For the use of rheumatologists, gastroenterologists, orthopaedicians, dermatologists, clinical immunologists and internal physicians and pediatricians experienced in the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis and plaque psoriasis patients only

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Adfrar
(**Adalimumab Injection 20/40mg)**
(For Subcutaneous use)

WARNING: SERIOUS INFECTIONS AND MALIGNANCY
SERIOUS INFECTIONS:
• With usage of adalimumab there is increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens.
• Discontinue adalimumab if a patient develops a serious infection or sepsis during treatment.
• Perform test for latent TB; if positive, start treatment for TB prior to starting adalimumab.
• Monitor all patients for active TB during treatment, even if initial latent TB test is negative.
MALIGNANCY:
• Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers including adalimumab.
• Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in adolescent and young adults with inflammatory bowel disease treated with TNF blockers including adalimumab.

COMPOSITION

Each single-dose, 1 mL prefilled glass syringe (PFS) providing 20 mg (0.4 mL)/40mg (0.8 mL) of Adfrar (adalimumab) for subcutaneous administration contains:

Table 1 –Composition

Excipient	Ouantity For each 20 mg in PFS	Quantity For each 40 mg in PFS
Monobasic sodium phosphate dihydrate I.P.	0.34mg	0.69 mg
Dibasic sodium phosphate dihydrate Ph.Eur.	0.61mg	1.22mg
Sodium Citrate I.P.	0.12mg	0.24mg
Citric acid monohydrate I.P.	0.52mg	1.04mg
Sodium Chloride I.P.	2.47mg	4.93mg
Mannitol I.P.	4.8mg	9.6mg
Polysorbate-80 I.P.	0.4mg	0.8mg
Water For Injection I.P.	QS to 0.4ml	QS to 0.8ml
pH	Target 5.2	Target 5.2

DESCRIPTION

Adfrar (adalimumab) is a humanized monoclonal antibody developed as a Similar Biological Medicinal Product to innovator adalimumab. Adfrar (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). Adfrar (adalimumab) was developed using phage display technology resulting in an antibody with human heavy and light chain variable regions and human constant regions. Adfrar (adalimumab) is produced by recombinant DNA technology in a mammalian cell expression system. It consists 1330 amino acids and the molecular weight is approximately 148 kilodaltons.

Adfrar (adalimumab) is supplied as a sterile, preservative-free solution of adalimumab for subcutaneous administration.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Adalimumab is a fully human monoclonal antibody of the IgG1 isotype that neutralizes the biological function of TNF-α by blocking its interaction with the p55 and p75 cell surface TNF receptors.

In the Phase III trial conducted on *Biosimilar* (adalimumab), after treatment with *Biosimilar* (adalimumab), a decrease in levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) was observed compared to baseline in patients with rheumatoid arthritis.

Pharmacokinetics

As per literature, following a single 40 mg subcutaneous injection of adalimumab, C max is approximately 4.7 mcg/mL, T max is approximately 131 hours and the average absolute bioavailability is 64%. The Mean terminal half-life is approximately 14 days. Systemic clearance is approximately 12 mL/h. No pharmacokinetic data are available for renal and hepatic function impaired patients. In patients with rheumatoid arthritis (RA), there is a trend toward lower clearance with increasing age in patients 40 to older than 75 years. In children 4 to 17 years of age with juvenile idiopathic arthritis, mean steady-state trough serum adalimumab concentrations are 6.8 and 6.6 mcg/mL for children receiving adalimumab 20 or 40 mg, respectively, every other week as monotherapy. No differences in pharmacokinetics have been observed based on gender.

NON-CLINICAL TOXICOLOGY

The toxicology studies conducted on Biosimilar (adalimumab) done by the manufacturer reveal no toxic effects at the highest dose tested. Biosimilar (adalimumab) did not cause any adverse acute toxicity in Wistar Rats at 70 mg/Kg and in Swiss Albino Mice at 140 mg/kg body weight. In repeated dose studies conducted in Wistar rats, the highest dose administered (25 mg/Kg for rats) was the 'No observed adverse effect level' (NOAEL). In New Zealand White rabbits NOAEL was 13 mg/Kg which was again the highest dose administered.

In the single dose toxicity studies on adalimumab done by the manufacturer, the undiluted concentration (59.485 mg/mL) of adalimumab was used for intradermal induction, topical induction and challenge exposure. No adverse visible signs of treatment such as changes in respiratory, circulatory, autonomic and central nervous system, behavioral pattern were observed. No mortality or morbidity was reported. There were no significant changes observed in the body weight as well as body weight gain between control and treated groups.

In repeat dose toxicity studies on adalimumab done by the manufacturer, there was absence of any treatment related biologically significant changes. In skin sensitization studies on adalimumab done by the manufacturer, no adverse general systemic clinical signs attributed to treatment were observed during the course of experimentation. The mean body weight gain was similar in treated and control group animals.

Long-term animal studies of Biosimilar (adalimumab) have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

INDICATIONS AND USAGE

Rheumatoid Arthritis

Adfrar (adalimumab) is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis. Adfrar (adalimumab) can be used alone or in combination with methotrexate or other disease-modifying antirheumatic drugs (DMARDs).

Juvenile Idiopathic Arthritis

Adfrar (adalimumab) is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. Adfrar (adalimumab) can be used alone or in combination with methotrexate.

Psoriatic Arthritis

Adfrar (adalimumab) is indicated for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis. Adfrar (adalimumab) can be used alone or in combination with DMARDs.

Ankylosing Spondylitis

Adfrar (adalimumab) is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Crohn's Disease

Adfrar (adalimumab) is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Adfrar (adalimumab) is indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.

Adfrar (adalimumab) is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients of 6 or more years of age with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine or methotrexate.

Ulcerative Colitis

Adfrar (adalimumab) is indicated for inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of adalimumab has not been established in patients who have lost response to or were intolerant to TNF blockers.

Plaque psoriasis
Adfrar (adalimumab) is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. Patients should be closely monitored by regular follow-up visits.

DOSAGE AND ADMINISTRATION
Adfrar (adalimumab) is administered by subcutaneous injection.

Rheumatoid arthritis, Ankylosing Spondylitis, psoriatic arthritis
For adults, 40 mg subcutaneously every other week. Methotrexate, glucocorticoids, salicylates, non-steroidal anti-inflammatory drugs, analgesics, or other disease modifying agents may be given concomitantly. Used for moderate to severe rheumatoid arthritis, as monotherapy, or in combination with methotrexate in psoriatic arthritis (PsA) and ankylosing spondylitis (AS). In the treatment of rheumatoid arthritis, some patients not taking concomitant methotrexate may derive additional benefit from increasing the dosing frequency to 40 mg every week.

Usual Pediatric Dose for Juvenile Idiopathic Arthritis
The recommended dose in patients 2 years of age and older with polyarticular juvenile idiopathic arthritis (JIA) is based on weight as shown below. Methotrexate (MTX), glucocorticoids, NSAIDs, and/or analgesics may be continued during treatment with Biosimilar (adalimumab).

Table 2 – Dose for Juvenile idiopathic arthritis

Patients (2 years of age and older)	**Dose**
10 kg to < 15 kg	10 mg every other week
15 kg to < 30 kg	20 mg every other week
> 30 kg	40 mg every other week

Adalimumab has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 1 0 kg.

Usual adult Dose for Crohn's Disease
- Initial dose: 160 mg subcutaneously on Day 1 (given as four 40 mg or eight 20 mg injections in one day or as two 40 mg or four 20 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15)

- Maintenance dose: Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week.
Aminosalicylates and/or corticosteroids may be continued during treatment. Azathioprine, 6-mercaptopurine (6-MP), or MTX may be continued during treatment if necessary. Treatment beyond one year in Crohn’s Disease has not been established.

Usual Pediatric Dose for Crohn's Disease (6 years of age and older)
The recommended dose regimen for paediatric patients 6 years of age and older with Crohn's disease (CD) is based on bodyweight as shown below:

Table 3 – Dose in pediatric patients 6 years of age and older with Crohn's disease (CD)

Pediatric Patients	**Induction Dose**	**Maintenance Dose Starting at Week 4 (Day 29)**
17 kg to < 40 kg	• 80 mg on Day 1 (administered as two • 40 mg injections in one day); and • 40 mg two week later (on Day 15)	• 20 mg every other week
> 40 kg	• 160 mg on Day 1 (administered as four injections per day for two consecutive day); and • 80 mg two weeks later (on Day 15) (administered as two 40mg injections in one day)	• 40 mg every other week

Usual Adult Dose for Ulcerative Colitis

- Initial dose: 160 mg subcutaneously on Day 1 (given as four 40 mg or eight 20 mg injections In one day or as two 40 mg or four 20 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15)
- Maintenance dose: Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week

Aminosalicylates and/or corticosteroids may be continued during treatment. Azathioprine, 6-mercaptopurine (6-MP), or MTX may be continued during treatment if necessary. Treatment in ulcerative colitis should only be continued in patients who have shown evidence of clinical remission by eight weeks (Day 57) of therapy.

Plaque psoriasis

Recommended dose for adult patients with plaque psoriasis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. The use of adalimumab in moderate to severe chronic plaque psoriasis beyond one year has not been evaluated.

General Considerations for Administration

Adfrar (adalimumab) is intended for use under the guidance and supervision of a physician. A patient may self-inject Biosimilar (adalimumab) if a physician determines that it is appropriate, and with medical follow-up, as necessary, after proper training in subcutaneous injection technique.

The solution in the prefilled syringe should be carefully inspected visually for particulate matter and discoloration prior to subcutaneous administration. If particulates and discolorations are noted, the product should not be used.

Adfrar (adalimumab) does not contain preservatives; therefore, unused portions of drug remaining from the syringe should be discarded. The needle cover of the syringe contains dry rubber (latex), which should not be handled by persons sensitive to this substance.

Patients using the prefilled syringe should be instructed to inject the full amount in the syringe (0.8 mL), which provides 40 mg of Adfrar (adalimumab), according to the directions provided.

Patients (15kg to <30 kg) using the paediatric pre-filled syringe, or their caregivers, should be instructed to inject the full amount in the syringe (0.4mL), which provides 20 mg of adalimumab biosimilar, according to the directions provided. Injection sites should be rotated and injections should never be given into areas where the skin is tender, bruised, red or hard.

CLINICAL STUDY

A prospective, multi-centre, randomized, double-blind, two-arm, parallel group, active-control, comparative clinical study was carried out by the manufacturer to evaluate efficacy and safety of biosimilar (adalimumab) (study arm)/ innovator adalimumab (reference arm) in patients with Active Rheumatoid Arthritis on a stable dose of Methotrexate in a total of 104 subjects (84 subjects on study arm and 20 subjects in the Reference arm). Both products (adalimumab) were administered at 40 mg dose as a single subcutaneous injection every other week. Subjects were treated as per treatment allocation with either study product or Reference product till week 16 at the recommended dose in a double-blind manner. Responders were continued on study arm in an open-label phase up to week 24, while non-responders were followed up for safety for 10 weeks after the last dose (at week 26).

The primary efficacy endpoint was to determine whether study product was comparable to Reference product in efficacy as determined by ACR20 (ACR- American College of Rheumatology) clinical response at week 16 when administered with a stable dose of methotrexate. Safety assessment included monitoring of adverse events, clinical laboratory parameters, anti-drug antibodies, vital signs and 12-lead ECG. Secondary endpoints were to evaluate the other efficacy parameters up to week 24 as well as safety and tolerability of study and Reference product up to week 34.

The total number of responders at week 16 achieving clinical response as per ACR20 criteria was 76 (90.48%) in study arm and 18 (90.00%) in the Reference arm. There was no significant difference between two treatment arms in terms of number of responders ($p > 0.05$). Hence, the two treatments are considered to be clinically equivalent. 46.43% of patients achieved clinical response as per ACR50 criteria at week 16 in the study arm as against 45.00%in the Reference arm. There was no significant difference between two treatment arms in the number of responders ($p > 0.05$). Hence, the two treatments are considered to be clinically equivalent.

13.10% patients achieved clinical response as per ACR70 criteria at week 16 in the study arm as against 15.00% in the Reference arm.

There was no significant difference between the two treatment arms in the number of responders ($p > 0.05$). Hence, the two treatments are considered to be clinically equivalent. The HAQ (Health Assessment Questionnaire) is one of the most widely used comprehensive, validated, patient-oriented outcome assessment instruments.

The mean of HAQ-DI (Disability Index) score in the study arm at baseline was 15.298 and improved to 7.225 at week 16. The mean of HAQ- Dl score in the Reference arm at baseline was 14.650 and improved to 7.684 at week 16.

There was no significant difference observed between rate of reduction of HAQ-DI scores between study and Reference groups at week 16. Hence, the observed reduction in HAQ-DI scores was comparable in both treatment arms.

The DAS28 is a measure of disease activity in rheumatoid arthritis (RA). DAS stands for 'Disease Activity Score' and the number 28 refers to the 28 joints (commonly affected by RA) that are examined in the assessment.

In the study, the mean of DAS28 score in the study arm at baseline was 5.5. The mean was reduced to 3.6 at week 16. The mean of DAS28 score in the Reference arm at baseline was 5.6. It was reduced to 3.6 at week 16. There was no statistically significant difference ($p > 0.05$) observed in reduction of mean DAS28 scores between both the treatment arms.

The study data showed comparable responses for both primary and secondary efficacy endpoints in both the treatment arms. Hence, the two treatments were considered clinically equivalent.
Phase III studies were not conducted in the other approved indications. The efficacy studies of the innovator in juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), plaque psoriasis (Ps), Crohn's disease and ulcerative colitis are summarized below.

For Juvenile Idiopathic Arthritis, the safety and efficacy of innovator product was assessed in two studies in patients with active polyarticular juvenile idiopathic arthritis (JIA). In study JIA-I, the safety and efficacy was done in patients stratified into two groups: MTX-treated or non-MTX-treated. The study included four phases: an open-label lead in phase (OL-LI; 16 weeks), a double-blind randomized withdrawal phase (DB; 32 weeks), an open-label extension phase (OLE-BSA; up to 136 weeks), and an open-label fixed dose phase (OLE-FD; 16 weeks). In the first three phases of the study, innovator product was administered based on body surface area at a dose of 24 mg/m2 up to a maximum total body dose of 40 mg subcutaneously (SC) every other week. In the OLE-FD phase, the patients were treated with 20 mg of innovator product SC every other week if their weight was less than 30 kg and with 40 mg of innovator product SC every other week if their weight was 30 kg or greater. Patients remained on stable doses of NSAIDs and or prednisone (≤0.2 mg/kg/day or 10 mg/day maximum). Patients demonstrating a Pediatric ACR 30 response at the end of OL-LI phase were randomized into the double blind (DB) phase of the study and received either innovator product or placebo every other week for 32 weeks or until disease flare. After 32 weeks or at the time of disease flare during the DB phase, patients were treated in the open-label extension phase based on the BSA regimen (OLE-BSA), before converting to a fixed dose regimen based on body weight (OLE-FD phase). At the end of the 16- week OL-LI phase, 94% of the patients in the MTX stratum and 74% of the patients in the non- MTX stratum were Pediatric ACR 30 responders. In the DB phase significantly fewer patients
who received innovator product experienced disease flare compared to placebo, both without MTX (43% *vs.* 71%) and with MTX (37% *vs.* 65%). More patients treated with innovator product continued to show pediatric ACR 30/50/70 responses at Week 48 compared to patients treated with placebo. Pediatric ACR responses were maintained for up to two years in the OLE phase in patients who received innovator product throughout the study.

In study JIA-II, innovator product was assessed in an open-label, multicenter study in patients who were 2 to <4 years of age or 4 years of age and older weighing <15 kg with moderately to severely active polyarticular JIA. The primary objective of the study was evaluation of safety.

The safety and efficacy of innovator product in psoriatic arthritis (PsA), was assessed in two randomized, double-blind, placebo controlled studies in patients with psoriatic arthritis. Study PsA-I enrolled adult patients with moderately to severely active PsA (>3 swollen and >3 tender joints) who had an inadequate response to NSAID. Patients on MTX therapy could continue MTX at the same dose. Doses of innovator product 40 mg or placebo every other week were administered during the 24-week double-blind period of the study. Compared to placebo, treatment with innovator product resulted in improvements in the measures of disease activity. Among patients with PsA who received innovator product, the clinical responses were apparent in some patients at the time of the first visit (two weeks) and were maintained up to 88 weeks. Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and ankylosing spondylitis-like subtypes. Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline. Patients with psoriatic involvement of at least three percent body surface area (BSA) were evaluated for Psoriatic Area and Severity Index (PASI) responses. At 24 weeks, the proportions of patients achieving a 75% or 90% improvement in the PASI were 59% and 42% respectively, in the innovator product group, compared to 1% and 0% respectively, in the placebo group ($p<0.001$). Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline. In study PsA-I, innovator product-treated patients demonstrated greater inhibition of radiographic progression compared to placebo-treated patients and this effect was maintained at 48 weeks. In Study PsA-I, physical function and disability were assessed using the HAQ Disability Index (HAQ-DI) and the SF-36 Health Survey. Patients treated with 40 mg of innovator product every other week showed greater improvement from baseline in the HAQ-DI score (mean decreases of 47% and 49% at Weeks 12 and 24 respectively) in comparison to placebo (mean decreases of 1% and 3% at Weeks 12 and 24 respectively).

In Ankylosing Spondylitis, safety and efficacy of innovator product 40 mg every other week was assessed in adult patients who had an inadequate response to glucocorticoids, NSAIDs, analgesics, methotrexate or sulfasalazine. Improvement in measures of disease activity was first observed at Week 2 and maintained through 24 weeks. At 12 weeks, the ASAS 20/50/70 responses were achieved by 58%, 38%, and 23%, respectively, of patients receiving innovator product, compared to 21%, 10%, and 5% respectively, of patients receiving placebo ($p <0.001$).

Similar responses were seen at Week 24 and were sustained in patients receiving open-label innovator product for up to 52 weeks. A greater proportion of patients treated with innovator product (22%) achieved a low level of disease activity at 24 weeks (defined as a value <20 [on a scale of 0 to 100 mm] in each of the four ASAS response parameters) compared to patients treated with placebo (6%).

A second double-blind, placebo-controlled study of 82 patients with ankylosing spondylitis showed similar results. Patients treated with innovator product achieved improvement from baseline in the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) score (-3.6 *vs.* - 1.1) and in the Short Form Health Survey (SF-36) Physical Component Summary (PCS) score (7.4 *vs.* 1.9) compared to placebo-treated patients at Week 24.

In adult Crohn's Disease, induction of clinical remission (defined as CDAI < 150) was evaluated in two studies. Maintenance of clinical remission was evaluated in Study III. A greater percentage of the patients treated with 160/80 mg innovator product achieved induction of clinical remission versus placebo at Week 4 regardless of whether the patients were TNF

blocker naïve (CD-I), or had lost response to or were intolerant to infliximab (CD-II). In Study III at Week 4, 58% of patients were in clinical response and were assessed in the primary analysis. At Weeks 26 and 56, greater proportions of patients who were in clinical response at Week 4 achieved clinical remission in the innovator product 40 mg every other week maintenance group compared to patients in the placebo maintenance group. The group that received innovator product therapy every week did not demonstrate significantly higher remission rates compared to the group that received innovator product every other week.

In pediatric Crohn's Disease, 52-week clinical study of 2 dose levels of innovator product (Study PCD-I) was conducted in pediatric patients (6 to 17 years of age) with moderately to severely active Crohn's disease (defined as Pediatric Crohn's Disease Activity Index (PCDAI) score > 30).

At Week 4, 28% of patients were in clinical remission (defined as PCDAI $\leq$ 10). The proportions of patients in clinical remission (defined as PCDAI $\leq$ 10) and clinical response (defined as reduction in PCDAI of at least 15 points from baseline) were assessed at Weeks 26 and 52. At both Weeks 26 and 52, the proportion of patients in clinical remission and clinical response was numerically higher in the high dose group compared to the low dose group.

In Ulcerative Colitis, the safety and efficacy of innovator product were assessed in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 on a 12 point scale, with an endoscopy sub score of 2 to 3 on a scale of 0 to 3) despite concurrent or prior treatment with immunosuppressants such as corticosteroids, azathioprine, or 6-MP in two randomized, doubleblind, placebo-controlled clinical studies (Studies UC-I and UC-II). In both Studies UC-I and UC-II, a greater percentage of the patients treated with 160/80 mg of innovator product compared to patients treated with placebo achieved induction of clinical remission. In Study UCII, a greater percentage of the patients treated with 160/80 mg of innovator product compared to patients treated with placebo achieved sustained clinical remission (clinical remission at both Weeks 8 and 52).

In Study UC-I, there was no statistically significant difference in clinical remission observed between the innovator product 80/40 mg group and the placebo group at Week 8. In Study UCII, 17.3% in the innovator product group were in clinical remission at Week 52 compared to 8.5% in the placebo group (treatment difference: 8.8%; 95% confidence interval (CI): [2.8%, 14.5%]; $p<0.05$). The subgroup of patients with prior TNF-blocker use achieved induction of clinical remission at 9% in the innovator product group versus 7% in the placebo group, and sustained clinical remission at 5% in the innovator product group versus 1% in the placebo group. In the subgroup of patients with prior TNF-blocker use, 10% were in clinical remission at Week 52 in the innovator product group versus 3% in the placebo group.

For Plaque Psoriasis, the safety and efficacy of innovator product were assessed in randomized, double-blind, placebo-controlled studies in adult subjects with moderate to severe chronic plaque psoriasis (Ps) who were candidates for systemic therapy or phototherapy. Studies Ps-I and II evaluated the proportion of subjects who achieved "clear" or "minimal" disease on the 6-point PGA scale and the proportion of subjects who achieved a reduction in PASI score of at least 75% (PASI 75) from baseline at Week 16. Additionally, Study Ps-I evaluated the proportion of subjects who maintained a PGA of "clear" or "minimal" disease or a PASI 75 response after Week 33 and on or before Week 52. Additionally, in Study Ps-I, subjects on innovator product who maintained a PASI 75 were re-randomized to innovator product (N = 250) or placebo (N = 240) at Week 33. After 52 weeks of treatment with innovator product,

more subjects on innovator product maintained efficacy when compared to subjects who were re-randomized to placebo based on maintenance of PGA of "clear" or "minimal" disease (68% *vs.* 28%) or a PASI
75 (79% *vs.* 43%). Subjects who relapsed re-initiated treatment with 80 mg of innovator product, then 40 mg eow beginning at week 1. At week 16, 69% of subjects had a response of PGA "clear" or "minimal".

CONTRAINDICATIONS
Adfrar (adalimumab) should not be administered to patients with known hypersensitivity to adalimumab or any of its components.
Adfrar (adalimumab) also is contraindicated in patients with active tuberculosis or other severe infections (such as sepsis and opportunistic infections) and moderate to severe heart failure (NYHA class III/IV).

WARNINGS AND PRECAUTIONS
Adfrar (adalimumab) treatment should only be under supervision of rheumatologists, gastroenterologists, orthopaedicians, dermatologists, clinical immunologists and internal physicians and pediatricians experienced in the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis and plaque psoriasis.

Serious infection: As per reports in literature, patients on TNF alpha blockers such as infliximab and adalimumab are at an increased risk of developing serious infections that may lead to hospitalization or death. Most patients take concomitant immunosuppressive agents (e.g. corticosteroids, methotrexate).

Discontinue Adfrar (adalimumab) if a patient develops a serious infection or sepsis. Reported infections include active TB (including reactivation of latent TB), invasive fungal infections (including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, and pneumocystosis), and bacterial, viral, or other infections caused by opportunistic pathogens. Carefully consider the risks and benefits of treatment with Adfrar (adalimumab) prior to initiating therapy in patients with chronic or recurrent infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with Biosimilar (adalimumab), including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

Malignancy: Lymphoma and other malignancies, some fatal, have been reported in children and adolescents treated with TNF blockers, including adalimumab. Post marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including adalimumab. These cases have had a very aggressive disease course and have been fatal. The majority of reported TNF blocker cases has occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine or 6- mercaptopurine concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other immunosuppressants. Closely monitor patients who develop a new infection during treatment, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and initiate appropriate antimicrobial therapy.

In the controlled portions of clinical trials of some TNF-blockers, including innovator, more cases of malignancies have been observed among TNF-blocker-treated adult patients compared to control-treated adult patients. During the controlled portions of global innovator clinical trials in adult patients in all approved indications, malignancies, other than non-melanoma (basal cell and squamous cell) skin cancer, were observed at a rate (95% confidence interval) of 0.7 (0.45, 1.01) per 100 patient-years among 7723 innovator product-treated patients versus a rate of 0.8 (0.48, 1.31) per 100 patient-years among 4598 control-treated patients (median duration of treatment of 4 months for innovator product-treated patients and 4 months for control-treated patients). In global controlled and uncontrolled clinical trials of innovator product in adult patients with all indications, the most frequently observed malignancies, other than lymphoma and non-melanoma skin cancer (NMSC) were breast, colon, prostate, lung, and melanoma.
Non-melanoma skin cancer (NMSC):
The rate (95% confidence interval) of NMSC was 0.8 (0.52, 1.11) per 100 patient-years among innovator product-treated patients and 0.3 (0.11, 0.63) per 100 patient-years among controltreated patients.

Lymphoma and Leukemia:
In the controlled portions of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In the controlled portions of global innovator clinical trials in adult patients with all indications, 2 lymphomas occurred among 7723 innovator product-treated patients versus 1 among 4598 control-treated patients.

In global controlled and uncontrolled clinical trials of innovator in adult patients with different indications, the observed rate of lymphomas was approximately 0.11 per 100 patient-years.
Hypersensitivity: Anaphylaxis and angioedema have been rarely reported.
Autoimmunity: May result in formation of autoantibodies and, rarely, in the development of a lupus-like syndrome.
Heart failure: Worsening of chronic heart failure (CHF) and new-onset CHF have occurred. Use with caution. Monitor patients with heart failure carefully.
Hematologic events: Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF-blocking agents. Adverse reactions of the hematologic system, including medically significant cytopenia (eg, leukopenia and thrombocytopenia), have been reported infrequently.
Hepatitis B: Risk of reactivation of hepatitis B virus (HBV) may be increased in chronic carriers of this virus. Use with caution in known HBV carriers. Evaluate patients at risk of hepatitis B virus (HBV) infection for prior evidence of HBV infection prior to initiating TNF blocker therapy. Closely monitor patients who are carriers of HBV and require treatment with TNF blocking agents for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of treatment.
Immunizations: If possible, bring juvenile idiopathic arthritis patients up to date with all immunizations prior to initiating therapy. Do not administer live vaccines concurrently with Biosimilar (adalimumab).
Neurologic events: Rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease, including multiple sclerosis, and peripheral demyelinating disease, including Guillain- Barré syndrome, have occurred. Exercise caution in considering the use of Biosimilar (adalimumab) in patients with pre existing or recent-onset central or peripheral nervous system demyelinating disorders.

ADVERSE REACTIONS

Although TNF blockers are generally well tolerated, the existence of any drawbacks to the use of these agents needs to be considered before the commencement of therapy. TNF-antagonist therapy is commonly associated with induction of auto antibodies, including anti-dsDNA antibodies; however, anti-TNF-induced lupus is not very common. Renal, cerebral and cutaneous involvement may occur more frequently than the classical drug-induced lupus.
The most common side effects of these therapies are injection site reactions to subcutaneously administered drugs (local erythema and swelling usually subside within 24 h, and can be lessened by antihistaminics), or infusion reactions with infliximab; it is not necessary to stop the treatment and these side effects do not interfere with the efficacy of the drugs. Development of antibodies against the drug – human antichimeric antibodies (HACA; infliximab) or human antihuman antibodies (HAHA; etanercept/adalimumab) – is a problem for TNF therapies. The incidence of HACA production to infliximab is reported to be approximately 10% and appears to be associated with lower serum infliximab concentrations and a slightly higher incidence of infusion reactions. Concomitant therapy with low-dose MTX greatly diminished the appearance of this antibody. The least HAHA antibody development has been observed in response to etanercept with an incidence of approximately 5%. Treatment with anti-TNF-α therapy can be used in HIV patients without advanced disease with associated rheumatic diseases. Use of TNF- α blockers in patients with HBV or HCV was associated with a transient transaminitis, but appeared to be safe overall.

In general, the most common side effects of Adalimumab are injection site reactions. Adalimumab increases the risk of rare serious infections. There is a two-fold risk of serious infections with the use of adalimumab. It should not be used during periods of active infection. Its most notable infectious complication is the reactivation of tuberculosis. Tuberculosis screening should be according to country standards and may or may not include purified protein derivative test or chest X-ray. Deep fungal and other serious and atypical infection can also be promoted by adalimumab. It has been associated infrequently with skin rashes. Rare side effects include: worsening or initiation of congestive heart failure, a lupus-like syndrome, a promotion of lymphoma, medically significant cytopenias, and worsening or initiation of a multiple sclerosis/neurological disease. There has been reported pancytopenia and elevated transamines with the use of adalimumab, which suggest that laboratory monitoring blood counts and liver functions, at least intermittently, is useful. In patients with any of the foregoing problems, its use should be extremely carefully considered.

In the clinical study of the manufacturer (refer to the clinical study section), 72 adverse events were reported. Out of 72 adverse events, 54 were reported in the adalimumab biosimilar (study arm) and 18 were reported in the Reference arm. There were 32 (38.10%) subjects in the study arm and 10 (50.00%) subjects in the Reference arm who had at least one adverse event in the study. There were 19 (22.62%) subjects in the study arm and 6 (30.00%) subjects in the Reference arm with at least one treatment emergent severe adverse event (TEAE) related to study medication. There were five (5.95%) subjects in the study arm and three (15.00%) subjects in the Reference arm with at least one TEAE in the study.

In this study, 17 serious adverse events (SAEs) were reported. One SAE was split into separate terms for the MedDRA (medical dictionary for regulatory activities) coding. As per the MedDRA coding, these 17 SAEs were coded into a total of 18 SAE terms (of which, 15 were reported in the study arm and 03 were reported in the Reference arm). There were 11 (13.10%) subjects in the study arm and 3 (15.00%) subjects in the Reference arm with at least one SAE

in the study. One death (Neutropenic sepsis with shock), was reported in the study i.e. 1 (1.19%) in study arm which was possibly related to methotrexate and/or study medication. There was one injection site reaction reported in this study. It was observed in study arm and found mild in severity.

All adverse events were classified according to MedDRA version 16.1. The most commonly reported adverse events according to preferred term reported in this study was pyrexia [5 (5.95%)] in the study arm and urinary tract infection [3 (15.00%)] in the Reference arm in this study. However, most commonly reported adverse events according to System Organ Class (SOC) reported was infection and infestation occurring in 15 (17.86%) subjects in the study arm and 5 (25.00%)] in the Reference arm in this study. The total numbers of infection and infestation event reports were 23 and nine in study arm and Reference arm, respectively.

Immunogenicity testing showed presence of antibodies only in one subject in the study arm. However, this subject was a clinical responder at week 16. Thus the immunogenicity profiling did not indicate any clinically significant concerns.

The summary of all adverse events is presented below in Table 4.

Table 4 - Summary of Biosimilar (adalimumab) TEAEs by Treatment, Body System and Preferred Term [safety population (N =84)]

Body System	Preferred Term	Biosimilar (adalimumab) (N=84) n % E
Subjects with at least one Adverse Event		32 (38.10%) 72
Blood and lymphatic system disorders		3 (3.57%) 3
	Anaemia	1 (1.19%) 1
	Leukocytosis	1 (1.19%) 1
	Pancytopenia	1 (1.19%) 1
Cardiac disorders		2 (2.38%) 2
	Myocardial infarction	1 (1.19%) 1
	Tachycardia	1 (1.19%) 1
Ear and labyrinth disorders		1 (1.19%) 1
	Vertigo	1 (1.19%) 1
Eye disorders		1 (1.19%) 1
	Dry eye	1 (1.19%) 1
Gastrointestinal disorders		4 (4.76%) 4
	Gastritis	1 (1.19%) 1
	Lip ulceration	1 (1.19%) 1
	Reflux gastritis	1 (1.19%) 1
	Stomatitis	1 (1.19%) 1
General disorders and administration site conditions		7 (8.33%) 11
	Injection site reaction	1 (1.19%) 1
	Local swelling	1 (1.19%) 1

	Pyrexia	5 (5.95%) 9
Infections and infestations		15 (17.86%) 23
	Acute sinusitis	1 (1.19%) 2
	Appendicitis	1 (1.19%) 1
	Cellulitis	1 (1.19%) 1
	Dengue fever	1 (1.19%) 2
	Erythema induratum	1 (1.19%) 1
	Gastroenteritis	1 (1.19%) 1
	Herpes zoster	1 (1.19%) 1
	Neutropenic sepsis	1 (1.19%) 1
	Pulmonary tuberculosis	1 (1.19%) 2
	Respiratory tract infection	1 (1.19%) 2
	Tuberculosis	1 (1.19%) 1
	Upper respiratory tract infection	1 (1.19%) 2
	Urinary tract infection	4 (4.76%) 6
Investigations		3 (3.57%) 5
	Alanine aminotransferase increased	1 (1.19%) 2
	Transaminases increased	2 (2.38%) 3
Metabolism and nutrition disorders		5 (5.95%) 9
	Diabetes mellitus	2 (2.38%) 4
	Dyslipidaemia	1 (1.19%) 2
	Hyperuricaemia	1 (1.19%) 2
	Vitamin D deficiency	1 (1.19%) 1
Musculoskeletal and connective tissue disorders		1 (1.19%) 2
	Neck pain	1 (1.19%) 2
Psychiatric disorders		1 (1.19%) 2
	Anxiety	1 (1.19%) 1
	Depression	1 (1.19%) 1
Renal and urinary disorders		2 (2.38%) 4
	Nephrolithiasis	1 (1.19%) 2
	Urate nephropathy	1 (1.19%) 2
Respiratory, thoracic and mediastinal disorders		2 (2.38%) 2
	Cough	1 (1.19%) 1
	Dyspnoea	1 (1.19%) 1
Skin and subcutaneous tissue disorders		2 (2.38%) 3
	Skin mass	1 (1.19%) 2
	Urticaria	1 (1.19%) 1

[N: Number of subjects in the safety population; n: number of subjects; E: number of events

Percentages calculated using the number of subjects in the safety population as the denominator (%= n/N*1 00)]

Phase III studies were not conducted by manufacturer in the other approved indications. In the controlled portions of the innovator product clinical trials in adult patients in all approved indications, the rate of serious infections was 4.4 per 100 patient-years in innovator product-treated patients versus a rate of 2.9 per 100 patient-years in control-treated patients. Serious infections observed included pneumonia, septic arthritis, prosthetic and post-surgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis.

Tuberculosis and Opportunistic Infections:
In all global controlled and uncontrolled clinical trials in all indications, the rate of reported active tuberculosis was 0.20 per 100 patient-years and the rate of positive PPD conversion was 0.10 per 100 patient-years.

Autoantibodies:
In the rheumatoid arthritis controlled trials, 12% of patients treated with innovator product and 7% of placebo-treated patients that had negative baseline ANA titers developed positive titers at week 24. The impact of long-term treatment with innovator product on the development of autoimmune diseases is unknown.

Liver Enzyme Elevations:
In controlled Phase 3 trials of innovator product (40 mg SC every other week) in patients with RA, PsA, and AS with control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.5% of innovator product-treated patients and 1.5% of control-treated patients. In a controlled Phase 3 trial of innovator product in patients with polyarticular JIA who were 4 to 17 years, ALT elevations ≥ 3 x ULN occurred in 4.4% of innovator product-treated patients and 1.5% of control-treated patients (ALT more common than AST); liver enzyme test elevations were more frequent among those treated with the combination of innovator product
and MTX than those treated with innovator product alone. In general, these elevations did not lead to discontinuation of innovator product treatment. In controlled Phase 3 trials of innovator product (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week) in adult patients with CD with a control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9% of innovator producttreated patients and 0.9% of control-treated patients. In the Phase 3 trial of innovator product in pediatric patients with Crohn's disease which evaluated efficacy and safety of two body weight based maintenance dose regimens following body weight based induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% (5/192) of patients, of whom 4 were receiving concomitant immunosuppressants at baseline; none of these patients discontinued due to abnormalities in ALT tests. In controlled Phase 3 trials of innovator product (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week) in patients with UC with control period duration ranging from 1 to 52 weeks, ALT elevations ≥3 x ULN occurred in 1.5% of innovator product-treated patients and 1.0% of control-treated patients. In controlled Phase 3 trials of innovator product (initial dose of 80 mg then 40 mg every other week) in patients with Ps with control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8% of innovator product-treated patients and 1.8% of control-treated patients. In controlled trials of innovator product (initial doses of 160 mg at Week

0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in subjects with HS with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of innovator product-treated subjects and 0.6% of control-treated subjects.

Immunogenicity:
Patients in rheumatoid arthritis studies of the innovator were tested at multiple time points for antibodies to adalimumab during the 6- to 12-month period. Approximately 5% (58 of 1062) of adult RA patients receiving innovator product developed low-titer antibodies to adalimumab at least once during treatment, which were neutralizing *in vitro*. Patients treated with concomitant methotrexate (MTX) had a lower rate of antibody development than patients on innovator product monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse reactions was observed. In patients with polyarticular JIA who were 4 to 17 years of age, adalimumab antibodies were identified in 16% of innovator product-treated patients. In patients receiving concomitant MTX, the incidence was 6% compared to 26% with innovator product monotherapy. In patients with polyarticular JIA who were 2 to <4 years of age or 4 years of age and older weighing <15 kg, adalimumab antibodies were identified in 7% (1 of 15) of innovator product-treated patients, and the one patient was receiving concomitant MTX. In patients with AS, the rate of development of antibodies to adalimumab in innovator producttreated patients was comparable to patients with RA. In patients with PsA, the rate of antibody development in patients receiving innovator product monotherapy was comparable to patients with RA; however, in patients receiving concomitant MTX the rate was 7% compared to 1% in RA.

In adult patients with CD, the rate of antibody development was 3%. In pediatric patients with Crohn's disease, the rate of antibody development in patients receiving innovator product was 3%. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 32% of total patients studied), the immunogenicity rate was 10%. In patients with moderately to severely active UC, the rate of antibody development in patients receiving innovator product was 5%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 25% of total patients studied), the immunogenicity rate was 20.7%. In patients with Ps, the rate of antibody development with innovator product monotherapy was 8%. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 mcg/mL. Among the patients whose serum adalimumab levels were < 2 mcg/mL (approximately 40% of total patients studied), the immunogenicity rate was 20.7%. In Ps patients who were on innovator product monotherapy and subsequently withdrawn from the treatment, the rate of antibodies to adalimumab after retreatment was similar to the rate observed prior to withdrawal. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions
In general, the adverse reactions in the innovator product-treated patients in the polyarticular juvenile idiopathic arthritis (JIA) trials included neutropenia, streptococcal pharyngitis, increased aminotransferases, herpes zoster, myositis, metrorrhagia, and appendicitis. Serious

infections were observed in 4% of patients within approximately 2 years of initiation of treatment with innovator product and included cases of herpes simplex, pneumonia, urinary tract infection, pharyngitis, and herpes zoster. In Study JIA-I, 45% of patients experienced an infection while receiving innovator product with or without concomitant MTX in the first 16 weeks of treatment. The types of infections reported in innovator product-treated patients were generally similar to those commonly seen in polyarticular JIA patients who are not treated with TNF blockers. Upon initiation of treatment, the most common adverse reactions occurring in this patient population treated with innovator product were injection site pain and injection site reaction (19% and 16%, respectively). A less commonly reported adverse event in patients receiving innovator product was granuloma annulare which did not lead to discontinuation of innovator product treatment. In the first 48 weeks of treatment in Study JIA-I, non-serious hypersensitivity reactions were seen in approximately 6% of patients and included primarily localized allergic hypersensitivity reactions and allergic rash. In Study JIA-I, 10% of patients treated with innovator product who had negative baseline anti-dsDNA antibodies developed positive titers after 48 weeks of treatment. No patient developed clinical signs of autoimmunity during the clinical trial.
Approximately 15% of patients treated with innovator product developed mild-to-moderate elevations of creatine phosphokinase (CPK) in Study JIA-I. Elevations exceeding 5 times the upper limit of normal were observed in several patients. CPK levels decreased or returned to normal in all patients. Most patients were able to continue innovator product without interruption. In Study JIA-II, the safety profile for this patient population was similar to the safety profile seen in patients 4 to 17 years of age with polyarticular JIA. In Study JIA-II, 78% of patients experienced an infection while receiving innovator product. These included nasopharyngitis, bronchitis, upper respiratory tract infection, otitis media, and were mostly mild to moderate in severity. Serious infections were observed in 9% of patients receiving innovator product in the study and included dental caries, rotavirus gastroenteritis, and varicella. In Study JIA-II, non-serious allergic reactions were observed in 6% of patients and included intermittent urticaria and rash, which were all mild in severity.

In Psoriatic Arthritis and Ankylosing Spondylitis Clinical Studies of innovator, the safety profile for patients treated with innovator product 40 mg every other week was similar to the safety profile seen in patients with RA, innovator product Studies RA-I through IV.

In adult Crohn's Disease Clinical Studies of innovator, safety profile for adult patients with CD treated with innovator product was similar to the safety profile seen in patients with RA.

In pediatric Crohn's Disease Clinical Studies of innovator, the safety profile for pediatric patients with Crohn's disease treated with innovator product was similar to the safety profile seen in adult patients with Crohn's disease.

In Ulcerative Colitis Clinical Studies of the innovator product, safety profile for patients with UC treated with innovator product was similar to the safety profile seen in patients with RA.

The safety profile for subjects with Plaque psoriasis treated with innovator product was similar to the safety profile seen in subjects with RA with the following exceptions. Innovator producttreated subjects had a higher incidence of arthralgia when compared to controls (3% *vs.* 1%).

The following adverse reactions have been identified during post-approval use of the innovator product. Because these reactions are reported voluntarily from a population of uncertain size,

it is not always possible to reliably estimate their frequency or establish a causal relationship.
Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis
General disorders and administration site conditions: Pyrexia
Hepato-biliary disorders: Liver failure, hepatitis
Immune system disorders: Sarcoidosis
Neoplasms benign, malignant and unspecified (including cysts and polyps): Merkel cell carcinoma (neuroendocrine carcinoma of the skin)
Nervous system disorders: Demyelinating disorders (e.g., optic neuritis, Guillain-Barré syndrome), cerebrovascular accident
Respiratory disorders: Interstitial lung disease, including pulmonary fibrosis, pulmonary embolism
Skin reactions: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), alopecia.

DRUG INTERACTIONS

Abatacept, tocilizumab: An increased rate of infection may occur. Concurrent therapy is not recommended. If co-administration occurs, closely monitor for signs of infection.
Anakinra: Do not use in combination; increased risk of serious infections and neutropenia.
Live vaccines: Do not give concurrently.
Methotrexate: Reduces apparent clearance of Adfrar (adalimumab); however, adjustments in the dose of either drug do not appear necessary.
Rituximab: A higher rate of serious infection has been observed in patients with RA treated with rituximab and subsequently receiving a TNF blocker (e.g. adalimumab).
There is insufficient information to provide recommendations for concurrent use of Adfrar (adalimumab) and other biologic products.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B - There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, Biosimilar (adalimumab) should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether Biosimilar (adalimumab) is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Biosimilar (adalimumab), a decision should be made whether to discontinue nursing or todiscontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and efficacy adalimumab in pediatric patients for uses other than polyarticular JIA and pediatric Crohn's disease have not been established. Adalimumab has not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg. Postmarketing cases of lymphoma, including hepatosplenic T-cell lymphoma and other malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including adalimumab.

Geriatric Use
Because there is a higher incidence of infections and malignancies in the elderly population in general, caution should be used when treating the elderly.

Effects on ability to drive and use machines
Adfrar (adalimumab) may have a minor influence on the ability to drive and use machines. Vertigo and visual impairment may occur following administration of adalimumab.

OVERDOSAGE
In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

PREPARATIONS
Adfrar (adalimumab) is supplied in prefilled syringes as a preservative free, sterile solution for subcutaneous administration. The following packaging configuration is available:
1 ml prefilled glass syringe providing 20 mg (0.4 mL)/40 mg (0.8 mL) of Adfrar (adalimumab) for subcutaneous administration.

STORAGE AND STABILITY
Do not use beyond the expiration date on the container. Adfrar (adalimumab) must be refrigerated at 2 to 8° C (36 to 46° F). DO NOT FREEZE.
Protect the prefilled syringe from exposure to light.

PRESENTATION:
Adalimumab Injection is available as 20 mg (0.4 mL)/40 mg (0.8 mL) in Pre-filled syringe.

EXPIRY DATE:
24 Months

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6. Clinical Study Report, Version 1.0 Dated 26 March 2015

Adfrar (adalimumab) PATIENT MEDICATION GUIDE
Read this Medication Guide of Adfrar (adalimumab) before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment.

What is the most important information I should know about Adfrar (adalimumab)?
Adfrar (adalimumab) is a medicine that affects your immune system. Adfrar (adalimumab) can lower the ability of your immune system to fight infections. **Serious infections have happened in people taking adalimumab. These serious infections include tuberculosis (TB) and infections caused by viruses, fungi or bacteria that have spread throughout the body. Some people have died from these infections.**

- Your doctor should test you for TB before starting Adfrar (adalimumab).

- Your doctor should check you closely for signs and symptoms of TB during treatment with Adfrar (adalimumab).

You should not start taking Adfrar (adalimumab) if you have any kind of infection unless your doctor says it is okay.

Before starting Adfrar (adalimumab), tell your doctor if you:

- think you have an infection or have symptoms of infection such as: fever, sweats, chills, sores on body, muscle aches, diarrhea, stomach pain, cough, burning urination, shortness of breath, tiredness, blood in phlegm and weight loss
- are being treated for an infection
- get a lot of infections or have infections that keep coming back
- have diabetes
- have TB, or have been in close contact with someone with TB
- Were born in, lived in, or traveled to countries where there is more risk for getting TB.
- Ask your doctor if you are not sure.
- Live or have lived in certain parts of the country where there is an increased risk for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, or blastomycosis). These infections may happen or become more severe if you use Adfrar (adalimumab). Ask your doctor if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis B
- Use the medicine abatacept, anakinra, rituximab, azathioprine, or 6–mercaptopurine.
- are scheduled to have major surgery

After starting Adfrar (adalimumab), call your doctor right away if you have an infection, or any sign of an infection.

Adfrar (adalimumab) can make you more likely to get infections or make any infection that you may have worse.

Cancer

- For children and adults taking TNF-blockers, including Adfrar (adalimumab), the chances of getting cancer may increase.
- There have been cases of unusual cancers in children, teenagers, and young adults using TNF-blockers.
- People with RA, especially more serious RA, may have a higher chance for getting a kind of cancer called lymphoma.
- If you use TNF blockers including Adfrar (adalimumab) your chance of getting two types of skin cancer may increase (basal cell cancer and squamous cell cancer of the skin). These types of cancer are generally not life-threatening if treated. Tell your doctor if you have a bump or open sore that doesn't heal.
- Some people receiving TNF blockers including adalimumab developed a rare type of cancer called hepatosplenic T-cell lymphoma. This type of cancer often results in death. Most of these people were male teenagers or young men. Also, most people were being treated for Crohn's disease or ulcerative colitis with another medicine called azathioprine or 6-mercaptopurine.

What is Adfrar (adalimumab)?

Adfrar (adalimumab) is a medicine called a Tumor Necrosis Factor (TNF) blocker. Adfrar (adalimumab) is used:

- To reduce the signs and symptoms of:
- **moderate to severe rheumatoid arthritis (RA) in adults.** Adfrar (adalimumab) can be used alone, with methotrexate, or with certain other medicines.
- **moderate to severe polyarticular juvenile idiopathic arthritis (JIA) in children** 4 years and older. Adfrar (adalimumab) can be used alone, with methotrexate, or with certain other medicines.
- **psoriatic arthritis (PsA) in adults.** Adfrar (adalimumab) can be used alone or with certain other medicines.
- **ankylosing spondylitis (AS) in adults.**
- **moderate to severe Crohn's disease (CD) in adults** when other treatments have not worked well enough.
- In adults, to help get **moderate to severe ulcerative colitis (UC)** under control (induce remission) and keep it under control (sustain remission) when certain other medicines have not worked well enough. It is not known if Biosimilar (adalimumab) is effective in people who stopped responding to or could not tolerate TNF-blocker medicines.
- **To treat moderate to severe chronic (lasting a long time) plaque psoriasis (Ps) in adults**
- who have the condition in many areas of their body and who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet light alone or with pills).

What should I tell my doctor before taking Adfrar (adalimumab)?

Adfrar (adalimumab) may not be right for you. Before starting Biosimilar (adalimumab), tell your doctor about all of your health conditions, including if you:

- have an infection.
- have or have had cancer.
- have any numbness or tingling or have a disease that affects your nervous system
- such as multiple sclerosis or Guillain-Barré syndrome.
- have or had heart failure.
- have recently received or are scheduled to receive a vaccine. You may receive vaccines, except for live vaccines while using Adfrar (adalimumab). Children with juvenile idiopathic arthritis should be brought up to date with all vaccines before starting Adfrar (adalimumab).
- are allergic to rubber or latex. The needle cover on the prefilled syringe contains dry natural rubber. Tell your doctor if you have any allergies to rubber or latex.
- are allergic to Adfrar (adalimumab) or to any of its ingredients. See the end of this Medication Guide for a list of ingredients in Adfrar (adalimumab).
- are pregnant or planning to become pregnant. It is not known if Adfrar (adalimumab) will harm your unborn baby. Adfrar (adalimumab) should only be used during a pregnancy if needed.
- breastfeeding or plan to breastfeed. You and your doctor should decide if you will breastfeed or use Adfrar (adalimumab). You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription
medicines, vitamins, and herbal supplements.

Especially tell your doctor if you use:

- Abatacept, anakinra, infliximab, etanercept, certolizumab pegol or golimumab, because you should not use Adfrar (adalimumab) while you are also taking one of these medicines.
- Your doctor may not want to give you Adfrar (adalimumab) if you have received rituximab recently.
- Azathioprine or 6–mercaptopurine, 6-MP.

Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I take Adfrar (adalimumab)?

- Adfrar (adalimumab) is given by an injection under the skin. Your doctor will tell you how often to take an injection of Adfrar (adalimumab). This is based on your condition to be treated. **Do not inject** Adfrar **(adalimumab) more often than you were prescribed.**
- Make sure you have been shown how to inject Adfrar (adalimumab) before you do it yourself.
- **Do not** try to inject Adfrar (adalimumab) yourself until you have been shown the right way to give the injections. If your doctor decides that you or a caregiver may be able to give your injections of Adfrar (adalimumab) at home, you should receive training on the right way to prepare and inject Adfrar (adalimumab).
- Do not miss any doses of Adfrar (adalimumab) unless your doctor says it is okay. If you

forget to take Adfrar (adalimumab), inject a dose as soon as you remember. Then, take your next dose at your regular scheduled time. This will put you back on schedule. In case you are not sure when to inject Adfrar (adalimumab), call your doctor or pharmacist.

- If you take more Adfrar (adalimumab) than you were told to take, call your doctor.

What are the possible side effects of Adfrar (adalimumab)?

Adfrar (adalimumab) can cause serious side effects, including:

- **Serious Infections.**

Your doctor will examine you for TB and perform a test to see if you have TB. If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with Adfrar (adalimumab) and during treatment with Adfrar (adalimumab). Even if your TB test is negative your doctor should carefully monitor you for TB infections while you are taking Adfrar (adalimumab). People who had a negative TB skin test before receiving adalimumab have developed active TB. Tell your doctor if you have any of the following symptoms while taking or after taking Adfrar (adalimumab):

o cough that does not go away
o low grade fever
o weight loss
o loss of body fat and muscle (wasting)

- **Hepatitis B infection in people who carry the virus in their blood.**

If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus can become active while you use Adfrar (adalimumab). Your doctor should do blood tests before you start treatment, while you are using Biosimilar (adalimumab), and for several months after you stop treatment with Adfrar (adalimumab). Tell your doctor if you have any of the following symptoms of a possible hepatitis B infection:

- **Allergic reactions.** Allergic reactions can happen in people who use Adfrar (adalimumab). Call your doctor or get medical help right away if you have any of these symptoms of a serious allergic reaction:
  o hives
  o swelling of your face, eyes, lips or mouth
  o trouble breathing
- **Nervous system problems.** Signs and symptoms of a nervous system problem include: numbness or tingling, problems with your vision, weakness in your arms or legs, and dizziness.
- **Blood problems.** Your body may not make enough of the blood cells that help fight infections or help to stop bleeding. Symptoms include a fever that does not go away, bruising or bleeding very easily, or looking very pale.
- **New heart failure or worsening of heart failure you already have. Call your doctor right away** if you get new worsening symptoms of heart failure while taking Adfrar (adalimumab), including:

o shortness of breath
o swelling of your ankles or feet
o Sudden weight gain.

- **Immune reactions including a lupus-like syndrome.** Symptoms include chest discomfort or pain that does not go away, shortness of breath, joint pain, or a rash on your cheeks or arms that gets worse in the sun. Symptoms may improve when you stop Adfrar (adalimumab).
- **Liver Problems.** Liver problems can happen in people who use TNF-blocker medicines. These problems can lead to liver failure and death. Call your doctor right away if you have any of these symptoms:

o feel very tired
o skin or eyes look yellow
o poor appetite or vomiting
o pain on the right side of your stomach (abdomen)

- **Psoriasis.** Some people using adalimumab had new psoriasis or worsening of psoriasis they already had. Tell your doctor if you develop red scaly patches or raised bumps that are filled with pus. Your doctor may decide to stop your treatment with Adfrar (adalimumab).

Call your doctor or get medical care right away if you develop any of the above symptoms.

Your treatment with Adfrar (adalimumab) may be stopped.
Common side effects with adalimumab include:

- Injection site reactions: redness, rash, swelling, itching, or bruising. These symptoms usually will go away within a few days. Call your doctor right away if you have pain, redness or swelling around the injection site that does not go away within a few days or gets worse.
- upper respiratory infections (including sinus infections)
- headaches
- rash
- nausea

These are not all the possible side effects with Adfrar (adalimumab). Tell your doctor if you have any side effect that bothers you or that does not go away. Ask your doctor or pharmacist for more information.

Call your doctor for medical advice about side effects.

How should I store Adfrar (adalimumab)?

- Store Adfrar (adalimumab) in a refrigerator at 36ºF to 46ºF (2ºC to 8ºC) in the original container until it is used. Protect from light.
- When travelling, Adfrar (adalimumab) should be stored in a cool carrier with an ice pack.
- **Do not freeze Adfrar (adalimumab).** Do not use Adfrar (adalimumab) if frozen, even if

it has been thawed.

- Refrigerated Adfrar (adalimumab) may be used until the expiration date printed on the Adfrar (adalimumab) carton or prefilled syringe.
- Do not use prefilled syringe if the liquid is cloudy, discolored, or has flakes or particles in it.
- Do not drop or crush Adfrar (adalimumab). The prefilled syringe is glass.

- **Keep Adfrar (adalimumab), injection supplies, and all other medicines out of the reach of children**

General information about Adfrar (adalimumab)

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Adfrar (adalimumab) for a condition for which it was not prescribed. Do not give Adfrar (adalimumab) to other people, even if they have the same condition. It may harm them. This Patient Medication Guide summarizes the most important information about Adfrar (adalimumab). If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Adfrar (adalimumab) that was written for healthcare professionals.

For more information go to www.torrentpharma.com

MARKETED BY:

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

MANUFACTURED BY:

Reliance Life Sciences Pvt. Ltd.
DALC, Plant 2, R-282, TTC Area of MIDC
Thane-Belapur Road, Rabale, Navi Mumbai - 400 701, INDIA

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