

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Enbrel 25 mg/ml powder and solvent for solution for injection for paediatric use.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 25 mg of etanercept. When reconstituted, the solution contains 25 mg/ml of etanercept.

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian expression system. Etanercept is a dimer of a chimeric protein genetically engineered by fusing the extracellular ligand binding domain of human tumour necrosis factor receptor-2 (TNFR2/p75) to the Fc domain of human IgG1. This Fc component contains the hinge, CH₂ and CH₃ regions but not the CH₁ region of IgG1. Etanercept contains 934 amino acids and has an apparent molecular weight of approximately 150 kilodaltons. The potency is determined by measuring the ability of etanercept to neutralise the TNF α -mediated growth inhibition of A375 cells. The specific activity of etanercept is 1.7×10^6 units/mg.

The solution contains benzyl alcohol 9 mg/ml as a preservative (see section 4.4). For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is white. The solvent is a clear, colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Polyarticular juvenile idiopathic arthritis

Treatment of active polyarticular juvenile idiopathic arthritis in children and adolescents aged 4 to 17 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. Enbrel has not been studied in children aged less than 4 years.

4.2 Posology and method of administration

Enbrel treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis. Patients treated with Enbrel should be given the Patient Alert Card.

Each vial of Enbrel 25 mg/ml should be used for a maximum of 2 doses administered to the same patient.

Comprehensive instructions for the preparation, administration and re-use of the reconstituted Enbrel vial are given in the package leaflet, section 7, "Instructions for preparation and giving an injection of Enbrel."

Children and adolescents (≥ 4 to <18 years)

0.4 mg/kg (up to a maximum of 25 mg per dose) after reconstitution of 25 mg Enbrel in 1 ml of solvent, given twice weekly as a subcutaneous injection with an interval of 3-4 days between doses.

Renal and hepatic impairment

No dose adjustment is required.

4.3 Contraindications

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

Sepsis or risk of sepsis.

Treatment with Enbrel should not be initiated in patients with active infections including chronic or localised infections.

Enbrel must not be given to premature babies or neonates as the solvent contains benzyl alcohol.

4.4 Special warnings and precautions for use

Infections

Patients should be evaluated for infections before, during, and after treatment with Enbrel, taking into consideration that the mean elimination half-life of etanercept is approximately 70 hours (range 7 to 300 hours).

Serious infections, sepsis, tuberculosis, and other opportunistic infections, have been reported with the use of Enbrel (see section 4.8). Some of these infections have been fatal. Patients who develop a new infection while undergoing treatment with Enbrel should be monitored closely. **Administration of Enbrel should be discontinued if a patient develops a serious infection.** Physicians should exercise caution when considering the use of Enbrel in patients with a history of recurring or chronic infections or with underlying conditions that may predispose patients to infections such as advanced or poorly controlled diabetes.

Tuberculosis

Cases of active tuberculosis including miliary tuberculosis and tuberculosis with extra-pulmonary location have been reported in patients treated with Enbrel.

Before starting treatment with Enbrel, all patients must be evaluated for both active and inactive ('latent') tuberculosis. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with 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's 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, Enbrel therapy must not be initiated. If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the

initiation of Enbrel, and in accordance with local recommendations. In this situation, the benefit/risk balance of Enbrel therapy should be very carefully considered.

All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g., persistent cough, wasting/weight loss, low-grade fever) appear during or after Enbrel treatment.

Hepatitis B virus reactivation

Reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus who are receiving TNF-antagonists including Enbrel has been reported. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating Enbrel therapy. Caution should be exercised when administering Enbrel to patients identified as carriers of HBV. If Enbrel is used in carriers of HBV, the patients should be monitored for signs and symptoms of active HBV infection and, if necessary, appropriate treatment should be initiated.

Worsening of hepatitis C

There have been reports of worsening of hepatitis C in patients receiving Enbrel.

Concurrent Enbrel and anakinra treatment

Concurrent administration of Enbrel and anakinra has been associated with an increased risk of serious infections and neutropenia compared to Enbrel alone. This combination has not demonstrated increased clinical benefit. Thus the combined use of Enbrel and anakinra is not recommended (see sections 4.5 and 4.8).

Concurrent Enbrel and abatacept treatment

In clinical studies, concurrent administration of abatacept and Enbrel resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.5).

Allergic reactions

Allergic reactions associated with Enbrel administration have been reported commonly. Allergic reactions have included angioedema and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, Enbrel therapy should be discontinued immediately and appropriate therapy initiated.

Immunosuppression

The possibility exists for TNF-antagonists, including Enbrel, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 adult patients with rheumatoid arthritis treated with Enbrel, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations.

Two juvenile idiopathic arthritis patients developed varicella infection and signs and symptoms of aseptic meningitis, which resolved without sequelae. Patients with a significant exposure to varicella virus should temporarily discontinue Enbrel therapy and be considered for prophylactic treatment with Varicella Zoster Immune Globulin.

The safety and efficacy of Enbrel in patients with immunosuppression or chronic infections have not been evaluated.

Malignancies and lymphoproliferative disorders

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have been received in the postmarketing period (see section 4.8).

In the controlled portions of clinical trials of TNF-antagonists, more cases of lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare, and the follow-up period of placebo patients was shorter than for patients receiving TNF-antagonist therapy. 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.

Vaccinations

Live vaccines should not be given concurrently with Enbrel. No data are available on the secondary transmission of infection by live vaccines in patients receiving Enbrel. It is recommended that juvenile idiopathic arthritis patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Enbrel therapy. In a double blind, placebo controlled, randomised clinical study in adult patients with psoriatic arthritis 184 patients also received a multivalent pneumococcal polysaccharide vaccine at week 4. In this study most psoriatic arthritis patients receiving Enbrel were able to mount effective B-cell immune response to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower and few patients had two-fold rises in titers compared to patients not receiving Enbrel. The clinical significance of this is unknown.

Autoantibody formation

Treatment with Enbrel may result in the formation of autoimmune antibodies (see section 4.8).

Haematologic reactions

Rare cases of pancytopenia and very rare cases of aplastic anaemia, some with fatal outcome, have been reported in patients treated with Enbrel. Caution should be exercised in patients being treated with Enbrel who have a previous history of blood dyscrasias. All patients and parents/caregivers should be advised that if the patient develops signs and symptoms suggestive of blood dyscrasias or infections (e.g. persistent fever, sore throat, bruising, bleeding, paleness) whilst on Enbrel, they should seek immediate medical advice. Such patients should be investigated urgently, including full blood count; if blood dyscrasias are confirmed, Enbrel should be discontinued.

CNS disorders

There have been rare reports of CNS demyelinating disorders in patients treated with Enbrel (see section 4.8). Although no clinical trials have been performed evaluating Enbrel therapy in patients with multiple sclerosis, clinical trials of other TNF antagonists in patients with multiple sclerosis have shown increases in disease activity. A careful risk/benefit evaluation, including a neurologic assessment, is recommended when prescribing Enbrel to patients with pre-existing or recent onset of CNS demyelinating disease, or to those who are considered to have an increased risk of developing demyelinating disease.

Combination therapy

In a controlled clinical trial of two years duration in adult rheumatoid arthritis patients, the combination of Enbrel and methotrexate did not result in unexpected safety findings, and the safety profile of Enbrel when given in combination with methotrexate was similar to the profiles reported in studies of Enbrel and methotrexate alone. Long-term studies to assess the safety of the combination are ongoing. The long-term safety of Enbrel in combination with other disease-modifying antirheumatic drugs (DMARD) has not been established.

Renal and hepatic impairment

Based on pharmacokinetic data (see section 5.2), no dosage adjustment is needed in patients with renal or hepatic impairment; clinical experience in such patients is limited.

Congestive heart failure

Physicians should use caution when using Enbrel in patients who have congestive heart failure (CHF). There have been postmarketing reports of worsening of CHF, with and without identifiable precipitating factors, in patients taking Enbrel. Two large clinical trials evaluating the use of Enbrel in the treatment of CHF were terminated early due to lack of efficacy. Although not conclusive, data from one of these trials suggest a possible tendency toward worsening CHF in those patients assigned to Enbrel treatment.

Wegener's granulomatosis

A placebo-controlled trial, in which 89 adult patients were treated with Enbrel in addition to standard therapy (including cyclophosphamide or methotrexate, and glucocorticoids) for a median duration of 25 months, has not shown Enbrel to be an effective treatment for Wegener's granulomatosis. The incidence of non-cutaneous malignancies of various types was significantly higher in patients treated with Enbrel than in the control group. Enbrel is not recommended for the treatment of Wegener's granulomatosis.

Benzyl alcohol

Enbrel contains benzyl alcohol as an excipient, which may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old and must not be given to premature babies or neonates.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent Enbrel and anakinra treatment

Adult patients treated with Enbrel and anakinra were observed to have a higher rate of serious infection when compared with patients treated with either Enbrel or anakinra alone (historical data).

In addition, in a double-blind placebo-controlled trial in adult patients receiving background methotrexate, patients treated with Enbrel and anakinra were observed to have a higher rate of serious infections (7%) and neutropenia than patients treated with Enbrel (see sections 4.4 and 4.8). The combination Enbrel and anakinra has not demonstrated increased clinical benefit and is therefore not recommended.

Concurrent Enbrel and abatacept treatment

In clinical studies, concurrent administration of abatacept and Enbrel resulted in increased incidences of serious adverse events. This combination has not demonstrated increased clinical benefit; such use is not recommended (see section 4.4).

Concurrent Enbrel and sulfasalazine treatment

In a clinical study of adult patients who were receiving established doses of sulfasalazine, to which Enbrel was added, patients in the combination group experienced a statistically significant decrease in mean white blood cell counts in comparison to groups treated with Enbrel or sulfasalazine alone. The clinical significance of this interaction is unknown.

Non-interactions

In clinical trials, no interactions have been observed when Enbrel was administered with glucocorticoids, salicylates (except sulfasalazine), nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, or methotrexate. See section 4.4 for vaccination advice.

No clinically significant pharmacokinetic drug-drug interactions were observed in studies with digoxin or warfarin.

4.6 Pregnancy and lactation

There are no studies of Enbrel in pregnant women. Developmental toxicity studies performed in rats and rabbits have revealed no evidence of harm to the foetus or neonatal rat due to etanercept. Preclinical data about peri- and postnatal toxicity of etanercept and of effects of etanercept on fertility and general reproductive performance are not available. Thus, the use of Enbrel in pregnant women is not recommended, and women of child-bearing potential should be advised not to get pregnant during Enbrel therapy.

Use during lactation

It is not known whether etanercept is excreted in human milk. Following subcutaneous administration to lactating rats, etanercept was excreted in the milk and detected in the serum of pups. Because immunoglobulins, in common with many medicinal products, can be excreted in human milk, a decision should be made whether to discontinue breast-feeding or to discontinue Enbrel while breast-feeding.

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

Undesirable effects in paediatric patients with polyarticular juvenile idiopathic arthritis

In general, the adverse events in paediatric patients were similar in frequency and type to those seen in adult patients (see below, Undesirable effects in adults). Differences from adults and other special considerations are discussed in the following paragraphs.

The types of infections seen in clinical trials in juvenile idiopathic arthritis patients aged 2 to 18 years were generally mild to moderate and consistent with those commonly seen in outpatient paediatric

populations. Severe adverse events reported included varicella with signs and symptoms of aseptic meningitis, which resolved without sequelae (see also section 4.4), appendicitis, gastroenteritis, depression/personality disorder, cutaneous ulcer, oesophagitis/gastritis, group A streptococcal septic shock, type I diabetes mellitus, and soft tissue and post-operative wound infection.

In one study in children with juvenile idiopathic arthritis aged 4 to 17 years, 43 of 69 (62%) children experienced an infection while receiving Enbrel during 3 months of the study (part 1 open-label), and the frequency and severity of infections was similar in 58 patients completing 12 months of open-label extension therapy. The types and proportion of adverse events in juvenile idiopathic arthritis patients were similar to those seen in trials of Enbrel in adult patients with rheumatoid arthritis, and the majority were mild. Several adverse events were reported more commonly in 69 juvenile idiopathic arthritis patients receiving 3 months of Enbrel compared to the 349 adult rheumatoid arthritis patients. These included headache (19% of patients, 1.7 events per patient year), nausea (9%, 1.0 event per patient year), abdominal pain (19%, 0.74 events per patient year), and vomiting (13%, 0.74 events per patient year).

There were 4 reports of macrophage activation syndrome in juvenile idiopathic arthritis clinical trials.

Undesirable effects in adults

Enbrel has been studied in 2,680 patients with rheumatoid arthritis in double-blind and open-label trials. This experience includes 2 placebo-controlled studies (349 Enbrel patients and 152 placebo patients) and 2 active-controlled trials, one active-controlled trial comparing Enbrel to methotrexate (415 Enbrel patients and 217 methotrexate patients) and another active-controlled trial comparing Enbrel (223 patients), methotrexate (228 patients) and Enbrel in combination with methotrexate (231 patients). The proportion of patients who discontinued treatment due to adverse events was the same in both the Enbrel and placebo treatment groups; in the first active-controlled trial, the dropout rate was significantly higher for methotrexate (10%) than for Enbrel (5%). In the second active-controlled trial, the rate of discontinuation for adverse events after 2 years of treatment was similar among all three treatment groups, Enbrel (16%), methotrexate (21%) and Enbrel in combination with methotrexate (17%). Additionally, Enbrel has been studied in 240 psoriatic arthritis patients who participated in 2 double-blind placebo-controlled studies and an open-label extension study. Five hundred and eight (508) ankylosing spondylitis patients were treated with Enbrel in 4 double-blind placebo-controlled studies. Enbrel has also been studied in 1,180 patients with plaque psoriasis for up to 6 months in 4 double-blind placebo-controlled studies.

In double-blind clinical trials comparing Enbrel to placebo, injection site reactions were the most frequent adverse events among Enbrel-treated patients. Among patients with rheumatoid arthritis treated in placebo-controlled trials, serious adverse events occurred at a frequency of 4% in 349 patients treated with Enbrel compared with 5% of 152 placebo-treated patients. In the first active-controlled trial, serious adverse events occurred at a frequency of 6% in 415 patients treated with Enbrel compared with 8% of 217 methotrexate-treated patients. In the second active-controlled trial the rate of serious adverse events after 2 years treatment was similar among the three treatment groups (Enbrel 16%, methotrexate 15% and Enbrel in combination with methotrexate 17%). Among patients with plaque psoriasis treated in placebo-controlled trials, the frequency of serious adverse events was about 1.2% of 1,029 patients treated with Enbrel compared with 1.5% of 460 placebo-treated patients.

The following list of adverse reactions is based on experience from clinical trials in adults and on postmarketing experience.

Within the organ system classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common (>1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10,000, <1/1000); very rare (<1/10,000); not known (could not be accurately estimated through clinical studies).

Infections and infestations:

Very common: Infections (including upper respiratory tract infections, bronchitis, cystitis, skin infections)*

Uncommon: Serious infections (including pneumonia, cellulitis, septic arthritis, sepsis)*

Rare: Tuberculosis

Blood and lymphatic system disorders:

Uncommon: Thrombocytopenia

Rare: Anaemia, leukopenia, neutropenia, pancytopenia*

Very rare: Aplastic anaemia*

Immune system disorders:

Common: Allergic reactions (see Skin and subcutaneous tissue disorders), autoantibody formation*

Rare: Serious allergic/anaphylactic reactions (including angioedema, bronchospasm)

Not known: Macrophage activation syndrome*, anti-neutrophilic cytoplasmic antibody positive vasculitis

Nervous system disorders:

Rare: Seizures

CNS demyelinating events suggestive of multiple sclerosis or localised demyelinating conditions such as optic neuritis and transverse myelitis (see section 4.4)

Respiratory, thoracic and mediastinal disorders:

Uncommon: Interstitial lung disease (including pneumonitis and pulmonary fibrosis)*

Hepatobiliary disorders:

Rare: Elevated liver enzymes

Skin and subcutaneous tissue disorders:

Common: Pruritus

Uncommon: Angioedema, urticaria, rash, psoriasiform rash, psoriasis (including new onset and pustular, primarily palms & soles)

Rare: Cutaneous vasculitis (including leukocytoclastic vasculitis), Stevens-Johnson syndrome, erythema multiforme

Very rare: Toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders:

Rare: Subacute cutaneous lupus erythematosus, discoid lupus erythematosus, lupus-like syndrome

General disorders and administration site conditions:

Very common: Injection site reactions (including bleeding, bruising, erythema, itching, pain, swelling)*

Common: Fever

Cardiac disorders:

There have been reports of worsening of congestive heart failure (see section 4.4).

*see Additional information, below.

Additional information

Serious adverse events reported in clinical trials

Among rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and plaque psoriasis patients in placebo-controlled, active-controlled, and open-label trials of Enbrel, serious adverse events reported included malignancies (see below), asthma, infections (see below), heart failure, myocardial infarction, myocardial ischaemia, chest pain, syncope, cerebral ischaemia, hypertension, hypotension, cholecystitis, pancreatitis, gastrointestinal haemorrhage, bursitis, confusion, depression, dyspnoea, abnormal healing, renal insufficiency, kidney calculus, deep vein thrombosis, pulmonary embolism, membranous glomerulonephropathy, polymyositis, thrombophlebitis, liver damage, leucopenia, paresis, paresthesia, vertigo, allergic alveolitis, angioedema, scleritis, bone fracture, lymphadenopathy, ulcerative colitis, intestinal obstruction, eosinophilia, haematuria, and sarcoidosis.

Malignancies

One hundred and twenty-nine new malignancies of various types were observed in 4,114 rheumatoid arthritis patients treated in clinical trials with Enbrel for up to approximately 6 years, including 231 patients treated with Enbrel in combination with methotrexate in the 2-year active-controlled study. The observed rates and incidences in these clinical trials were similar to those expected for the population studied. A total of 2 malignancies were reported in clinical studies of approximately 2 years duration involving 240 Enbrel-treated psoriatic arthritis patients. In clinical studies conducted for more than 2 years with 351 ankylosing spondylitis patients, 6 malignancies were reported in Enbrel-treated patients. Twenty-three malignancies were reported in plaque psoriasis patients treated with Enbrel in double-blind and open-label studies of up to 15 months involving 1,261 Enbrel-treated patients.

There were a total of 15 lymphomas reported in 5,966 patients treated with Enbrel in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and psoriasis clinical trials.

Reports of various malignancies (including breast and lung carcinoma and lymphoma) have also been received in the postmarketing period (see section 4.4).

Injection site reactions

Compared to placebo, patients with rheumatic diseases treated with Enbrel had a significantly higher incidence of injection site reactions (36% vs. 9%). Injection site reactions usually occurred in the first month. Mean duration was approximately 3 to 5 days. No treatment was given for the majority of injection site reactions in the Enbrel treatment groups, and the majority of patients who were given treatment received topical preparations such as corticosteroids, or oral antihistamines. Additionally, some patients developed recall injection site reactions characterised by a skin reaction at the most recent site of injection along with the simultaneous appearance of injection site reactions at previous injection sites. These reactions were generally transient and did not recur with treatment.

In controlled trials in patients with plaque psoriasis, approximately 14.5% of patients treated with Enbrel developed injection site reactions compared with 5.2% of placebo-treated patients during the first 12 weeks of treatment.

Serious infections

In placebo-controlled trials, no increase in the incidence of serious infections (fatal, life threatening, or requiring hospitalisation or intravenous antibiotics) was observed. Serious infections occurred in 6.3% of rheumatoid arthritis patients treated with Enbrel for up to 48 months. These included abscess (at various sites), bacteraemia, bronchitis, bursitis, cellulitis, cholecystitis, diarrhoea, diverticulitis, endocarditis (suspected), gastroenteritis, hepatitis B, herpes zoster, leg ulcer, mouth infection, osteomyelitis, otitis, peritonitis, pneumonia, pyelonephritis, sepsis, septic arthritis, sinusitis, skin infection, skin ulcer, urinary tract infection, vasculitis, and wound infection. In the 2-year active-controlled study where patients were treated with either Enbrel alone, methotrexate alone or Enbrel in combination with methotrexate, the rates of serious infections were similar among the treatment groups. However, it cannot be excluded that the combination of Enbrel with methotrexate could be associated with an increase in the rate of infections.

There were no differences in rates of infection among patients treated with Enbrel and those treated with placebo for plaque psoriasis in placebo controlled trials of up to 24 weeks duration. Serious infections experienced by Enbrel-treated patients included cellulitis, gastroenteritis, pneumonia, cholecystitis, osteomyelitis, gastritis, appendicitis, Streptococcal fasciitis, myositis, septic shock, diverticulitis and abscess. In the double-blind and open-label psoriatic arthritis trials, 1 patient reported a serious infection (pneumonia).

Serious and fatal infections have been reported during use of Enbrel; reported pathogens include bacteria, mycobacteria (including tuberculosis), viruses and fungi. Some have occurred within a few weeks after initiating treatment with Enbrel in patients who have underlying conditions (e.g. diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis (see section 4.4). Enbrel treatment may increase mortality in patients with established sepsis.

Autoantibodies

Adult patients had serum samples tested for autoantibodies at multiple timepoints. Of the rheumatoid arthritis patients evaluated for antinuclear antibodies (ANA), the percentage of patients who developed new positive ANA ($\geq 1:40$) was higher in patients treated with Enbrel (11%) than in placebo-treated patients (5%). The percentage of patients who developed new positive anti-double-stranded DNA antibodies was also higher by radioimmunoassay (15% of patients treated with Enbrel compared to 4% of placebo-treated patients) and by *Crithidia luciliae* assay (3% of patients treated with Enbrel compared to none of placebo-treated patients). The proportion of patients treated with Enbrel who developed anticardiolipin antibodies was similarly increased compared to placebo-treated patients. The impact of long-term treatment with Enbrel on the development of autoimmune diseases is unknown.

There have been rare reports of patients, including rheumatoid factor positive patients, who have developed other autoantibodies in conjunction with a lupus-like syndrome or rashes that are compatible with subacute cutaneous lupus or discoid lupus by clinical presentation and biopsy.

Pancytopenia and aplastic anaemia

There have been postmarketing reports of pancytopenia and aplastic anaemia, some of which had fatal outcomes (see section 4.4)

Interstitial lung disease

There have been postmarketing reports of interstitial lung disease (including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes.

Laboratory evaluations

Based on the results of clinical studies, normally no special laboratory evaluations are necessary in addition to careful medical management and supervision of patients.

Concurrent Enbrel and anakinra treatment

In studies when adult patients received concurrent treatment with Enbrel plus anakinra, a higher rate of serious infections compared to Enbrel alone was observed and 2% of patients (3/139) developed neutropenia (absolute neutrophil count < 1000 / mm³). While neutropenic, one patient developed cellulitis that resolved after hospitalisation (see sections 4.4 and 4.5).

4.9 Overdose

No dose-limiting toxicities were observed during clinical trials of rheumatoid arthritis patients. The highest dose level evaluated has been an intravenous loading dose of 32 mg/m² followed by subcutaneous doses of 16 mg/m² administered twice weekly. One rheumatoid arthritis patient mistakenly self-administered 62 mg Enbrel subcutaneously twice weekly for 3 weeks without experiencing undesirable effects. There is no known antidote to Enbrel.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tumor Necrosis Factor alpha (TNF- α) inhibitors.

ATC code: L04AB01

Tumour necrosis factor (TNF) is a dominant cytokine in the inflammatory process of rheumatoid arthritis. Elevated levels of TNF are also found in the synovium and psoriatic plaques of patients with psoriatic arthritis and in serum and synovial tissue of patients with ankylosing spondylitis. In plaque psoriasis, infiltration by inflammatory cells including T-cells leads to increased TNF levels in psoriatic lesions compared with levels in uninvolved skin. Etanercept is a competitive inhibitor of TNF-binding to its cell surface receptors and thereby inhibits the biological activity of TNF. TNF and lymphotoxin are pro-inflammatory cytokines that bind to two distinct cell surface receptors: the 55-kilodalton (p55) and 75-kilodalton (p75) tumour necrosis factor receptors (TNFRs). Both TNFRs exist naturally in membrane-bound and soluble forms. Soluble TNFRs are thought to regulate TNF biological activity.

TNF and lymphotoxin exist predominantly as homotrimers, with their biological activity dependent on cross-linking of cell surface TNFRs. Dimeric soluble receptors such as etanercept possess a higher affinity for TNF than monomeric receptors and are considerably more potent competitive inhibitors of TNF binding to its cellular receptors. In addition, use of an immunoglobulin Fc region as a fusion element in the construction of a dimeric receptor imparts a longer serum half-life.

Mechanism of action

Much of the joint pathology in rheumatoid arthritis and ankylosing spondylitis and skin pathology in plaque psoriasis is mediated by pro-inflammatory molecules that are linked in a network controlled by TNF. The mechanism of action of etanercept is thought to be its competitive inhibition of TNF binding to cell surface TNFR, preventing TNF-mediated cellular responses by rendering TNF biologically inactive. Etanercept may also modulate biologic responses controlled by additional downstream molecules (e.g., cytokines, adhesion molecules, or proteinases) that are induced or regulated by TNF.

Clinical trials

This section presents data from one study in polyarticular juvenile idiopathic arthritis and four randomised controlled trials in adults with rheumatoid arthritis.

Paediatric patients with polyarticular juvenile idiopathic arthritis

The safety and efficacy of Enbrel were assessed in a two-part study in 69 children with polyarticular juvenile idiopathic arthritis who had a variety of juvenile idiopathic arthritis onset types. Patients aged 4 to 17 years with moderately to severely active polyarticular juvenile idiopathic arthritis refractory to or intolerant of methotrexate were enrolled; patients remained on a stable dose of a single nonsteroidal anti-inflammatory drug and/or prednisone (< 0.2 mg/kg/day or 10 mg maximum). In part 1, all patients received 0.4 mg/kg (maximum 25 mg per dose) Enbrel subcutaneously twice weekly. In part 2, patients with a clinical response at day 90 were randomised to remain on Enbrel or receive placebo for four months and assessed for disease flare. Responses were measured using the JRA Definition of Improvement (DOI), defined as $\geq 30\%$ improvement in at least three of six and $\geq 30\%$ worsening in no more than one of six JRA core set criteria, including active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment, and erythrocyte sedimentation rate (ESR). Disease flare was defined as a $\geq 30\%$ worsening in three of six JRA core set criteria and $\geq 30\%$ improvement in not more than one of the six JRA core set criteria and a minimum of two active joints.

In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2. In part 2, 6 of 25 (24%) patients remaining on Enbrel experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo ($p=0.007$). From the start of part 2, the median time to flare was ≥ 116 days for patients who received Enbrel and 28 days for patients who received placebo. Of patients who demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients remaining on Enbrel continued to improve from month 3 through month 7, while those who received placebo did not improve.

Studies have not been done in patients with polyarticular juvenile idiopathic arthritis to assess the effects of continued Enbrel therapy in patients who do not respond within 3 months of initiating Enbrel therapy or to assess the combination of Enbrel with methotrexate.

Adult patients with rheumatoid arthritis

The efficacy of Enbrel was assessed in a randomised, double-blind, placebo-controlled study. The study evaluated 234 adult patients with active rheumatoid arthritis who had failed therapy with at least one but no more than four disease-modifying antirheumatic drugs (DMARDs). Doses of 10 mg or 25 mg Enbrel or placebo were administered subcutaneously twice a week for 6 consecutive months. The results of this controlled trial were expressed in percentage improvement in rheumatoid arthritis using American College of Rheumatology (ACR) response criteria.

ACR 20 and 50 responses were higher in patients treated with Enbrel at 3 and 6 months than in patients treated with placebo (ACR 20: Enbrel 62% and 59%, placebo 23% and 11% at 3 and 6 months respectively; ACR 50: Enbrel 41% and 40%, placebo 8% and 5% at months 3 and 6 respectively; $p < 0.01$ Enbrel vs placebo at all time points for both ACR 20 and ACR 50 responses).

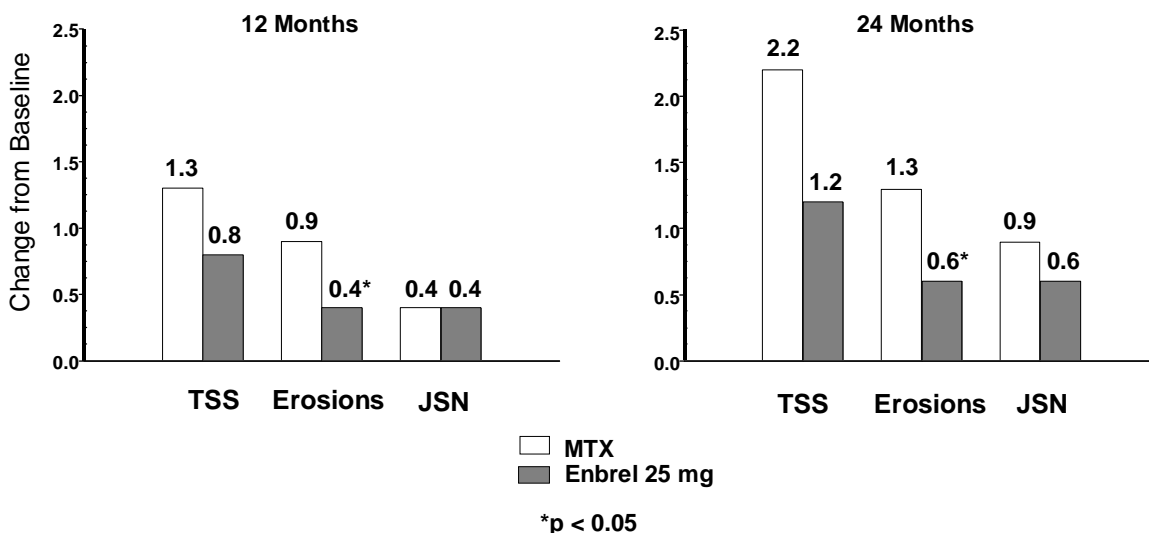
Approximately 15% of subjects who received Enbrel achieved an ACR 70 response at month 3 and month 6 compared to fewer than 5% of subjects in the placebo arm. Among patients receiving Enbrel, the clinical responses generally appeared within 1 to 2 weeks after initiation of therapy and nearly always occurred by 3 months. A dose response was seen; results with 10 mg were intermediate between placebo and 25 mg. Enbrel was significantly better than placebo in all components of the ACR criteria as well as other measures of rheumatoid arthritis disease activity not included in the ACR response criteria, such as morning stiffness. A Health Assessment Questionnaire (HAQ), which included disability, vitality, mental health, general health status, and arthritis-associated health status subdomains, was administered every 3 months during the trial. All subdomains of the HAQ were improved in patients treated with Enbrel compared to controls at 3 and 6 months.

After discontinuation of Enbrel, symptoms of arthritis generally returned within a month. Re-introduction of treatment with Enbrel after discontinuation of up to 24 months resulted in the same magnitudes of responses as patients who received Enbrel without interruption of therapy based on results of open-label studies. Continued durable responses have been seen for up to 48 months in open-label extension treatment trials when patients received Enbrel without interruption; longer-term experience is not available.

The efficacy of Enbrel was compared to methotrexate in a randomised, active-controlled study with blinded radiographic evaluations as a primary endpoint in 632 adult patients with active rheumatoid arthritis (<3 years duration) who had never received treatment with methotrexate. Doses of 10 mg or 25 mg Enbrel were administered SC twice a week for up to 24 months. Methotrexate doses were escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial and continued for up to 24 months. Clinical improvement including onset of action within 2 weeks with Enbrel 25 mg was similar to that seen in the previous trials, and was maintained for up to 24 months. At baseline, patients had a moderate degree of disability, with mean HAQ scores of 1.4 to 1.5. Treatment with Enbrel 25 mg resulted in substantial improvement at 12 months, with about 44% of patients achieving a normal HAQ score (less than 0.5). This benefit was maintained in Year 2 of this study.

In this study, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and joint space narrowing score (JSN). Radiographs of hands/wrists and feet were read at baseline and 6, 12, and 24 months. The 10 mg Enbrel dose had consistently less effect on structural damage than the 25 mg dose. Enbrel 25 mg was significantly superior to methotrexate for erosion scores at both 12 and 24 months. The differences in TSS and JSN were not statistically significant between methotrexate and Enbrel 25 mg. The results are shown in the figure below.

RADIOGRAPHIC PROGRESSION: COMPARISON OF ENBREL vs METHOTREXATE IN PATIENTS WITH RA OF <3 YEARS DURATION



In another active-controlled, double-blind, randomised study, clinical efficacy, safety, and radiographic progression in RA patients treated with Enbrel alone (25 mg twice weekly), methotrexate alone (7.5 to 20 mg weekly, median dose 20 mg), and of the combination of Enbrel and methotrexate initiated concurrently were compared in 682 adult patients with active rheumatoid arthritis of 6 months to 20 years duration (median 5 years) who had a less than satisfactory response to at least 1 disease-modifying antirheumatic drug (DMARD) other than methotrexate.

Patients in the Enbrel in combination with methotrexate therapy group had significantly higher ACR 20, ACR 50, ACR 70 responses and improvement for DAS and HAQ scores at both 24 and 52 weeks than patients in either of the single therapy groups (results shown in table below). Significant advantages for Enbrel in combination with methotrexate compared with Enbrel monotherapy and methotrexate monotherapy were also observed after 24 months.

CLINICAL EFFICACY RESULTS AT 12 MONTHS: COMPARISON OF ENBREL vs
METHOTREXATE vs ENBREL IN COMBINATION WITH METHOTREXATE IN
PATIENTS WITH RA OF 6 MONTHS TO 20 YEARS DURATION

Endpoint	Methotrexate (n = 228)	Enbrel (n = 223)	Enbrel + Methotrexate (n = 231)
ACR Responses^a			
ACR 20	58.8%	65.5%	74.5% ^{†,ϕ}
ACR 50	36.4%	43.0%	63.2% ^{†,ϕ}
ACR 70	16.7%	22.0%	39.8% ^{†,ϕ}
<u>DAS</u>			
Baseline score ^b	5.5	5.7	5.5
Week 52 score ^b	3.0	3.0	2.3 ^{†,ϕ}
Remission ^c	14%	18%	37% ^{†,ϕ}
<u>HAQ</u>			
Baseline	1.7	1.7	1.8
Week 52	1.1	1.0	0.8 ^{†,ϕ}

a: Patients who did not complete 12 months in the study were considered to be non-responders.

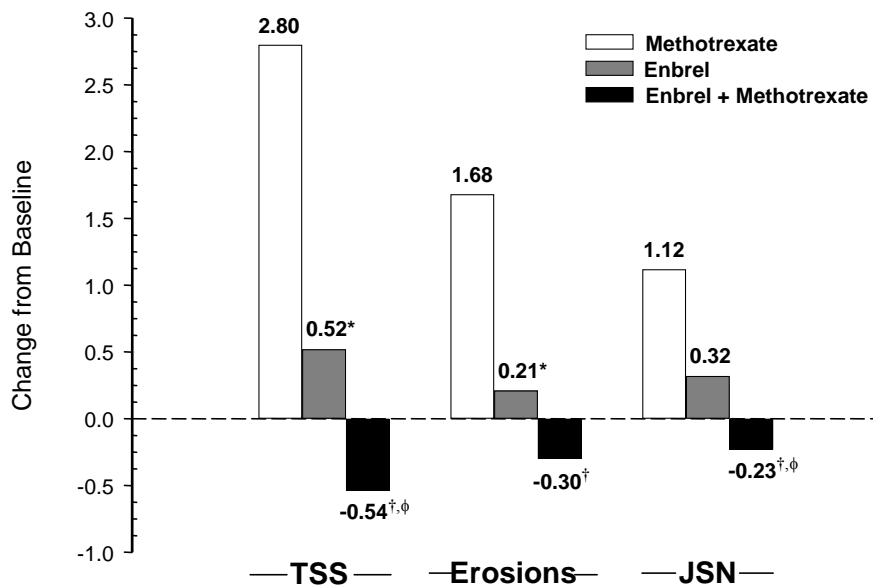
b: Values for Disease Activity Score (DAS) are means.

c: Remission is defined as DAS <1.6

Pairwise comparison p-values: † = p < 0.05 for comparisons of Enbrel + methotrexate vs methotrexate and ϕ = p < 0.05 for comparisons of Enbrel + methotrexate vs Enbrel

Radiographic progression at 12 months was significantly less in the Enbrel group than in the methotrexate group, while the combination was significantly better than either monotherapy at slowing radiographic progression (see figure below).

RADIOGRAPHIC PROGRESSION: COMPARISON OF ENBREL vs METHOTREXATE vs ENBREL IN COMBINATION WITH METHOTREXATE IN PATIENTS WITH RA OF 6 MONTHS TO 20 YEARS DURATION (12 MONTH RESULTS)



Pairwise comparison p-values: * = $p < 0.05$ for comparisons of Enbrel vs methotrexate, [†] = $p < 0.05$ for comparisons of Enbrel + methotrexate vs methotrexate and ϕ = $p < 0.05$ for comparisons of Enbrel + methotrexate vs Enbrel

Significant advantages for Enbrel in combination with methotrexate compared with Enbrel monotherapy and methotrexate monotherapy were also observed after 24 months. Similarly, the significant advantages for Enbrel monotherapy compared with methotrexate monotherapy were also observed after 24 months.

In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change ≤ 0.5) at 24 months was higher in the Enbrel in combination with methotrexate group compared with the Enbrel alone and methotrexate alone groups (62%, 50%, and 36%, respectively; $p < 0.05$). The difference between Enbrel alone and methotrexate alone was also significant ($p < 0.05$). Among patients who completed a full 24 months of therapy in the study, the non-progression rates were 78%, 70%, and 61%, respectively.

The safety and efficacy of 50mg Enbrel (two 25 mg SC injections) administered once weekly were evaluated in a double-blind, placebo-controlled study of 420 patients with active RA. In this study, 53 patients received placebo, 214 patients received 50 mg Enbrel once weekly and 153 patients received 25 mg Enbrel twice weekly. The safety and efficacy profiles of the two Enbrel treatment regimens were comparable at week 8 in their effect on signs and symptoms of RA; data at week 16 did not show comparability (non-inferiority) between the two regimens.

Antibodies to Enbrel

Antibodies to etanercept have been detected in the sera of some subjects treated with etanercept. These antibodies have all been non-neutralising and are generally transient. There appears to be no correlation between antibody development and clinical response or adverse events.

In subjects treated with approved doses of etanercept in clinical trials for up to 12 months, cumulative rates of anti-etanercept antibodies were approximately 6% of subjects with rheumatoid arthritis, 7.5% of subjects with psoriatic arthritis, 2.0% of subjects with ankylosing spondylitis, 7% of subjects with psoriasis, and 3% of subjects with juvenile idiopathic arthritis.

The proportion of subjects who developed antibodies to etanercept in longer-term trials (of up to 3.5 years) increases over time, as expected. However, due to their transient nature, the incidence of antibodies detected at each assessment point was typically less than 7% in rheumatoid arthritis subjects and psoriasis subjects.

In a long-term psoriasis study in which patients received 50 mg twice weekly for 96 weeks, the incidence of antibodies observed at each assessment point was up to approximately 9%.

5.2 Pharmacokinetic properties

Etanercept serum values were determined by an ELISA method, which may detect ELISA-reactive degradation products as well as the parent compound.

Paediatric patients with polyarticular juvenile idiopathic arthritis

In a polyarticular juvenile idiopathic arthritis trial with Enbrel, 69 patients (aged 4 to 17 years) were administered 0.4 mg Enbrel/kg twice weekly for three months. Serum concentration profiles were similar to those seen in adult rheumatoid arthritis patients. The youngest children (4 years of age) had reduced clearance (increased clearance when normalised by weight) compared with older children (12 years of age) and adults. Simulation of dosing suggests that while older children (10-17 years of age) will have serum levels close to those seen in adults, younger children will have appreciably lower levels.

Adults

Etanercept is slowly absorbed from the site of subcutaneous injection, reaching maximum concentration approximately 48 hours after a single dose. The absolute bioavailability is 76%. With twice weekly doses, it is anticipated that steady-state concentrations are approximately twice as high as those observed after single doses. After a single subcutaneous dose of 25 mg Enbrel, the average maximum serum concentration observed in healthy volunteers was $1.65 \pm 0.66 \mu\text{g/ml}$, and the area under the curve was $235 \pm 96.6 \mu\text{g}\cdot\text{hr/ml}$. Dose proportionality has not been formally evaluated, but there is no apparent saturation of clearance across the dosing range.

A biexponential curve is required to describe the concentration time curve of etanercept. The central volume of distribution of etanercept is 7.6 l, while the volume of distribution at steady-state is 10.4 l. Etanercept is cleared slowly from the body. The half-life is long, approximately 70 hours. Clearance is approximately 0.066 l/hr in patients with rheumatoid arthritis, somewhat lower than the value of 0.11 l/hr observed in healthy volunteers. Additionally, the pharmacokinetics of Enbrel in rheumatoid arthritis patients, ankylosing spondylitis and plaque psoriasis patients are similar.

Mean serum concentration profiles at steady state in treated RA patients were C_{max} of 2.4 mg/l vs 2.6 mg/l, C_{min} of 1.2 mg/l vs 1.4 mg/l, and partial AUC of 297 mgh/l vs 316 mgh/l for 50 mg Enbrel once weekly (n=21) vs 25 mg Enbrel twice weekly (n=16), respectively. In an open-label, single-dose, two-treatment, crossover study in healthy volunteers, etanercept administered as a single 50 mg/ml injection was found to be bioequivalent to two simultaneous injections of 25 mg/ml.

In a population pharmacokinetics analysis in ankylosing spondylitis patients the etanercept steady state AUCs were 466 µg•hr/ml and 474 µg•hr/ml for 50 mg Enbrel once weekly (N= 154) and 25 mg twice weekly (N = 148), respectively.

Although there is elimination of radioactivity in urine after administration of radiolabelled etanercept to patients and volunteers, increased etanercept concentrations were not observed in patients with acute renal or hepatic failure. The presence of renal and hepatic impairment should not require a change in dosage. There is no apparent pharmacokinetic difference between males and females. Methotrexate has no effect on the pharmacokinetics of etanercept. The effect of Enbrel on the human pharmacokinetics of methotrexate has not been investigated.

5.3 Preclinical safety data

In the toxicological studies with Enbrel, no dose-limiting or target organ toxicity was evident. Enbrel was considered to be non-genotoxic from a battery of *in vitro* and *in vivo* studies. Carcinogenicity studies, and standard assessments of fertility and postnatal toxicity, were not performed with Enbrel due to the development of neutralising antibodies in rodents.

Enbrel did not induce lethality or notable signs of toxicity in mice or rats following a single subcutaneous dose of 2000 mg/kg or a single intravenous dose of 1000 mg/kg. Enbrel did not elicit dose-limiting or target organ toxicity in cynomolgus monkeys following twice weekly subcutaneous administration for 4 or 26 consecutive weeks at a dose (15 mg/kg) that resulted in AUC-based serum drug concentrations that were over 27-fold higher than that obtained in humans at the recommended dose of 25 mg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Mannitol
Sucrose
Trometamol.

Solvent:
Water for injections
Benzyl alcohol.

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

After reconstitution, chemical and physical stability has been demonstrated for 14 days at 2°C – 8°C. From a microbiological point of view, once reconstituted, the product may be stored for a maximum of 14 days at 2°C – 8°C. Other storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze

For storage conditions of the reconstituted medicinal product see section 6.3.

6.5 Nature and contents of container

Clear glass vial (4 ml, type I glass) with rubber stoppers, aluminium seals, and flip-off plastic caps. Enbrel is supplied with pre-filled syringes containing bacteriostatic water for injections. The syringes are type I glass-fitted with stainless steel needles. Cartons contain 4 vials of Enbrel with 4 pre-filled solvent syringes, 8 empty plastic syringes, 20 stainless steel needles and 24 alcohol swabs.

6.6 Special precautions for disposal and other handling

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

Instructions for use and handling

Enbrel is reconstituted with 1 ml bacteriostatic water for injections before use, and administered by subcutaneous injection. The solution should be clear and colourless to pale yellow, with no lumps, flakes or particles. Some white foam may remain in the vial – this is normal. Enbrel should not be used if all the powder in the vial is not dissolved within 10 minutes. Start again with another vial.

Comprehensive instructions for the preparation, administration and re-use of the reconstituted Enbrel vial are given in the package leaflet, section 7, "Instructions for preparation and giving an injection of Enbrel.

7. MARKETING AUTHORISATION HOLDER

Wyeth Europa Ltd.
Huntercombe Lane South
Taplow, Maidenhead
Berkshire, SL6 0PH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/126/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3 February 2000

Date of last renewal: 3 February 2005

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMA) <http://www.emea.europa.eu>