ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Trudexa 40 mg solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.8 ml single dose vial contains 40 mg of adalimumab.
Adalimumab is a recombinant human monoclonal antibody expressed in Chinese Hamster Ovary cells.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

Trudexa in combination with methotrexate, is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Trudexa can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Trudexa has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Psoriatic arthritis

Trudexa is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

Ankylosing spondylitis

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

Crohn's disease

Trudexa is indicated for treatment of severe, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. For induction treatment, Trudexa should be given in combination with cortiocosteroids. Trudexa can be given as monotherapy in case of intolerance to corticosteroids or when continued treatment with corticosteroids is inappropriate (see section 4.2).

4.2 Posology and method of administration

Trudexa treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or Crohn's disease. Patients treated with Trudexa should be given the special alert card.

After proper training in injection technique, patients may self-inject with Trudexa if their physician determines that it is appropriate and with medical follow-up as necessary.

During treatment with Trudexa, other concomitant therapies (e.g., corticosteroids and/or immunomodulatory agents) should be optimised.

Adults

Rheumatoid arthritis

The recommended dose of Trudexa for adult patients with rheumatoid arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection. Methotrexate should be continued during treatment with Trudexa.

Glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, or analgesics can be continued during treatment with Trudexa. Regarding combination with disease modifying anti-rheumatic drugs other than methotrexate see sections 4.4 and 5.1.

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.

Psoriatic arthritis and ankylosing spondylitis

The recommended dose of Trudexa for patients with psoriatic arthritis and ankylosing spondylitis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection.

For all of the above indications, available data suggest that the 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.

Crohn's disease

The recommended Trudexa induction dose regimen for adult patients with severe 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 Trudexa and signs and symptoms of disease recur, Trudexa 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 dose intensity to 40 mg Trudexa 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.

Elderly patients

No dose adjustment is required.

Children and adolescents

There is no experience in children.

Impaired renal and/or hepatic function

Trudexa has not been studied in these patient populations. No dose recommendations can be made.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Active tuberculosis or other severe infections such as sepsis, and opportunistic infections (see section 4.4).

Moderate to severe heart failure (NYHA class III/IV) (see section 4.4).

4.4 Special warnings and precautions for use

Infections

Patients must be monitored closely for infections, including tuberculosis, before, during and after treatment with Trudexa. Because the elimination of adalimumab may take up to five months, monitoring should be continued throughout this period.

Treatment with Trudexa should not be initiated in patients with active infections including chronic or localized infections until infections are controlled.

Patients who develop a new infection while undergoing treatment with Trudexa should be monitored closely. Administration of Trudexa should be discontinued if a patient develops a new serious infection until infections are controlled. Physicians should exercise caution when considering the use of Trudexa 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, sepsis, tuberculosis and other opportunistic infections, including fatalities, have been reported with Trudexa.

Serious infections:

In clinical trials an increased risk of serious infections in patients receiving Trudexa has been shown, and reports from the post-marketing setting support this finding. Of particular importance are infections such as pneumonia, pyelonephritis, septic arthritis and septicaemia.

Tuberculosis:

There have been reports of tuberculosis in patients receiving Trudexa. It should be noted that in the majority of those reports, tuberculosis was extra-pulmonary, i.e. disseminated.

Before initiation of therapy with Trudexa, all patients must be evaluated for both active or inactive (latent) tuberculosis infection. This evaluation should include a detailed medical history with a personal history of tuberculosis or possible previous exposure to patients 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 of these tests should be 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, Trudexa therapy must not be initiated (see section 4.3).

If latent tuberculosis is diagnosed, appropriate anti-tuberculosis prophylaxis in accordance with local recommendations must be initiated before starting treatment with Trudexa. In this situation, the benefit/risk balance of therapy with Trudexa should be very carefully considered.

Patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur during or after therapy with Trudexa.

Other opportunistic infections:

There have been reports of serious and severe opportunistic infections associated with Trudexa therapy, for example pneumocystis carinii pneumonia, disseminated histoplasmosis, listeriosis and aspergillosis.

If a patient receiving Trudexa shows prolonged/atypical symptoms/signs of infections or general deterioration, prevalent opportunistic conditions must be considered.

Hepatitis B Reactivation

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including Trudexa, who are chronic carriers of this virus. Some cases have had fatal outcome. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating Trudexa therapy. Carriers of HBV who require treatment with Trudexa should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data of 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, Trudexa should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Neurological events

TNF-antagonists including Trudexa have been associated in rare cases with new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease. Prescribers should exercise caution in considering the use of Trudexa in patients with pre-existing or recent-onset central nervous system demyelinating disorders.

Allergic reactions

Serious allergic adverse reactions have not been reported with subcutaneous administration of Trudexa during clinical trials. Non-serious allergic reactions associated with Trudexa were uncommon during clinical trials. In postmarketing, serious allergic reactions including anaphylaxis have been reported very rarely following Trudexa administration. If an anaphylactic reaction or other serious allergic reaction occurs, administration of Trudexa should be discontinued immediately and appropriate therapy initiated.

The needle cover of the syringe contains natural rubber (latex). This may cause severe allergic reactions in patients sensitive to latex.

Immunosuppression

In a study of 64 patients with rheumatoid arthritis that were treated with Trudexa, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T-and B cells and NK-cells, monocyte/macrophages, and neutrophils.

Malignancies and lymphoproliferative disorders

In the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies including lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare. Furthermore, there is an increased background lymphoma risk 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 or other malignancies in patients treated with a TNF-antagonist cannot be excluded.

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving Trudexa. Thus additional caution should be exercised in considering Trudexa treatment of these patients (see section 4.8).

In an exploratory clinical trial evaluating the use of another anti-TNF agent, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. 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.

Haematologic reactions

Rare reports of pancytopenia including aplastic anaemia have been reported with TNF blocking agents. Adverse events of the haematologic system, including medically significant cytopoenia (e.g. thrombocytopaenia, leucopaenia) have been infrequently reported with Trudexa. All 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 Trudexa. Discontinuation of Trudexa therapy should be considered in patients with confirmed significant haematologic abnormalities.

Vaccinations

Similar antibody responses to the standard 23-valent pneumococcal vaccine and the influenza trivalent virus vaccination were observed in a study in 226 adult subjects with rheumatoid arthritis who were treated with adalimumab or placebo. No data are available on the secondary transmission of infection by live vaccines in patients receiving Trudexa. Patients on Trudexa may receive concurrent vaccinations, except for live vaccines.

Congestive heart failure

In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Cases of worsening congestive heart failure have also been reported in patients receiving Trudexa. Trudexa should be used with caution in patients with mild heart failure (NYHA class I/II). Trudexa is contraindicated in moderate to severe heart failure (see section 4.3). Treatment with Trudexa must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Autoimmune processes

Treatment with Trudexa may result in the formation of autoimmune antibodies. The impact of long-term treatment with Trudexa on the development of autoimmune diseases is unknown. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Trudexa and is positive for antibodies against double-stranded DNA, further treatment with Trudexa should not be given (see section 4.8).

Concurrent administration of TNF-antagonists and anakinra

Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF-antagonist, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNF-antagonists. Therefore, the combination of adalimumab and anakinra is not recommended.

Surgery

There is limited safety experience of surgical procedures in patients treated with Trudexa. The long half-life of adalimumab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on Trudexa should be closely monitored for infections, and appropriate actions should be taken. There is limited safety experience in patients undergoing arthroplasty while receiving Trudexa.

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 Trudexa does not worsen or cause strictures.

4.5 Interaction with other medicinal products and other forms of interaction

Trudexa has been studied both in rheumatoid arthritis and psoriatic arthritis patients taking Trudexa as monotherapy and those taking concomitant methotrexate. Antibody formation was lower when Trudexa was given together with methotrexate in comparison with use as monotherapy. Administration of Trudexa without methotrexate resulted in increased formation of antibodies, increased clearance and reduced efficacy of adalimumab (see section 5.1).

4.6 Pregnancy and lactation

For Trudexa, no 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 and fertility effects of adalimumab are not available (see section 5.3).

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. 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 Trudexa treatment.

Use during lactation

It is not known whether adalimumab is excreted in human milk or absorbed systemically after ingestion.

However, because human immunoglobulins are excreted in milk, women must not breast-feed for at least five months after the last Trudexa treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Clinical Trials

Trudexa was studied in 5293 patients in controlled and open label trials for up to 60 months. These trials included rheumatoid arthritis patients with short term and long standing disease as well as psoriatic arthritis, ankylosing spondylitis and Crohn's disease patients. The data in Table 1 is based on the controlled Studies (I−IX,CLASSIC I, GAIN AND CHARM) (described in section 5.1) involving 3271 patients receiving Trudexa and 1809 patients receiving placebo or active comparator during the controlled period.

The proportion of patients who discontinued treatment due to adverse events during the double-blind, controlled portion of Studies I−IX, CLASSIC I, GAIN and CHARM was 5.7% for patients taking Trudexa and 5.3% for control treated patients.

Adverse events at least possibly causally-related to adalimumab for Studies I−IX, CLASSIC I, GAIN and CHARM, both clinical and laboratory, are displayed by system organ class and frequency (very common ≥ 1/10; common≥ 1/100 < 1/10; uncommon≥ 1/1000 to ≤ 1/100) and rare < 1/1000 in Table 1 below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1
Undesirable Effects in Clinical Studies

System Organ Class	Frequency	Adverse Reaction
Infections and infestations	Common	lower respiratory infections (including pneumonia, bronchitis), viral infections (including influenza, herpes infections), candidiasis, bacterial infections (including urinary tract infections), upper respiratory infection
	Uncommon	opportunistic infections (including tuberculosis, histoplasmosis), sepsis, abscess, joint infection, wound infection, skin infection (including cellulitis and impetigo), superficial fungal infections (including skin, nail and foot)
	Rare	necrotising fasciitis, viral meningitis, diverticulitis
Neoplasms benign and malignant (including cysts and polyps)	Uncommon	skin papilloma
	Rare	lymphoma, solid organ tumours (including breast, ovarian, testicular), squamous cell carcinoma of the skin

Blood and the lymphatic system disorders	Common	lymphopaenia
	Uncommon	neutropaenia (including agranulocytosis), leucopaenia, thrombocytopaenia, anaemia, , lymphadenopathy, leucocytosis
	Rare	pancytopaenia, idiopathic thrombocytopaenia purpura
Immune system disorders	Uncommon	systemic lupus erythematosus, angioedema, drug hypersensitivity, seasonal allergy
	Rare	serum sickness
Endocrine disorders	Rare	thyroid disorder (including goitre)
Metabolism and nutrition disorders	Uncommon	Hypokalaemia, lipids increased, appetite disorders (including anorexia), hyperuricaemia
	Rare	hypercalcaemia
Psychiatric disorders	Uncommon	mood disorders, anxiety (including nervousness and agitation)
Nervous system disorders	Common	dizziness (including vertigo), headache, neurologic sensation disorders (including paraesthesias)
	Uncommon	syncope, migraine, tremor, sleep disturbances
	Rare	multiple sclerosis
Eye disorders	Common	infection, irritation or inflammation of the eye
	Uncommon	vision disorder, ocular sensation disorders
	Rare	Panophthalmitis, iritis, glaucoma
Ear and labyrinth disorders	Uncommon	tinnitus, ear discomfort (including pain and swelling)
	Rare	hearing loss
Cardiac disorders	Uncommon	arrhythmias, tachycardia, palpitations
	Rare	cardiac arrest, coronary artery insufficiency, angina pectoris, pericardial effusion
Vascular disorders	Uncommon	hypertension, flushing, haematoma
	Rare	vascular occlusion, aortic stenosis, thrombophlebitis, aortic aneurysm
Respiratory, thoracic and mediastinal disorders	Common	cough, nasopharyngeal pain

	Uncommon	asthma, dyspnoea, dysphonia, nasal congestion
	Rare	pulmonary oedema, pharyngeal oedema, pleural effusion, pleurisy
Gastrointestinal disorders	Common	diarrhoea, abdominal pain, stomatitis and mouth ulceration, nausea
	Uncommon	rectal haemorrhage, gastritis, vomiting, dyspepsia, abdominal bloating, constipation,
	Rare	intestinal stenosis, colitis, enteritis, oesophagitis
Hepato-biliary disorders	Common	hepatic enzymes increased
	Rare	hepatic necrosis, hepatitis
Skin and subcutaneous tissue disorders	Common	rash, dermatitis and eczema, pruritus, hair loss
	Uncommon	urticaria, psoriasis, ecchymosis and increased bruising, purpura
	Rare	erythema multiforme, panniculitis
Musculoskeletal, connective tissue and bone disorders	Common	musculoskeletal pain
	Rare	rhabdomyolysis
Renal and urinary disorders	Uncommon	haematuria, renal impairment, bladder and urethral symptoms
	Rare	proteinuria, renal pain
Reproductive system and breast disorders	Uncommon	menstrual cycle and uterine bleeding disorders
General disorders and administration site conditions	Very Common	injection site reaction (including pain, swelling, redness or pruritus)
	Common	pyrexia, fatigue (including asthenia and malaise)
	Uncommon	chest pain, oedema, influenza like illness
Investigations	Uncommon	blood creatine phosphokinase increased, activated partial thromboplastin time prolonged, autoantibodies present
Injury and poisoning	Uncommon	accidental injury, impaired healing

Injection site reactions

In the twelve controlled trials, 16% of patients treated with Trudexa developed injection site reactions (erythema and/or itching, haemorrhage, pain or swelling), compared to 10% of patients receiving placebo or active control. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

Infections

In the twelve controlled trials, the rate of infection was 1.49 per patient year in the Trudexa treated patients and 1.42 per patient year in the placebo and active control-treated patients. The infections consisted primarily of upper respiratory tract infections, bronchitis and urinary tract infections. Most patients continued on Trudexa after the infection resolved.

The incidence of serious infections was 0.03 per patient year in Trudexa treated patients and 0.03 per patient year in placebo and active control−treated patients.

In controlled and open label studies with Trudexa, serious infections (including fatal infections, which occurred rarely) have been reported, which include reports of tuberculosis (including miliary and extra-pulmonary locations) and invasive opportunistic infections (e.g. disseminated histoplasmosis, pneumocystis carinii pneumonia, aspergillosis and listeriosis). Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease.

Malignancies and lymphoproliferative disorders

During the controlled portions of ten Trudexa trials at least 12 weeks in duration (I-IX and CHARM) in patients with moderately to severely active rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and Crohn's disease, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 5.7 (3.3, 10.1) per 1000 patient-years among 2887 Trudexa treated patients versus a rate of 4.1 (1.5, 10.9) 1 per 1000 patient-years among 1570 control patients (median duration of treatment was 5.7 months for Trudexa and 5.5 months for control-treated patients). The rate (95% confidence interval) of non-melanoma skin cancers was 7.6 (4.7, 12.4) per 1000 patient-years among Trudexa-treated patients and 2.0 (0.5, 8.2) per 1000 patient-years among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates (95% confidence interval) of 2.4 (1.0, 5.7) per 1000 patient-years among Trudexa-treated patients and 0 per 1000 patient-years among control patients. The rate (95% confidence interval) of lymphomas was 1.0 (0.2, 3.8) per 1000 patient-years among Trudexa-treated patients and 1.0 (0.1, 7.3) per 1000 patient-years among control patients.

When combining controlled portions of ten trials (I-IX and CHARM) and ongoing open label extension studies with a median duration of approximately 2. years including 4843 patients and over 13000 patient-years of therapy, the observed rate of malignancies, other than lymphoma and non-melanoma skin cancers is approximately 13.6 per 1000 patient years. The observed rate of non-melanoma skin cancers is approximately 9.0 per 1000 patient years, and the observed rate of lymphomas is approximately 1.2 per 1000 patient years.

In post-marketing experience from January 2003, predominately in patients with rheumatoid arthritis, the reported rate of malignancies other than lymphomas and non-melanoma skin cancers is approximately 1.7 per 1000 patient years. The reported rates for non-melanoma skin cancers and lymphomas are approximately 0.2 and 0.4 per 1000 patient years, respectively (see section 4.4).

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple time points in rheumatoid arthritis Studies I−V. In these trials, 11.9% of patients treated with Trudexa and 8.1% of placebo and active control−treated patients that had negative baseline anti-nuclear antibody titres reported positive titres at week 24. Two patients out of 3441 treated with Trudexa in all rheumatoid arthritis and psoriatic arthritis studies developed clinical signs suggestive of new-onset lupus-like syndrome. The patients

improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms.

Liver Enzyme Elevations

Rheumatoid arthritis clinical trials: in controlled rheumatoid arthritis clinical trials (Studies I–IV), elevations of ALT were similar in patients receiving adalimumab or placebo. In patients with early rheumatoid arthritis (disease duration of less than 3 years) (Study V), elevations of ALT were more common in the combination arm (Trudexa /methotrexate) compared to the methotrexate monotherapy arm or the Trudexa monotherapy arm.

Psoriatic arthritis clinical trials: elevations in ALT were more common in psoriatic arthritis patients (Studies VI-VII) compared with patients in rheumatoid arthritis clinical studies.

In all studies (I-VII), patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment.

Crohn's disease clinical trials: in controlled clinical trials, elevations of ALT were similar in patients receiving adalimumab or placebo.

Additional Adverse Reactions from Postmarketing Surveillance or Phase IV Clinical Trials

The additional adverse reactions in Table 2 have been reported from postmarketing surveillance or Phase IV clinical trials:

Table 2
Undesirable Effects in Postmarketing Surveillance and Phase IV Clinical Studies

System Organ Class	**Adverse Reaction**
Hepatobiliary Disorders	reactivation of hepatitis B
Nervous system disorders	demyelinating disorders (e.g. optic neuritis)
Respiratory, thoracic and mediastinal disorders	interstitial lung disease, including pulmonary fibrosis
Skin and subcutaneous tissue disorders	cutaneous vasculitis
Immune system disorders	anaphylaxis

4.9 Overdose

No dose-limiting toxicity was observed during clinical trials. The highest dose level evaluated has been multiple intravenous doses of 10 mg/kg.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressive agents. ATC code: L04AA17

Mechanism of action

Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

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 IC_{50} of 1-2 X 10^{-10} M).

Pharmacodynamic effects

After treatment with Trudexa, a rapid decrease in levels of acute phase reactants of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) and serum cytokines (IL-6) was observed compared to baseline in patients with rheumatoid arthritis. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodelling responsible for cartilage destruction were also decreased after Trudexa administration. Patients treated with Trudexa usually experienced improvement in haematological signs of chronic inflammation.

A rapid decrease in CRP levels was also observed in patients with Crohn's disease.

Clinical trials

Rheumatoid arthritis

Trudexa was evaluated in over 3000 patients in all rheumatoid arthritis clinical trials. Some patients were treated for up to 60 months duration. The efficacy and safety of Trudexa for the treatment of rheumatoid arthritis were assessed in five randomised, double-blind and well-controlled studies.

Study I evaluated 271 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, had failed therapy with at least one disease-modifying, anti rheumatic drug and had insufficient efficacy with methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate dose remained constant at 10 to 25 mg every week. Doses of 20, 40 or 80 mg of Trudexa or placebo were given every other week for 24 weeks.

Study II evaluated 544 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old and had failed therapy with at least one disease-modifying, anti-rheumatic drugs. Doses of 20 or 40 mg of Trudexa were given by subcutaneous injection every other week with placebo on alternative weeks or every week for 26 weeks; placebo was given every week for the same duration. No other disease-modifying anti-rheumatic drugs were allowed.

Study III evaluated 619 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, had insufficient efficacy to methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate dose remained constant at 12.5 to 25 mg every week. There were three groups in this study. The first received placebo injections every week for 52 weeks. The second received 20 mg of Trudexa every week for 52 weeks. The third group received 40 mg of Trudexa every other week with placebo injections on alternate weeks. Thereafter, patients enrolled in an open-label extension phase in which 40 mg of Trudexa was administered every other week up to 60 months.

Study IV primarily assessed safety in 636 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old. Patients were permitted to be either disease-modifying, anti-rheumatic drug-naïve or to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. These therapies include methotrexate, leflunomide, hydroxychloroquine, sulfasalazine and/or gold salts. Patients were randomised to 40 mg of Trudexa or placebo every other week for 24 weeks.

Study V evaluated 799 methotrexate-naïve, adult patients with moderate to severely active early rheumatoid arthritis (mean disease duration less than 9 months). This study evaluated the efficacy of Trudexa 40 mg every other week/methotrexate combination therapy, Trudexa 40 mg every other week monotherapy and methotrexate monotherapy in reducing the signs and symptoms and rate of progression of joint damage in rheumatoid arthritis for 104 weeks.

The primary end point in Studies I, II and III and the secondary endpoint in Study IV was the percent of patients who achieved an ACR 20 response at week 24 or 26. The primary endpoint in Study V was the percent of patients who achieved an ACR 50 response at week 52. Study III and V had an

additional primary endpoint at 52 weeks of retardation of disease progression (as detected by X-ray results). Study III also had a primary endpoint of changes in quality of life.

ACR response

The percent of Trudexa-treated patients achieving ACR 20, 50 and 70 responses was consistent across trials I, II and III. The results for the 40 mg every other week dose are summarised in Table 3.

Table 3: ACR Responses in Placebo-Controlled Trials (Percent of Patients)

Response	Study I[a]**		Study II[a]**		Study III[a]**	
	Placebo/ MTX[c] n=60	Trudexa[b]/ MTX[c] n=63	Placebo n=110	Trudexa[b] n=113	Placebo/ MTX[c] n=200	Trudexa[b]/ MTX[c] n=207
ACR 20						
6 months	13.3%	65.1%	19.1%	46.0%	29.5%	63.3%
12 months	NA	NA	NA	NA	24.0%	58.9%
ACR 50						
6 months	6.7%	52.4%	8.2%	22.1%	9.5%	39.1%
12 months	NA	NA	NA	NA	9.5%	41.5%
ACR 70						
6 months	3.3%	23.8%	1.8%	12.4%	2.5%	20.8%
12 months	NA	NA	NA	NA	4.5%	23.2%

[a] Study I at 24 weeks, Study II at 26 weeks , and Study III at 24 and 52 weeks
[b] 40 mg Trudexa administered every other week
[c] MTX = methotrexate
**p < 0.01, Trudexa versus placebo

In Studies I-IV, all individual components of the ACR response criteria (number of tender and swollen joints, physician and patient assessment of disease activity and pain, disability index (HAQ) scores and CRP (mg/dl) values) improved at 24 or 26 weeks compared to placebo. In Study III, these improvements were maintained throughout 52 weeks. In addition, ACR response rates were maintained in the majority of patients followed in the open-label extension phase to week 104. There were 114 out of 207 patients who continued on Humira 40 mg every other week for 60 months. Among those, 86, 72, and 41 patients had ACR 20/50/70 response, respectively at month 60.

In Study IV, the ACR 20 response of patients treated with Trudexa plus standard of care was statistically significantly better than patients treated with placebo plus standard of care ($p < 0.001$).

In Studies I-IV, Trudexa-treated patients achieved statistically significant ACR 20 and 50 responses compared to placebo as early as one to two weeks after initiation of treatment.

In Study V with early rheumatoid arthritis patients who were methotrexate naïve, combination therapy with Trudexa and methotrexate led to faster and significantly greater ACR responses than methotrexate monotherapy and Trudexa monotherapy at week 52 and responses were sustained at week 104 (see Table 4).

Table 4: ACR Responses in Study V (percent of patients)

Response	**MTX n=257**	**Trudexa n=274**	**Trudexa/MTX n=268**	**p-value[a]**	**p-value[b]**	**p-value[c]**
ACR 20						

Week 52	62.6%	54.4%	72.8%	0.013	< 0.001	0.043
Week 104	56.0%	49.3%	69.4%	0.002	< 0.001	0.140
ACR 50						
Week 52	45.9%	41.2%	61.6%	< 0.001	< 0.001	0.317
Week 104	42.8%	36.9%	59.0%	< 0.001	< 0.001	0.162
ACR 70						
Week 52	27.2%	25.9%	45.5%	< 0.001	< 0.001	0.656
Week 104	28.4%	28.1%	46.6%	< 0.001	< 0.001	0.864

a. p-value is from the pairwise comparison of methotrexate monotherapy and Trudexa/methotrexate combination therapy using the Mann-Whitney U test.
b. p-value is from the pairwise comparison of Trudexa monotherapy and Trudexa/methotrexate combination therapy using the Mann-Whitney U test
c. p-value is from the pairwise comparison of Trudexa monotherapy and methotrexate monotherapy using the Mann-Whitney U test

At week 52, 42.9% of patients who received Trudexa/methotrexate combination therapy achieved clinical remission (DAS28 < 2.6) compared to 20.6% of patients receiving methotrexate monotherapy and 23.4% of patients receiving Trudexa monotherapy. Trudexa/methotrexate combination therapy was clinically and statistically superior to methotrexate ($p < 0.001$) and Trudexa monotherapy ($p < 0.001$) in achieving a low disease state in patients with recently diagnosed moderate to severe rheumatoid arthritis. The response for the two monotherapy arms was similar ($p = 0.447$).

Radiographic response

In Study III, where Trudexa treated patients had a mean duration of rheumatoid arthritis of approximately 11 years, structural joint damage was assessed radiographically and expressed as change in modified total Sharp score and its components, the erosion score and joint space narrowing score. Trudexa/methotrexate patients demonstrated significantly less radiographic progression than patients receiving methotrexate alone at 6 and 12 months (see Table 5). Data from the open-label extension phase indicate that the reduction in rate of progression of structural damage is maintained for 60 months in a subset of patients. 113/207 of patients originally treated with 40 mg Humira every other week were evaluated radiographically at 5 years. Among those, 66 patients showed no progression of structural damage defined by a change in the TSS of zero or less.

Table 5: Radiographic Mean Changes Over 12 Months in Study III

	Placebo/ MTX[a]	TRUDEXA/MTX 40 mg every other week	Placebo/MTX-TRUDEXA/MTX (95% Confidence Interval[b])	P-value
Total Sharp score	2.7	0.1	2.6 (1.4, 3.8)	< 0.001[c]
Erosion score	1.6	0.0	1.6 (0.9, 2.2)	< 0.001
JSN[d] score	1.0	0.1	0.9 (0.3, 1.4)	0.002

[a]methotrexate
[b]95% confidence intervals for the differences in change scores between methotrexate and Trudexa.
[c]Based on rank analysis
[d]Joint Space Narrowing

In Study V, structural joint damage was assessed radiographically and expressed as change in modified total Sharp score (see Table 6).

Table 6: Radiographic Mean Changes at Week 52 in Study V

	MTX n=257 (95% confidence interval)	Trudexa n=274 (95% confidence interval)	Trudexa/MTX n=268	p-value[a]	p-value[b]	p-value[c]

			(95% confidence interval)			
Total Sharp score	5.7 (4.2-7.3)	3.0 (1.7-4.3)	1.3 (0.5-2.1)	< 0.001	0.0020	< 0.001
Erosion score	3.7 (2.7-4.7)	1.7 (1.0-2.4)	0.8 (0.4-1.2)	< 0.001	0.0082	< 0.001
JSN score	2.0 (1.2-2.8)	1.3 (0.5-2.1)	0.5 (0-1.0)	< 0.001	0.0037	0.151

a. p-value is from the pairwise comparison of methotrexate monotherapy and Trudexa/methotrexate combination therapy using the Mann-Whitney U test.
b. p-value is from the pairwise comparison of Trudexa monotherapy and Trudexa/methotrexate combination therapy using the Mann-Whitney U test
c. p-value is from the pairwise comparison of Trudexa monotherapy and methotrexate monotherapy using the Mann-Whitney U test

Following 52 weeks and 104 weeks of treatment, the percentage of patients without progression (change from baseline in modified total Sharp score ≤ 0.5) was significantly higher with Trudexa/methotrexate combination therapy (63.8% and 61.2% respectively) compared to methotrexate monotherapy (37.4% and 33.5% respectively, $p < 0.001$) and Trudexa monotherapy (50.7%, $p < 0.002$ and 44.5%, $p < 0.001$ respectively).

Quality of life and physical function

Health-related quality of life and physical function was assessed using the disability index of the Health Assessment Questionnaire (HAQ) in the four original adequate and well-controlled trials, which was a pre-specified primary endpoint at week 52 in Study III. All doses/schedules of Trudexa in all four studies showed statistically significantly greater improvement in the disability index of the HAQ from baseline to Month 6 compared to placebo and in Study III the same was seen at week 52. Results from the Short Form Health Survey (SF 36) for all doses/schedules of Trudexa in all four studies support these findings, with statistically significant physical component summary (PCS) scores, as well as statistically significant pain and vitality domain scores for the 40 mg every other week dose. A statistically significant decrease in fatigue as measured by functional assessment of chronic illness therapy (FACIT) scores was seen in all three studies in which it was assessed (Studies I, III, IV).

In Study III, improvement in physical function was maintained through week 260 (60 months) of open-label treatment. Improvement in quality of life was measured up to week 156 (36 months) and improvement was maintained through that time.

In Study V, the improvement in the HAQ disability index and the physical component of the SF 36 showed greater improvement ($p < 0.001$) for Trudexa/methotrexate combination therapy versus methotrexate monotherapy and Trudexa monotherapy at week 52, which was maintained through week 104.

Psoriatic arthritis

Trudexa, 40 mg every other week, was studied in patients with moderately to severely active psoriatic arthritis in two placebo-controlled studies, Studies VI and VII. Study VI with 24 week duration, treated 313 adult patients who had an inadequate response to non-steroidal anti-inflammatory drug therapy and of these, approximately 50% were taking methotrexate. Study VII with 12-week duration, treated 100 patients who had an inadequate response to DMARD therapy.

There is insufficient evidence of the efficacy of Trudexa in patients with ankylosing spondylitis-like psoriatic arthropathy due to the small number of patients studied (see Table 7).

Table 7: ACR Response in Placebo-Controlled Psoriatic Arthritis Studies (Percent of Patients)

	Study VI	Study VII

Response	Placebo N=162	Trudexa N=151	Placebo N=49	Trudexa N=51
ACR 20				
Week 12	14%	58%***	16%	39%*
Week 24	15%	57%***	N/A	N/A
ACR 50				
Week 12	4%	36%***	2%	25%***
Week 24	6%	39%***	N/A	N/A
ACR 70				
Week 12	1%	20%***	0%	14%*
Week 24	1%	23%***	N/A	N/A

*** $p < 0.001$ for all comparisons between Trudexa and placebo
* $p < 0.05$ for all comparisons between Trudexa and placebo
N/A not applicable

ACR responses in Study VI were similar with and without concomitant methotrexate therapy. Trudexa treated patients demonstrated improvement in physical function as assessed by HAQ and Short Form Health Survey (SF 36), from base-line to week 24.

Ankylosing spondylitis

Trudexa 40 mg every other week was assessed in 393 patients in two randomised, 24 week double−blind, placebo−controlled studies in patients with active ankylosing spondylitis (mean baseline score of disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)] was 6.3 in all groups) who have had an inadequate response to conventional therapy. Seventy-nine (20.1%) patients were treated concomitantly with disease modifying anti-rheumatic drugs, and 37 (9.4%) patients with glucocorticoids. The blinded period was followed by an open−label period during which patients received Trudexa 40 mg every other week subcutaneously for up to an additional 28 weeks. Subjects (n = 215, 54.7%) who failed to achieve ASAS 20 at Weeks 12, or 16 or 20 received early escape open-label adalimumab 40 mg every other week subcutaneously and were subsequently treated as non-responders in the double-blind statistical analyses.

In the larger study (VIII) with 315 patients, results showed statistically significant improvement of the signs and symptoms of ankylosing spondylitis in patients treated with Trudexa compared to placebo. Significant response was first observed at Week 2 and maintained through 24 weeks (Table 8).

Table 8 - Efficacy Responses in Placebo-Controlled AS Study – Study VIII Reduction of Signs and Symptoms

Response	**Placebo N=107**	**Trudexa N=208**
ASAS[a] 20		
Week 2	16%	42%***
Week 12	21%	58%***
Week 24	19%	51%***
ASAS 50		
Week 2	3%	16%***
Week 12	10%	38%***
Week 24	11%	35%***
ASAS 70		
Week 2	0%	7%**
Week 12	5%	23%***
Week 24	8%	24%***
BASDAI[b] 50		

Week 2	4%	20%***
Week 12	16%	45%***
Week 24	15%	42%***

***,** Statistically significant at $p < 0.001$, < 0.01 for all comparisons between Trudexa and placebo at Weeks 2, 12 and 24

[a] ASsessments in Ankylosing Spondylitis

[b] Bath Ankylosing Spondylitis Disease Activity Index

Trudexa treated patients had significantly greater improvement at Week 12 which was maintained through Week 24 in both the SF36 and Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL).

Similar trends (not all statistically significant) were seen in the smaller randomised, double−blind, placebo controlled study (IX) of 82 adult patients with active ankylosing spondylitis.

Crohn's Disease

The safety and efficacy of Trudexa were assessed in over 1400 patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450) in randomised, double-blind, placebo-controlled studies. 478 of the enrolled patients (32%) were defined as having a severe disease (CDAI score > 300 and concomitant corticosteroid and/or immunosuppressants) corresponding to the population defined in the indication (see section 4.1). Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted and 79% of patients continued to receive at least one of these medications.

Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies, CLASSIC I and GAIN. In CLASSIC I, 299 TNF-antagonist naive patients were randomised to one of four treatment groups; placebo at weeks 0 and 2, 160 mg Trudexa at week 0 and 80 mg at week 2, 80 mg at week 0 and 40 mg at week 2, and 40 mg at week 0 and 20 mg at week 2. In GAIN, 325 patients who had lost response or were intolerant to infliximab were randomised to receive either 160 mg Trudexa at week 0 and 80 mg at week 2 or placebo at weeks 0 and 2. The primary non-responders were excluded from the studies and therefore these patients were not further evaluated.

Maintenance of clinical remission was evaluated in CHARM. In CHARM, 854 patients received open-label 80 mg at week 0 and 40 mg at week 2. At week 4 patients were randomised to 40 mg every other week, 40 mg every week, or placebo with a total study duration of 56 weeks. Patients in clinical response (decrease in CDAI ≥ 70) at week 4 were stratified and analysed separately from those not in clinical response at week 4. Corticosteroid taper was permitted after week 8.

CLASSIC I and GAIN induction of remission and response rates are presented in Table 9.

Table 9: Induction of Clinical Remission and Response

(Percent of Patients)

	CLASSIC I: Infliximab Naive Patients			GAIN: Infliximab Experienced Patients	
	Placebo N=74	**Trudexa 80/40 mg N = 75**	**Trudexa 160/80 mg N=76**	**Placebo N=166**	**Trudexa 160/80 mg N=159**
Week 4					
Clinical remission	12%	24%	36%*	7%	21%*
Clinical response (CR-100)	24%	37%	49%**	25%	38%**

All p-values are pairwise comparisons of proportions for Trudexa *versus* placebo

* $p < 0.001$

** $p < 0.01$

Similar remission rates were observed for the 160/80 mg and 80/40 mg induction regimens by week 8 and adverse events were more frequently noted in the 160/80 mg group.

In CHARM, at week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. Of those in clinical response at week 4, 48% had been previously exposed to other anti-TNF therapy. Maintenance of remission and response rates are presented in Table 10. Clinical remission results remained relatively constant irrespective of previous TNF antagonist exposure.

Table 10: Maintenance of Clinical Remission and Response

(Percent of Patients)

	Placebo	**40 mg Trudexa every other week**	**40 mg Trudexa every week**
Week 26	**N=170**	**N=172**	**N=157**
Clinical remission	17%	40%*	47%*
Clinical response (CR-100)	27%	52%*	52%*
Patients in steroid-free remission for >=90 days[a]	3% (2/66)	19% (11/58)**	15% (11/74)**
Week 56	**N=170**	**N=172**	**N=157**
Clinical remission	12%	36%*	41%*
Clinical response (CR-100)	17%	41%*	48%*
Patients in steroid-free remission for >=90 days[a]	5% (3/66)	29% (17/58)*	20% (15/74)**

* $p < 0.001$ for Trudexa *versus* placebo pairwise comparisons of proportions

** $p < 0.02$ for Trudexa *versus* placebo pairwise comparisons of proportions

[a] Of those receiving corticosteroids at baseline

Among patients who were not in response at week 4, 43% of Trudexa maintenance patients responded by week 12 compared to 30% of placebo maintenance patients. These results suggest that some patients who have not responded by week 4 benefit from continued maintenance therapy through week 12. Therapy continued beyond 12 weeks did not result in significantly more responses (see section 4.2).

Quality of Life

In CLASSIC I and GAIN, statistically significant improvement in the disease-specific inflammatory bowel disease questionnaire (IBDQ) total score was achieved at week 4 in patients randomised to

Trudexa 80/40 mg and 160/80 mg compared to placebo and was seen at weeks 26 and 56 in CHARM as well among the adalimumab treatment groups compared to the placebo group.

Immunogenicity

Formation of anti-adalimumab antibodies is associated with increased clearance and reduced efficacy of adalimumab. There is no apparent correlation between the presence of anti-adalimumab antibodies and adverse events.

Patients in Studies I, II and III were tested at multiple timepoints for antibodies to adalimumab during the 6 to 12 month period. In the pivotal trials, anti-adalimumab antibodies were identified in 58/1053 (5.5%) patients treated with adalimumab, compared to 2/370 (0.5%) on placebo. In patients not given concomitant methotrexate, the incidence was 12.4%, compared to 0.6% when adalimumab was used as add-on to methotrexate.

In patients with psoriatic arthritis, adalimumab antibodies were identified in 38/376 subjects (10%) treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 13.5% (24/178 subjects), compared to 7% (14 of 198 subjects) when adalimumab was used as add-on to methotrexate.

In patients with ankylosing spondylitis antibodies were identified in 17/204 subjects (8.3%) treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 16/185 (8.6%), compared to 1/19 (5.3%) when adalimumab was used as add-on to methotrexate.

In patients with Crohn's disease, adalimumab antibodies were identified in 7/269 subjects (2.6%) treated with adalimumab.

Because immunogenicity analyses are product-specific, comparison of antibody rates with those from other products is not appropriate.

5.2 Pharmacokinetic properties

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 Trudexa every other week in 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 every other week and every week subcutaneous dosing.

In patients with Crohn's disease, the loading dose of 80 mg Trudexa on week 0 followed by 40 mg Trudexa on week 2 achieves serum adalimumab trough concentrations of approximately 5.5 µg/ml during the induction period. A loading dose of 160 mg Trudexa on week 0 followed by 80 mg Trudexa on week 2 achieves serum adalimumab trough concentrations of approximately 12 µg/ml during the induction period. Mean steady-state trough levels of approximately 7 µg/ml were observed in Crohn's disease patients who received a maintenance dose of 40 mg Trudexa every other week.

Population pharmacokinetic analyses with data from over 1300 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. Trudexa has not been studied in children or in patients with hepatic or renal impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of single dose toxicity, repeated dose toxicity, and genotoxicity.

An embryo-foetal developmental toxicity/perinatal developmental study has been performed in cynomologous monkeys at 0, 30 and 100 mg/kg (9-17 monkeys/group) and has revealed no evidence of harm to the foetuses due to adalimumab. Carcinogenicity studies, and standard assessment of fertility and postnatal toxicity, were not performed with adalimumab due to the lack of appropriate models for an antibody with limited cross-reactivity to rodent TNF and the development of neutralizing antibodies in rodents.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Citric acid monohydrate
Sodium citrate
Sodium dihydrogen phosphate dihydrate
Disodium phosphate dihydrate
Sodium chloride
Polysorbate 80
Sodium hydroxide
Water for injections.

6.2 Incompatibilities

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

6.3 Shelf life

18 months

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Keep the vial in the outer carton. Do not freeze.

6.5 Nature and contents of container

Trudexa 40 mg solution for injection in single-use vial (type I glass), fitted with rubber stoppers, aluminium crimps and flip-off seals.

Packs of:
1 vial (0.8 ml sterile solution), 1 empty sterile injection syringe in pouch and 2 alcohol pads, all in a blister.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Abbott Laboratories Ltd.
Queenborough
Kent ME11 5EL
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/257/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1 September 2003

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

1. NAME OF THE MEDICINAL PRODUCT

Trudexa 40 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.8 ml single dose pre-filled syringe contains 40 mg of adalimumab.

Adalimumab is a recombinant human monoclonal antibody expressed in Chinese Hamster Ovary cells.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

Trudexa in combination with methotrexate, is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

Trudexa can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Trudexa has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Psoriatic arthritis

Trudexa is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

Ankylosing spondylitis

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

Crohn's disease

Trudexa is indicated for treatment of severe, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. For induction treatment, Trudexa should be given in combination with corticosteroids. Trudexa can be given as monotherapy in case of intolerance to corticosteroids or when continued treatment with corticosteroids is inappropriate (see section 4.2).

4.2 Posology and method of administration

Trudexa treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or Crohn's disease. Patients treated with Trudexa should be given the special alert card.

After proper training in injection technique, patients may self-inject with Trudexa if their physician determines that it is appropriate and with medical follow-up as necessary.

During treatment with Trudexa, other concomitant therapies (e.g., corticosteroids and/or immunomodulatory agents) should be optimised.

Adults

Rheumatoid arthritis

The recommended dose of Trudexa for adult patients with rheumatoid arthritis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection. Methotrexate should be continued during treatment with Trudexa.

Glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, or analgesics can be continued during treatment with Trudexa. Regarding combination with disease modifying anti-rheumatic drugs other than methotrexate see sections 4.4 and 5.1.

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.

Psoriatic arthritis and ankylosing spondylitis

The recommended dose of Trudexa for patients with psoriatic arthritis and ankylosing spondylitis is 40 mg adalimumab administered every other week as a single dose via subcutaneous injection.

For all of the above indications, available data suggest that the 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.

Crohn's disease

The recommended Trudexa induction dose regimen for adult patients with severe 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 Trudexa and signs and symptoms of disease recur, Trudexa 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 dose intensity to 40 mg Trudexa 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.

Elderly patients

No dose adjustment is required.

Children and adolescents

There is no experience in children.

Impaired renal and/or hepatic function

Trudexa has not been studied in these patient populations. No dose recommendations can be made.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Active tuberculosis or other severe infections such as sepsis, and opportunistic infections (see section 4.4).

Moderate to severe heart failure (NYHA class III/IV) (see section 4.4).

4.4 Special warnings and precautions for use

Infections

Patients must be monitored closely for infections, including tuberculosis, before, during and after treatment with Trudexa. Because the elimination of adalimumab may take up to five months, monitoring should be continued throughout this period.

Treatment with Trudexa should not be initiated in patients with active infections including chronic or localized infections until infections are controlled.

Patients who develop a new infection while undergoing treatment with Trudexa should be monitored closely. Administration of Trudexa should be discontinued if a patient develops a new serious infection until infections are controlled. Physicians should exercise caution when considering the use of Trudexa 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, sepsis, tuberculosis and other opportunistic infections, including fatalities, have been reported with Trudexa.

Serious infections:

In clinical trials an increased risk of serious infections in patients receiving Trudexa has been shown, and reports from the post-marketing setting support this finding. Of particular importance are infections such as pneumonia, pyelonephritis, septic arthritis and septicaemia.

Tuberculosis:

There have been reports of tuberculosis in patients receiving Trudexa. It should be noted that in the majority of those reports, tuberculosis was extra-pulmonary, i.e. disseminated.

Before initiation of therapy with Trudexa, all patients must be evaluated for both active or inactive (latent) tuberculosis infection. This evaluation should include a detailed medical history with a personal history of tuberculosis or possible previous exposure to patients 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 of these tests should be 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, Trudexa therapy must not be initiated (see section 4.3).

If latent tuberculosis is diagnosed, appropriate anti-tuberculosis prophylaxis in accordance with local recommendations must be initiated before starting treatment with Trudexa. In this situation, the benefit/risk balance of therapy with Trudexa should be very carefully considered.

Patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur during or after therapy with Trudexa.

Other opportunistic infections:

There have been reports of serious and severe opportunistic infections associated with Trudexa therapy, for example pneumocystis carinii pneumonia, disseminated histoplasmosis, listeriosis and aspergillosis.

If a patient receiving Trudexa shows prolonged/atypical symptoms/signs of infections or general deterioration, prevalent opportunistic conditions must be considered.

Hepatitis B Reactivation

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including Trudexa, who are chronic carriers of this virus. Some cases have had fatal outcome. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating Trudexa therapy. Carriers of HBV who require treatment with Trudexa should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data of 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, Trudexa should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Neurological events

TNF-antagonists including Trudexa have been associated in rare cases with new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease. Prescribers should exercise caution in considering the use of Trudexa in patients with pre-existing or recent-onset central nervous system demyelinating disorders.

Allergic reactions

Serious allergic adverse reactions have not been reported with subcutaneous administration of Trudexa during clinical trials. Non-serious allergic reactions associated with Trudexa were uncommon during clinical trials. In postmarketing, serious allergic reactions including anaphylaxis have been reported very rarely following Trudexa administration. If an anaphylactic reaction or other serious allergic reaction occurs, administration of Trudexa should be discontinued immediately and appropriate therapy initiated.

The needle cover of the syringe contains natural rubber (latex). This may cause severe allergic reactions in patients sensitive to latex.

Immunosuppression

In a study of 64 patients with rheumatoid arthritis that were treated with Trudexa, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T-and B cells and NK-cells, monocyte/macrophages, and neutrophils.

Malignancies and lymphoproliferative disorders

In the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies including lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare. Furthermore, there is an increased background lymphoma risk 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 or other malignancies in patients treated with a TNF-antagonist cannot be excluded.

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving Trudexa. Thus additional caution should be exercised in considering Trudexa treatment of these patients (see section 4.8).

In an exploratory clinical trial evaluating the use of another anti-TNF agent, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. 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.

Haematologic reactions

Rare reports of pancytopenia including aplastic anaemia have been reported with TNF blocking agents. Adverse events of the haematologic system, including medically significant cytopoenia (e.g. thrombocytopaenia, leucopaenia) have been infrequently reported with Trudexa. All 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 Trudexa. Discontinuation of Trudexa therapy should be considered in patients with confirmed significant haematologic abnormalities.

Vaccinations

Similar antibody responses to the standard 23-valent pneumococcal vaccine and the influenza trivalent virus vaccination were observed in a study in 226 adult subjects with rheumatoid arthritis who were treated with adalimumab or placebo. No data are available on the secondary transmission of infection by live vaccines in patients receiving Trudexa. Patients on Trudexa may receive concurrent vaccinations, except for live vaccines.

Congestive heart failure

In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Cases of worsening congestive heart failure have also been reported in patients receiving Trudexa. Trudexa should be used with caution in patients with mild heart failure (NYHA class I/II). Trudexa is contraindicated in moderate to severe heart failure (see section 4.3). Treatment with Trudexa must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Autoimmune processes

Treatment with Trudexa may result in the formation of autoimmune antibodies. The impact of long-term treatment with Trudexa on the development of autoimmune diseases is unknown. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Trudexa and is positive for antibodies against double-stranded DNA, further treatment with Trudexa should not be given (see section 4.8).

Concurrent administration of TNF-antagonists and anakinra

Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF-antagonist, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNF-antagonists. Therefore, the combination of adalimumab and anakinra is not recommended.

Surgery

There is limited safety experience of surgical procedures in patients treated with Trudexa. The long half-life of adalimumab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on Trudexa should be closely monitored for infections, and appropriate actions should be taken. There is limited safety experience in patients undergoing arthroplasty while receiving Trudexa.

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 Trudexa does not worsen or cause strictures.

4.5 Interaction with other medicinal products and other forms of interaction

Trudexa has been studied both in rheumatoid arthritis and psoriatic arthritis patients taking Trudexa as monotherapy and those taking concomitant methotrexate. Antibody formation was lower when Trudexa was given together with methotrexate in comparison with use as monotherapy. Administration of Trudexa without methotrexate resulted in increased formation of antibodies, increased clearance and reduced efficacy of adalimumab (see section 5.1).

4.6 Pregnancy and lactation

For Trudexa, no 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 and fertility effects of adalimumab are not available (see section 5.3).

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. 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 Trudexa treatment.

Use during lactation

It is not known whether adalimumab is excreted in human milk or absorbed systemically after ingestion.

However, because human immunoglobulins are excreted in milk, women must not breast-feed for at least five months after the last Trudexa treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Clinical Trials

Trudexa was studied in 5293 patients in controlled and open label trials for up to 60 months. These trials included rheumatoid arthritis patients with short term and long standing disease as well as psoriatic arthritis, ankylosing spondylitis and Crohn's disease patients. The data in Table 1 is based on the controlled Studies (I−IX,CLASSIC I, GAIN AND CHARM) (described in section 5.1) involving 3271 patients receiving Trudexa and 1809 patients receiving placebo or active comparator during the controlled period.

The proportion of patients who discontinued treatment due to adverse events during the double-blind, controlled portion of Studies I−IX, CLASSIC I, GAIN and CHARM was 5.7% for patients taking Trudexa and 5.3% for control treated patients.

Adverse events at least possibly causally-related to adalimumab for Studies I−IX, CLASSIC I, GAIN and CHARM, both clinical and laboratory, are displayed by system organ class and frequency (very common ≥ 1/10; common≥ 1/100 < 1/10; uncommon≥ 1/1000 to ≤ 1/100) and rare < 1/1000 in Table 1 below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1
Undesirable Effects in Clinical Studies

System Organ Class	Frequency	Adverse Reaction
Infections and infestations	Common	lower respiratory infections (including pneumonia, bronchitis), viral infections (including influenza, herpes infections), candidiasis, bacterial infections (including urinary tract infections), upper respiratory infection
	Uncommon	opportunistic infections (including tuberculosis, histoplasmosis), sepsis, abscess, joint infection, wound infection, skin infection (including cellulitis and impetigo), superficial fungal infections (including skin, nail and foot)
	Rare	necrotising fasciitis, viral meningitis, diverticulitis
Neoplasms benign and malignant (including cysts and polyps)	Uncommon	skin papilloma
	Rare	lymphoma, solid organ tumours (including breast, ovarian, testicular), squamous cell carcinoma of the skin

Blood and the lymphatic system disorders	Common	lymphopaenia
	Uncommon	neutropaenia (including agranulocytosis), leucopaenia, thrombocytopaenia, anaemia, , lymphadenopathy, leucocytosis
	Rare	pancytopaenia, idiopathic thrombocytopaenia purpura
Immune system disorders	Uncommon	systemic lupus erythematosus, angioedema, drug hypersensitivity, seasonal allergy
	Rare	serum sickness
Endocrine disorders	Rare	thyroid disorder (including goitre)
Metabolism and nutrition disorders	Uncommon	Hypokalaemia, lipids increased, appetite disorders (including anorexia), hyperuricaemia
	Rare	hypercalcaemia
Psychiatric disorders	Uncommon	mood disorders, anxiety (including nervousness and agitation)
Nervous system disorders	Common	dizziness (including vertigo), headache, neurologic sensation disorders (including paraesthesias)
	Uncommon	syncope, migraine, tremor, sleep disturbances
	Rare	multiple sclerosis
Eye disorders	Common	infection, irritation or inflammation of the eye
	Uncommon	vision disorder, ocular sensation disorders
	Rare	Panophthalmitis, iritis, glaucoma
Ear and labyrinth disorders	Uncommon	tinnitus, ear discomfort (including pain and swelling)
	Rare	hearing loss
Cardiac disorders	Uncommon	arrhythmias, tachycardia, palpitations
	Rare	cardiac arrest, coronary artery insufficiency, angina pectoris, pericardial effusion
Vascular disorders	Uncommon	hypertension, flushing, haematoma
	Rare	vascular occlusion, aortic stenosis, thrombophlebitis, aortic aneurysm
Respiratory, thoracic and mediastinal disorders	Common	cough, nasopharyngeal pain

	Uncommon	asthma, dyspnoea, dysphonia, nasal congestion
	Rare	pulmonary oedema, pharyngeal oedema, pleural effusion, pleurisy
Gastrointestinal disorders	Common	diarrhoea, abdominal pain, stomatitis and mouth ulceration, nausea
	Uncommon	rectal haemorrhage, gastritis, vomiting, dyspepsia, abdominal bloating, constipation,
	Rare	intestinal stenosis, colitis, enteritis, oesophagitis
Hepato-biliary disorders	Common	hepatic enzymes increased
	Rare	hepatic necrosis, hepatitis
Skin and subcutaneous tissue disorders	Common	rash, dermatitis and eczema, pruritus, hair loss
	Uncommon	urticaria, psoriasis, ecchymosis and increased bruising, purpura
	Rare	erythema multiforme, panniculitis
Musculoskeletal, connective tissue and bone disorders	Common	musculoskeletal pain
	Rare	rhabdomyolysis
Renal and urinary disorders	Uncommon	haematuria, renal impairment, bladder and urethral symptoms,
	Rare	proteinuria, renal pain
Reproductive system and breast disorders	Uncommon	menstrual cycle and uterine bleeding disorders
General disorders and administration site conditions	Very Common	injection site reaction (including pain, swelling, redness or pruritus)
	Common	pyrexia, fatigue (including asthenia and malaise)
	Uncommon	chest pain, oedema, influenza like illness
Investigations	Uncommon	blood creatine phosphokinase increased, activated partial thromboplastin time prolonged, autoantibodies present
Injury and poisoning	Uncommon	accidental injury, impaired healing

Injection site reactions

In the twelve controlled trials, 16% of patients treated with Trudexa developed injection site reactions (erythema and/or itching, haemorrhage, pain or swelling), compared to 10% of patients receiving placebo or active control. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

Infections

In the twelve controlled trials, the rate of infection was 1.49 per patient year in the Trudexa treated patients and 1.42 per patient year in the placebo and active control-treated patients. The infections consisted primarily of upper respiratory tract infections, bronchitis and urinary tract infections. Most patients continued on Trudexa after the infection resolved.

The incidence of serious infections was 0.03 per patient year in Trudexa treated patients and 0.03 per patient year in placebo and active control−treated patients.

In controlled and open label studies with Trudexa, serious infections (including fatal infections, which occurred rarely) have been reported, which include reports of tuberculosis (including miliary and extra-pulmonary locations) and invasive opportunistic infections (e.g. disseminated histoplasmosis, pneumocystis carinii pneumonia, aspergillosis and listeriosis). Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease.

Malignancies and lymphoproliferative disorders

During the controlled portions of ten Trudexa trials at least 12 weeks in duration (I-IX and CHARM) in patients with moderately to severely active rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and Crohn's disease, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 5.7 (3.3, 10.1) per 1000 patient-years among 2887 Trudexa treated patients versus a rate of 4.1 (1.5, 10.9) 1 per 1000 patient-years among 1570 control patients (median duration of treatment was 5.7 months for Trudexa and 5.5 months for control-treated patients). The rate (95% confidence interval) of non-melanoma skin cancers was 7.6 (4.7, 12.4) per 1000 patient-years among Trudexa-treated patients and 2.0 (0.5, 8.2) per 1000 patient-years among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates (95% confidence interval) of 2.4 (1.0, 5.7) per 1000 patient-years among Trudexa-treated patients and 0 per 1000 patient-years among control patients. The rate (95% confidence interval) of lymphomas was 1.0 (0.2, 3.8) per 1000 patient-years among Trudexa-treated patients and 1.0 (0.1, 7.3) per 1000 patient-years among control patients.

When combining controlled portions of ten trials (I-IX and CHARM) and ongoing open label extension studies with a median duration of approximately 2. years including 4843 patients and over 13000 patient-years of therapy, the observed rate of malignancies, other than lymphoma and non-melanoma skin cancers is approximately 13.6 per 1000 patient years. The observed rate of non-melanoma skin cancers is approximately 9.0 per 1000 patient years, and the observed rate of lymphomas is approximately 1.2 per 1000 patient years.

In post-marketing experience from January 2003, predominately in patients with rheumatoid arthritis, the reported rate of malignancies other than lymphomas and non-melanoma skin cancers is approximately 1.7 per 1000 patient years. The reported rates for non-melanoma skin cancers and lymphomas are approximately 0.2 and 0.4 per 1000 patient years, respectively (see section 4.4).

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple time points in rheumatoid arthritis Studies I−V. In these trials, 11.9% of patients treated with Trudexa and 8.1% of placebo and active control−treated patients that had negative baseline anti-nuclear antibody titres reported positive titres at week 24. Two patients out of 3441 treated with Trudexa in all rheumatoid arthritis and psoriatic arthritis studies developed clinical signs suggestive of new-onset lupus-like syndrome. The patients

improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms.

Liver Enzyme Elevations

Rheumatoid arthritis clinical trials: in controlled rheumatoid arthritis clinical trials (Studies I–IV), elevations of ALT were similar in patients receiving adalimumab or placebo. In patients with early rheumatoid arthritis (disease duration of less than 3 years) (Study V), elevations of ALT were more common in the combination arm (Trudexa /methotrexate) compared to the methotrexate monotherapy arm or the Trudexa monotherapy arm.

Psoriatic arthritis clinical trials: elevations in ALT were more common in psoriatic arthritis patients (Studies VI-VII) compared with patients in rheumatoid arthritis clinical studies.

In all studies (I-VII), patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment.

Crohn's disease clinical trials: in controlled clinical trials, elevations of ALT were similar in patients receiving adalimumab or placebo.

Additional Adverse Reactions from Postmarketing Surveillance or Phase IV Clinical Trials

The additional adverse reactions in Table 2 have been reported from postmarketing surveillance or Phase IV clinical trials:

Table 2
Undesirable Effects in Postmarketing Surveillance and Phase IV Clinical Studies

System Organ Class	**Adverse Reaction**
Hepatobiliary Disorders	reactivation of hepatitis B
Nervous system disorders	demyelinating disorders (e.g. optic neuritis)
Respiratory, thoracic and mediastinal disorders	interstitial lung disease, including pulmonary fibrosis
Skin and subcutaneous tissue disorders	cutaneous vasculitis
Immune system disorders	anaphylaxis

4.9 Overdose

No dose-limiting toxicity was observed during clinical trials. The highest dose level evaluated has been multiple intravenous doses of 10 mg/kg.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressive agents. ATC code: L04AA17

Mechanism of action

Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

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 IC_{50} of 1-2 X 10^{-10} M).

Pharmacodynamic effects

After treatment with Trudexa, a rapid decrease in levels of acute phase reactants of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) and serum cytokines (IL-6) was observed compared to baseline in patients with rheumatoid arthritis. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodelling responsible for cartilage destruction were also decreased after Trudexa administration. Patients treated with Trudexa usually experienced improvement in haematological signs of chronic inflammation.

A rapid decrease in CRP levels was also observed in patients with Crohn's disease.

Clinical trials

Rheumatoid arthritis

Trudexa was evaluated in over 3000 patients in all rheumatoid arthritis clinical trials. Some patients were treated for up to 60 months duration. The efficacy and safety of Trudexa for the treatment of rheumatoid arthritis were assessed in five randomised, double-blind and well-controlled studies.

Study I evaluated 271 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, had failed therapy with at least one disease-modifying, anti rheumatic drug and had insufficient efficacy with methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate dose remained constant at 10 to 25 mg every week. Doses of 20, 40 or 80 mg of Trudexa or placebo were given every other week for 24 weeks.

Study II evaluated 544 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old and had failed therapy with at least one disease-modifying, anti-rheumatic drugs. Doses of 20 or 40 mg of Trudexa were given by subcutaneous injection every other week with placebo on alternative weeks or every week for 26 weeks; placebo was given every week for the same duration. No other disease-modifying anti-rheumatic drugs were allowed.

Study III evaluated 619 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old, had insufficient efficacy to methotrexate at doses of 12.5 to 25 mg (10 mg if methotrexate-intolerant) every week and whose methotrexate dose remained constant at 12.5 to 25 mg every week. There were three groups in this study. The first received placebo injections every week for 52 weeks. The second received 20 mg of Trudexa every week for 52 weeks. The third group received 40 mg of Trudexa every other week with placebo injections on alternate weeks. Thereafter, patients enrolled in an open-label extension phase in which 40 mg of Trudexa was administered every other week up to 60 months.

Study IV primarily assessed safety in 636 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old. Patients were permitted to be either disease-modifying, anti-rheumatic drug-naïve or to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. These therapies include methotrexate, leflunomide, hydroxychloroquine, sulfasalazine and/or gold salts. Patients were randomised to 40 mg of Trudexa or placebo every other week for 24 weeks.

Study V evaluated 799 methotrexate-naïve, adult patients with moderate to severely active early rheumatoid arthritis (mean disease duration less than 9 months). This study evaluated the efficacy of Trudexa 40 mg every other week/methotrexate combination therapy, Trudexa 40 mg every other week monotherapy and methotrexate monotherapy in reducing the signs and symptoms and rate of progression of joint damage in rheumatoid arthritis for 104 weeks.

The primary end point in Studies I, II and III and the secondary endpoint in Study IV was the percent of patients who achieved an ACR 20 response at week 24 or 26. The primary endpoint in Study V was the percent of patients who achieved an ACR 50 response at week 52. Study III and V had an

additional primary endpoint at 52 weeks of retardation of disease progression (as detected by X-ray results). Study III also had a primary endpoint of changes in quality of life.

ACR response

The percent of Trudexa-treated patients achieving ACR 20, 50 and 70 responses was consistent across trials I, II and III. The results for the 40 mg every other week dose are summarised in Table 3.

Table 3: ACR Responses in Placebo-Controlled Trials (Percent of Patients)

Response	Study I[a]**		Study II[a]**		Study III[a]**	
	Placebo/ MTX[c] n=60	Trudexa[b]/ MTX[c] n=63	Placebo n=110	Trudexa[b] n=113	Placebo/ MTX[c] n=200	Trudexa[b]/ MTX[c] n=207
ACR 20						
6 months	13.3%	65.1%	19.1%	46.0%	29.5%	63.3%
12 months	NA	NA	NA	NA	24.0%	58.9%
ACR 50						
6 months	6.7%	52.4%	8.2%	22.1%	9.5%	39.1%
12 months	NA	NA	NA	NA	9.5%	41.5%
ACR 70						
6 months	3.3%	23.8%	1.8%	12.4%	2.5%	20.8%
12 months	NA	NA	NA	NA	4.5%	23.2%

[a] Study I at 24 weeks, Study II at 26 weeks , and Study III at 24 and 52 weeks
[b] 40 mg Trudexa administered every other week
[c] MTX = methotrexate
**p < 0.01, Trudexa versus placebo

In Studies I-IV, all individual components of the ACR response criteria (number of tender and swollen joints, physician and patient assessment of disease activity and pain, disability index (HAQ) scores and CRP (mg/dl) values) improved at 24 or 26 weeks compared to placebo. In Study III, these improvements were maintained throughout 52 weeks. In addition, ACR response rates were maintained in the majority of patients followed in the open-label extension phase to week 104. There were 114 out of 207 patients who continued on Humira 40 mg every other week for 60 months. Among those, 86, 72, and 41 patients had ACR 20/50/70 response, respectively at month 60.

In Study IV, the ACR 20 response of patients treated with Trudexa plus standard of care was statistically significantly better than patients treated with placebo plus standard of care ($p < 0.001$).

In Studies I-IV, Trudexa-treated patients achieved statistically significant ACR 20 and 50 responses compared to placebo as early as one to two weeks after initiation of treatment.

In Study V with early rheumatoid arthritis patients who were methotrexate naïve, combination therapy with Trudexa and methotrexate led to faster and significantly greater ACR responses than methotrexate monotherapy and Trudexa monotherapy at week 52 and responses were sustained at week 104 (see Table 4).

Table 4: ACR Responses in Study V (percent of patients)

Response	**MTX n=257**	**Trudexa n=274**	**Trudexa/MTX n=268**	**p-value[a]**	**p-value[b]**	**p-value[c]**
ACR 20						

Week 52	62.6%	54.4%	72.8%	0.013	< 0.001	0.043
Week 104	56.0%	49.3%	69.4%	0.002	< 0.001	0.140
ACR 50						
Week 52	45.9%	41.2%	61.6%	< 0.001	< 0.001	0.317
Week 104	42.8%	36.9%	59.0%	< 0.001	< 0.001	0.162
ACR 70						
Week 52	27.2%	25.9%	45.5%	< 0.001	< 0.001	0.656
Week 104	28.4%	28.1%	46.6%	< 0.001	< 0.001	0.864

a. p-value is from the pairwise comparison of methotrexate monotherapy and Trudexa/methotrexate combination therapy using the Mann-Whitney U test.
b. p-value is from the pairwise comparison of Trudexa monotherapy and Trudexa/methotrexate combination therapy using the Mann-Whitney U test
c. p-value is from the pairwise comparison of Trudexa monotherapy and methotrexate monotherapy using the Mann-Whitney U test

At week 52, 42.9% of patients who received Trudexa/methotrexate combination therapy achieved clinical remission (DAS28 < 2.6) compared to 20.6% of patients receiving methotrexate monotherapy and 23.4% of patients receiving Trudexa monotherapy. Trudexa/methotrexate combination therapy was clinically and statistically superior to methotrexate ($p < 0.001$) and Trudexa monotherapy ($p < 0.001$) in achieving a low disease state in patients with recently diagnosed moderate to severe rheumatoid arthritis. The response for the two monotherapy arms was similar ($p = 0.447$).

Radiographic response

In Study III, where Trudexa treated patients had a mean duration of rheumatoid arthritis of approximately 11 years, structural joint damage was assessed radiographically and expressed as change in modified total Sharp score and its components, the erosion score and joint space narrowing score. Trudexa/methotrexate patients demonstrated significantly less radiographic progression than patients receiving methotrexate alone at 6 and 12 months (see Table 5). Data from the open-label extension phase indicate that the reduction in rate of progression of structural damage is maintained for 60 months in a subset of patients. 113/207 of patients originally treated with 40 mg Humira every other week were evaluated radiographically at 5 years. Among those, 66 patients showed no progression of structural damage defined by a change in the TSS of zero or less.

Table 5: Radiographic Mean Changes Over 12 Months in Study III

	Placebo/ MTX[a]	TRUDEXA/MTX 40 mg every other week	Placebo/MTX-TRUDEXA/MTX (95% Confidence Interval[b])	P-value
Total Sharp score	2.7	0.1	2.6 (1.4, 3.8)	< 0.001[c]
Erosion score	1.6	0.0	1.6 (0.9, 2.2)	< 0.001
JSN[d] score	1.0	0.1	0.9 (0.3, 1.4)	0.002

[a]methotrexate
[b]95% confidence intervals for the differences in change scores between methotrexate and Trudexa.
[c]Based on rank analysis
[d]Joint Space Narrowing

In Study V, structural joint damage was assessed radiographically and expressed as change in modified total Sharp score (see Table 6).

Table 6: Radiographic Mean Changes at Week 52 in Study V

	MTX n=257 (95% confidence interval)	Trudexa n=274 (95% confidence interval)	Trudexa/MTX n=268	p-value[a]	p-value[b]	p-value[c]

			(95% confidence interval)			
Total Sharp score	5.7 (4.2-7.3)	3.0 (1.7-4.3)	1.3 (0.5-2.1)	< 0.001	0.0020	< 0.001
Erosion score	3.7 (2.7-4.7)	1.7 (1.0-2.4)	0.8 (0.4-1.2)	< 0.001	0.0082	< 0.001
JSN score	2.0 (1.2-2.8)	1.3 (0.5-2.1)	0.5 (0-1.0)	< 0.001	0.0037	0.151

a. p-value is from the pairwise comparison of methotrexate monotherapy and Trudexa/methotrexate combination therapy using the Mann-Whitney U test.
b. p-value is from the pairwise comparison of Trudexa monotherapy and Trudexa/methotrexate combination therapy using the Mann-Whitney U test
c. p-value is from the pairwise comparison of Trudexa monotherapy and methotrexate monotherapy using the Mann-Whitney U test

Following 52 weeks and 104 weeks of treatment, the percentage of patients without progression (change from baseline in modified total Sharp score ≤ 0.5) was significantly higher with Trudexa/methotrexate combination therapy (63.8% and 61.2% respectively) compared to methotrexate monotherapy (37.4% and 33.5% respectively, $p < 0.001$) and Trudexa monotherapy (50.7%, $p < 0.002$ and 44.5%, $p < 0.001$ respectively).

Quality of life and physical function

Health-related quality of life and physical function was assessed using the disability index of the Health Assessment Questionnaire (HAQ) in the four original adequate and well-controlled trials, which was a pre-specified primary endpoint at week 52 in Study III. All doses/schedules of Trudexa in all four studies showed statistically significantly greater improvement in the disability index of the HAQ from baseline to Month 6 compared to placebo and in Study III the same was seen at week 52. Results from the Short Form Health Survey (SF 36) for all doses/schedules of Trudexa in all four studies support these findings, with statistically significant physical component summary (PCS) scores, as well as statistically significant pain and vitality domain scores for the 40 mg every other week dose. A statistically significant decrease in fatigue as measured by functional assessment of chronic illness therapy (FACIT) scores was seen in all three studies in which it was assessed (Studies I, III, IV).

In Study III, improvement in physical function was maintained through week 260 (60 months) of open-label treatment. Improvement in quality of life was measured up to week 156 (36 months) and improvement was maintained through that time.

In Study V, the improvement in the HAQ disability index and the physical component of the SF 36 showed greater improvement ($p < 0.001$) for Trudexa/methotrexate combination therapy versus methotrexate monotherapy and Trudexa monotherapy at week 52, which was maintained through week 104.

Psoriatic arthritis

Trudexa, 40 mg every other week, was studied in patients with moderately to severely active psoriatic arthritis in two placebo-controlled studies, Studies VI and VII. Study VI with 24 week duration, treated 313 adult patients who had an inadequate response to non-steroidal anti-inflammatory drug therapy and of these, approximately 50% were taking methotrexate. Study VII with 12-week duration, treated 100 patients who had an inadequate response to DMARD therapy.

There is insufficient evidence of the efficacy of Trudexa in patients with ankylosing spondylitis-like psoriatic arthropathy due to the small number of patients studied (see Table 7).

Table 7: ACR Response in Placebo-Controlled Psoriatic Arthritis Studies (Percent of Patients)

	Study VI	Study VII

Response	Placebo N=162	Trudexa N=151	Placebo N=49	Trudexa N=51
ACR 20				
Week 12	14%	58%***	16%	39%*
Week 24	15%	57%***	N/A	N/A
ACR 50				
Week 12	4%	36%***	2%	25%***
Week 24	6%	39%***	N/A	N/A
ACR 70				
Week 12	1%	20%***	0%	14%*
Week 24	1%	23%***	N/A	N/A

*** $p < 0.001$ for all comparisons between Trudexa and placebo
* $p < 0.05$ for all comparisons between Trudexa and placebo
N/A not applicable

ACR responses in Study VI were similar with and without concomitant methotrexate therapy. Trudexa treated patients demonstrated improvement in physical function as assessed by HAQ and Short Form Health Survey (SF 36), from base-line to week 24.

Ankylosing spondylitis

Trudexa 40 mg every other week was assessed in 393 patients in two randomised, 24 week double−blind, placebo−controlled studies in patients with active ankylosing spondylitis (mean baseline score of disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)] was 6.3 in all groups) who have had an inadequate response to conventional therapy. Seventy-nine (20.1%) patients were treated concomitantly with disease modifying anti − rheumatic drugs, and 37 (9.4%) patients with glucocorticoids. The blinded period was followed by an open−label period during which patients received Trudexa 40 mg every other week subcutaneously for up to an additional 28 weeks. Subjects (n=215, 54.7%) who failed to achieve ASAS 20 at Weeks 12, or 16 or 20 received early escape open-label adalimumab 40 mg every other week subcutaneously and were subsequently treated as non-responders in the double-blind statistical analyses.

In the larger study (VIII) with 315 patients, results showed statistically significant improvement of the signs and symptoms of ankylosing spondylitis in patients treated with Trudexa compared to placebo. Significant response was first observed at Week 2 and maintained through 24 weeks (Table 8).

Table 8 - Efficacy Responses in Placebo-Controlled AS Study – Study VIII Reduction of Signs and Symptoms

Response	**Placebo N=107**	**Trudexa N=208**
ASAS[a] 20		
Week 2	16%	42%***
Week 12	21%	58%***
Week 24	19%	51%***
ASAS 50		
Week 2	3%	16%***
Week 12	10%	38%***
Week 24	11%	35%***
ASAS 70		
Week 2	0%	7%**
Week 12	5%	23%***
Week 24	8%	24%***
BASDAI[b] 50		

Week 2	4%	20%***
Week 12	16%	45%***
Week 24	15%	42%***

***,** Statistically significant at $p < 0.001$, < 0.01 for all comparisons between Trudexa and placebo at Weeks 2, 12 and 24

[a] ASsessments in Ankylosing Spondylitis

[b] Bath Ankylosing Spondylitis Disease Activity Index

Trudexa treated patients had significantly greater improvement at Week 12 which was maintained through Week 24 in both the SF36 and Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL).

Similar trends (not all statistically significant) were seen in the smaller randomised, double−blind, placebo controlled study (IX) of 82 adult patients with active ankylosing spondylitis.

Crohn's Disease

The safety and efficacy of Trudexa were assessed in over 1400 patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450) in randomised, double-blind, placebo-controlled studies. 478 of the enrolled patients (32%) were defined as having a severe disease (CDAI score > 300 and concomitant corticosteroid and/or immunosuppressants) corresponding to the population defined in the indication (see section 4.1). Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted and 79% of patients continued to receive at least one of these medications.

Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies, CLASSIC I and GAIN. In CLASSIC I, 299 TNF-antagonist naive patients were randomised to one of four treatment groups; placebo at weeks 0 and 2, 160 mg Trudexa at week 0 and 80 mg at week 2, 80 mg at week 0 and 40 mg at week 2, and 40 mg at week 0 and 20 mg at week 2. In GAIN, 325 patients who had lost response or were intolerant to infliximab were randomised to receive either 160 mg Trudexa at week 0 and 80 mg at week 2 or placebo at weeks 0 and 2. The primary non-responders were excluded from the studies and therefore these patients were not further evaluated.

Maintenance of clinical remission was evaluated in CHARM. In CHARM, 854 patients received open-label 80 mg at week 0 and 40 mg at week 2. At week 4 patients were randomised to 40 mg every other week, 40 mg every week, or placebo with a total study duration of 56 weeks. Patients in clinical response (decrease in CDAI ≥ 70) at week 4 were stratified and analysed separately from those not in clinical response at week 4. Corticosteroid taper was permitted after week 8.

CLASSIC I and GAIN induction of remission and response rates are presented in Table 9.

Table 9: Induction of Clinical Remission and Response

(Percent of Patients)

	CLASSIC I: Infliximab Naive Patients			GAIN: Infliximab Experienced Patients	
	Placebo N=74	**Trudexa 80/40 mg N = 75**	**Trudexa 160/80 mg N=76**	**Placebo N=166**	**Trudexa 160/80 mg N=159**
Week 4					
Clinical remission	12%	24%	36%*	7%	21%*
Clinical response (CR-100)	24%	37%	49%**	25%	38%**

All p-values are pairwise comparisons of proportions for Trudexa *versus* placebo

* $p < 0.001$

** $p < 0.01$

Similar remission rates were observed for the 160/80 mg and 80/40 mg induction regimens by week 8 and adverse events were more frequently noted in the 160/80 mg group.

In CHARM, at week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. Of those in clinical response at week 4, 48% had been previously exposed to other anti-TNF therapy. Maintenance of remission and response rates are presented in Table 10. Clinical remission results remained relatively constant irrespective of previous TNF antagonist exposure.

Table 10: Maintenance of Clinical Remission and Response

(Percent of Patients)

	Placebo	**40 mg Trudexa every other week**	**40 mg Trudexa every week**
Week 26	**N=170**	**N=172**	**N=157**
Clinical remission	17%	40%*	47%*
Clinical response (CR-100)	27%	52%*	52%*
Patients in steroid-free remission for >=90 days[a]	3% (2/66)	19% (11/58)**	15% (11/74)**
Week 56	**N=170**	**N=172**	**N=157**
Clinical remission	12%	36%*	41%*
Clinical response (CR-100)	17%	41%*	48%*
Patients in steroid-free remission for >=90 days[a]	5% (3/66)	29% (17/58)*	20% (15/74)**

* $p < 0.001$ for Trudexa *versus* placebo pairwise comparisons of proportions

** $p < 0.02$ for Trudexa *versus* placebo pairwise comparisons of proportions

[a] Of those receiving corticosteroids at baseline

Among patients who were not in response at week 4, 43% of Trudexa maintenance patients responded by week 12 compared to 30% of placebo maintenance patients. These results suggest that some patients who have not responded by week 4 benefit from continued maintenance therapy through week 12. Therapy continued beyond 12 weeks did not result in significantly more responses (see section 4.2).

Quality of Life

In CLASSIC I and GAIN, statistically significant improvement in the disease-specific inflammatory bowel disease questionnaire (IBDQ) total score was achieved at week 4 in patients randomised to