Summary of Product Characteristics

1.0 Name of the Medicinal Product

PAMERA 40

2.0 Physical Appearance:

PAMERA 40 is a clear solution free from visible particles that can be observed by visual inspection

2.1 Qualitative and Quantitative Composition

Each pre-filled glass syringe of 0.8 mL contains;

Adalimumab (r-DNA Origin) ……40 mg

3.0 Pharmaceutical Form

Injectable, single use pre-filled syringes and vials and it is administered by subcutaneous injection.

4.1 Clinical Particulars

4.2 Therapeutic indications

Adalimumab is indicated for treatment of:

- Rheumatoid Arthritis (RA)
- Juvenile Idiopathic Arthritis (JIA)
- Axial Spondyloarthritis (AS)
- Psoriatic Arthritis (PsA)
- Psoriasis
- Paediatric Plaque Psoriasis
- Hidradenitis Suppurativa (HS)
- Crohn's disease
- Paediatric Crohn's disease
- Ulcerative colitis
- Uveitis

4.3 Posology and method of administration

Rheumatoid arthritis:

The recommended dose of Adalimumab 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 adalimumab.
In monotherapy, some patients who experience a decrease in their response may benefit from an increase in dose intensity to 40 mg adalimumab 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 suggest that re-introduction of adalimumab after discontinuation for 70 days or longer resulted in the same magnitudes of clinical response and similar safety profile as before dose interruption.

Ankylosing spondylitis, axial spondyloarthritis without radiographic evidence of AS and Psoriatic Arthritis
The recommended dose of adalimumab for patients with ankylosing spondylitis axial spondyloarthritis without radiographic evidence of AS 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 reconsidered in a patient not responding within this time period.

Psoriasis
The recommended dose of adalimumab for adult patients is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week starting one 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 adalimumab therapy should be carefully reconsidered in a patient with an inadequate response after the 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.

Hidradenitis suppurativa

The recommended adalimumab dose regimen for adult patients with hidradenitis suppurativa (HS) is 160 mg initially at Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later at Day 15 (given as two 40 mg injections in one day). Two weeks later (Day 29) continue with a dose of 40 mg every week. Antibiotics may be continued during treatment with adalimumab if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS 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 40 mg every week may be re-introduced. The benefit and risk of continued long-term treatment should be periodically evaluated.

Crohn's disease

The recommended adalimumab 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 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days), 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 disease recur, adalimumab 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 decrease in their response may benefit from an increase in dosing frequency to 40 mg adalimumab 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.

Ulcerative colitis

The recommended adalimumab 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 one day or as two injections per day for two 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 adalimumab every week.

Available data suggest that clinical response is usually achieved within 2-8 weeks of treatment. Adalimumab therapy should not be continued in patients failing to respond within this time period.

Uveitis

The recommended dose of adalimumab for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. There is limited experience in the initiation of treatment with adalimumab alone. Treatment with adalimumab 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 adalimumab.

It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis.

Method of administration

Adalimumab is administered by subcutaneous injection.

4.4 Contraindications

Adalimumab is contraindicated in patients with:

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

4.5 Special warnings and precautions for use

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded.

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 four 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. Hospitalisation 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 disorder; 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 occurs, 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 leukemia 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, leukemia, 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 PUVA 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 COPD 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 (for example,

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 hematologic 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.

4.6 Interaction with other medicinal products and other forms of interaction

PAMERA 40 has been studied in rheumatoid arthritis, polyarticular juvenile idiopathic arthritis and psoriatic arthritis patients taking PAMERA 40 as monotherapy and those taking concomitant methotrexate. Antibody formation was lower when PAMERA 40 was given together with methotrexate in comparison with use as monotherapy. Administration of PAMERA 40 without methotrexate resulted in increased formation of antibodies, increased clearance and reduced efficacy of adalimumab.

The combination of PAMERA 40 and anakinra is not recommended.

The combination of PAMERA 40 and abatacept is not recommended.

4.7 Usage in 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.

Paediatrics

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis from 2 to 12 years of age:

The recommended dose of adalimumab for patients with polyarticular juvenile idiopathic arthritis, aged 2 - 12 years, is 24 mg/m2 body surface area up to a

maximum single dose of 20 mg adalimumab (for patients aged 2 - < 4) and up to a maximum single dose of 40 mg adalimumab (for patients aged 4-12) administered every other week via subcutaneous injection. The volume for injection is selected based on the patients' 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

Height (cm)	Total Body Weight (kg)												
	10	15	20	25	30	35	40	45	50	55	60	65	70
80	0.2	0.3	0.3	0.3									
90	0.2	0.3	0.3	0.4	0.4	0.4							
100	0.3	0.3	0.3	0.4	0.4	0.4	0.5	0.5					
110	0.3	0.3	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.6	0.6		
120	0.3	0.4	0.4	0.4	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.7	0.7
130		0.4	0.4	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.7	0.7	0.7
140		0.4	0.4	0.5	0.5	0.6	0.6	0.6	0.7	0.7	0.7	0.7	0.8*
150			0.5	0.5	0.6	0.6	0.6	0.7	0.7	0.7	0.7	0.8*	0.8*
160			0.5	0.5	0.6	0.6	0.7	0.7	0.7	0.8*	0.8*	0.8*	0.8*
170				0.6	0.6	0.6	0.7	0.7	0.8*	0.8*	0.8*	0.8*	0.8*
180					0.6	0.7	0.7	0.8*	0.8*	0.8*	0.8*	0.8*	0.8*

*Maximum single dose is 40 mg (0.8 mL)

Polyarticular juvenile idiopathic arthritis from 13 years of age

For [redacted] from 13 years of age, a dose of 40 mg is administered every other week [redacted] 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 retreatment 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 less than 4 years for this indication.

The volume for injection is selected based on the patients' weight (Table 2).

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

Body Weight (kg)	Paediatric Psoriasis Dose
13 –	0.2 mL (10
17 –	0.3 mL (15
23 –	0.4 mL (20
29 –	0.5 mL (25
35 –	0.6 mL (30
41 –	0.7 mL (35
47+	0.8 mL (40

Adolescent hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)

There are no clinical trials with adalimumab in adolescent patients with HS.

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 HS 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 less than 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 80 mg at Week 0 (dose can be administered as two injections in one day), 40 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 20 mg every other week via subcutaneous injection. Some subjects who experience insufficient 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 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days), 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 below 6 years for this indication.

Paediatric ulcerative colitis

The safety and efficacy of adalimumab in children aged 4-17 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 2-17 years have not yet been established. No data are available.

Women of child bearing 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 five 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.

Breast feeding

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 breast- feed for at least five months after the last adalimumab treatment.

4.8 Effects on ability to drive and use machines

Adalimumab has no or negligible influence on the ability to drive and use machines.

4.9 Undesirable effects

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

Blood and the lymphatic system disorders: Leucopoenia (including neutropenia and agranulocytosis), anemia, leucocytosis, thrombocytopenia, idiopathic thrombocytopenic purpura, pancytopenia, polycythemia

Cardiac disorders: Arrhythmia, atrial fibrillation, chest pain, coronary artery disorder, heart arrest, hypertensive encephalopathy, myocardial infarct, palpitation, pericardial effusion, pericarditis, syncope, tachycardia, congestive heart failure

Endocrine System: Parathyroid disorder

Metabolism And Nutritional Disorders: Dehydration, healing abnormal, ketosis, paraproteinemia, peripheral edema, lipids increased, hypokalemia, uric acid

increased, blood sodium abnormal, hypocalcaemia, hyperglycemia, hypophosphatemia

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

Respiratory, thoracic and mediastinal disorders: Asthma, bronchospasm, dyspnea, 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, hematuria, nocturia, cystitis, kidney calculus, menstrual disorder

Gastrointestinal disorders: Diverticulitis, large bowel perforations including perforations associated with diverticulitis and appendiceal perforations associated with appendicitis, pancreatitis, cholecystitis, cholelithiasis, esophagitis, gastroenteritis, gastrointestinal hemorrhage, vomiting, abdominal pain, nausea, dyspepsia, gastro esophageal reflux disease, sicca syndrome, dysphagia, face edema

General disorders and administration site conditions: Pyrexia, injection site reaction

(including injection site erythema), chest pain, edema, inflammation

Hepato-biliary disorders: Liver failure, hepatitis, hepatic necrosis, elevated liver enzymes, hepatic steatosis, bilirubin increased, reactivation of hepatitis B, autoimmune hepatitis

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: Stevens Johnson Syndrome, cutaneous vasculitis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), alopecia, rash (including exfoliative rash), urticaria, bruising (including purpura), dermatitis (including eczema), onychoclasis, hyperhydrosis, pruritus, night sweats, scar, erythema multiforme, angioedema, cutaneous vasculitis, worsening of symptoms of dermatomyositis

Vascular disorders: Systemic vasculitis, deep vein thrombosis, hypertension, flushing, hematoma, 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 tissue infections (including paronychia, cellulitis, impetigo, necrotising 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 coccidioidomycosis, histoplasmosis and mycobacterium avium complex infection), bacterial infections, eye infections

Psychiatric disorders: Mood alterations (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), autoantibody test positive (including double stranded DNA antibody), blood lactate dehydrogenase increased Injury, poisoning and procedural complications: Impaired healing

Safety data from Hetero- Adalimumab clinical study in Rheumatoid Arthritis

A total of 14 adverse events were reported in 11 subjects (13.8%) with Hetero Adalimumab. Two patients reported two serious adverse events (Hetero Adalimumab - sinusitis and Reference Adalimumab - viral infection) during the study and resolved completely. There were no deaths and no life threatening adverse events were reported.

4.10 Overdose

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.

5.1 Pharmacological Properties

5.2 Pharmacodynamics properties

Mechanism of Action

Adalimumab binds specifically to TNF-alpha and blocks its interaction with the 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 RA, JIA, PsA, and AS and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques. In PsA, treatment with adalimumab may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamics 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 leukocyte 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 levels of acute phase reactants of inflammation (Creactive protein [CRP] and erythrocyte sedimentation rate [ESR])

and serum cytokines (IL-6) was observed compared to baseline in patients with Rheumatoid Arthritis. A decrease in CRP levels was also observed in patients with Crohn's disease and ulcerative colitis. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were 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.

5.3 Pharmacokinetic properties

Absorption and distribution

After subcutaneous administration of a single 40 mg dose, absorption and distribution of adalimumab was slow, with peak serum concentrations 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 (~40 mg), clearances ranged from 11 to 15 ml/hour, the distribution volume (V_{ss}) ranged from 5 to 6 litres and the mean terminal phase half-life was approximately two weeks. Adalimumab concentrations in the synovial fluid from several rheumatoid arthritis patients ranged from 31-96% of those in serum.

Following subcutaneous administration of 40 mg of adalimumab every other week in adult rheumatoid arthritis (RA) patients 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 roughly proportionally with dose following 20, 40 and 80 mg subcutaneous dosing every other week 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 (JIA) who were

4 to 17 years the mean trough steady-state (values measured from Week 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 JIA who were 2 to < 4 years old or aged 4 and above weighing < 15 kg dosed with adalimumab 24 mg/m2 , the mean trough steady-state serum adalimumab concentrations 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, the mean trough steady-state (values measured at Week 24) serum adalimumab Concentrations were 8.8±6.6µg/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 pediatric 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 trough concentrations of approximately 7 to 8 µg/mL at Week 2 and Week 4. The mean steady-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 HS patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other pediatric patients (pediatric psoriasis, juvenile idiopathic arthritis, pediatric Crohn's disease, and enthesitis-related arthritis). The recommended adolescent HS 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 on Week 0 followed by 40 mg adalimumab on Week 2 achieves serum adalimumab trough concentrations of approximately 5.5 µg/ml during the induction period. A loading dose of
160 mg adalimumab on Week 0 followed by 80 mg adalimumab on Week 2 achieves serum adalimumab trough concentrations of approximately 12 µg/ml during the induction period. Mean steady-state trough levels of approximately 7µg/ml were observed in Crohn's disease patients who received a maintenance dose of 40 mg adalimumab every other week.
In pediatric patients with moderate to severe CD, 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 randomised 1:1 to either the Standard Dose (40/20 mg eow) or Low Dose (20/10 mg eow) 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±2.2µg/ml for the low dose group. The mean trough concentrations were maintained in patients who continued to receive adalimumab treatment eow for 52 weeks. For patients who dose escalated from eow to 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 on Week 0 followed by 80 mg adalimumab on Week 2 achieves serum adalimumab trough concentrations of approximately 12 µg/ml during the induction period. Mean steady-state trough levels of approximately 8µg/ml were observed in ulcerative colitis patients who received a maintenance dose of 40 mg adalimumab every other week.
In patients with uveitis, a loading dose of 80 mg adalimumab on 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 over 1,300 RA 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, AAA) were observed to be lower in patients with measurable AAA.

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

5.4 Preclinical safety 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.

6.1 Pharmaceutical Particulars

6.2 List of excipients

S. No.	Ingredients	Function
1	Monobasic sodium phosphate dihydrate	Buffering agent
2	Dibasic sodium phosphate dihydrate	Buffering agent
3	Sodium citrate	Buffering agent
4	Citric acid monohydrate	Buffering agent
5	Mannitol	Stabilizing agent
6	Sodium chloride	Tonicity agent
7	Polysorbate 80	Stabilizing agent
8	Water for injection	Diluent

6.3 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.4 Shelf life

24 months from the date of manufacture.

6.5 Special precautions for storage

Store in a refrigerator (2°C to 8°C). Keep the container in the outer carton in order to protect from light. Keep out of reach of children. Do not freeze or shake.

6.6 Nature and contents of container

The following presentations are available:

S.	Strength/Dosa
1	Adalimumab Injection 10 mg/0.2 mL Adalimumab injection 0.2 ml single-use prefilled glass syringe Each 0.2 ml contains 10 mg of Adalimumab (concentration: 50mg/ml).
2	Adalimumab injection: 20 mg/0.4 mL Adalimumab injection 0.4 ml single use pre-filled syringe Each 0.4 ml contains 20 mg of Adalimumab (concentration: 50mg/ml).
3	Adalimumab injection: 40 mg/0.8 mL Adalimumab injection 0.8 ml single use pre-filled syringe Each 0.8 ml contains 40 mg of Adalimumab (concentration: 50mg/ml).
4	Adalimumab injection: 40 mg mg/0.8 mL Adalimumab injection 0.8 ml single use glass vial Each 0.8 ml contains 40 mg of Adalimumab (concentration: 50mg/ml).

5	Adalimumab injection: 40 mg mg/0.8 mL Adalimumab injection 0.8 ml single use Pre filled Pen Each 0.8 ml contains 40 mg of Adalimumab (concentration: 50mg/ml).

Adalimumab drug product is available in different dose strengths in USP Type 1 glass single use pre-filled syringes and single use vials. Container closure system is the primary packaging item of the Adalimumab drug product. 2 ml clear glass vial: Neutral (USP Type I) with 13mm rubber stopper is used to fill Adalimumab drug product. The rubber stopper is formulated with elastomer butyl coated with FluroTec®, which doesn't affect the product quality. The complete glass vial is placed onto the plastic tray, which holds the neck of glass vial and the tray is placed into the carton box, which acts as secondary packing system.

Adalimumab drug product of different strengths is filled in a pre-sterilized pre-fillable glass syringes of 1 ml capacity, which is with fixed stainless steel needle and needle shield (make: BD, USA). Upon filling of the drug product into the pre-filled syringe, the syringe is stoppered with a pre-sterilized elastomeric butyl rubber stopper. Then to this syringe, plunger rod is inserted. The complete pre-filled syringe is placed into the plastic tray, which holds the syringe intact at all times and the tray is placed into the carton box, which acts as secondary packing system.

6.7 Special precautions for disposal

Parenteral medicinal products should be inspected visually for particulate matter and discoloration prior to administration.

Adalimumab is for single-use only, as the product contains no preservatives. Any unused medicinal product or waste material should be disposed in accordance with local requirements.

7.0 Marketing Authorisation / Prequalification Holder

Manufactured by:

HETERO BIOPHARMA LIMITED
Sy.No. 458 (part), TSIIC-Formulation
SEZ, Polepally Village, Jadcherla
Mandal Mahaboobnagar District – 509
301, Telangana State, India.

8.0 Marketing Authorization Number

TAN 22 HM 0020

9.0 Date of renewal of the authorisation

Not Applicable

10. Date of revision of the test

April, 2022