The recommended initial dose is 40 mg every other week q.s. to pH 5.2. Some patients who experience insufficient response may benefit from an increase to 80 mg every other week starting from week 6 (Day 15) can be used. Two weeks later (Day 29), a maintenance dose of 40 mg every other week can be initiated if TNF-antagonist treatment is being considered in such cases.

**THERAPEUTIC INDICATIONS**

Exemptia™ is indicated for Rheumatoid Arthritis (RA) in adults:
- Severe, active and progressive RA
- Juvenile idiopathic arthritis
- Moderate to severe active polyarthritic JIA in pediatric patients of 2 years of age and older
- Active enthesal-related arthritis in patients of 5 years of age and older

**PHARMACEUTICAL FORM AND COMPOSITION**

Exemptia™ contains Adalimumab as its active ingredient. Adalimumab is a fully human monoclonal antibody that is produced recombinantly in CHO (Chinese hamster ovary) cells. Adalimumab consists of 1330 amino acid containing glycoprotein which has two copies of heavy and two copies of light chain in heterodimer form with a molecular weight of 144.367 g/mol.

**POSSIBLE MEANS OF ADMINISTRATION**

Example: To be administered subcutaneously.

**Rheumatoid Arthritis (RA)**

- The recommended dose in adults is 40 mg every other week. Patients with RA not receiving methotrexate may benefit from increasing the frequency to 40 mg every week.
- For a more rapid response, an initial dose (Day 1) of 160 mg (four 40 mg injections in one day or two 80 mg injections on two consecutive days), followed by 40 mg every other week (Day 15), can be used. Two weeks later (Day 29), a maintenance dose of 40 mg every other week can be initiated.
- Some patients who experience insufficient response may benefit from an increase in dosing frequency to 40 mg every week.

**Elderly patients**

- No dose adjustment is required
- Initial rapid and/or hepatitis C infection
- Adalimumab has not been studied in these patients. No dose recommendations can be made.

**CONTRAINDICATIONS**

- Active tuberculosis or other severe infections such as sepsis and opportunistic infections

**SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

- Patients taking TNF-antagonists or with impaired lung function are susceptible to serious infections and therefore should be monitored throughout Adalimumab treatment including before and after vaccination.
- Patients should only be treated with Adalimumab after active infections including chronic or localized infections are controlled.
- Risks and benefits of Adalimumab therapy should be re-evaluated after vaccination in patients who have been previously exposed to infections including the case of patients who travelled high-risk tuberculosis areas or endemic mycoses such as blastomycosis, histoplasmosis and coccidioidomycosis.

- When patients develop a new infection while being treated with Adalimumab, a complete diagnostic evaluation should be performed and the patient should be closely monitored. Adalimumab should be discontinued in cases where a new infection or sepsis develops, and appropriate antibacterial or antifungal therapy should be started to control the infection.
- Physicians should prescribe Adalimumab with caution after patients’ history to infections including the use of combined immunosuppressive medications.

**UNDESIRABLE EFFECTS**

- Adverse reactions that have been seen with concurrent use of Adalimumab with Etanercept, Infliximab, Abatacept, Certolizumab pegol, Adalimumab with another TNF blocker (infliximab or etanercept). Short bowel obstruction

- Failure to respond to treatment for Crohn’s disease may result in the presence of focal or superficial fistulization and may require surgical intervention.
- Adalimumab does not vorsen or cause stenosis.

**PREGNANCY AND LACTATION**

- Risk of infection in elderly patients over 65 years of age is higher than those below 65 years of age, and patients with some heavy lymphatic disease or other serious systemic illness with or without concomitant shock, and an invasive immune reaction such as Crohn’s disease and psoriasis may benefit from early and appropriate care in such cases. It is advised that the patients who were treated with infliximab who had moderate to severe chronic obstructive pulmonary disease (COPD) and were heavy smokers. Therefore, caution should be used after initiation of Adalimumab therapy in such cases.

**INTERACTION WITH OTHER MEDICAL PRODUCTS AND OTHER FORMS OF TREATMENT**

Adalimumab treatment as monotherapy and in combination with methotrexate has been studied in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and ankylosing spondylitis in pediatric patients. For patients who need to be considered prior to planning a surgery and the patient should be monitored for infections.

**ADVERSE EVENTS OBSERVED IN CLINICAL TRIAL TREATING DISEASES**

Adalimumab can affect normal immune responses of the newborn if administered after the 36th week of gestation. There is no data suggesting whether Adalimumab is excreted in human milk in any significant amounts.

- It is not recommended for women to breastfeed for at least five months after the last dose of Adalimumab (initiation of breastfeeding is allowed at least five months after the last dose of Adalimumab treatment). The infant’s weight gain may be greater than those of the exposed group of infants.

**EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

Adalimumab may result in visual impairment which can affect the ability to drive one’s own car or operate machinery.

**UNDESIRABLE EFFECTS**

- The most common reported undesirable effects in patients taking Adalimumab include infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (itching, stinging, haematoma, pain or swelling), headache and local injection site reactions (such as swelling, redness, pain, induration, bruising, oedema and abscess). For patients who have been treated with infliximab who had moderate to severe chronic obstructive pulmonary disease (COPD) and were heavy smokers. Therefore, caution should be used after initiation of Adalimumab therapy in such cases.

- Rare instances of malignancies such as lymphoma and leukemia have been seen in patients treated with TNF-antagonists. RA patients with long-standing, highly active inflammatory diseases were at a higher risk of experiencing these malignancies.

- Infections and infestations
- Infections and infestations
**Pharmacodynamic effects**

**Adalimumab** treatment, the levels of acute phase reactants of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)), and serum cytokines (IL-6) declined rapidly in comparison to baseline levels in patients with RA. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce remodeling responsible for osteoarticular destruction were also decreased after Adalimumab administration.

A rapid decrease in CRP levels was also observed in patients with polyarticular juvenile idiopathic arthritis. Crohn’s disease and ulcerative colitis after treatment with Adalimumab. In patients with Crohn’s disease, a reduction of the number of cells expressing inflammatory markers in the colon including a significant reduction of expression of TNF-α was seen. Markers of intestinal mucosa have shown evidence of mucosal healing in Adalimumab treated patients.

**Clinical Efficacy and Safety**

**Clinical Trial of CHL’s Adalimumab in Indian Patients**

A total 162 subjects were screened on a single visit at different sites in India, of whom 120 subjects were enrolled in the study. 82 subjects in each group; 63 CHL’s Adalimumab and innovator’s Adalimumab. Total 103 subjects were qualified as per protocol (N=51) and 119 subjects qualified for intent to treat (ITT) which were included for efficacy analysis, respectively.

**Efficacy Conclusions of CHL Trials**

The American College of Rheumatology (ACR) response was significantly improved for each group at each evaluation throughout the study. After treatment with CHL’s Adalimumab, at Visit 5 (day 84), 62% of patients treated with ACR 20, 49% with ACR 50 and 19% with ACR 70. In innovator’s Adalimumab group, Visit 5 (day 84), 72% of patient had an ACR 20, 43% had an ACR 50 and 15.7% had an ACR 70 response. No statistically significant differences between the treatment groups were observed in ACR responses.

In addition to these parameters, significant improvement was noted in all ACR 20 responders. The difference in treatment groups was not significant.

**Safety conclusions of CHL Trials**

**Adalimumab** was well tolerated and no new safety signals were observed. A total of 31 adverse events (AEs) including 3 serious adverse events (SAEs) were reported during the study, which were completely resolved. The distribution of AEs was comparable between the treatment groups. There were 15 AEs (including 2 SAEs) reported by 9 subjects in CHL’s Adalimumab treated group, whereas in innovator’s Adalimumab treated group 18 AEs (including 1 SAE) were reported by 11 subjects. Pyrexia, headache and cough were commonly reported in both the groups, but there were no differences in the incidence of AEs in both the groups. No serious systemically adverse events were observed throughout the study except in one patient in the study. However, the incidence of SAEs was comparable in both treatment groups.

**Pharmacodynamics**

**Adalimumab properties required for Adalimumab**

Absorption and distribution of a single 40 mg dose is slow and serum concentration reaches peak after 1 day upon subcutaneous administration with an average bioavailability of about 84%. Serum concentrations were dose proportional when single doses ranging from 0.25 to 10 mg were administered. The distribution volume (V) ranges from 3 to 6 liters, clearance range from 11 to 15 liters/hour and the mean terminal phase half-life was approximately 180 days. The selected dose levels were 1X, 5X & 10X of the human equivalent dose for comparative purpose in repeated dose toxicity studies.

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**OVERDOSE**

No dose-limiting toxicity was observed in patients and the highest dose evaluated was intravenous dose of 10 mg/kg administered over 30 minutes. (n=7) The selected dose levels were 1X, 5X & 10X of the human equivalent dose for comparative purpose in repeated dose toxicity studies. Repeated dose toxicity studies by subcutaneous route comprising weekly dosing schedule over a period of four weeks was performed in rat and rabbit. Local tolerance evaluation was a part of repeated dose toxicity studies and by an independent skin sensitization study in guinea pigs. In general, CHL’s Adalimumab revealed a good safety margin in terms of body weight, brain and major organs were unaffected in rabbits. A comparative study of CHL’s Adalimumab was performed at different sites in India, of whom 120 subjects were enrolled in the study. 82 subjects in each group; 63 CHL’s Adalimumab and innovator’s Adalimumab.

**Pharmacodynamics**

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- Approximately 5 mg/L without concomitant methotrexate and 5 to 9 mg/L with concomitant methotrexate with a dosage of 10 mg every other week.
- Secure trough levels at steady-state increase proportionally with dose increase (30, 40 and 80 mg subcutaneous dose every other week and every week).
- Parenteral adverse effects: patients of 65 years or age and older.
- Approximately 0.1 mg/L without concomitant methotrexate and 0.6 to 2 mg/L with concomitant methotrexate (c) measured from week 2 to week 4 with a dose of 24 mg/week (up to a maximum of 40 mg) every other week.
- Loading dose of 80 mg Adalimumab on week 2 followed by 40 mg Adalimumab on week 2 and 2 weeks with 25 mg, trough concentration
- Loading dose of 160 mg Adalimumab on week 2 followed by 80 mg Adalimumab on week 2 and 2 weeks with 25 mg, trough concentration
- Loading dose of 160 mg Adalimumab on week 2 followed by 80 mg Adalimumab on week 2 and 2 weeks with 25 mg, trough concentration
- Plasma trough concentration was observed in patients receiving 40 mg Adalimumab every other week.
- Approximately 0.1 mg/L without concomitant methotrexate and 0.6 to 2 mg/L with concomitant methotrexate.
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