For the use of a Rheumatologist or an Orthopaedician or a Gastroenterologist or a Dermatologist only
Rx

ADALIMUMAB

Exemptia™

Solution for subcutaneous use
40 mg/0.8 mL single-use pre-filled syringe
20 mg/0.4 mL single-use pre-filled syringe

DESCRIPTION

Exemptia™ contains Adalimumab as an active ingredient. Adalimumab is a fully human monoclonal IgG1 antibody produced recombinantly by Chinese Hamster Ovary (CHO)cells.Adalimumab consists of 1330 amino acid containing glycoprotein which has two copies of heavy- and two copies of light-chains in heterodimeric form with a molecular weight of 148 kDa (approx.). Adalimumab binds specifically to Tumor Necrosis Factor-alpha (TNF-α) and blocks its interaction with the p55 and p75 cell surface TNF receptors.

PHARMACEUTICAL FORM AND COMPOSITION

Exemptia™ is a clear, colorless, sterile, liquid, solution presented in single-dose pre-filled syringes for subcutaneous use.

Each pre-filled syringe of Exemptia™ contains:

Ingredients	**40 mg strength**	**20 mg strength**
Active ingredient		
Adalimumab	40 mg	20 mg
Inactive ingredients		
Succinic acid NF	0.944 mg	0.472 mg
Sodium hydroxide NF	q.s. to pH 5.2	q.s. to pH 5.2
Sodium chloride USP	4.672 mg	2.336 mg
L-Arginine monohydrochloride USP	4 mg	2 mg
Sorbitol NF	8 mg	4 mg
Polysorbate 80 NF	0.08 mg	0.04 mg
WFI	q.s. to 0.8 mL	q.s. to 0.4 mL

THERAPEUTIC INDICATIONS: Exemptia™ is indicated for

Rheumatoid Arthritis (RA) (in adults)
- Moderate to severe, active RA
- Severe, active and progressive RA

Juvenile Idiopathic Arthritis (JIA)
- Moderate to severe active polyarticular JIA in pediatric patients of 2 years of age and older.
- Active enthesitis related arthritis in patients of 6 years of age and older

Psoriatic Arthritis (PsA)
- Active and progressive PsA in adults.

Ankylosing Spondylitis (AS) and axial spondyloarthritis without radiographic evidence of AS
- Active AS and axial spondyloarthritis without radiographic evidence of AS in adults.

Crohn's Disease (CD)
- Patients (adult patients and pediatric patients of 6 years and older) with moderate to severe active CD who have had inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies.

Ulcerative Colitis (UC)
- Adult patients with moderate to severe active UC who have had an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies.

Plaque Psoriasis (Ps)
- Moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy

Hidradenitis Suppurativa (HS)
- Moderate to severe Hidradenitis Suppurativa.

POSOLOGY AND METHOD OF ADMINISTRATION

Exemptia™ needs to be administered as a subcutaneous injection.

Rheumatoid arthritis (RA)
- The recommended dose in adult patients is 40 mg every other week. Patients with RA not receiving methotrexate may benefit from increasing the frequency to 40 mg every week. Drugs such as methotrexate, glucocorticoids, salicylates, non-steroidal anti-inflammatory drugs, or analgesics can be continued during Adalimumab treatment.

Juvenile Idiopathic Arthritis
- The recommended dose of Adalimumab for patients 2 years of age and older with polyarticular JIA is based on weight as shown below:

Patients (2 years of age and older)	**Dose**
10 kg (22 lbs) to <15 kg (33 lbs)	10 mg every other week
15 kg (33 lbs) to <30 kg (66 lbs)	20 mg every other week
≥30 kg (66 lbs)	40 mg every other week

Enthesitis related arthritis
- The recommended dose is 24 mg/m² up to a maximum single dose of 40 mg administered every other week

Psoriatic Arthritis
- The recommended dose in adult patients is 40 mg every other week. Drugs such as methotrexate, glucocorticoids, salicylates, non-steroidal anti-inflammatory drugs, or analgesic can be continued during Adalimumab treatment

Ankylosing Spondylitis (AS) and axial spondyloarthritis without radiographic evidence of AS
- The recommended dose in adult patients is 40 mg every other week

Crohn's disease

Adult patients and pediatric patients ≥ 40 kg:
- The recommended initial dose is 80 mg (Day 1) followed by 40 mg on Day 15, and further followed by 40 mg every other week
- For a more rapid response, an initial dose (Day 1) of 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15) can be used. Two weeks later (Day 29), begin a maintenance dose of 40 mg every other week.
- Some patients who experience insufficient response may benefit from an increase in dosing frequency to 40 mg every week

Pediatric patients < 40 kg:
- The recommended initial dose is 40 mg (Day 1) followed by 20 mg on Day 15, and further followed by 20 mg every other week
- For a more rapid response, an initial dose (Day 1) of 80 mg (two 40 mg injections in one day), followed by 40 mg two weeks later (Day 15) can be used. Two weeks later (Day 29), begin a maintenance dose of 20 mg every other week
- Some patients who experience insufficient response may benefit from an increase in dosing frequency to 20 mg every week

Ulcerative colitis
- The recommended initial dose is 160 mg (Day 1) (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg every other week.
- Some patients who experience insufficient response may benefit from an increase in dosing frequency to 40 mg every week

Plaque Psoriasis
- Initial dose of 80 mg, followed by 40 mg every other week starting from week one after initial dose

Hidradenitis Suppurativa (HS)
- 160 mg (Day 1) (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15).
- Two weeks later (Day 29) begin a maintenance dose of 40 mg every other week.

Elderly patients
- No dose adjustment is required

Impaired renal and/or hepatic function
- Adalimumab has not been studied in these patients. No dose recommendations can be made.

CONTRAINDICATIONS

Adalimumab, sterile solution for injection is contraindicated in the following conditions:
- Hypersensitivity to the active substance or to any of the excipients.
- Moderate to severe heart failure
- Active tuberculosis or other severe infections such as sepsis and opportunistic infections

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Infections

Patients taking TNF-antagonists or with impaired lung function are susceptible to serious infections and therefore should be monitored throughout Adalimumab treatment including before, during and after treatment.

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 reviewed prior to initiating the treatment in patients who have been exposed to tuberculosis (including the ones who have travelled through high-risk tuberculosis areas) or endemic mycoses such as histoplasmosis, blastomycosis 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 serious infection or sepsis develops, and appropriate antifungal or antimicrobial therapy should be initiated to control the infection. Physicians should prescribe Adalimumab with caution after examining patient's history to infections including the use of concomitant immunosuppressive medications.

Serious infections

Patients receiving Adalimumab have encountered hospitalization, fatal outcomes, serious infections such as pneumonia, pyelonephritis, septic arthritis and septicemia due to bacterial, mycobacterial, invasive fungal, parasitic, viral, or other opportunistic infections such as listeriosis, legionellosis and pneumocystis.

Tuberculosis

All patients must be examined in detail (including medical history) for both, active or inactive (latent) tuberculosis infection and current immunosuppressive therapy prior to administering Adalimumab as tuberculosis has been reported in patients receiving Adalimumab. The patient's file should have records of tuberculin skin test and chest X-ray. Adalimumab therapy should not be initiated in those 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.

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.

Patients should be instructed to seek medical advice for symptoms such as persistent cough, wasting/weight loss, low grade fever etc. that occur during or after Adalimumab treatment.

Other opportunistic infections

Adalimumab treatment can result in opportunistic infections including invasive fungal infections in patients which if left untreated may prove fatal.

Adalimumab treatment should be discontinued in patients who show symptoms of fever, malaise, weight loss, sweats, cough, dyspnea, and/or pulmonary infiltrates or other serious systemic illness with or without concomitant shock, and an invasive fungal infection should be suspected. Antifungal therapy should be initiated under extreme care and expertise in patients who show invasive fungal infections.

Hepatitis B reactivation

Patients who are chronic carriers of Hepatitis B virus (i.e., surface antigen positive) can show reactivation of hepatitis B while being treated with TNF-antagonists such as Adalimumab,which in the past have sometimes resulted in fatal outcomes. Therefore, HBV infection test should be performed prior to administration of Adalimumab and an expert in treatment of hepatitis B should be consulted for patients who test positive for hepatitis B virus infection.

Signs and symptoms for active HBV infection should be monitored in carriers of HBV throughout Adalimumab treatment and for several months after termination of therapy. Adalimumab treatment should be discontinued and anti-viral therapy should be initiated if HBV reactivation occurs in a patient.

Neurological events

Rarely, Adalimumab and other TNF-antagonists have been shown to be associated with exacerbation or new onset of central or peripheral nervous system demyelinating disorders such as multiple sclerosis and Guillain-Barré syndrome. Thus, Adalimumab should be prescribed with caution in such cases.

Allergic reactions

Only rare incidents of serious/non-serious allergic reactions such as anaphylaxis have been reported with Adalimumab treatment. Adalimumab treatment should be discontinued if serious allergic reactions such as anaphylaxis, allergic rash, fixed drug reaction, non-specified drug reaction or urticaria are observed in patients.

Immunosuppression

Adalimumab treatment is not reported to be associated with depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T, B, NK cells, monocyte/macrophages, and neutrophils in clinical studies.

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.

Malignancies in Adults: Cases of malignancies other than lymphoma that have been observed in patients with RA, psoriatic arthritis, ankylosing spondylitis, Crohn'sdisease and plaque psoriasis are breast cancer, colon cancer, prostate cancer, lung cancer and melanoma. Malignancies in the lung or head and neck were reported in patients treated with infliximab who had moderate to severe chronic obstructive pulmonary disease (COPD) and were heavy smokers. Therefore, caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with increased risk for malignancy due to heavy smoking.

Non-melanoma skin cancer: Prior to and during treatment with Adalimumab, patients should be examined for non-melanoma skin cancer especially if they have a history of extensive immunosuppressant therapy or psoriasis patients with a history of PUVA treatment.

Lymphoma and Leukemia: The risk of lymphoma development is higher in patients with RA, other chronic inflammatory diseases particularly with highly active disease or chronic exposure to immunosuppressant therapies than general population even when a TNF blocker is not used. Acute and chronic leukemia were also reported with TNF-antagonist in RA and other indications.

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-antagonists (initiation of therapy ≤ 18 years of age), including Adalimumab. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression.

Rare cases of hepatosplenic T-cell lymphoma (HSTCL) have occurred in patients treated with Adalimumab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Some of these HSTCL with Adalimumab have occurred in young adult patients on concomitant treatment with azathioprine or 6-mercaptopurine.

Haematologic reactions

The following haematologic reactions have been reported with TNF-antagonists: pancytopenia, aplastic anaemia, cytopenia (e.g. thrombocytopenia, leucopenia) and blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor). Medical attention should be sought upon observation of these symptoms and Adalimumab should be discontinued.

Vaccinations

Similar antibody responses to the standard 23-valent pneumococcal vaccine and the influenza trivalent virus vaccination were observed in a study in adult subjects with RA who were treated with Adalimumab or placebo. Therefore, patients can receive vaccination (except live vaccines) while on Adalimumab treatment.

Congestive heart failure

Increased mortality and worsening congestive heart failure have been reported in patients treated with TNF-antagonists including Adalimumab. Treatment must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Autoimmune processes

Autoantibodies may develop in patients taking Adalimumab with rare instances of symptoms of lupus-like syndrome. Adalimumab treatment should be discontinued in such cases.

Concurrent administration of TNF-antagonists or other biological DMARDs

Serious infections have been seen with concurrent use of Anakinra with Etanercept. Therefore Adalimumab is not recommended to be used with Anakinra. Adalimumab should also not be used with Infliximab, Etanercept, Abatacept, Certolizumab pegol, or Golimumab.

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.

Surgery

There is little or no safety experience in patients undergoing surgical procedures or arthroplasty during Adalimumab treatment. The long half-life of Adalimumab should be considered prior to planning a surgery and the patient should be monitored for infections.

Elderly Population

Risk of infection in elderly patients over 65 years of age is higher than those below this age with some having fatal outcomes. Thus, particular attention should be given.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Adalimumab treatment as monotherapy and with concomitant methotrexate has been studied in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and psoriatic arthritis patients. Adalimumab when given with methotrexate results in lower antibody formation, decreased clearance and increased efficacy of Adalimumab in comparison to Adalimumab monotherapy treatment. Combinations of Adalimumab with Anakinra, and Adalimumab with Abatacept are not recommended.

PREGNANCY AND LACTATION

Pregnancy

Limited clinical data is available on exposed pregnancies for Adalimumab.

Preclinical studies conducted in monkeys revealed no indication of maternal toxicity, embryotoxicity or teratogenicity; postnatal toxicity and fertility effects of Adalimumab are unavailable.

Adalimumab can affect normal immune responses of the newborn if administered during pregnancy due to its inhibition of TNF and hence it is not recommended in pregnancy. Women should use adequate contraception during Adalimumab treatment and for a further five months after the last dose to prevent pregnancy as it bears the potential to cross the placenta into the serum of infants. This could lead to increased risk of infection to the infant. Live vaccinations to infants exposed to Adalimumab in utero is not recommended for at least 5 months after the mother's last injection.

Lactation

It is not recommended for women to breast-feed for at least five months after the last Adalimumab injection as human immunoglobulins are excreted in milk and there is no data suggesting whether Adalimumab is excreted in human milk or absorbed systemically after ingestion.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Administration of Adalimumab may result in vertigo and visual impairment which can influence the ability to drive and use machines.

ADVERSE EVENTS OBSERVED IN CHL's CLINICAL TRIAL WERE:

Dyspnoea, fungal infection, gastritis, headache, injection site reaction, joint swelling, oligomenorrhoea, pollakiuria, polymenorrhoea, pulmonary tuberculosis, pyrexia, rash, urinary tract infection, vomiting, abdominal discomfort, abdominal pain, accelerated hypertension, arthralgia, asthenia, body tinea, chest pain, cough, diarrhoea and dyspepsia.

UNDESIRABLE EFFECTS

The most commonly reported undesirable effects in patients taking Adalimumab include: infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache and musculoskeletal pain. Some fatal infections (including sepsis, opportunistic infections, TB), HBV reactivation and various malignancies (including leukaemia, lymphoma and HSTCL) have been reported. Serious reactions such as haematological, neurological and autoimmune reactions were also reported. Some rare reactions include pancytopenia, aplastic anaemia, central and peripheral demyelinating events, lupus, lupus-related conditions and Stevens-Johnson syndrome.

Table: Undesirable Effects

System Organ Class	**Frequency**	**Adverse Reaction**
Infections and infestations	Very common	Respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral)
	Common	Systemic infections (including sepsis, candidiasis and influenza), intestinal infections (including gastroenteritis viral), skin and soft tissue 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
	Uncommon	Neurological infections (including viral meningitis), opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avum complex infection), bacterial infections, eye infections, joint infections, diverticulitis

System Organ Class	Frequency	Adverse Reaction
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common	Skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma), benign neoplasm
	Uncommon	Lymphoma, solid organ neoplasm (including breast cancer, lung neoplasm and thyroid neoplasm), melanoma
	Rare	Leukaemia
	Not known	hepatosplenic T-cell lymphoma
Blood and the lymphatic system disorders	Very common	leucopenia (including neutropenia and agranulocytosis), anaemia
	Common	leucocytosis, thrombocytopenia
	Uncommon	Idiopathic thrombocytopenic purpura
	Rare	Pancytopenia
Immune system disorders	Common	Hypersensitivity, allergies (including seasonal allergy)
	Uncommon	Sarcoidosis
	Rare	Anaphylaxis
Metabolism and nutrition disorders	Very common	Lipids increased
	Common	Hypokalemia, uric acid increased, blood sodium abnormal, hypocalcemia, hyperglycemia, hypophosphatemia, dehydration
Psychiatric disorders	Common	Mood alterations (including depression), anxiety, insomnia
Nervous system disorders	Very common	Headache
	Common	Paraesthesias (including hypoaesthesia), migraine, sciatica
	Uncommon	Cerebrovascular accident , tremor, neuropathy
	Rare	Multiple sclerosis, demyelinating disorder (e.g. optic neuritis, Guillain-Barré syndrome)
Eye disorders	Common	Visual impairment, conjunctivitis
	Uncommon	Blepharitis, eye swelling, diplopia
Ear and labyrinth disorders	Common	Vertigo
	Uncommon	Deafness, tinnitus
Cardiac disorders	Common	Tachycardia
	Uncommon	Myocardial infarction, arrhythmia, congestive heart failure
	Rare	Cardiac arrest
Vascular disorders	Common	Hypertension, flushing, haematoma
	Uncommon	Aortic aneurysm, vascular arterial occlusion, thrombophlebitis
Respiratory, thoracic and mediastinal disorders	Common	Asthma, dyspnoea, cough
	Uncommon	Pulmonary embolism, interstitial lung disease, chronic obstructive pulmonary disease, pneumonitis pleural effusion
	Rare	Pulmonary fibrosis
Gastrointestinal disorders	Very common	Abdominal pain, nausea and vomiting
	Common	GI haemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome
	Uncommon	Pancreatitis, dysphagia, face oedema
	Rare	Intestinal perforation
Hepato-biliary disorders	Very common	Elevated liver enzymes
	Uncommon	Cholecystitis and cholelithiasis, hepatic steatosis, bilirubin increased
	Rare	Reactivation of hepatitis B
Skin and subcutaneous tissue disorders	Very common	Rash (including exfoliative rash)
	Common	Worsening or new onset of psoriasis (including palmplantar pustular psoriasis), urticaria, bruising (including purpura), dermatitis (including eczema), onychoclasis, hyperhydrosis, alopecia, pruritus
	Uncommon	Night sweats, scar
	Rare	Erythema multiforme, Stevens-Johnson syndrome, angioedema, cutaneous vasculitis
Musculoskeletal, connective tissue and bone disorders	Very common	Musculoskeletal pain
	Common	Muscle spasms (including blood creatine phosphokinase increased)
	Uncommon	Rhabdomyolysis, systemic lupus erythematosus
	Rare	Lupus-like syndrome
Renal and urinary disorders	Common	Renal impairment, haematuria
	Uncommon	Nocturia
Reproductive system and breast disorders	Uncommon	Erectile dysfunction
General disorders and administration site conditions	Very common	Injection site reaction (including injection site erythema)
	Common	Chest pain, oedema
	Uncommon	Inflammation
Investigations	Common	Coagulation and bleeding disorders (including activated partial thromboplastin time prolonged), autoantibody test positive (including double stranded DNA antibody), blood lactate dehydrogenase increased
Injury and poisoning	Common	Impaired healing

OVERDOSE

No dose-limiting toxicity was observed in patients and the highest dose level evaluated was intravenous dose of 10 mg/kg, approximately 15 times the recommended dose.

PHARMACOLOGICAL PROPERTIES

Pharmacokinetic properties reported for Adalimumab

Absorption and distribution of a single 40 mg dose is slow and serum concentration reaches its peak after 5 days upon subcutaneous administration with an average bioavailability of about 64 %. Serum concentrations were dose proportional when single intravenous dose ranging from 0.25 to 10 mg/kg was administered. The distribution volume (Vss) ranges from 5 to 6 litres, clearances range from 11 to 15 ml/hour and the mean terminal phase half-life was approximately two weeks with a single dose of Adalimumab administration. Concentration of Adalimumab measured from synovial fluid of rheumatoid arthritis patients ranges from 31-96% of those in serum.

The mean steady-state trough concentrations after subcutaneous administration of Adalimumab have been calculated from serum of the following patients:

RA patients:

- Approximately 5 µg/ml without concomitant methotrexate) and 8 to 9 µg/ml (with concomitant methotrexate with a dose of 40 mg every other week
- Serum trough levels at steady-state increase proportionally with dose increase (20, 40 and 80 mg subcutaneous dosing every other week and every week)

Polyarticular juvenile idiopathic arthritis patients of 4-17 years age:

- 5.6 ± 5.6 µg/mL (102 % CV) without concomitant methotrexate and 10.9 ±5.2 µg/mL (47.7% CV) with concomitant methotrexate (values measured from week 20 to 48) with a dose of 24 mg/m^2 (up to a maximum of 40 mg) every other week

Crohn's disease patients:

- Loading dose of 80 mg Adalimumab on week 0 followed by 40 mg Adalimumab on week 2 results in approximately 5.5 µg/mL trough concentration
- Loading dose of 160 mg Adalimumab on week 0 followed by 80 mg Adalimumab on week 2 achieves12 µg/mL trough concentration
- 7 µg/mL trough concentration was observed in patients receiving 40 mg Adalimumab every other week

Ulcerative colitis patients:

- Loading dose of 160 mg Adalimumab on week 0 followed by 80 mg Adalimumab on week 2 achieves 12 µg/mL trough concentration
- 8 µg/mL trough concentration was observed in patients receiving 40 mg Adalimumab every other week

Adalimumab has not been studied in patients with hepatic or renal impairment.

Pharmacodynamics properties

Pharmacotherapeutic group: Selective immunosuppressive agents.

Mechanism of action:

Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Upon binding to human TNF, Adalimumab either neutralizes the biological function of TNF by blocking its interaction with the cell surface TNF-receptors or modulates biological responses involving changes in leukocyte migration of adhesion molecules (ELAM-1, VCAM-1, and ICAM-1 with an IC50 of 0.1-0.2 nM). TNF plays a central role in initiation, maintenance and progression of several inflammatory diseases and treatment with Adalimumab improves the signs and symptoms of these TNF-associated diseases in patients.

Pharmacodynamics 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-6) declined rapidly as compared to baseline in patients with RA. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodelling responsible for cartilage 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. Endoscopic studies in 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 at 11 investigational sites in India, of which, 120 subjects were enrolled in the study, 60 subjects in each group viz. CHL's Adalimumab and Innovator's Adalimumab. Total 103 subjects were qualified as per protocol (PP) criteria and 119 subjects qualified for intend to treat (ITT) criteria 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 (on day 84), 82% of patient had an ACR20, 46% had an ACR50 and 14% had an ACR 70. Whereas, in Innovator's Adalimumab group at Visit 5 (on Day 84), 79.2% of patient had an ACR20, 43.4% had an ACR50 and 15.1% had an ACR70 response. No statistically significant differences between the treatment groups were observed in ACR response.

In addition to swollen joints and tender joints, significant improvement was noted in all ACR core components. The difference in both treatment groups was not significant.

Significant improvement was observed in Disease Activity Score 28 C-Reactive Protein (DAS28 CRP) score from the baseline in both the groups. The DAS28 CRP score in CHL's Adalimumab group was 5.8± 0.88 and in Innovator's Adalimumab group was 5.8 ± 0.83. Over a period of 84 days the score was decreased to 3.7 ± 1.12 and 3.7 ± 0.94 in CHL's Adalimumab and Innovator's Adalimumab group, respectively. No significant difference was observed between treatment groups at baseline and end of the study.

Similarly, at baseline Disease Activity Score 28 Erythrocyte Sedimentation Rate (DAS28ESR) score in CHL's Adalimumab group was 6.8 ± 0.78 and in Innovator's Adalimumab group it was 6.9 ± 0.81. Over a period of 84 days the score was decreased to 4.8 ± 1.04 and 4.8 ± 0.89 in CHL's Adalimumab and Innovator's Adalimumab group, respectively. No significant difference was observed between treatment groups at baseline and end of the study.

An efficacy subset analysis showed no significant difference between the treatment groups with respect to age groups, gender and weight on ACR criteria response and DAS 28 (CRP/ESR).

In this study, no significant difference was observed for anti-drug antibodies detected in samples from CHL's Adalimumab treated and Innovator's Adalimumab treated RA patients.

Anti-drug antibody was observed in two samples of patients treated with CHL's Adalimumab on Visit 5 with titer value of 25 and 800, and one sample of patient treated with Innovator's Adalimumab on Visit 5 with titer values of 200. These results indicate that both the drug products CHL's Adalimumab and Innovator's Adalimumab are similar with respect to immunogenic response in patients.

Summary of ACR response by treatment groups and visit (PP population)

	Visit	Responder	Adalimumab (CHL) (N = 50) n (%)	Adalimumab (Innovator) (N = 53) n (%)
ACR20	Visit 3 (Day 28)	Yes	25 (50.0%)	24 (45.3%)
		No	25 (50.0%)	29 (54.7%)
	Visit 4 (Day 56)	Yes	37 (74.0%)	37 (69.8%)
		No	13 (26.0%)	16 (30.2%)
	Visit 5 (Day 84)	Yes	41 (82.0%)	42 (79.2%)
		No	9 (18.0%)	11 (20.8%)
ACR50	Visit 3 (Day 28)	Yes	4 (8.0%)	5 (9.4%)
		No	46 (92.0%)	48 (90.6%)
	Visit 4 (Day 56)	Yes	17 (34.0%)	10 (18.9%)
		No	33 (66.0%)	43 (81.1%)
	Visit 5 (Day 84)	Yes	23 (46.0%)	23 (43.4%)
		No	27 (54.0%)	30 (56.6%)
ACR70	Visit 3 (Day 28)	Yes	1 (2.0%)	3 (5.7%)
		No	49 (98.0%)	50 (94.3%)
	Visit 4 (Day 56)	Yes	6 (12.0%)	6 (11.3%)
		No	44 (88.0%)	47 (88.7%)
	Visit 5 (Day 84)	Yes	7 (14.0%)	8 (15.1%)
		No	43 (86.0%)	45 (84.9%)

Abbreviations: N = number of subjects in specified treatment; n = number of subjects at specified category. **ACR20, ACR50 and ACR70 responders:** ≥20%, ≥50% and ≥70%, respectively, improvement in tender and swollen joint count; and ≥20%, ≥50% and ≥70%, respectively, improvement in at least 3 of 5 remaining ACR core measures: patient assessment of pain; patient and physician global assessment of disease activity; self-assessed disability [HAQ]; and CRP.

Summary of ACR Core Component: Baseline value and change from baseline to Visit 5 (Day 84) (PP Population)

ACR Core component	Adalimumab (CHL) (N=50)	Adalimumab (Innovator) (N=53)
Tender joint count score (0-28)		
Visit 1 (Day 1)	16.6 ± 6.09	17.4 ± 6.32
Change from baseline at Visit 5 (Day 84)	-10.5 ± 5.95*	-11.7 ± 7.19*
Swollen joint count score		
Visit 1 (Day 1)	11.7 ± 5.57	12.4 ± 5.24
Change from baseline at Visit 5 (Day 84)	-8.2 ± 5.77*	-9.2 ± 6.02*
Patient Assessment of pain		
Visit 1 (Day 1)	66.5 ± 12.38	66.4 ± 11.11
Change from baseline at Visit 5 (Day 84)	-30.0 ± 17.66*	-28.4 ± 16.75*
Patient global assessment of disease activity		
Visit 1 (Day 1)	66.2 ± 11.91	64.8 ± 10.57
Change from baseline at Visit 5 (Day 84)	-30.5 ± 16.75*	-28.3 ± 18.11*
Physician global assessment of disease activity		
Visit 1 (Day 1)	63.4 ± 12.02	63.9 ± 10.39
Change from baseline at Visit 5 (Day 84)	-29.2 ± 18.35*	-28.6 ± 18.02*
Disability Index of the HAQ		
Visit 1 (Day 1)	1.7 ± 0.62	1.6 ± 0.61
Change from baseline at Visit 5 (Day 84)	-0.8 ± 0.63*	-0.7 ± 0.60*
ACR Core component	**Adalimumab (CHL) (N=50)**	**Adalimumab (Innovator) (N=53)**
CRP		
Visit 1 (Day 1)	11.0 ± 12.72	10.5 ± 12.90
Change from baseline at Visit 5 (Day 84)	-5.5 ± 12.66*	0.7 ± 26.98
ESR		
Visit 1 (Day 1)	53.9 ± 21.45	53.2 ± 20.33
Change from baseline at Visit 5 (Day 84)	-8.6 ± 19.76*	-5.4 ± 17.35*
DAS 28-CRP		
Visit 1 (Day 1)	5.8 ± 0.88	5.8 ± 0.83
Change from baseline at Visit 5 (Day 84)	-2.1 ± 1.09*	-2.1 ± 1.21*
DAS 28-ESR		
Visit 1 (Day 1)	6.8 ± 0.78	6.9 ± 0.81
Change from baseline at Visit 5 (Day 84)	-2.0 ± 1.10*	-2.1 ± 1.15*

Values presented in Mean ± SD.

* Significant compared to baseline.

Safety conclusions of CHL Trials

Overall, CHL's Adalimumab and Innovator's Adalimumab were safe and well tolerated in this study. 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 16 AEs (including 1 SAE) were reported by 11 subjects. Pyrexia, headache and cough were commonly reported in both the treatment groups. The 3 SAEs reported were pyrexia, dizziness and cough. Majority of AEs were mild in intensity and not related to the study drugs.

Three system organ class (SOC) with higher number of AEs were gastrointestinal disorder, general disorder and administration site condition, and infection and infestation.

There were no persistent changes from baseline in laboratory parameters in both treatment groups. General examination shows no significant sign in any treatment groups except 2 cases of pallor at visit 3 in Innovator's Adalimumab treated group. No other systemic abnormality was observed throughout the study except musculoskeletal; however, the proportion of abnormality was comparable in both treatment groups.

PRECLINICAL SAFETY DATA OF CHL's ADALIMUMAB

The safety profile of CHL's Adalimumab was assessed using a battery of toxicological studies.

Preclinical studies for CHL's Adalimumab were performed as per the recommendations set forth in Schedule Y/ ICH guidelines in compliance with GLP standards at Zydus Research Centre, Cadila Healthcare Limited, Ahmedabad. Toxicological studies included independent acute toxicity studies in mice and rats by intended subcutaneous route and by alternate intravenous route of administration. Repeated dose toxicity studies by subcutaneous route comprising weekly dosing schedule over a period of four weeks was performed in rats and rabbits. 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 mortality over the acute dose of 830 mg/kg in mice & 410 mg/kg in rats by both subcutaneous and intravenous routes and were approximately 100 times of the human equivalent dose. No mortality, apparent signs of toxicity, adverse changes in body weights and gross pathological lesions were noticed in both mice and rats when compared to vehicle control groups. CHL's Adalimumab did not induce any dermal sensitization in guinea pigs. No adverse local tolerance effects were noticed at the site of injection in both rats and rabbits.

Repeated weekly subcutaneous administration of CHL's Adalimumab was conducted over a period of four weeks at dose levels of 4.1, 20.5 & 41 mg/kg in rats and 2.1, 10.5 & 21 mg/kg in rabbits. The selected dose levels were 1X, 5X & 10X of the human equivalent dose. A recovery group was maintained for a period of two weeks at 10X of the human equivalent dose. Vehicle control groups were maintained with main study & recovery groups. Innovator's Adalimumabwas used at 1X of the human equivalent dose for comparative purpose in repeated dose toxicity studies.

No mortality occurred in both rats and rabbits. No adverse changes were noticed during detailed clinical examination, body weight and feed intake determinations, hematological, biochemical, organ weight estimations, bone marrow examination and gross or histo-pathological evaluation. No differences were noticed in both the groups treated with CHL's Adalimumab and Innovator's Adalimumabin both rats and rabbits. No delayed toxicity was noticed during treatment free recovery period of two weeks.

The immunogenic response in CHL's Adalimumab treated groups was comparable to that of Innovator's Adalimumab treated group. No immunogenicity titers were noticed against host cell proteins (HCP) which demonstrates that the product have extremely low levels of HCP contaminants.

NOAEL was considered to be more than 10X of human equivalent dose (41 mg/kg in rats and 21 mg/kg in rabbits) by weekly subcutaneous administration over a period of four weeks.

Thus, the overall pre-clinical profile of CHL's Adalimumab seems to be non-inferior with the Innovator's Adalimumab and considered to be safe at the recommended dose in humans.

PHARMACEUTICAL PARTICULARS

Active Ingredients

Adalimumab

List of excipients

Succinic acid, Sodium hydroxide, Sodium chloride, L-Arginine monohydrochloride, Sorbitol, Polysorbate 80, WFI

INCOMPATIBILITIES

This medicinal product should not be mixed with other medicinal products.

SHELF LIFE

24 months

SPECIAL PRECAUTIONS FOR STORAGE

Store between + 2 °C and + 8 °C, in the carton to protect from light.

Do not freeze **Exemptia™**. Do not use **Exemptia™** if frozen, even if it has been thawed.

KEEP OUT OF REACH OF CHILDREN.

NATURE AND CONTENTS OF CONTAINER

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

SPECIAL PRECAUTIONS FOR DISPOSAL

Exemptia™ does not contain any preservative. Any unused product or waste material should be discarded.

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Size : 190x290 mm – Back side

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