The recommended dose in adult patients is 40 mg every other week. Drugs such as methotrexate, glucocorticoids, salicylates, non-steroidal anti-inflammatory drugs, or other serious systemic illnesses/conditions are not to be used in these patients who have been diagnosed with active tuberculosis. An expert in tuberculosis should be consulted if latent tuberculosis is suspected when Adalimumab treatment is being considered.

Tuberculosis

All patients must be evaluated in detail (including medical history) for both active or latent tuberculosis before treatment with Adalimumab. The patient’s file should have records of tuberculosis skin test and chest X-rays. This history should be reviewed by the treating physician. Adalimumab therapy should not be initiated in patients who have been treated with tuberculosis or have active tuberculosis as well as in patients who have had a positive test for tuberculosis. When initiating Adalimumab therapy in patients with a history of tuberculosis, fully evaluate the patient to determine whether tuberculosis is active or latent; if positive, patients should be treated with appropriate antimycobacterial therapy before starting Adalimumab.

Adalimumab is contraindicated in patients with active, untreated tuberculosis, as well as those with known or suspected latent tuberculosis infection. Adalimumab is also contraindicated in patients with severe active tuberculosis or those who have had tuberculosis within the past 5 years.

Malignancies

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 disease are at a higher risk of experiencing these malignancies. In Adalimumab-treated patients, there have been reports of lymphomas and leukemias. Malignancies were reported in patients treated with TNF-antagonists who had moderate to severe chronic inflammatory disease. RA patients who have been treated with TNF-antagonists are at increased risk of infections to the infant. Live vaccinations to infants exposed to Adalimumab should not also be used with Infliximab, Etanercept, Alemtuzumab, Certolizumab pegol, or golimumab.

Pregnancy

There is a lack of sufficient experience in pediatric or adults undergoing surgical procedures or with impaired lung function. Any patient receiving Adalimumab should be discharged with infection to the infant. Live vaccinations to infants exposed to Adalimumab in the uterus are not recommended for at least 5 months after the mother’s last injection.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Adalimumab may cause dizziness or loss of balance, which may result in falls. These effects are more common with higher doses or in patients with a history of nervous system disorders. Therefore, patients should be advised to use caution while driving or using machinery.

ADVERSE EVENTS OBSERVED IN CHILD, CLINICAL TRIAL WERE: Dyspnoea, fungal infection, injection site reaction, joint swelling, omphalitis, polymyositis, polynephritis, pulmonary tuberculosis, pyrexia, rash, sinus tract infection, vomiting, abdominal distention, abdominal pain, accelerated hypertension, anemia, azotemia, blood loss, chest pain, cough, dysphonia, dyspepsia, dysuria, headache, hypothermia, hypertension, hypertension in renal transplant patients, hypothermia, hypotension, hypovolemia, infection, insomnia, injection site edema, injection site reaction, injection site pain, injection site swelling, jaw pain, joint swelling, leucopenia, lymphadenopathy, myalgia, myositis, nausea, neuropathy, nail disorder, paresthesia, peripheral neuropathy, pharyngitis, pneumonia, pseudomembranous colitis, pyrexia, rash, rhinitis, sinusitis, stomatitis, sweating, tinnitus, urticaria, upper respiratory tract infection, vertigo, vomiting, weight gain, weight loss. There is no data suggesting whether Adalimumab is excreted in human milk or absorbed through the breast.

UNDESIRABLE EFFECTS

The most common reported undesirable effects in patients taking Adalimumab includes: nausea (such as nasopharyngitis, upper respiratory tract infection and sinusitis), vomiting, headache, myalgia, arthralgia, back pain, pruritus, vomiting, abdominal pain, diarrhea, dyspepsia, hypertension, insomnia, pyrexia, urticaria, upper respiratory tract infection, vertigo, abdominal distention, abdominal pain, accelerated hypertension, anemia, azotemia, blood loss, chest pain, cough, dysphonia, dyspepsia, dysuria, headache, hypothermia, hypertension, hypertension in renal transplant patients, hypotension, hypovolemia, infection, insomnia, injection site edema, injection site reaction, injection site pain, injection site swelling, jaw pain, joint swelling, leucopenia, lymphadenopathy, myalgia, myositis, nausea, neuropathy, nail disorder, paresthesia, peripheral neuropathy, pharyngitis, pneumonia, pseudomembranous colitis, pyrexia, rash, rhinitis, sinusitis, stomatitis, sweating, tinnitus, urticaria, upper respiratory tract infection, vertigo, vomiting, weight gain, weight loss. There is no data suggesting whether Adalimumab is excreted in human milk or absorbed through the breast.
**Pharmacodynamic effects:**

Upon Adalimumab treatment, the levels of acute phase reactants of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)), and serum cytokines (IL-1α and TNFα) declined rapidly in both concomitant and non-concomitant patients. Levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce remodeling responsible for osteoporosis decreased as well after Adalimumab administration.

A rapid decrease in CRP levels was also observed in patients with polymyositis/dermatomyositis. Cough's disease and ulcerative colitis after treatment with Adalimumab. In patients with Cushing’s disease, the reduction of the number of cells expressing inflammatory markers in the colon including a significant reduction of expression of TNFα-was seen when compared to baseline. Adalimumab improves the signs and symptoms of these TNFα-associated diseases in patients.

**OVERDOSE:**

No dose-limiting toxicity was observed in patients and the highest dose evaluated was 70 mg/kg without concomitant methotrexate.

**PHARMACOLOGICAL PROPERTIES:**

**Pharmacokinetic properties:** of Adalimumab

- **Absorption:** Absorption and distribution of a single 40 mg dose is slow and serum concentration reaches its peak after 1 day upon subcutaneous administration with an average bioavailability of about 64%. Serum concentrations were dose proportional when single intravenous doses ranging from 0.25 to 10 mg/kg were administered.

- **Distribution:** The distribution volume (Vd) ranges from 5 to 6 L/kg, clearance ranges from 11 to 15 mL/min and half-life was approximately 14 hours with a single dose of Adalimumab administration. Concentration of Adalimumab measured from post-infusion levels of macromolecular antibody ranges from 31-49% of these levels.

- **Elimination:** The mean steady-state trough concentrations after subcutaneous administration of Adalimumab have been calculated from the serum of the following patients:
  - Approximately 5 μg/mL without concomitant methotrexate and 15 μg/mL (with concomitant methotrexate) with a dose of 40 mg every other week.
  - Serum trough levels of steady-state increase proportionally with dose increase (20, 40 and 80 mg subcutaneous dosing every other week and every week).

- **Population pharmacokinetic analysis:** of patients aged 17 years or above:
  - Serum creatinine clearance of <50 mL/min/1.73 m²: 9.6 μg/mL and 25 μg/mL for 40 mg and 80 mg subcutaneous dosing every other week.

**Summary of ACR response by treatment group and visit:**

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**Adalimumab:** N = number of subjects in specified treatment; n = number of patients in whom ACR 20, 50, 70, responders were counted. The 3 ACR criteria and 119 subjects qualified for intent to treat (ITT) criteria which were included for efficacy analysis. For Adalimumab, the NOAEL was considered to be more than 10X of human equivalent dose (41 mg/kg). The selected dose was 15, 50 and 150 mg/kg equivalent dose.

**Safety profiles:** of Adalimumab

- **Adalimumab:** The safety profile of Adalimumab was assessed using a battery of toxicological studies.

  - **Preclinical studies:** for CHL's Adalimumab were performed as per the recommendations set in both Schenk V1 & V2 guidelines in compliance with GLP standards. Muller Labs, Cadila Healthcare Limited.

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  - **Clinical Trial of CHL's Adalimumab in Indian Patients:**

    1,012 subjects were screened and 419 subjects were randomized into 2 arms, of which, 120 subjects enrolled in the study. 419 subjects distributed equally between 2 arms in the Adalimumab and Innovator's Adalimumab arm. The study included 3 equal arms and treatment groups were 3:1 ratio for each of the treatment groups.

- **Immediate or delayed injection site reactions:** observed in 12% of patients in both treatment arms. There were no persistent changes from baseline in laboratory parameters in both treatment arms. General examination showed no significant signs in any treatment group. 2 cases of palp at visit 3 in Innovator's Adalimumab treated arm.

  - **No adverse systemic events was observed throughout the study except for injection site reactions which were comparably divided in both treatment arms.

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**SPECIAL PRECAUTIONS FOR DISPOSAL:**

- **Adalimumab:** Exemptia™ is supplied in pre-filled syringe (borosilicate USP Type I glass barrel) with integrated needle and coated rubber stopper.

  - **Shelf life:** for the medicinal product should not be mixed with other medicinal products.

**SPECIAL PRECAUTIONS FOR STORAGE:**

- **Adalimumab:** Store at 2°C - 8°C (and in the protected from light). Do not freeze Exemptia™. Do not use Exemptia™ if it has frozen, even if the label has not been tampered with.

**KEEP OUT OF REACH OF CHILDREN:**

**NATURAL CONTENTS OF CONTAINER:**

- **Exemptia™** is supplied in pre-filled syringes (technically USP Type I glass barrels) with integrated needle and coated rubber stopper.

**SPECIAL PRECAUTIONS FOR DISPOSAL:**

- **Exemptia™** does not contain any preservatives. Any unused product or waste material should be disposed of in accordance with local regulations.

**MANUFACTURED & MARKETED BY:**

- **Cadila Healthcare Limited** TM - Trademark of Cadila Healthcare Limited

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**Clinical Efficacy and Safety:**

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

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