CIPLÉUMAB Subcutaneous Injection (Adalimumab)

**Description**

Adalimumab is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF-alpha). Adalimumab was created using phage display technology resulting in an antibody with human derived heavy and light chain variable regions and human IgG1:k constant regions. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons.

**Composition**

Each pre-filled glass syringe of 0.8 mL contains:
- Adalimumab (r-DNA Origin) IH ......................... 40 mg
- Monobasic Sodium Phosphate Dihydrate IP .... 0.69 mg
- Dibasic Sodium Phosphate Dihydrate USP ...... 1.22 mg
- Sodium Citrate IP .............................................. 0.24 mg
- Citric Acid Monohydrate IP ......................... 1.04 mg
- Mannitol IP ..................................................... 9.6 mg
- Sodium Chloride IP ........................................ 4.93 mg
- Polysorbate 80 IP ........................................... 0.8 mg
- Water for Injections IP ............................... q.s. to 0.8 mL

The pH is 5.2 ± 0.2.

**Dosage Form**

Injectable

**Pharmacology**

- **Mechanism of Action**

  Adalimumab binds specifically to TNF-alpha and blocks its interaction with p55 and p75 cell surface TNF receptors. Adalimumab also lyses surface TNF expressing cells *in vitro* in the presence of complement. Adalimumab does not bind or inactivate lymphotoxin (TNF-beta). TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of patients with rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) and play an important role in both the pathological inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques. In psoriatic arthritis, treatment with adalimumab may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s)
by which adalimumab exerts its clinical effects is unknown. Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leucocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC50 of 1-2 X 10-10M).

**Pharmacodynamics**

After treatment with adalimumab, a decrease in the levels of acute-phase reactants of inflammation (C-reactive protein and erythrocyte sedimentation rate) and serum cytokines (IL-6) was observed compared to baseline in patients with rheumatoid arthritis. A decrease in CRP was also observed in patients with Crohn’s disease and ulcerative colitis. Serum levels of matrix metalloproteinases (MMP-1 and MMP-2) that produce tissue remodeling responsible for cartilage destruction was also decreased after adalimumab administration.

**Clinical Efficacy**

**Efficacy Data from Hetero-Adalimumab Clinical Study in Rheumatoid Arthritis**

In a phase-III study, Hetero Adalimumab ACR 20 response and other efficacy parameters (ACR 50, ACR 70, Interleukin-6, DAS 28-CRP and HAQ-DI) is comparable with Reference Adalimumab at the end of 12 weeks. Development of anti-drug antibodies was similar in Hetero Adalimumab and Reference Adalimumab at the end of 12 weeks.

**Pharmacokinetics**

**Absorption and Distribution**

After subcutaneous administration of a single 40 mg dose, absorption and distribution of adalimumab was slow, with peak serum concentration 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 (around 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 2 weeks. Adalimumab concentrations in the synovial fluid from rheumatoid arthritis patients ranged from 31 to 96% of those in serum. Following subcutaneous administration of 40 mg of adalimumab every other week in adult rheumatoid arthritis 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 proportionally with dose following 20, 40 and 80 mg subcutaneous dosing every other week (eow) and every week. Following the administration of 24 mg/m2 (up to a maximum of 40 mg) subcutaneously every other week to patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years of age, the mean trough steady-state (values measured from weeks 20 to 48) serum adalimumab concentration was 5.6 ± 5.6 μg/ml (102% CV) for adalimumab without concomitant methotrexate and 10.9 ± 5.2 μg/ml (47.7% CV) with concomitant methotrexate. In patients with polyarticular juvenile idiopathic arthritis who were 2 to <4 years old or aged 4 years and above, weighing <15 kg and dosed with adalimumab 24 mg/m2, the mean trough steady-state serum adalimumab concentration was 6.0 ± 6.1 μg/ml (101% CV) for adalimumab without concomitant methotrexate and 7.9 ± 5.6 μg/ml (71.2% CV) with concomitant methotrexate. Following the administration of 24 mg/m2 (up to a maximum of 40 mg) subcutaneously every other week to patients with enthesitis-related arthritis who were 6 to 17 years of age, the mean trough steady-state (values measured at week 24) serum adalimumab concentrations were 8.8 ± 6.6 μg/ml for adalimumab without concomitant methotrexate and 11.8 ± 4.3 μg/ml with concomitant methotrexate. In adult patients with psoriasis, the mean steady-state trough concentration was 5 μg/ml during adalimumab 40 mg every other week-monotherapy treatment. Following the administration of 0.8 mg/kg (up to a maximum of 40 mg) subcutaneously every other week to paediatric patients with chronic plaque psoriasis, the mean ± SD steady-state adalimumab trough concentration was approximately 7.4 ± 5.8 μg/ml (79% CV).

In adult patients with hidradenitis suppurativa, a dose of 160 mg adalimumab on week 0 followed by 80 mg on week 2
achieved serum adalimumab concentrations of approximately 7 to 8 μg/ml at week 2 and week 4. The mean-state trough concentration at week 12 through week 36 were approximately 8 to 10 μg/ml during adalimumab 40 mg every week treatment. Adalimumab exposure in adolescent hidradenitis suppurativa patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paediatric psoriasis, juvenile idiopathic arthritis, paediatric Crohn's disease, and enthesitis-related arthritis). The recommended adolescent hidradenitis suppurativa dosing schedule is 40 mg every other week. Since exposure to adalimumab can be affected by body size, adolescents with higher body weight and inadequate response may benefit from receiving the recommended adult dose of 40 mg every week. In patients with Crohn's disease, the loading dose of 80 mg adalimumab at week 0 followed by 40 mg adalimumab at week 2 achieved serum adalimumab trough concentrations of approximately 5.5 μg/ml during the induction period. A loading dose of 160 mg adalimumab at week 0 followed by 80 mg adalimumab at week 2 achieves serum adalimumab trough concentrations of approximately 12 μg/ml during the induction period. Mean steady-state trough levels of approximately 7 μg/ml were observed in Crohn's disease patients who received a maintenance dose of adalimumab 40 mg every other week. In paediatric patients with moderate-to-severe Crohn's disease, the open-label adalimumab induction dose was 160/80 mg or 80/40 mg at weeks 0 and 2, respectively, dependent on a body weight cut-off of 40 kg. At week 4, patients were randomized 1:1 to either the standard dose (40/20 mg every other week) or low dose (20/10 mg every other week) maintenance treatment groups based on their body weight. The mean (± SD) serum adalimumab trough concentrations achieved at week 4 were 15.7 ± 6.6 μg/ml for patients ≥40 kg (160/80 mg) and 10.6 ± 6.1 μg/ml for patients < 40 kg (80/40 mg). For patients who stayed on their randomized therapy, the mean (± SD) adalimumab trough concentrations at week 52 were 9.5 ± 5.6 μg/ml for the Standard Dose group and 3.5 ± 2.2 μg/ml for the low-dose group. The mean trough concentrations were maintained in patients who continued to receive adalimumab treatment every other week for 52 weeks. For patients who dose-escalated from every other week therapy to a weekly regimen, the mean (± SD) serum concentrations of adalimumab at week 52 were 15.3 ± 11.4 μg/ml (40/20 mg, weekly) and 6.7 ± 3.5 μg/ml (20/10 mg, weekly). In patients with ulcerative colitis, a loading dose of 160 mg adalimumab at week 0 followed by 80 mg adalimumab at week 2 achieves serum adalimumab concentrations of approximately 12 μg/ml during the induction period. Mean steady-state trough levels of approximately 8 μg/ml were observed in ulcerative colitis patients who received a maintenance dose of adalimumab 40 mg every other week. In patients with uveitis, a loading dose of 80 mg adalimumab at week 0 followed by 40 mg adalimumab every other week starting at week 1 resulted in mean steady-state concentrations of approximately 8 to 10 μg/ml.

Elimination
Population pharmacokinetic analyses with data from 1,300 rheumatoid arthritis 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) were observed to be lower in patients with measurable anti-adalimumab antibodies. Adalimumab has not been studied in patients with hepatic or renal impairment.

Indications
CIPLEUMAB is indicated for the following:

1. Rheumatoid Arthritis

CIPLEUMAB in combination with methotrexate 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; and,
the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. CIPLEUMAB can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. CIPLEUMAB has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

2. Patients with Juvenile Idiopathic Arthritis

*Polyarticular Juvenile Idiopathic Arthritis*

CIPLEUMAB in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). CIPLEUMAB can be given as monotherapy, in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. CIPLEUMAB has not been studied in patients aged less than 2 years.

*Enthesitis-Related Arthritis*

CIPLEUMAB is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy.

3. Patients with Axial Spondyloarthritis

*Ankylosing Spondylitis*

CIPLEUMAB is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

*Axial Spondyloarthritis without Radiographic Evidence of Ankylosing Spondylitis*

CIPLEUMAB is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

4. Psoriatic Arthritis

CIPLEUMAB is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. CIPLEUMAB has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function.

5. Psoriasis

CIPLEUMAB is indicated for the treatment of moderate-to-severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy.

6. Paediatric Plaque Psoriasis

CIPLEUMAB is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.

7. Hidradenitis Suppurativa

CIPLEUMAB is indicated for the treatment of active moderate-to-severe hidradenitis suppurativa (acne inversa) in adults and adolescents from 12 years of age with an inadequate response to conventional systemic hidradenitis suppurativa therapy.
8. Crohn’s Disease

CIPLEUMAB is indicated for treatment of moderately or severely active Crohn’s disease in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant, or who are intolerant to or have medical contraindications for such therapies.

9. Paediatric Crohn’s Disease

CIPLEUMAB is indicated for the treatment of moderately to severely active Crohn’s disease, in paediatric patients (from 6 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy and a corticosteroid and/or immunomodulator, or who are intolerant to or have contraindications for such therapies.

10. Ulcerative Colitis

CIPLEUMAB is indicated for the treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

11. Uveitis

CIPLEUMAB is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing or in whom corticosteroid treatment is inappropriate.

Dosage And Administration

CIPLEUMAB is administered by subcutaneous injection.

1. Patients with Rheumatoid Arthritis

The recommended dose of CIPLEUMAB for adult patients with rheumatoid arthritis is 40 mg administered every other week as a single dose via subcutaneous injection. Methotrexate should be continued during treatment with adalimumab. Glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs or analgesics can be continued during treatment with CIPLEUMAB. In monotherapy, some patients who experience a decrease in their response may benefit from an increase in dose intensity to 40 mg CIPLEUMAB every week. Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be reconsidered in a patient not responding within this time period.

Dose Interruption

There may be a need for dose interruption, for instance, before surgery or if a serious infection occurs. Available data suggests that re-introduction of CIPLEUMAB after discontinuation for 70 days or longer resulted in the same magnitude of clinical response and similar safety profile as before dose interruption.

2. Patients with Ankylosing Spondylitis and Axial Spondyloarthritis without Radiographic Evidence of Ankylosing Spondylitis, and Psoriatic Arthritis

The recommended dose of CIPLEUMAB for patients with ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, and for patients with psoriatic arthritis is 40 mg administered every other week as a single dose via subcutaneous injection. Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be considered in a patient not responding within this time period.
3. Patients with Psoriasis

The recommended dose of CIPLEUMAB for adult patients is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week, starting 1 week after the initial dose. Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period. Beyond 16 weeks, patients with inadequate response may benefit from an increase in dosing frequency to 40 mg every week. The benefits and risks of continued weekly CIPLEUMAB therapy should be carefully reconsidered in a patient with an inadequate response after an increase in dosing frequency. If adequate response is achieved with an increased dosing frequency, the dose may subsequently be reduced to 40 mg every other week.

4. Patients with Juvenile Idiopathic Arthritis

The recommended dose for patients 2 years of age and older with polyarticular juvenile idiopathic arthritis is based on the patient’s height and weight (Table 1).

Table 1: Adalimumab Dose in Millilitres (mL) by Height and Weight of Patients for Polyarticular Juvenile Idiopathic Arthritis and Enthesitis-Related Arthritis

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* Maximum single dose is 40 mg (0.8 mL)

5. Patients with Hidradenitis Suppurativa

The recommended CIPLEUMAB dose regimen for adult patients with hidradenitis suppurativa is 160 mg initially at day 1 (given as four 40 mg injections in 1 day or as two 40 mg injections per day for 2 consecutive days), followed by 80 mg, 2 weeks later, at day 15 (given as two 40 mg injections in one day). After 2 weeks (day 29), continue with a dose of 40 mg every week. Antibiotics may be continued during treatment with CIPLEUMAB, if necessary. It is recommended that the patient should use a topical antiseptic wash on their hidradenitis suppurativa lesions daily during treatment with CIPLEUMAB. Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement.
within this time period. Should treatment be interrupted, CIPLEUMAB 40 mg every week may be re-introduced. The benefit and risk of continued long-term treatment should be periodically evaluated.

6. Patients with Crohn’s Disease

The recommended CIPLEUMAB induction-dose regimen for adult patients with moderately to severely active Crohn’s disease is 80 mg at week 0 followed by 40 mg at week 2. In case there is a need for a more rapid response to therapy, the regimen of 160 mg at week 0 (dose can be administered as four injections in 1 day or as two injections per day for 2 consecutive days) and 80 mg at week 2 can be used with the awareness that the risk for adverse events is higher during induction. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Alternatively, if a patient has stopped adalimumab and signs and symptoms of the disease recur, CIPLEUMAB may be re-administered. There is little experience from re-administration after more than 8 weeks since the previous dose. During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines. Some patients who experience a decrease in their response may benefit from an increase in dosing frequency to 40 mg CIPLEUMAB every week. Some patients who have not responded by week 4 may benefit from continued maintenance therapy through week 12. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

7. Patients with Ulcerative Colitis

The recommended CIPLEUMAB induction-dose regimen for adult patients with moderate-to-severe ulcerative colitis is 160 mg at week 0 (dose can be administered as four injections in 1 day or as two injections for 2 consecutive days) and 80 mg at week 2. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines. Some patients who experience decrease in their response may benefit from an increase in dosing frequency to 40 mg CIPLEUMAB every week. Available data suggest that clinical response is usually achieved within 2 to 8 weeks of treatment. CIPLEUMAB therapy should not be continued in patients failing to respond within this time period.

8. Patients with Uveitis

The recommended dose of CIPLEUMAB for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given every other week after the initial dose. There is limited experience in the initiation of treatment with CIPLEUMAB alone. Treatment with CIPLEUMAB can be initiated in combination with corticosteroids and/or with other non-biologic immunomodulatory agents. Concomitant corticosteroids may be tapered in accordance with clinical practice starting two weeks after initiating treatment with CIPLEUMAB. It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis.

Special Populations

Elderly
No dose adjustment is required.
Renal and/or Hepatic Impairment
Adalimumab has not been studied in these patient populations. No dose recommendations can be made.
Paediatric
Juvenile Idiopathic Arthritis
Polyarticular Juvenile Idiopathic Arthritis (from age 2 to 12 years of age)
The recommended dose of adalimumab for patients with polyarticular juvenile idiopathic arthritis, aged 2 to 12 years, is 24 mg/m² body surface area up to a maximum single dose of 20 mg adalimumab (for patients aged 2 to <4 years) and up to a maximum single dose of 40 mg adalimumab (for patients aged 4 to 12 years) administered every other week via subcutaneous injection. The volume for injection is selected based on the patients’ height and weight (Table 1).
Polyarticular Juvenile Idiopathic Arthritis (from 13 years of age)
For patients from 13 years of age, a dose of 40 mg is administered every other week regardless of body surface area. Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period. There is no relevant use of adalimumab in patients aged <2 years for this indication.

Enthesitis-Related Arthritis
The recommended dose of adalimumab for patients with enthesitis-related arthritis, 6 years of age and older, is 24 mg/m² body surface area up to a maximum single dose of 40 mg adalimumab administered every other week via subcutaneous injection. The volume for injection is selected based on the patients’ height and weight. Adalimumab has not been studied in patients with enthesitis-related arthritis, aged less than 6 years.

Paediatric Plaque Psoriasis
The recommended adalimumab dose is 0.8 mg per kg body weight (up to a maximum of 40 mg per dose) administered subcutaneously weekly for the first two doses and every other week thereafter. Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this time period. If re-treatment with adalimumab is indicated, the above guidance on dose and treatment duration should be followed. The safety of adalimumab in paediatric patients with plaque psoriasis has been assessed for a mean of 13 months. There is no relevant use of adalimumab in children aged <4 years for this indication. The volume for injection is selected based on the patients’ weight (Table 2).

Table 2: Adalimumab Dose in Millilitres (mL) by Weight for Patients with Paediatric Psoriasis

<table>
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<tr>
<th>Body Weight (kg)</th>
<th>Paediatric Psoriasis Dose</th>
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<tr>
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<td>0.2 mL (10 mg)</td>
</tr>
<tr>
<td>17 - 22</td>
<td>0.3 mL (15 mg)</td>
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<td>23 - 28</td>
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</table>

Adolescent Hidradenitis Suppurativa (from 12 years of age, weighing at least 30 kg)
There are no clinical trials with adalimumab in adolescent patient with hidradenitis suppurativa. The recommended adalimumab dose is 80 mg at week 0 followed by 40 mg every other week, starting at week 1 via subcutaneous injection. In adolescent patients with inadequate response to adalimumab 40 mg every other week, an increase in dosing frequency to 40 mg every week may be considered. Antibiotics may be continued during treatment with adalimumab, if necessary. It is recommended that the patient should use a topical antiseptic wash on their hidradenitis suppurativa lesions on a daily basis during treatment with adalimumab. Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period. Should treatment be interrupted, adalimumab may be re-introduced as appropriate. The benefit and risk of continued long-term treatment should be periodically evaluated.

There is no relevant use of adalimumab in children aged <12 years in this indication.
**Paediatric Crohn’s Disease**

**Paediatric Crohn’s Disease Patients <40 kg**
The recommended adalimumab induction dose regimen for paediatric subjects with moderately to severely active Crohn’s disease is 40 mg at week 0 followed by 20 mg at week 2. In case there is a need for a more rapid response to therapy, the regimen of 80 mg at week 0 (dose can be administered as two injections in 1 day) and 40 mg at week 2 can be used, with the awareness that the risk for adverse events may be higher with the use of the higher induction dose. After induction treatment, the recommended dose is 20 mg every other week via subcutaneous injection. Some subjects who experience inadequate response may benefit from an increase in dosing frequency to 20 mg adalimumab every week.

**Paediatric Crohn’s Disease Patients ≥40 kg**
The recommended adalimumab induction dose regimen for paediatric subjects with moderately to severely active Crohn’s disease is 80 mg at week 0 followed by 40 mg at week 2. In case there is a need for a more rapid response to therapy, the regimen of 160 mg at week 0 (dose can be administered as four injections in 1 day or as two injections per day for 2 consecutive days) and 80 mg at week 2 can be used, with the awareness that the risk for adverse events may be higher with use of the higher induction dose. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Some subjects who experience insufficient response may benefit from an increase in dosing frequency to 40 mg adalimumab every week. Continued therapy should be carefully considered in a subject not responding by week 12. There is no relevant use of adalimumab in children aged <6 years for this indication.

**Paediatric Ulcerative Colitis**
The safety and efficacy of adalimumab in children aged 4 to 17 years have not yet been established. No data are available. There is no relevant use of adalimumab in children aged <4 years for this indication.

**Psoriatic Arthritis and Axial Spondyloarthritis, Including Ankylosing Spondylitis**
There is no relevant use of adalimumab in the paediatric population for the indications of ankylosing spondylitis and psoriatic arthritis.

**Paediatric Uveitis**
The safety and efficacy of adalimumab in children aged 2 to 17 years have not yet been established. No data are available.

**Women of Childbearing Potential/Contraception in Males and Females**
Women of childbearing potential are strongly recommended to use adequate contraception to prevent pregnancy and continue its use for at least 5 months after the last adalimumab treatment.

**Pregnancy**
For adalimumab, limited clinical data on exposed pregnancies are available. In a developmental toxicity study conducted in monkeys, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. Preclinical data on postnatal toxicity of adalimumab are not available. 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. Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection. Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother’s last adalimumab injection during pregnancy.

**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 breastfeed for at least 5 months after the last adalimumab treatment.
Contraindications

Hypersensitivity to the active substance or to any of the excipients
Active tuberculosis or other severe infections such as sepsis, or opportunistic infections
Moderate-to-severe heart failure (NYHA class III/IV)

Warnings And Precautions

General

Infections
Patients taking TNF-antagonists are more susceptible to serious infections. Impaired lung function may increase the risk for developing infections. Patients must, therefore, be monitored closely for infections, including tuberculosis, before, during and after treatment with adalimumab. Because the elimination of adalimumab may take up to 4 months, monitoring should be continued throughout this period. Treatment with adalimumab should not be initiated in patients with active infections, including chronic or localized infections, until infections are controlled. In patients who have been exposed to tuberculosis and patients who have travelled in areas of high risk of tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, the risk and benefits of treatment with adalimumab should be considered prior to initiating therapy. Patients who develop a new infection while undergoing treatment with adalimumab, should be monitored closely and undergo a complete diagnostic evaluation. Administration of adalimumab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled. Physicians should exercise caution when considering the use of adalimumab in patients with a history of recurring infection or with underlying conditions, which may predispose patients to infections, including the use of concomitant immunosuppressive medications.

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

Tuberculosis
Tuberculosis, including reactivation and new onset of tuberculosis, has been reported in patients receiving adalimumab. Reports included cases of pulmonary and extra-pulmonary (i.e. disseminated) tuberculosis. Before initiation of therapy with adalimumab, all patients must be evaluated for either active or inactive (latent) tuberculosis infection. This evaluation should include a detailed medical assessment of patient history of tuberculosis or possible previous exposure to people with active tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests (i.e. tuberculin skin test and chest X-ray) should be performed in all patients (local recommendations may apply). It is recommended that the conduct and results of these tests are recorded in the patient 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, adalimumab therapy must not be initiated. In all situations described below, the benefit/risk balance of therapy should be very carefully considered. If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted. If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylaxis treatment before the initiation of adalimumab, and in accordance with local recommendations. Use of anti-tuberculosis prophylaxis treatment should also be considered before the initiation of adalimumab in patients with several or significant risk factors for tuberculosis.
despite a negative test for tuberculosis and in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with adalimumab. Some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with adalimumab. Patients should be instructed to seek medical advice if signs/symptoms suggestive of a tuberculosis infection (e.g. persistent cough, wasting/weight loss, low-grade fever, listlessness) occur during or after therapy with adalimumab.

**Other Opportunistic Infections**

Opportunistic infections, including invasive fungal infections, have been observed in patients receiving adalimumab. These infections have not consistently been recognized in patients taking TNF-antagonists and this resulted in delays in appropriate treatment, sometimes resulting in fatal outcomes. For patients who develop the signs and symptoms such as fever, malaise, weight loss, sweats, cough, dyspnoea, and/or pulmonary infiltrates or other serious systemic illness with or without concomitant shock, an invasive fungal infection should be suspected and administration of adalimumab should be promptly discontinued. Diagnosis and administration of empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the care of patients with invasive fungal infections.

**Hepatitis B Reactivation**

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including adalimumab, who are chronic carriers of this virus (i.e. surface antigen-positive). Some cases have had a fatal outcome. Patients should be tested for HBV infection before initiating treatment with adalimumab. For patients who test positive for hepatitis B infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Carriers of HBV who require treatment with adalimumab should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data from treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, adalimumab should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

**Neurological Events**

TNF-antagonists, including adalimumab, have been associated in rare instances with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis and optic neuritis, and peripheral demyelinating disease, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of adalimumab in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of adalimumab should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders. Neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of adalimumab therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.

**Allergic Reactions**

Serious allergic reactions associated with adalimumab were rare during clinical trials. Non-serious allergic reactions associated with adalimumab were uncommon during clinical trials. Reports of serious allergic reactions, including anaphylaxis, have been received following adalimumab administration. If an anaphylactic reaction or other serious allergic reaction administration of adalimumab should be discontinued immediately and appropriate therapy initiated.

**Immunosuppression**

No evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T-, B-, NK-cells, monocyte/macrophages, and neutrophils.

**Malignancies and Lymphoproliferative Disorders**

There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates the risk estimation. With the current knowledge, a possible risk
for the development of lymphomas, leukaemia, and other malignancies in patients treated with a TNF-antagonist cannot be excluded. The potential risk with the combination of azathioprine or 6-mercaptopurine and adalimumab should be carefully considered. A risk for the development of hepatosplenic T-cell lymphoma in patients treated with adalimumab cannot be excluded. No studies have been conducted that include patients with a history of malignancy or in whom treatment with adalimumab is continued following development of malignancy. Thus, additional caution should be exercised in considering adalimumab treatment of these patients. All patients, and in particular patients with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of psoralen and ultraviolet A radiation treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with adalimumab. Melanoma and Merkel cell carcinoma have also been reported in patients treated with TNF-antagonists, including adalimumab. Caution should be exercised when using any TNF-antagonist in chronic obstructive pulmonary disease patients as well as in patients with increased risk for malignancy due to heavy smoking. With current data, it is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (e.g. patients with long-standing ulcerative colitis or primary sclerosing cholangitis) or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. Haematologic Reactions Patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor) while on adalimumab. Discontinuation of adalimumab therapy should be considered in patients with confirmed significant haematologic abnormalities. Vaccinations Patients on adalimumab may receive concurrent vaccinations, except for live vaccines. Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy. Congestive Heart Failure Adalimumab should be used with caution in patients with mild heart failure (NYHA class I/II). Treatment with adalimumab must be discontinued in patients who develop new or worsening symptoms of congestive heart failure. Autoimmune Processes Treatment with adalimumab may result in the formation of autoimmune antibodies. The impact of long-term treatment with adalimumab on the development of autoimmune diseases is unknown. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with adalimumab and is positive for antibodies against double-stranded DNA, further treatment with adalimumab should not be given. Concurrent Administration of Biologic DMARDS or TNF-Antagonists Concomitant administration of adalimumab with other biologic DMARDS (e.g. anakinra and abatacept) or other TNF-antagonists is not recommended based upon the possible increased risk for infections, including serious infections and other potential pharmacological interactions. Surgery There is limited safety experience of surgical procedures in patients treated with adalimumab. The long half-life of adalimumab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on adalimumab should be closely monitored for infections, and appropriate actions should be taken. There is limited safety experience in patients undergoing arthroplasty while receiving adalimumab. Small Bowel Obstruction
Failure to respond to treatment for Crohn's disease may indicate the presence of fixed fibrotic stricture that may require surgical treatment. Available data suggest that adalimumab does not worsen or cause strictures.

**Elderly**

Particular attention regarding the risk for infection should be paid when treating the elderly.

### Drug Interactions

**Methotrexate**

Adalimumab has been studied in rheumatoid arthritis patients taking concomitant methotrexate. Although methotrexate reduced the apparent adalimumab clearance, the data do not suggest the need for dose adjustment of either adalimumab or methotrexate.

**Biological Products**

In clinical studies with rheumatoid arthritis, an increased risk of serious infections has been seen with the combination of TNF blockers with anakinra or abatacept, with no added benefit; therefore, use of adalimumab with abatacept or anakinra is not recommended in patents with rheumatoid arthritis. A higher rate of serious infections has also been observed in patients with rheumatoid arthritis treated with rituximab who received subsequent treatment with a TNF blocker. There is insufficient information regarding the concomitant use of adalimumab and other biological products for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, uveitis and plaque psoriasis. Concomitant administration of adalimumab with other biologic DMARDs (e.g., anakinra, and abatacept) or other TNF blockers is not recommended based upon the possible increased risk of infections and other potential pharmacological interactions.

**Live Vaccines**

Avoid the use of live vaccines with adalimumab.

**Cytochrome (CYP) P450 Substrates**

The formation of CYP450 enzymes maybe suppressed by increased levels of cytokines (e.g. TNF alpha, IL-6) during chronic inflammation. It is possible for a molecule that antagonizes cytokine activity, such as adalimumab, to influence the formation of CYP450 enzymes. Upon initiation or discontinuation of adalimumab in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g. warfarin) or drug concentration (e.g. cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

### Preclinical Data

In single dose toxicity studies with adalimumab in rats and mice, no clinical signs of toxicity and mortality were observed at doses up to 165.3 mg/kg and 328 mg/kg respectively. In repeated dose toxicity studies with adalimumab in rats and rabbits, no significant toxic effects were observed at doses up to 82.7 mg/kg and 41.3 mg/kg respectively. No significant immunogenic reactions were observed in rats treated with test and reference items at 16.5 mg/kg body weight. In guinea pigs, adalimumab was observed to have no skin sensitization potential. These observations were observed with studies involving in-house adalimumab product.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term animal studies of adalimumab have not been conducted to evaluate the carcinogenic potential or its effect on fertility. No clastogenic or mutagenic effects of adalimumab were observed in the in vivo mouse micronucleus test or the Salmonella-Escherichia coli (Ames) assay, respectively. No studies of impairment of fertility with adalimumab have been conducted.

### Undesirable Effects

**Body as a Whole**
Pain in extremity, pelvic pain, surgery, thorax pain.

Blood and the Lymphatic System Disorders
Leucopaenia (including neutropaenia and agranulocytosis), anaemia, leukocytosis, thrombocytopenia, idiopathic thrombocytopenic purpura, pancytopenia, polycythaemia.

Cardiac Disorders
Arrhythmia, atrial fibrillation, chest pain, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, tachycardia, CHF.

Endocrine System
Parathyroid disorder.

Metabolism and Nutritional Disorders
Dehydration, healing abnormal ketosis, paraproteinaemia, peripheral oedema, lipids increased, hypokalaemia, uric acid increased, blood sodium abnormal, hypocalcaemia, hyperglycaemia, hypophosphataemia.

Musculoskeletal and Connective Tissue Disorders
Arthritis, bone disorder, bone fracture, (not spontaneous), bone necrosis, joint disorder, muscle cramps, myasthenia, pyogenic arthritis, synovitis, tendon disorder, musculoskeletal pain, muscle spasms (including blood creatine phosphokinase increased), rhabdomyolysis, systemic lupus erythematosus, lupus-like syndrome.

Nervous System Disorders
Confusion, subdural haematoma, tremor, demyelinating disorders (e.g. optic neuritis, Guillain-Barré syndrome), cerebrovascular accident, headache, paraesthesias (including hypoesthesia), migraine, nerve root compression, neuropathy, multiple sclerosis.

Respiratory, Thoracic and Mediastinal Disorders
Asthma, bronchospasm, dyspnoea, lung function decreased, pleural effusion, interstitial lung disease, including pulmonary fibrosis, pulmonary embolism, cough, chronic obstructive pulmonary disease, pneumonitis.

Renal and Urinary Disorders
Renal impairment, haematuria, nocturia, cystitis, kidney calculus, menstrual disorder.

Gastrointestinal Disorders
Diverticulitis, large bowel perforations, including perforation associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis, cholecystitis, cholelithiasis, oesophagitis, gastrointestinal haemorrhage, vomiting, abdominal pain, nausea, dyspepsia, gastro-oesophageal reflux disease, sicca syndrome, dysphagia, face oedema.

General Disorders and Administration Site Conditions
Pyrexia, injection site reaction (including injection site erythema), chest pain, oedema, inflammation.

Hepatobiliary Disorders
Liver failure, hepatitis, hepatic necrosis, elevated liver enzymes, hepatic steatosis, bilirubin increased, reactivation of hepatitis B, autoimmune disease.

Immune System Disorders
Sarcoidosis, hypersensitivity, allergies (including seasonal allergy), vasculitis, anaphylaxis.

Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)
Merkel cell carcinoma (neuroendocrine carcinoma of the skin), adenoma, skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma); benign neoplasm, lymphoma, solid organ neoplasm (including breast cancer, lung neoplasm and thyroid neoplasm), melanoma, leukaemia, hepatosplenic T-cell lymphoma.

Skin and Subcutaneous Tissue Disorders
Steven-Johnson syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all subtypes including pustular and palmoplantar), alopecia, rash (including exfoliative rash), urticaria, bruising (including purpura), dermatitis
(including eczema), onychoclasis, hyperhidrosis, pruritus, night sweats, scar, erythema multiforme, angio-oedema, cutaneous vasculitis, worsening of symptoms of dermatomyositis.

Vascular Disorders
Systemic vasculitis, deep vein thrombosis, hypertension, flushing, haematoma, aortic aneurysm, vascular arterial occlusion, thrombophlebitis.

Infections and Infestations
Respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis, and pneumonia herpes viral), systemic infections (including sepsis, candidiasis and influenza), intestinal infections (including gastroenteritis viral), skin and soft infections (including paronychia, cellulitis, impetigo, necrotizing fasciitis and herpes zoster), ear infections, oral infections (including herpes simplex, oral herpes and tooth infections), reproductive tract infections (including vulvovaginal mycotic infection), urinary tract infections (including pyelonephritis), fungal infections, joint infections, neurological infections (including viral meningitis), opportunistic infections and tuberculosis (including coccidiodomycosis, histoplasmosis and mycobacterium avium complex infection), bacterial infections, eye infections.

Psychiatric Disorders
Mood disorders (including depression), anxiety, insomnia.

Eye Disorders
Visual impairment, conjunctivitis, blepharitis, eye swelling, diplopia, cataract.

Ear and Labyrinth Disorders
Vertigo, deafness, tinnitus.

Reproductive System and Breast Disorders
Erectile dysfunction.

Investigations
Coagulation and bleeding disorders (including activated partial thromboplastin time prolonged), auto-antibody test positive (including double-stranded DNA antibody), blood lactate dehydrogenase increased.

Injury, Poisoning and Procedural Complications
Impaired healing.

Safety Data from CIPLEUMAB Clinical Study in Rheumatoid Arthritis
A total of 14 adverse events were reported in 11 subjects (13.8%) with CIPLEUMAB. In 2 patients, two serious adverse events (CIPLEUMAB – sinusitis; Reference adalimumab – viral infection) were reported during the study and these were resolved completely. There were no deaths, and no life-threatening adverse events were reported. If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024. By reporting side effects you can help provide more information on the safety of this product.

Overdosage
No dose-limiting toxicity was observed during clinical trials. The highest dose level evaluated has been multiple intravenous doses of 10 mg/kg, which is approximately 15 times the recommended dose.

Incompatibility
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
**Storage And Handling Instructions**

CIPLEUMAB should be stored in a refrigerator. Store between 2°C to 8°C. Do not freeze or shake. Protect from light. Keep out of reach of children.

**Packaging Information**

CIPLEUMAB is available in the following strength: 40 mg/0.8 ml. CIPLEUMAB is supplied as a preservative-free, sterile solution for subcutaneous administration.

The following packaging configuration is available:
- 40 mg/0.8 ml in a single-use, prefilled glass syringe

Last Updated: *March 2018*

**CIPLEUMAB Subcutaneous Injection**

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