopenia, lymphadenopathy, lymphocytosis, platelet count decreased, purpura</td>
</tr>
<tr>
<td>Metabolic and Nutritional Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperlipidaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypercholesterolaemia, alkaline phosphatase increased, BUN increased, hyperuricaemia, peripheral oedema, weight gain, creatinine phosphokinase increased, healing abnormal, hypokalaemia, lactic dehydrogenase increased</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td>Depression, somnolence, insomnia, agitation</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td>Headache, dizziness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paresthaesia, vertigo, hypeaesthesia, neuralgia, tremor</td>
</tr>
<tr>
<td>Special senses</td>
<td></td>
<td>Conjunctivitis, eye disorder*, otitis media, taste perversion, abnormal vision, blurred vision, dry eye, ear disorder*, eye pain</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td></td>
<td>Hypertension, vasodilatation, chest pain, migraine</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td></td>
<td>Ecchymosis</td>
</tr>
<tr>
<td>Respiratory System</td>
<td></td>
<td>Upper respiratory infection, rhinitis, sinusitis, bronchitis, cough increased, pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pharyngitis, dyspnoea, lung disorder*, asthma</td>
</tr>
<tr>
<td>Digestive System</td>
<td></td>
<td>Nausea, diarrhoea, sore throat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver function test abnormal, SGPT increased, SGOT increased, mouth ulceration, oesophagitis, vomiting, dyspepsia, constipation, gastrointestinal pain, tooth disorder*, gastritis, gastroenteritis, tongue disorder*, oral moniliasi, aphthous stomatitis, dysphagia, stomatitis, ulcerative stomatitis</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td></td>
<td>Rash, pruritis, herpes simplex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin disorder*, herpes zoster, maculopapular rash, nail disorder*, dry skin, sweating increased, alopecia, fungal dermatitis, urticaria, skin nodule, skin ulcer, eczema, subcutaneous haematoma</td>
</tr>
<tr>
<td>Musculo-skeletal System</td>
<td></td>
<td>Arthralgia, muscle cramps, myalgia, joint disorder, synovitis, tendon disorder*</td>
</tr>
<tr>
<td>Urogenital System</td>
<td></td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vaginal moniliasi, haematuria, cystitis, menorrhagia, proteinuria, increased urinary frequency</td>
</tr>
<tr>
<td>Body as a whole</td>
<td></td>
<td>Laboratory test abnormal, asthenia, clinical flare reaction, flu syndrome, abdominal pain,</td>
</tr>
</tbody>
</table>
**Injection site reactions**

In placebo-controlled trials, 20% of patients treated with Humira developed injection site reactions (erythema and/or itching, haemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

**Infections**

In placebo-controlled trials, the rate of infection was 1 per patient year in the Humira treated patients and 0.9 per patient year in the placebo-treated patients. The incidence of serious infections was 0.04 per patient year in Humira treated patients and 0.02 per patient year in placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, bronchitis and urinary tract infections. Most patients continued on Humira after the infection resolved.

**Malignancies**

Twenty-four (24) non-melanoma skin cancers and 30 other malignancies of various types were observed in 2334 rheumatoid arthritis patients treated in clinical trials with Humira for up to 53 months. The observed rates and incidences were similar to those expected for the population studied.

**Autoantibodies**

Patients had serum samples tested for autoantibodies at multiple time points. In the adequate and well-controlled trials, 12.6% of patients treated with Humira and 7.3% of placebo-treated patients that had negative baseline anti-nuclear antibody titres reported positive titres at week 24. One patient out of 2334 treated with Humira developed clinical signs suggestive of new-onset lupus-like syndrome. The patient improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms.

**4.9 Overdose**

No dose-limiting toxicity was observed during clinical trials of rheumatoid arthritis patients. The highest dose level evaluated has been multiple intravenous doses of 10 mg/kg.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Selective immunosuppressive agents. ATC code: L04AA17

**Mechanism of action**
Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC$_{50}$ of 1-2 X 10$^{-10}$ M).

**Pharmacodynamic effects**

After treatment with Humira, a rapid decrease in levels of acute phase reactants of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) and serum cytokines (IL-6) was observed compared to baseline in patients with rheumatoid arthritis. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodelling responsible for cartilage destruction were also decreased after Humira administration. Patients treated with Humira usually experienced improvement in haematological signs of chronic inflammation.

**Clinical trials**

Humira was evaluated in over 2330 patients in all clinical trials. Some patients were treated for greater than 36 months duration. The efficacy and safety of Humira were assessed in four randomised, double-blind and well-controlled studies.

Study I evaluated 271 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, had failed therapy with at least one disease-modifying, anti-rheumatic drugs and had insufficient efficacy with methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate dose remained constant at 10 to 25 mg every week. Doses of 20, 40 or 80 mg of Humira or placebo were given every other week for 24 weeks.

Study II evaluated 544 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old and had failed therapy with at least one disease-modifying, anti-rheumatic drug. Doses of 20 or 40 mg of Humira were given by subcutaneous injection every other week with placebo on alternative weeks or every week for 26 weeks; placebo was given every week for the same duration. No other disease-modifying anti-rheumatic drugs were allowed.

Study III evaluated 619 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, had insufficient efficacy to methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate dose remained constant at 12.5 to 25 mg every week. There were three groups in this study. The first received placebo injections every week for 52 weeks. The second received 20 mg of Humira every week for 52 weeks. The third group received 40 mg of Humira every other week with placebo injections on alternate weeks.

Study IV primarily assessed safety in 636 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old. Patients were permitted to be either disease-modifying, anti-rheumatic drug-naïve or to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. These therapies include methotrexate, leflunomide, hydroxychloroquine, sulfasalazine and/or gold salts. Patients were randomised to 40 mg of Humira or placebo every other week for 24 weeks.

The primary end point in Studies I, II and III and the secondary endpoint in Study IV was the percent of patients who achieved an ACR 20 response at Week 24 or 26. Study III had additional primary endpoints at 52 weeks of retardation of disease progression (as detected by x-ray results) and changes in quality of life.

**ACR response**

The percent of Humira-treated patients achieving ACR 20, 50 and 70 responses was consistent across trials I, II and III. The results for the 40 mg every other week dose are summarized in Table 2.
Table 2: ACR Responses in Placebo-Controlled Trials (Percent of Patients)

<table>
<thead>
<tr>
<th>Response</th>
<th>Study I**</th>
<th>Study II**</th>
<th>Study III**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo/ MTXc</td>
<td>Humira/ MTXc</td>
<td>Placebo/ MTXc</td>
</tr>
<tr>
<td>ACR 20</td>
<td>n=60</td>
<td>n=63</td>
<td>n=110</td>
</tr>
<tr>
<td>6 months</td>
<td>13.3%</td>
<td>65.1%</td>
<td>19.1%</td>
</tr>
<tr>
<td>12 months</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ACR 50</td>
<td>n=100</td>
<td>n=101</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>6.7%</td>
<td>52.4%</td>
<td>8.2%</td>
</tr>
<tr>
<td>12 months</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ACR 70</td>
<td>n=150</td>
<td>n=151</td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>3.3%</td>
<td>23.8%</td>
<td>1.8%</td>
</tr>
<tr>
<td>12 months</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Study I at 24 weeks, Study II at 26 weeks, and Study III at 24 and 52 weeks
b 40 mg Humira administered every other week
c MTX = methotrexate
*p<0.01, Humira versus placebo

In Studies I-IV, all individual components of the ACR response criteria (number of tender and swollen joints, physician and patient assessment of disease activity and pain, disability index (HAQ) scores and CRP (mg/dl) values) improved at 24 or 26 weeks compared to placebo. In Study III, these improvements were maintained throughout 52 weeks.

In Study IV, the ACR 20 response of patients treated with Humira plus standard of care was statistically significantly better than patients treated with placebo plus standard of care (p<0.001).

In all four studies, Humira-treated patients achieved statistically significant ACR 20 and 50 responses compared to placebo as early as one to two weeks after initiation of treatment.

**Quality of life and physical function**

Health-related quality of life and physical function was assessed using the disability index of the Health Assessment Questionnaire (HAQ) in all four adequate and well-controlled trials, which was a pre-specified primary endpoint at Week 52 in Study III. All doses/schedules of Humira in all four studies showed statistically significantly greater improvement in the disability index of the HAQ from baseline to Month 6 compared to placebo and in Study III the same was seen at Week 52. Results from the Short Form Health Survey (SF 36) for all doses/schedules of Humira in all four studies support these findings, with statistically significant physical component summary (PCS) scores, as well as statistically significant pain and vitality domain scores for the 40 mg every other week dose. A statistically significant decrease in fatigue as measured by functional assessment of chronic illness therapy (FACIT) scores was seen in all three studies in which it was assessed (Studies I, III, IV).

**Immunogenicity**

Patients in Studies I, II and III were tested at multiple timepoints for antibodies to adalimumab during the 6 to 12 month period. In the pivotal trials, anti-adalimumab antibodies were identified in 58/1053 (5.5%) patients treated with adalimumab, compared to 2/370 (0.5%) on placebo. In patients not given concomitant methotrexate, the incidence was 12.4%, compared to 0.6% when adalimumab was used as add-on to methotrexate.

Because immunogenicity analyses are product-specific, comparison of antibody rates with those from other products is not appropriate.

5.2 Pharmacokinetic properties
After subcutaneous administration of a single 40 mg dose, absorption and distribution of adalimumab was slow, with peak serum concentrations being reached about 5 days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. After single intravenous doses ranging from 0.25 to 10 mg/kg, concentrations were dose proportional. After doses of 0.5 mg/kg (~40 mg), clearances ranged from 11 to 15 ml/hour, the distribution volume (Vss) ranged from 5 to 6 litres and the mean terminal phase half-life was approximately two weeks. Adalimumab concentrations in the synovial fluid from several rheumatoid arthritis patients ranged from 31-96% of those in serum.

Following subcutaneous administration of 40 mg of Humira every other week the mean steady-state trough concentrations were approximately 5 μg/ml (without concomitant methotrexate) and 8 to 9 μg/ml (with concomitant methotrexate), respectively. The serum adalimumab trough levels at steady-state increased roughly proportionally with dose following 20, 40 and 80 mg every other week and every week subcutaneous dosing.

Population pharmacokinetic analyses with data from over 1300 patients revealed a trend toward higher apparent clearance of adalimumab with increasing body weight. After adjustment for weight differences, gender and age appeared to have a minimal effect on adalimumab clearance. The serum levels of free adalimumab (not bound to anti-adalimumab antibodies, AAA) were observed to be lower in patients with measurable AAA. Humira has not been studied in children or in patients with hepatic or renal impairment.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on studies of single dose toxicity, repeated dose toxicity, and genotoxicity.

An embryo-foetal developmental toxicity/perinatal developmental study has been performed in cynomologous monkeys at 0, 30 and 100 mg/kg (9-17 monkeys / group) and has revealed no evidence of harm to the foetuses due to adalimumab. Carcinogenicity studies, and standard assessment of fertility and postnatal toxicity, were not performed with adalimumab due to the lack of appropriate models for an antibody with limited cross-reactivity to rodent TNF and the development of neutralizing antibodies in rodents.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Citric acid monohydrate
Sodium citrate
Sodium dihydrogen phosphate dihydrate
Disodium phosphate dihydrate
Sodium chloride
Polysorbate 80
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
6.4 Special precautions for storage

Store at 2°C – 8°C (in a refrigerator). Keep the container in the outer carton. Do not freeze.

6.5 Nature and contents of container

Humira 40 mg solution for injection in single-use pre-filled syringe (type I glass) for patient use:

Packs of:
- 1 pre-filled syringe (0.8 ml sterile solution) with 1 alcohol pad in a blister.
- 2 pre-filled syringes (0.8 ml sterile solution), each with 1 alcohol pad, in a blister.
- 4 pre-filled syringes (0.8 ml sterile solution), each with 1 alcohol pad, in a blister.
- 6 pre-filled syringes (0.8 ml sterile solution), each with 1 alcohol pad, in a blister.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Abbott Laboratories Ltd.
Queenborough
Kent ME11 5EL
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
1. **NAME OF THE MEDICINAL PRODUCT**

Humira 40 mg solution for injection in pre-filled syringe with needleguard

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each 0.8 ml single dose pre-filled syringe contains 40 mg of adalimumab.

Adalimumab is a recombinant human monoclonal antibody expressed in Chinese Hamster Ovary cells.

For excipients, see 6.1.

3. **PHARMACEUTICAL FORM**

Solution for injection in pre-filled syringe with needleguard

4. **CLINICAL PARTICULARS**

4.1 Therapeutic indications

Humira is indicated 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.

To ensure maximum efficacy, Humira is given in combination with methotrexate. Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

4.2 Posology and method of administration

Humira treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis. Patients treated with Humira should be given the special alert card.

After proper training in injection technique, patients may self-inject with Humira if their physician determines that it is appropriate and with medical follow-up as necessary.

**Adults**

The recommended dose of Humira for adult patients with rheumatoid arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection. Methotrexate should be continued during treatment with Humira.

Glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, or analgesics can be continued during treatment with Humira. Regarding combination with disease modifying anti-rheumatic drugs other than methotrexate see 4.4 and 5.1.

In monotherapy, some patients who experience decrease in their response to Humira may benefit from an increase in dose intensity to 40 mg adalimumab every week.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

**Elderly patients**
No dose adjustment is required.

**Children and adolescents**

Humira has not been studied in this patient population. Therefore, use of Humira cannot be recommended in patients aged below 18 years until further data become available.

**Impaired renal and/or hepatic function**

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

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Active tuberculosis or other severe infections such as sepsis, and opportunistic infections (see 4.4).

Moderate to severe heart failure (NYHA class III/IV) (see 4.4).

### 4.4 Special warnings and special precautions for use

**Infections**

Patients must be monitored closely for infections, including tuberculosis, before, during and after treatment with Humira. Because the elimination of adalimumab may take up to five months, monitoring should be continued throughout this period.

Treatment with Humira should not be initiated in patients with active infections including chronic or localized infections until infections are controlled.

Patients who develop a new infection while undergoing treatment with Humira should be monitored closely. Administration of Humira should be discontinued if a patient develops a new serious infection until infections are controlled. Physicians should exercise caution when considering the use of Humira in patients with a history of recurring infection or with underlying conditions which may predispose patients to infections.

Serious infections, sepsis, and opportunistic infections, including fatalities, have been reported with Humira. Tuberculosis has been observed in patients treated with Humira. All patients recovered after standard antimicrobial therapy. No deaths due to tuberculosis occurred during the clinical trials.

Before initiation of therapy with Humira, all patients must be evaluated for both active or inactive (latent) tuberculosis infection. This evaluation should include a detailed medical history with a personal history of tuberculosis or possible previous exposure to patients with active tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e. tuberculin skin test and chest x-ray, should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the patient’s alert card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, Humira therapy must not be initiated (see 4.3).

If latent tuberculosis is diagnosed, appropriate anti-tuberculosis prophylaxis in accordance with local recommendations must be initiated before starting treatment with Humira. In this situation, the benefit/risk balance of therapy with Humira should be very carefully considered.
Patients should be instructed to seek medical advice if signs/symptoms (eg, persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur during or after therapy with Humira.

Neurological events

TNF-antagonists including Humira have been associated in rare cases with exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease. Prescribers should exercise caution in considering the use of Humira in patients with pre-existing or recent-onset central nervous system demyelinating disorders.

Allergic reactions

Serious allergic adverse reactions have not been reported with subcutaneous administration of Humira during clinical trials. Non-serious allergic reactions associated with Humira were uncommon during clinical trials. If an anaphylactic reaction or other serious allergic reaction occurs, administration of Humira should be discontinued immediately and appropriate therapy initiated.

Immunosuppression

In a study of 64 patients with rheumatoid arthritis that were treated with Humira, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T-and B cells and NK-cells, monocyte/macrophages, and neutrophils. It is not known whether exposure to adalimumab can increase the risk of developing malignancies and lymphoproliferative disorders.

Vaccinations

Sixty-one patients with rheumatoid arthritis were given pneumococcal vaccinations against a background of Humira and methotrexate therapy. Most patients receiving Humira were able to mount effective B-cell immune responses to pneumococcal polysaccharide vaccine. Since no data are available, concurrent administration of live vaccines and Humira is not recommended.

Congestive heart failure

In a clinical trial with another TNF antagonist worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Humira should be used with caution in patients with mild heart failure (NYHA class I/II). Humira is contraindicated in moderate or severe heart failure (see 4.3). Treatment with Humira must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Autoimmune processes

Treatment with Humira may result in the formation of autoimmune antibodies. The impact of long-term treatment with Humira on the development of autoimmune diseases is unknown.

Concurrent administration of TNF-alpha inhibitor and anakinra

Concurrent administration of etanercept (another agent that inhibits TNFα) and anakinra (a recombinant, non-glycosylated form of the human interleukin-1 receptor antagonist) has been associated with an increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared to these medicinal products alone. The safety and efficacy of anakinra used in combination with adalimumab has not been established. Therefore, combination of adalimumab and anakinra is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction
Humira has been studied both in rheumatoid arthritis patients taking Humira as monotherapy and those taking concomitant methotrexate. Antibody formation was low (< 1%) when Humira was given together with methotrexate in comparison with use as monotherapy. Administration of Humira without methotrexate resulted in increased formation of antibodies and increased clearance of adalimumab (see 5.1).

There is no experience with the efficacy and safety in patients previously treated with other TNF-antagonists.

4.6 Pregnancy and lactation

For adalimumab, there is no experience in pregnant women.

In a developmental toxicity study conducted in monkeys, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. Preclinical data on postnatal toxicity and fertility effects of adalimumab are not available (see 5.3).

Due to its inhibition of TNFα, adalimumab administered during pregnancy could affect normal immune responses in the newborn. Administration of adalimumab is not recommended during pregnancy. Women of childbearing potential are strongly recommended to use adequate contraception to prevent pregnancy and continue its use for at least five months after the last Humira treatment.

Use during lactation

It is not known whether adalimumab is excreted in human milk or absorbed systemically after ingestion.

However, because human immunoglobulins are excreted in milk, women must not breast-feed for at least five months after the last Humira treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Humira was studied in 2334 patients in placebo-controlled trials and in long term follow-up studies, including 2073 patients exposed for six months and 1497 patients exposed for greater than one year. The data in the table is based on the adequate and well-controlled studies I, II, III and IV (see 5.1) involving 1380 patients receiving adalimumab during the placebo-controlled period by randomised treatment. The population had a mean age of 54.5 years, 77% were female, 91% were Caucasian and had moderate to severely active rheumatoid arthritis. Most patients received 40 mg Humira every other week.

The proportion of patients who discontinued treatment due to adverse events during the double-blind, placebo controlled portion of Studies I, II, III and IV was 6.6% for patients taking Humira and 4.2% for placebo-treated patients.

Adverse events at least possibly causally-related to adalimumab, both clinical and laboratory, are displayed by system organ class and frequency (very common > 1/10; common > 1/100 ≤ 1/10; uncommon > 1/1000 ≤ 1/100) in Table 1 below.

<p>| Table 1 |
| Undesirable Effects in Clinical Studies |</p>
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<th>Body system</th>
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<td>Skin benign neoplasm</td>
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<tr>
<td>Haemic and Lymphatic system</td>
<td></td>
<td>Decreased haemoglobin, granulocytopenia, coagulation time increased, antinuclear antibody present</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>, leukopenia, lymphadenopathy, lymphocytosis, platelet count decreased, purpura</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Metabolic and Nutritional</td>
<td>Common</td>
<td>Hyperlipidaemia</td>
</tr>
<tr>
<td>Disorders</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypercholesterolaemia, alkaline phosphatase increased, BUN increased, hyperuricaemia, peripheral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>oedema, weight gain, creatinine phosphokinase increased, healing abnormal, hypokalaemia, lactic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dehydrogenase increased</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Uncommon</td>
<td>Depression, somnolence, insomnia, agitation</td>
</tr>
<tr>
<td>Nervous System</td>
<td>Common</td>
<td>Headache, dizziness</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paresthesia, vertigo, hypeaesthesia, neuralgia, tremor</td>
</tr>
<tr>
<td>Special senses</td>
<td>Uncommon</td>
<td>Conunctivitis, eye disorder*, otitis media, taste perversion, abnormal vision, blurred vision, dry</td>
</tr>
<tr>
<td></td>
<td></td>
<td>eye, ear disorder*, eye pain</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td>Uncommon</td>
<td>Hypertension, vasodilatation, chest pain, migraine</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>Uncommon</td>
<td>Ecchymosis</td>
</tr>
<tr>
<td>Respiratory System</td>
<td>Common</td>
<td>Upper respiratory infection, rhinitis, sinusitis, bronchitis, cough increased, pneumonia</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Pharyngitis, dyspnoea, lung disorder*, asthma</td>
</tr>
<tr>
<td>Digestive System</td>
<td>Common</td>
<td>Nausea, diarrhoea, sore throat</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Liver function test abnormal, SGPT increased, SGOT increased, mouth ulceration, oesophagitis,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>vomiting, dyspepsia, constipation, gastrointestinal pain, tooth disorder*, gastritis, gastroenteritis,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tongue disorder*, oral moniliasis, aphthous stomatitis, dysphagia, stomatitis, ulcerative stomatitis</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td>Common</td>
<td>Rash, pruritis, herpes simplex</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Skin disorder*, herpes zoster, maculopapular rash, nail disorder*, dry skin, sweating increased,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>alopecia, fungal dermatitis, urticaria, skin nodule, skin ulcer, eczema, subcutaneous haematoma</td>
</tr>
<tr>
<td>Musculo-skeletal System</td>
<td>Uncommon</td>
<td>Arthralgia, muscle cramps, myalgia, joint disorder*, synovitis, tendon disorder</td>
</tr>
<tr>
<td>Urogenital System</td>
<td>Common</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Vaginal moniliasis, haematuria, cystitis, menorrhagia, proteinuria, increased urinary frequency</td>
</tr>
<tr>
<td>Body as a whole</td>
<td>Common</td>
<td>Laboratory test abnormal, asthenia, clinical flare reaction, flu syndrome, abdominal pain, infection</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Fever, mucous membrane disorder*, pain in extremity, face oedema, back pain, cellulites, chills, sepsis, surgery</td>
<td></td>
</tr>
<tr>
<td>Injection Site Reaction</td>
<td>Very common</td>
<td>Injection site pain</td>
</tr>
<tr>
<td>Common</td>
<td>Injection site reaction, injection site haemorrhage, injection site eruption</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity, general</td>
<td>Uncommon</td>
<td>Allergic reaction</td>
</tr>
</tbody>
</table>

* (not otherwise specified).

**Injection site reactions**

In placebo-controlled trials, 20% of patients treated with Humira developed injection site reactions (erythema and/or itching, haemorrhage, pain or swelling), compared to 14% of patients receiving placebo. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

**Infections**

In placebo-controlled trials, the rate of infection was 1 per patient year in the Humira treated patients and 0.9 per patient year in the placebo-treated patients. The incidence of serious infections was 0.04 per patient year in Humira treated patients and 0.02 per patient year in placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, bronchitis and urinary tract infections. Most patients continued on Humira after the infection resolved.

**Malignancies**

Twenty-four (24) non-melanoma skin cancers and 30 other malignancies of various types were observed in 2334 rheumatoid arthritis patients treated in clinical trials with Humira for up to 53 months. The observed rates and incidences were similar to those expected for the population studied.

**Autoantibodies**

Patients had serum samples tested for autoantibodies at multiple time points. In the adequate and well-controlled trials, 12.6% of patients treated with Humira and 7.3% of placebo-treated patients that had negative baseline anti-nuclear antibody titres reported positive titres at week 24. One patient out of 2334 treated with Humira developed clinical signs suggestive of new-onset lupus-like syndrome. The patient improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms.

**4.9 Overdose**

No dose-limiting toxicity was observed during clinical trials of rheumatoid arthritis patients. The highest dose level evaluated has been multiple intravenous doses of 10 mg/kg.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Selective immunosuppressive agents. ATC code: L04AA17
Mechanism of action

Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC₅₀ of 1-2 X 10⁻¹⁰ M).

Pharmacodynamic effects

After treatment with Humira, a rapid decrease in levels of acute phase reactants of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) and serum cytokines (IL-6) was observed compared to baseline in patients with rheumatoid arthritis. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodelling responsible for cartilage destruction were also decreased after Humira administration. Patients treated with Humira usually experienced improvement in haematological signs of chronic inflammation.

Clinical trials

Humira was evaluated in over 2330 patients in all clinical trials. Some patients were treated for greater than 36 months duration. The efficacy and safety of Humira were assessed in four randomised, double-blind and well-controlled studies.

Study I evaluated 271 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, had failed therapy with at least one disease-modifying, anti-rheumatic drug and had insufficient efficacy with methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate dose remained constant at 10 to 25 mg every week. Doses of 20, 40 or 80 mg of Humira or placebo were given every other week for 24 weeks.

Study II evaluated 544 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old and had failed therapy with at least one disease-modifying, anti-rheumatic drugs. Doses of 20 or 40 mg of Humira were given by subcutaneous injection every other week with placebo on alternative weeks or every week for 26 weeks; placebo was given every week for the same duration. No other disease-modifying anti-rheumatic drugs were allowed.

Study III evaluated 619 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, had insufficient efficacy to methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate dose remained constant at 12.5 to 25 mg every week. There were three groups in this study. The first received placebo injections every week for 52 weeks. The second received 20 mg of Humira every week for 52 weeks. The third group received 40 mg of Humira every other week with placebo injections on alternate weeks.

Study IV primarily assessed safety in 636 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old. Patients were permitted to be either disease-modifying, anti-rheumatic drug-naïve or to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. These therapies include methotrexate, leflunomide, hydroxychloroquine, sulfasalazine and/or gold salts. Patients were randomised to 40 mg of Humira or placebo every other week for 24 weeks.

The primary end point in Studies I, II and III and the secondary endpoint in Study IV was the percent of patients who achieved an ACR 20 response at Week 24 or 26. Study III had additional primary endpoints at 52 weeks of retardation of disease progression (as detected by x-ray results) and changes in quality of life.

ACR response
The percent of Humira-treated patients achieving ACR 20, 50 and 70 responses was consistent across trials I, II and III. The results for the 40 mg every other week dose are summarized in Table 2.

<table>
<thead>
<tr>
<th>Response</th>
<th>Study I*</th>
<th>Study II*</th>
<th>Study III*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo/ MTXc</td>
<td>Humira/ MTXc</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>n=60</td>
<td>n=63</td>
<td>n=110</td>
</tr>
<tr>
<td>ACR 20 6 months</td>
<td>13.3%</td>
<td>65.1%</td>
<td>19.1%</td>
</tr>
<tr>
<td>ACR 20 12 months</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ACR 50 6 months</td>
<td>6.7%</td>
<td>52.4%</td>
<td>8.2%</td>
</tr>
<tr>
<td>ACR 50 12 months</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ACR 70 6 months</td>
<td>3.3%</td>
<td>23.8%</td>
<td>1.8%</td>
</tr>
<tr>
<td>ACR 70 12 months</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Study I at 24 weeks, Study II at 26 weeks, and Study III at 24 and 52 weeks

b 40 mg Humira administered every other week

c MTX = methotrexate

*p<0.01, Humira versus placebo

In Studies I-IV, all individual components of the ACR response criteria (number of tender and swollen joints, physician and patient assessment of disease activity and pain, disability index (HAQ) scores and CRP (mg/dl) values) improved at 24 or 26 weeks compared to placebo. In Study III, these improvements were maintained throughout 52 weeks.

In Study IV, the ACR 20 response of patients treated with Humira plus standard of care was statistically significantly better than patients treated with placebo plus standard of care (p<0.001).

In all four studies, Humira-treated patients achieved statistically significant ACR 20 and 50 responses compared to placebo as early as one to two weeks after initiation of treatment.

Quality of life and physical function

Health-related quality of life and physical function was assessed using the disability index of the Health Assessment Questionnaire (HAQ) in all four adequate and well-controlled trials, which was a pre-specified primary endpoint at Week 52 in Study III. All doses/schedules of Humira in all four studies showed statistically significantly greater improvement in the disability index of the HAQ from baseline to Month 6 compared to placebo and in Study III the same was seen at Week 52. Results from the Short Form Health Survey (SF 36) for all doses/schedules of Humira in all four studies support these findings, with statistically significant physical component summary (PCS) scores, as well as statistically significant pain and vitality domain scores for the 40 mg every other week dose. A statistically significant decrease in fatigue as measured by functional assessment of chronic illness therapy (FACIT) scores was seen in all three studies in which it was assessed (Studies I, III, IV).

Immunogenicity

Patients in Studies I, II and III were tested at multiple timepoints for antibodies to adalimumab during the 6 to 12 month period. In the pivotal trials, anti-adalimumab antibodies were identified in 58/1053 (5.5%) patients treated with adalimumab, compared to 2/370 (0.5%) on placebo. In patients not given concomitant methotrexate, the incidence was 12.4%, compared to 0.6% when adalimumab was used as add-on to methotrexate.

Because immunogenicity analyses are product-specific, comparison of antibody rates with those from other products is not appropriate.
5.2 Pharmacokinetic properties

After subcutaneous administration of a single 40 mg dose, absorption and distribution of adalimumab was slow, with peak serum concentrations being reached about 5 days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. After single intravenous doses ranging from 0.25 to 10 mg/kg, concentrations were dose proportional. After doses of 0.5 mg/kg (~40 mg), clearances ranged from 11 to 15 ml/hour, the distribution volume (Vss) ranged from 5 to 6 litres and the mean terminal phase half-life was approximately two weeks. Adalimumab concentrations in the synovial fluid from several rheumatoid arthritis patients ranged from 31-96% of those in serum.

Following subcutaneous administration of 40 mg of Humira every other week the mean steady-state trough concentrations were approximately 5 μg/ml (without concomitant methotrexate) and 8 to 9 μg/ml (with concomitant methotrexate), respectively. The serum adalimumab trough levels at steady-state increased roughly proportionally with dose following 20, 40 and 80 mg every other week and every week subcutaneous dosing.

Population pharmacokinetic analyses with data from over 1300 patients revealed a trend toward higher apparent clearance of adalimumab with increasing body weight. After adjustment for weight differences, gender and age appeared to have a minimal effect on adalimumab clearance. The serum levels of free adalimumab (not bound to anti-adalimumab antibodies, AAA) were observed to be lower in patients with measurable AAA. Humira has not been studied in children or in patients with hepatic or renal impairment.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on studies of single dose toxicity, repeated dose toxicity, and genotoxicity.

An embryo-foetal developmental toxicity/perinatal developmental study has been performed in cynomologous monkeys at 0, 30 and 100 mg/kg (9-17 monkeys/group) and has revealed no evidence of harm to the foetuses due to adalimumab. Carcinogenicity studies, and standard assessment of fertility and postnatal toxicity, were not performed with adalimumab due to the lack of appropriate models for an antibody with limited cross-reactivity to rodent TNF and the development of neutralizing antibodies in rodents.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Citric acid monohydrate
Sodium citrate
Sodium dihydrogen phosphate dihydrate
Disodium phosphate dihydrate
Sodium chloride
Polysorbate 80
Sodium hydroxide
Water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
6.3 Shelf life

18 months

6.4 Special precautions for storage

Store at 2°C – 8°C (in a refrigerator). Keep the container in the outer carton. Do not freeze.

6.5 Nature and contents of container

Humira 40 mg solution for injection in single-use pre-filled syringe (type I glass) with needleguard for hospital and caregiver use:

Packs of:
1 pre-filled syringe with needleguard (0.8 ml sterile solution) in a blister, and 1 alcohol pad.

6.6 Instructions for use and handling and disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Abbott Laboratories Ltd.
Queenborough
Kent ME11 5EL
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT
ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION
A MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Abbott Bioresearch Center
100 Research Drive
Worcester
MA 01605
USA

Name and address of the manufacturer responsible for batch release

Abbott GmbH & Co. KG
Max-Planck-Ring 2
D-65205 Wiesbaden
Germany

B CONDITIONS OF THE MARKETING AUTHORISATION

- CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2).

- OTHER CONDITIONS

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outer carton</td>
</tr>
</tbody>
</table>

### 1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection  
Adalimumab

### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 0.8 ml vial contains 40 mg adalimumab

### 3. LIST OF EXCIPIENTS

Excipients: mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections

### 4. PHARMACEUTICAL FORM AND CONTENTS

1 vial containing 40 mg adalimumab  
1 sterile injection syringe with fixed needle  
2 alcohol pads

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.  
Read the package leaflet before use.

### 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY


### 8. EXPIRY DATE

EXP {MM/YYYY}
9. SPECIAL STORAGE CONDITIONS

Store at 2°C – 8°C (in a refrigerator) and store the vial in the outer carton. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Abbott Laboratories Ltd
Queenborough
Kent ME11 5EL
United Kingdom

12. MARKETING AUTHOURISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER’S BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Humira 40 mg solution for injection
Adalimumab

Store at 2°C – 8°C.

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Abbott Laboratories Ltd.

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

LOT:
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial label

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Humira 40 mg injection
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/ YYYY}

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 mg/0.8 ml
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 0.8 ml pre-filled syringe contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled syringe containing 40 mg adalimumab
1 alcohol pad

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY


8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS
Store at 2°C – 8°C (in a refrigerator) and store the syringe in the outer carton.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Queenborough
Kent ME11 5EL
United Kingdom

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EU/0/00/000/000

13. MANUFACTURER’S BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING**

Outer carton

1. **NAME OF THE MEDICINAL PRODUCT**

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

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   One 0.8 ml pre-filled syringe contains 40 mg adalimumab

3. **LIST OF EXCIPIENTS**

   Excipients: mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate
   dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and
   water for injections

4. **PHARMACEUTICAL FORM AND CONTENTS**

   2 pre-filled syringes, each containing 40 mg adalimumab
   2 alcohol pads

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   Subcutaneous use
   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

   EXP {MM/YYYY}

9. **SPECIAL STORAGE CONDITIONS**
Store at 2°C – 8°C (in a refrigerator) and store the syringe in the outer carton. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Abbott Laboratories Ltd
Queenborough
Kent ME11 5EL
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER’S BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 0.8 ml pre-filled syringe contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

4 pre-filled syringes, each containing 40 mg adalimumab
4 alcohol pads

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS
Store at 2°C – 8°C (in a refrigerator) and store the syringe in the outer carton. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Abbott Laboratories Ltd
Queenborough
Kent ME11 5EL
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER’S BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE
<table>
<thead>
<tr>
<th><strong>PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outer carton</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Humira 40 mg solution for injection in pre-filled syringe</td>
</tr>
<tr>
<td>Adalimumab</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>2. STATEMENT OF ACTIVE SUBSTANCE(S)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>One 0.8 ml pre-filled syringe contains 40 mg adalimumab</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>3. LIST OF EXCIPIENTS</strong></th>
</tr>
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<tbody>
<tr>
<td>Excipients: mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th><strong>4. PHARMACEUTICAL FORM AND CONTENTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>6 pre-filled syringes, each containing 40 mg adalimumab</td>
</tr>
<tr>
<td>6 alcohol pads</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>5. METHOD AND ROUTE(S) OF ADMINISTRATION</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous use</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</strong></th>
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</thead>
<tbody>
<tr>
<td>Keep out of the reach and sight of children.</td>
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<tr>
<th><strong>7. OTHER SPECIAL WARNING(S), IF NECESSARY</strong></th>
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<tr>
<th><strong>8. EXPIRY DATE</strong></th>
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<tbody>
<tr>
<td>EXP {MM/YYYY}</td>
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</tbody>
</table>

| **9. SPECIAL STORAGE CONDITIONS** |
Store at 2°C – 8°C (in a refrigerator) and store the syringe in the outer carton.
Do not freeze.

<table>
<thead>
<tr>
<th>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</th>
</tr>
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</table>

<table>
<thead>
<tr>
<th>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott Laboratories Ltd</td>
</tr>
<tr>
<td>Queenborough</td>
</tr>
<tr>
<td>Kent ME11 5EL</td>
</tr>
<tr>
<td>United Kingdom</td>
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<tr>
<th>12. MARKETING AUTHORISATION NUMBER(S)</th>
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<tbody>
<tr>
<td>EU/0/00/000/000</td>
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</table>

<table>
<thead>
<tr>
<th>13. MANUFACTURER’S BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOT:</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>14. GENERAL CLASSIFICATION FOR SUPPLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicinal product subject to medical prescription.</td>
</tr>
</tbody>
</table>

| 15. INSTRUCTIONS ON USE |
### Minimum Particulars to Appear on Blisters or Strips

#### Tray backing text

<table>
<thead>
<tr>
<th>1. Name of the Medicinal Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humira 40 mg solution for injection in pre-filled syringe</td>
</tr>
<tr>
<td>Adalimumab</td>
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<tr>
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</table>

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<tr>
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<tr>
<td>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Syringe label</td>
</tr>
</tbody>
</table>

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Humira 40 mg injection

Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

LOT:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 mg/0.8 ml
PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 0.8 ml pre-filled syringe with needleguard contains 40 mg adalimumab

3. LIST OF EXCIPIENTS

Excipients: mannitol, citric acid monohydrate, sodium citrate, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80, sodium hydroxide and water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

1 pre-filled syringe containing 40 mg adalimumab
1 alcohol pad

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS
Store at 2°C – 8°C (in a refrigerator) and store the syringe in the outer carton.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Abbott Laboratories Ltd
Queenborough
Kent ME11 5EL
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER’S BATCH NUMBER

LOT:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE
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1. **NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

   Humira 40 mg injection  
   Subcutaneous use

2. **METHOD OF ADMINISTRATION**

3. **EXPIRY DATE**

   EXP {MM/YYYY}

4. **BATCH NUMBER**

   LOT:

5. **CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

   40 mg/0.8 ml
Humira

Mark your calendar with the stickers provided to remind you of the date for your next dose.
**Humira Patient Alert Card**

This alert card contains important safety information that you need to be aware of before you are given Humira and during treatment with Humira.

- Show this card to any doctor involved in your treatment.

**Infections**

Humira increases the risk of getting infections. Infections may progress more rapidly and be more severe. This includes tuberculosis.

*Prior to Humira treatment:*
- You should not be treated with Humira if you have a severe infection.
- You should be screened for tuberculosis. 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. Please record the dates of the last screening for tuberculosis below:
  - Tuberculin test: _______________
  - Chest x-ray: _______________

*During Humira treatment:*
- If you develop symptoms suggestive of infections, such as fever, persistent cough, weight loss, or listlessness, seek medical attention immediately.

**Heart Failure**

*Prior to Humira treatment:*
- Humira should not be used if you have moderate to severe heart failure.

*During Humira treatment:*
- If you develop symptoms of heart failure (shortness of breath or swelling of the feet) seek medical attention immediately.

**Dates of Humira treatment:**
- 1st injection: _______________________
- Following injections: _______________________
- _______________________
- _______________________
- _______________________

- See the Humira package leaflet for more information.
- Please make sure you also have a list of all your other medicines with you at any visit to a health care professional.

Patient’s Name: _______________________
Doctor’s Name: _______________________
Doctor’s Phone: _______________________

- Keep this card with you for 5 months after the last Humira dose, since side effects may occur a long time after your last dose of Humira.
B. PACKAGE LEAFLET
PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.

- 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 together with the package leaflet.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:
1. What Humira is and what it is used for
2. Before you use Humira
3. How to use Humira
4. Possible side effects
5 Storing Humira
6. Further information

Humira 40 mg solution for injection

Adalimumab

- The active substance is adalimumab
- Each vial contains 40 mg 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.

Marketing Authorisation Holder:

Abbott Laboratories Ltd
Queenborough
Kent ME11 5EL
United Kingdom

Manufacturer:

Abbott GmbH & Co. KG
Max-Planck-Ring 2
D - 65205Wiesbaden
Germany

1. WHAT HUMIRA IS AND WHAT IT IS USED FOR

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

Each pack contains 1 vial with an empty sterile injection syringe and 2 alcohol pads.

Humira is intended for treatment of rheumatoid arthritis. It is a medicine that decreases the inflammation process of the disease. 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 collects in your joints and is thought to make your rheumatoid arthritis worse.

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.

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

2. BEFORE YOU USE HUMIRA

Do not use Humira:

- If you are hypersensitive (allergic) to adalimumab or any of the other ingredients of Humira.
- If you have a severe infection, including active tuberculosis (see “Take special care with Humira”). 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 “Take special care with Humira”).

Take special care with Humira:

- If you experience allergic reactions 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. It is important to tell your doctor if you get symptoms such as fever, wounds, feeling tired or dental problems.
- 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 history, a chest x-ray and a tuberculin test. The conduct 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. 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 have a history of recurrent infections or other conditions that increase the risk of infections.
- If you have multiple sclerosis, your doctor will decide if you should receive Humira.
- Some vaccines should not be given while receiving Humira. Please check with your doctor before you receive any vaccines.
- 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.
Pregnancy

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.

Breast-feeding

It is not known whether adalimumab passes into breast milk.

If you are a nursing mother, you should stop nursing during Humira treatment and for at least 5 months after the last Humira treatment.

Using other medicines

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

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.

3. HOW TO USE HUMIRA

Always take Humira exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Humira is injected under the skin (subcutaneous use). The usual dose for adults with rheumatoid arthritis is 40 mg adalimumab given every other week as a single dose. You should continue to inject Humira for as long as instructed by your doctor.

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

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

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 vial of Humira for injection
  - One syringe with fixed needle
  - Two alcohol pads
Look at the expiry date on the vial. 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

Preparing the Humira dose for injection

- Do NOT shake the vial.
- Remove the plastic cap from the Humira vial. Do NOT remove the grey stopper or aluminium ring around the top of the vial.
- Use a new alcohol pad to clean the grey stopper on the vial. After cleaning, do not touch the stopper with your hands.
- Remove cap from needle syringe, being careful not to touch needle or let it touch any surface.
- Make sure that the plunger is fully inserted into the syringe. With the vial upright on a flat surface, such as a table, insert the needle straight through the centre ring of the grey stopper. If the needle is correctly lined up, you should feel a slight resistance and then a “pop” as the needle goes through the centre of the stopper. Look for the needle tip inside the stopper window. If the needle is not correctly lined up with the centre of the stopper, you will feel constant resistance as it goes through the stopper and no “pop.” The needle may then enter at an angle and bend, break or prevent proper removal of the vial contents. If this happens, do not use the syringe or vial.
• With the needle still in the vial, turn the vial upside down at eye level. Check that the needle is below the surface of the solution. Slowly pull the plunger back to draw solution into the syringe.
• With the needle still inserted in the vial, check the syringe for air bubbles. Gently tap the syringe to make any bubbles rise to the top of the syringe near the needle. Slowly press the plunger to push the bubbles out of the syringe and into the vial. When you do this, if you accidentally push some solution back into the vial, pull slowly back in the plunger to draw the entire contents of the vial back into the syringe.
• Pull the needle completely out of the vial. Again, do NOT touch the needle or let it touch any surface.

Injecting Humira
• 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 of children

If you use more Humira than you should:
If you accidentally inject Humira more frequently than told to by your doctor, you should call your doctor. Always take the outer carton or the vial of medicine with you, even if it is empty.

If you forget to take 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.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Humira can have side effects. Most side effects are mild to moderate. However, some may be serious and require treatment. Side effects may occur at least up to 5 months after the last treatment.

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, malaise, wounds, dental problems, burning on urination
- Feeling weak or tired
- Coughing
- Tingling
- Numbness
- Double vision
- Arm or leg weakness

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

Very common (> 1/10 patients): Injection site reactions (inflammation at the injection site)

Common (> 1/100 and < 1/10 patients): Infection, e.g. urinary tract infection, respiratory tract infections (cold, rhinitis, sinusitis, bronchitis, pneumonia), headache, rash, dizziness, nausea, diarrhoea, sore throat, itching, cold blisters, abdominal pain, anaemia.

Uncommon (> 1/1000 and < 1/100 patients): Tuberculosis, other serious infections (e.g. sepsis), allergic reactions, nerve disorders (e.g. multiple sclerosis), low blood cell counts including anaemia, swelling of the feet, weight gain, depression, difficulty sleeping, agitation, eye disorders, ear disorders, taste disturbances, vision disturbances, high blood pressure, asthma, abnormal liver function, abdominal symptoms (e.g. vomiting, indigestion, constipation), mouth disorder, skin disorders (e.g. eczema), hair loss, urinary disturbances (e.g. blood or protein in urine, increased urinary frequency).

Your doctor may also do tests to examine your liver function and/or blood values.

If any side effects worry you, if you have any unusual effects or you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING HUMIRA

Keep out of the reach and sight of children.

Store at 2°C – 8°C (in a refrigerator) and store the vial in the outer carton. Do not freeze.

Do not use after the expiry date stated on the label/blister/carton.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien Luxembourg/Luxemburg
(Latina)
Tel: + 39 06 928921

This leaflet was last approved on {date}
PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.
- 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 together with the package leaflet.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:
1. What Humira is and what it is used for
2. Before you use Humira
3. How to use Humira
4. Possible side effects
5. Storing Humira
6. Further information

Humira 40 mg solution for injection in pre-filled syringe

Adalimumab

- The active substance is adalimumab.
- Each pre-filled syringe contains 40 mg 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.

Marketing Authorisation Holder:
Abbott Laboratories Ltd
Queenborough
Kent ME11 5EL
United Kingdom

Manufacturer:
Abbott GmbH & Co. KG
Max-Planck-Ring 2
D - 65205 Wiesbaden
Germany

1. WHAT HUMIRA IS AND WHAT IT IS USED FOR

Humira 40 mg solution for injection is supplied as a sterile solution of 40 mg adalimumab dissolved in 0.8 ml solution in the following presentation:

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 intended for treatment of rheumatoid arthritis. It is a medicine that decreases the inflammation process of the disease. 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 collects in your joints and is thought to make your rheumatoid arthritis worse.

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.

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

2. BEFORE YOU USE HUMIRA

Do not use Humira:

- If you are hypersensitive (allergic) to adalimumab or any of the other ingredients of Humira.
- If you have a severe infection, including active tuberculosis (see “Take special care with Humira”). 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 “Take special care with Humira”).

Take special care with Humira:

- If you experience allergic reactions 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. It is important to tell your doctor if you get symptoms such as fever, wounds, feeling tired or dental problems.
- 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 history, a chest x-ray and a tuberculin test. The conduct 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. 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 have a history of recurrent infections or other conditions that increase the risk of infections.
- If you have multiple sclerosis, your doctor will decide if you should receive Humira.
- Some vaccines should not be given while receiving Humira. Please check with your doctor before you receive any vaccines.
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.

Pregnancy

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.

Breast-feeding

It is not known whether adalimumab passes into breast milk.

If you are a nursing mother, you should stop nursing during Humira treatment and for at least 5 months after the last Humira treatment.

Using other medicines

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

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.

3. HOW TO USE HUMIRA

Always take Humira exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Humira is injected under the skin (subcutaneous use). The usual dose for adults with rheumatoid arthritis is 40 mg adalimumab given every other week as a single dose. You should continue to inject Humira for as long as instructed by your doctor.

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

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

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
  o One pre-filled syringe of Humira for injection
  o 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.
  o Do not inject in an area where the skin is reddened, bruised, or hard. This may mean there is an infection.
  o Wipe the injection site with the enclosed alcohol pad, using a circular motion.
  o Do not touch the area again before injecting.

3) Injecting Humira
• 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 of children

If you use more Humira than you should:

If you accidentally inject Humira more frequently than told to by your doctor, you should call your doctor. Always take the outer carton of medicine with you, even if it is empty.

If you forget to take 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.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Humira can have side effects. Most side effects are mild to moderate. However, some may be serious and require treatment. Side effects may occur at least up to 5 months after the last treatment.

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, malaise, wounds, dental problems, burning on urination
• Feeling weak or tired
The symptoms described above can be signs of the below listed side effects, which have been observed with Humira:

Very common (> 1/10 patients): Injection site reactions (inflammation at the injection site)

Common (> 1/100 and < 1/10 patients): Infection, e.g. urinary tract infection, respiratory tract infections (cold, rhinitis, sinusitis, bronchitis, pneumonia), headache, rash, dizziness, nausea, diarrhoea, sore throat, itching, cold blisters, abdominal pain, anaemia.

Uncommon (> 1/1000 and < 1/100 patients): Tuberculosis, other serious infections (e.g. sepsis), allergic reactions, nerve disorders (e.g. multiple sclerosis), low blood cell counts including anaemia, swelling of the feet, weight gain, depression, difficulty sleeping, agitation, eye disorders, ear disorders, taste disturbances, vision disturbances, high blood pressure, asthma, abnormal liver function, abdominal symptoms (e.g. vomiting, indigestion, constipation), mouth disorder, skin disorders (e.g. eczema), hair loss, urinary disturbances (e.g. blood or protein in urine, increased urinary frequency).

Your doctor may also do tests to examine your liver function and/or blood values.

If any side effects worry you, if you have any unusual effects, or if you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING HUMIRA

Keep out of the reach and sight of children.

Store at 2°C – 8°C (in a refrigerator) and store the pre-filled syringe in the outer carton. Do not freeze.

Do not use after the expiry date stated on the label/blister/carton.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.
Read all of this leaflet carefully before you start using this medicine.
- 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 the package leaflet.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:
1. What Humira is and what it is used for
2. Before you use Humira
3. How to use Humira
4. Possible side effects
5. Storing Humira
6. Further information

Humira 40 mg solution for injection in pre-filled syringe with needleguard

Adalimumab

- The active substance is adalimumab.
- Each pre-filled syringe contains 40 mg 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.

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1. WHAT HUMIRA IS AND WHAT IT IS USED FOR
Humira 40 mg solution for injection is supplied as a sterile solution of 40 mg adalimumab dissolved in 0.8 ml solution.

Each pack contains 1 pre-filled syringe with needleguard for hospital administration or administration by a caregiver, with 1 alcohol pad.

Humira is intended for treatment of rheumatoid arthritis. It is a medicine that decreases the inflammation process of the disease. 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 collects in your joints and is thought to make your rheumatoid arthritis worse.

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.

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

2. BEFORE YOU USE HUMIRA

Do not use Humira:

- If you are hypersensitive (allergic) to adalimumab or any of the other ingredients of Humira.
- If you have a severe infection, including active tuberculosis (see “Take special care with Humira”). 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 “Take special care with Humira”).

Take special care with Humira:

- If you experience allergic reactions 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. It is important to tell your doctor if you get symptoms such as fever, wounds, feeling tired or dental problems.
- 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 history, a chest x-ray and a tuberculin test. The conduct 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. 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 have a history of recurrent infections or other conditions that increase the risk of infections.
- If you have multiple sclerosis, your doctor will decide if you should receive Humira.
- Some vaccines should not be given while receiving Humira. Please check with your doctor before you receive any vaccines.
- 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.

**Pregnancy**

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.

**Breast-feeding**

It is not known whether adalimumab passes into breast milk.

If you are a nursing mother, advise you should stop nursing during Humira treatment, and for at least 5 months after the last Humira treatment.

**Using other medicines**

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

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.

### 3. **HOW TO USE HUMIRA**

Always take Humira exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Humira is injected under the skin (subcutaneous use). The usual dose for adults with rheumatoid arthritis is 40 mg adalimumab given every other week as a single dose. Your should continue to inject Humira for as long as instructed by your doctor.

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

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

**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

- 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
• Hold the syringe in one hand and with the other hand slide the outer protective shield over the exposed needle until it locks in place
• 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 of children

If you use more Humira than you should:

If you accidentally inject Humira more frequently than told to by your doctor, you should call your doctor. Always take the outer carton of medicine with you, even if it is empty.

If you forget to take 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.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Humira can have side effects. Most side effects are mild to moderate. However, some may be serious and require treatment. Side effects may occur at least up to 5 months after the last treatment.

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, malaise, wounds, dental problems, burning on urination
• Feeling weak or tired
• Coughing
• Tingling
• Numbness
• Double vision
• Arm or leg weakness

The symptoms described above can be signs of the below listed side effects, which have been observed with Humira:
Very common (> 1/10 patients): Injection site reactions (inflammation at the injection site)

Common (> 1/100 and < 1/10 patients): Infection, e.g. urinary tract infection, respiratory tract infections (cold, rhinitis, sinusitis, bronchitis, pneumonia), headache, rash, dizziness, nausea, diarrhoea, sore throat, itching, cold blisters, abdominal pain, anemia.

Uncommon (> 1/1000 and < 1/100 patients): Tuberculosis, other serious infections (e.g. sepsis), allergic reactions, nerve disorders (e.g. multiple sclerosis), low blood cell counts including anaemia, swelling of the fee, weight gain, depression, difficulty sleeping, agitation, eye disorders, ear disorders, taste disturbances, vision disturbances, high blood pressure, asthma, abnormal liver function, abdominal symptoms (e.g. vomiting, indigestion, constipation), mouth disorder, skin disorders (e.g. eczema), hair loss, urinary disturbances (e.g. blood or protein in urine, increased urinary frequency).

Your doctor may also do tests to examine your liver function and/or blood values.

If any side effects worry you, if you have any unusual effects or you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING HUMIRA

Keep out of the reach and sight of children.

Store at 2°C – 8°C (in a refrigerator) and store the pre-filled syringe in the outer carton. Do not freeze.

Do not use after the expiry date stated on the label/blister/carton.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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