SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures which have been finalised before 1 October 2004. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

Remicade contains the active substance infliximab. It is a chimeric human-murine monoclonal antibody directed against tumour necrosis factor alpha (TNFα), manufactured from a recombinant cell line. Infliximab contains approximately 30% murine variable region amino acid sequence, which confers antigen-binding specificity to human TNFα. The remaining 70% correspond to a human IgG1 heavy chain constant region and a human kappa light chain constant region. Remicade is presented as powder for concentrate for solution for infusion (100 mg/vial), to be reconstituted with water for injections, diluted with saline and thereafter administered via intravenous infusion.

Infliximab has high affinity for human TNFα, which is a cytokine with multiple biologic actions including mediation of inflammatory responses and modulation of the immune system. There is evidence that TNFα plays a role in autoimmune and inflammatory diseases.

Remicade has currently been approved for use in the following therapeutic areas:

Crohn's disease is a chronic medically incurable inflammatory bowel disease, which appears periodically with a varying course. The symptoms range from mild inflammatory symptoms to disabling conditions involving large parts of the gastro-intestinal tract and with severe subsequent complications such as the occurrence of fistulae. Conventional therapies include corticosteroids, aminosalisylates, antibiotics and immunosuppressive drugs. Only when medical treatment is not successful or in certain complications, surgery is indicated. Despite this fact, surgery is needed in a number of patients. A fulminate life-threatening course of the disease is rare, but due to therapeutic failure and severe and disabling side effects of corticosteroids and immunosuppressant medicinal products alternative therapies are needed.

Rheumatoid Arthritis (RA) is characterised by chronic inflammation of several joints and is often complicated by the involvement of internal organs. The underlying aetiology of this inflammatory process remains unknown, but there is evidence that points to immunological reactions against still unidentified antigens. It should therefore be possible to reduce the consequences of the disease process both by blocking important steps in the inflammatory reaction and by modifying the specific immunological mechanisms that are involved in the development of the disease. In RA there are increased levels of TNFα secreted by infiltrating lymphocytes and macrophages which is implicated in synovial proliferation, inflammation and joints destruction. The pharmacological management of RA involves mainly symptomatic treatment and disease modification.

RA is a progressive disease but the rate of progression varies from one individual to another. Characteristic X-ray findings are seen in more than half of the patients 2 years after the onset and in 80% after 5 years. Joint erosion often occurs early in RA, affecting up to 40% of patients destined to develop erosive RA, during the first year and 90% during the first 2 years (Plant *et al*.,1998). Functional disability occurs early, and the disease is also associated with premature mortality (Goldbach-Mansky and Lipsky, 2003; Pincus, 1995) mainly due to cardiovascular disease.

Ankylosing Spondylitis (AS) is a chronic inflammatory disease of the spine and tendons characterised by progressive, stiffening of the sacroiliac, intervertebral and costovertebral joints and leading to bony ankylosis. AS is a systemic rheumatic disease and may also effect enthesis (tendon insertions) and peripheral joints, as well as other organs such as the eyes, heart, and lungs. The long-term outcome of AS (10-20 years) is severe handicap and disability in 25-30% of cases, and AS is associated with an increased mortality rate. The goal of conventional treatments such as physiotherapy, non-steroidal

anti-inflammatory drugs, glucocorticoids, DMARDs is pain control. Oral agents employed to modify disease progression in RA are prescribed for AS patients with refractory symptoms. Modest benefit is achieved in some patients, particularly in peripheral joint symptoms. Axial symptoms are inconsistently improved in patients treated with second-line agents, and there is little evidence these medicinal products slow the progression of structural damage. Abundance of TNF-alpha mRNA in sacroiliac joints biopsies from AS patients, suggests a pathogenic role for TNF.

Psoriatic arthritis (PsA) is an inflammatory arthritis, associated with psoriasis. With the exception of the distal interphalangeal joints there are no predictable joints for involvement in PsA and the signs of inflammation are often non-symmetrical and more difficult to detect compared with RA. Pain and tenderness is often more pronounced than in other joint inflammation. Spondylarthropathy is often present. Some typical features of PsA occur, such as dactylitis, i.e. swelling of a whole digit. Treatment approaches include physical therapy, NSAIDs, DMARDs and corticosteroids. There is an increased risk for flares of psoriasis when tapering steroid treatment. The outcome of the disease varies from low activity to severe disabling disease including mutilating joint disease.

In August 1999, a Marketing Authorisation under "exceptional circumstances" was granted for Remicade. The approved indications were for the treatment of severe, active Crohn's disease and for fistulising Crohn's disease in patients who have not responded despite a full and adequate course of therapy with conventional treatment such as a corticosteroid and/or an immunosuppressant. Due to the limited safety and efficacy data available at the time of approval, the Marketing Authorisation Holder (MAH) committed to provide additional data when they became available; the benefit–risk balance was to be reassessed on a yearly basis. Following the authorisation of Remicade for treatment of Crohn's disease, subsequent type II variation applications have been submitted and reviewed to extend the indication for use in RA, Ankylosing Spondylitis and Psoriatic Arthritis.

Within the first and second annual reassessment, further safety and efficacy data for Remicade have been reviewed. Based on post marketing experience as well as new clinical trial data, safety concerns identified during the initial approval procedures, have been confirmed and new concerns have emerged. The main safety concerns, which apply for both Crohn's disease patients and RA patients, include serious infections including tuberculosis (TB), infusion-related reactions including anaphylactic/toid reactions, antibody development, worsening of heart failure, neurological disorders, blood disorder, possible increased risk of malignancies and the fact that long-term consequences of Remicade treatment are unknown.

Because of these safety concerns, and due to the limited efficacy data in Crohn's disease and upon advice from an Expert Group convened by the EMEA, the indications for treatment of Crohn's disease were restricted via an urgent safety restriction on 17 January 2002, while the indication for RA remained unchanged.

In light of the available knowledge of the safety profile of Remicade, and considering the post marketing experience so far, it was considered necessary to find ways to improve the awareness of the patients and health care professionals about the risks with Remicade use. Therefore, a patient alert card was introduced in February 2002.

Since then additional data from clinical studies and post-marketing data have been submitted. The additional data, assessed within PSURs, various variation applications and follow-up measures/ specific obligations, 2 further annual reassessments and the five year renewal of the Marketing Authorisation allowed to better characterise the benefits and risks with Remicade. Further to the fourth annual reassessment the CHMP lifted the need for annual reassessments. Based on new data from clinical studies, the therapeutic indications were updated to include ankylosing spondylitis, MTX-naïve RA and psoriatic arthritis. Information from clinical trial experience with repeated administration in severe active Crohn`s disease and long-term treatment of Crohn`s disease has also been added to the relevant sections of the product information.

By the cut-off date of this report, the following therapeutic indications apply :

Rheumatoid arthritis:
Remicade, in combination with methotrexate, is indicated for:
the reduction of signs and symptoms as well as the improvement in physical function in:

- patients with active disease when the response to disease-modifying drugs, including methotrexate, has been inadequate.
- patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.

In these patient populations, a reduction in the rate of the progression of joint damage, as measured by x-ray, has been demonstrated (see section 5.1).

Crohn's disease:
Remicade 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 an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.
- treatment of fistulising, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).
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Ankylosing spondylitis:
Remicade is indicated for:
Treatment of ankylosing spondylitis, in patients who have severe axial symptoms, elevated serological markers of inflammatory activity and who have responded inadequately to conventional therapy.

Psoriatic arthritis:
Remicade, in combination with methotrexate, is indicated for:
Treatment of active and progressive psoriatic arthritis in patients who have responded inadequately to disease-modifying anti-rheumatic drugs.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

Remicade is supplied as a sterile lyophilised cake for reconstitution and dilution prior to administration. Each vial of the product contains 100 mg infliximab, monobasic sodium phosphate monohydrate, dibasic sodium phosphate dihydrate, sucrose, and polysorbate 80. No preservatives are added. The primary container/closure system consists of a 20 ml Type I glass vial, a rubber stopper and a flip-off cap.

Development pharmaceutics
During development different cell clones, manufacturing processes and formulations were used. Comparability between product used in clinical trials and that produced using the current process was demonstrated by the extended batch analyses and in characterisation studies.

During the licensing process, delayed hypersensitivity reactions were reported for a small group of Crohn´s disease patients treated in early clinical trials, and re-treated two to four years later. All but one (9 out of 10) of the affected patients had in their initial treatment received a liquid formulation of Remicade. It was noticed that the liquid formulation had a higher turbidity (possibly caused by infliximab self-association) than lyophilised Remicade used in other studies where no delayed hypersensitivity reactions were observed, and a contribution of the liquid formulation to the development of hypersensitivity reactions could not be excluded. Characterisation of the molecular integrity of the reconstituted lyophilised product intended for marketing showed that the monomer

content of the product is at least 98%, which is considered acceptable. To control that undue aggregation of the product does not occur, the applicant limits the product specification for turbidity to "opalescent" (Ph.Eur.) and tighten the product specification for monomer content by gel filtration (GF) - HPLC to ≥98.0%. Delayed hypersensitivity is further addressed in the Clinical section below.

Method of preparation

Remicade is manufactured in production batches of 10,000 to 63,000 vials. An acceptable description of the manufacturing process has been given. Briefly, frozen infliximab pre-formulated bulk (PFB) is thawed, formulated to the final batch size, sterilised by filtration, filled and dried by lyophilisation to yield infliximab finished product; 100 mg/vial.

Adequate in-process control tests are performed throughout the manufacturing process, including control of the integrity of all filters both prior to and after use. The test methods used are considered acceptable.

Validation
The lyophilisation, the aseptic filling processes as well as the manufacturing conditions are satisfactorily validated.

Control of starting materials

Specifications and routine tests
The specifications for release cover all tests commonly applied to purified protein solutions. Specifications for: endotoxin, bioburden, pH, protein concentration, infliximab charge heterogeneity, bioactivity, purity by SDS-PAGE, reduced and non-reduced, purity by GF-HPLC and identity by GF-HPLC must be met for release of the active substance.

During the evaluation process, a number of questions were raised regarding specifications and routine testing. Most of these have been adequately solved, while some remaining issues will be addressed on an ongoing basis.

Results from finished product testing including the bulk substance, from three full-scale batches have been submitted.

Development genetics
The infliximab monoclonal antibody is expressed using chimeric antibody genes consisting of the variable region sequences cloned from the murine anti-TNFα hybridoma A2, and human antibody constant region sequences supplied by the plasmid expression vectors.

Generation of the murine anti-TNF α hybridoma was performed according to standard procedures by immunisation of BALB/c mice with purified recombinant human TNFα. The anti-TNFα hybridoma cell line A2 was established after subcloning of cells yielding the highest specific activity, and a cell clone found to be 98% homogenous with regard to expression of IgG1 was selected for further processing.

A description is given of the different steps starting from the preparation of the infliximab genomic libraries used for isolation of the light and heavy chain variable regions, and ending at the isolation of the two expression vectors carrying infliximab chimeric light chain or heavy chain genes.

The procedures used for transfection and isolation of the C-168-J producer cell clone included steps where the heavy and light chain vector constructs were linearised and transfected into Sp2/0 cells by electroporation. The subclone C-168C was selected and the high antibody producing subpopulation was enriched using serial cell sorting by flow cytometry. The highest-producing cell clone was used to create the research cell bank from which the current master cell bank (MCB; C168J) was established.

Cell bank system
The studies reported on the safety of the producer cell line have been performed in accordance with the EU guideline "Note for guidance of production and quality control of monoclonal antibodies". The MCB has been characterised for the absence of microbial and viral contaminants as well as inherent characteristics of the cell line as karyotype, isoenzyme patterns, authenticity, clonality and stability. Each master working cell bank (MWCB) is prepared from a single vial of the MCB. The routine analyses performed on new MWCB´s are found acceptable and include tests for viability, mycoplasma, sterility, MAP, murine thymic agent, *in vitro* and *in vivo* tests for adventitious virus, bovine virus, karyology, isoenzymes, as well as the stable production and the identity of the secreted antibody. In view of the tests applied for qualification of each new MWCB, omission of stability studies on frozen cell banks is acceptable.

Fermentation and harvesting
Infliximab is a recombinant antibody produced and secreted from mouse myeloma cells (SP2/0 cells). The antibody is manufactured by continuous perfusion cell culture. Collected harvests are clarified by filtration before further purification.

A satisfactory description is given of the different steps of the process, including in-process tests, e.g. cell viability, cell density and microbial contamination. Each harvest is tested for pH, bioburden and endotoxin content. Maximum ranges are specified for operation parameters including temperature, dissolved oxygen, pH, and agitation rate during cultivation in the fermentors. Criteria are set for termination of the cultures.

For each new MWCB, at the end of the first three fermentation runs, samples are withdrawn and tested for mycoplasma, xenotropic retrovirus, ecotropic retrovirus as well as for positive reaction *in vitro* assays using MRC-5, Vero 76, HeLa and the host cell line as indicator cells. In these analyses, all samples tested so far have been found negative.

Data for in-process tests and operating parameters have been provided and are considered adequate.
As a result of the evaluation process, a maximum limit for the viral load of the unpurified bulk harvest was defined (see Viral safety).

Purification
The different steps of the purification process include affinity and anion chromatography, as well as two robust virus removal steps that are capable of removing adventitious agents and other contaminants. The documentation of the purification process contains a satisfactory presentation of the conditions applied during each step. All materials and equipment used in the different steps are specified. Intermediates of the process are 0.2 µm filtered before storage.

Characterisation
Data presented on the characterisation of infliximab were of high quality. This refers both to the studies shown on aspects of microheterogeneity associated with fermentation, and to identification of degraded/modified forms of infliximab. Most of the techniques used for characterisation are applied in the extended batch analysis indicated for demonstration of the consistency of the current process as well as for comparability with products derived from different processes. The discriminating capacity of the proposed consistency/comparability testings is supported by the high quality of the characterisation studies.

Analytical Development
Validation reports were submitted for all methods used to control the in process and release specifications (active ingredient and the finished product). Furthermore, a survey was given on the qualification tests performed on a selection of non-routine assays.

Process validation
The process validation is divided into four sections covering:

- Facilities, and cleaning and microbial control of equipment. An overview of the systems in place to fulfil Good Manufacturing Practice (GMP) requirements is presented.
- Cell growth and harvesting. The cell growth kinetics and antibody productivity profiles are shown for each of nine bioreactors for time periods of up to 86 days.
- Removal of media components/additives during purification
- Capacity of the purification process to remove contaminating virus

Control tests on the finished product

For the finished product, release tests and specifications are provided. Release tests include tests of samples at the end of fermentation and sterility testing of final bulk. The final lyophilised product is tested for sterility, endotoxin, appearance, residual moisture and reconstitution time. After reconstitution the product is tested for colour, visible particles and turbidity. Protein content, pH, uniformity, identity and immunoreactivity are determined. SDS-PAGE, gel filtration (GF) -HPLC and isoelectric focussing (IEF) are performed. Release results for seven batches of drug product were provided.

Stability

The reports on the ongoing stability studies on the pre-formulated bulk product will be submitted when available, as a follow up measure. Shipment of frozen infliximab PFB from Centocor BV in Leiden, The Netherlands, to a contract site is satisfactorily validated.

The stability of the finished product has been tested in an adequate number of batches to support the shelf-life of 18 months when stored at 2 - 8 °C. During the post-authorisation phase, the shelf-life of the product was extended to 36 months by submission of supportive stability data. Stability was demonstrated for reconstituted product for up to 24 hours at room temperature.

Viral safety
The virus removal/inactivation capacity of the manufacturing process was investigated using the following model viruses: ecotropic recombinant retrovirus (ERV), reovirus type 3 (Reo 3) and poliovirus type 1 (Polio).

The submitted data indicated that, in the normal case, there is sufficient safety margin for retrovirus removal during manufacture. To ensure that this margin will not be exceeded, the applicant has agreed to include a test for quantification by transmission electron microscopy in each case that a positive result is obtained in any of the analyses for infectious retrovirus applied for in process control of fermentor harvests.

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics

Various *in vitro* studies have shown that infliximab has a high avidity for human transmembrane TNFα and high affinity for soluble TNFα. Infliximab has also been shown to bind to monomeric TNFα in addition to trimeric TNFα (Kd values were in the pM or nM range). The binding to both transmembrane and soluble forms of TNFα was shown to be saturable and concentration-dependent.

Infliximab was shown to inhibit the binding of recombinant human (rh)TNFα to human TNFα p55 and p75 receptors constructs. Infliximab-TNFα complexes were stable *in vitro*, also in the presence of sTNFR-p55-receptor. Limited data in mice also indicated that the infliximab-TNFα complexes were stable.

Infliximab inhibited functional activities of TNFα in a variety of *in vitro* cell assays (human fibroblasts, endothelial cells, epithelial cells, neutrophils, and peripheral blood mononuclear cells). In most cases, full inhibition was seen at concentrations lower than 5 µg/ml infliximab. In one *in vitro* study, infliximab in combination with either complement or effector cells induced lysis of SP2/0 cells expressing recombinant transmembrane TNFα. This property appeared to be dependent on both the infliximab antigen-binding site and on the IgG1 Fc domain.

In standard cytotoxicity tests, infliximab inhibited the cytotoxic effects of human recombinant or natural TNFα (50% inhibition at 10-20 ng/ml infliximab). As expected, infliximab (up to 1.5 mg/ml) had no effect on recombinant human lymphotoxin α-induced toxicity. It was also shown that infliximab could neutralise human and chimpanzee TNFα with similar potency, while TNFα from a number of other species (rhesus cynomolgous, pigtail macaque, cotton-top tamarin, baboon, marmoset, pig, rabbit, rat and mouse) was not affected by infliximab.

Studies in normal mice given rhTNFα and different transgenic mice models that expressed recombinant forms of soluble or transmembrane human TNFα showed that infliximab inhibited the pathological effects mediated by human TNFα. In a mouse model of colitis, a monoclonal antibody against mouse TNFα significantly reduced the severity of colitis as indicated by a composite disease activity index.

New pharmacodynamic data in transgenic mice serving as models for arthritis were submitted after approval for Crohn's disease. These data indicated that the murine anti-human TNFα monoclonal antibody (mA2) inhibited effects mediated by human TNFα, which also resulted in joint healing. Thus, these preclinical data would support the use of infliximab in RA.

The reactivity of infliximab with a number of human tissues was studied by *in vitro* immunohistochemical assays. Consistent with the known distribution of TNFα, reactivity was observed with mononuclear and stromal cells in most tissues as well as in smooth musculature associated with vascular walls or selected muscle bundles in a number of tissues.

Pharmacokinetics

The preclinical pharmacokinetic documentation is limited. Since the relevance of animal pharmacokinetic data on infliximab is marginal for the safety assessment, this was considered acceptable.

Toxicology

General toxicity
The lack of binding of infliximab with TNFα from other species than human and chimpanzee has restricted the possibilities to evaluate its toxicity profile. Although single and repeated dose toxicity studies were performed in rats, these studies are not considered to have any relevance for the human safety assessment. A small number of chimpanzees, the only relevant species identified for safety testing, were given single or up to 5 once daily repeated doses of infliximab. There were no clinical or biochemical indications of toxicity. However, due to the study designs (e.g. sub-optimal dose regimens, short follow-up period; no post mortem data as animals were not sacrificed) and uncertainties regarding the conduct of the experiments, these data were of marginal value for the human safety assessment. Due to the lack of relevant animal models, the absence of more detailed toxicity data with infliximab was considered acceptable.

Since TNFα plays an important role in the defence against various infections, long-term inhibition of TNFα may be associated with an increased susceptibility for infectious disease. Data from the literature have shown that anti-TNFα monoclonal antibodies reduce host defence in various clinically relevant intracellular infection models, which in several experiments led to an increased infection-induced mortality. These aspects are further addressed in the clinical section below.

A 6 months toxicity study with an anti-mouse TNFα monoclonal antibody (chimeric V1q muG2a, which has functional characteristics similar to infliximab) was submitted in year 2001. In this study, CD-1 mice were given 25 weekly i.v. doses of 10 or 40 mg/kg cV1q. No cV1q treatment-related mortality or clinical signs of toxicity were observed. Furthermore, post mortem examinations did not indicate any treatment related findings. However, ophthalmic examinations revealed a dose-related increase of bilateral crystalline deposits in the lens capsule of treated male mice. The relevance of this finding for humans is not known.

Reproductive toxicity
Standard reproductive/developmental toxicity studies have not been performed with infliximab due to lack of relevant animal models. In an attempt to mimic the clinical situation of TNFα inhibition, studies were conducted in mice using a monoclonal antibody against mouse TNFα (cV1q). In these experiments, it was demonstrated that cV1q crossed the placenta but there was no indication of impairment of reproductive function, embryotoxicity or teratogenicity.

During the review process, concerns were expressed regarding the use of infliximab in pregnancy as well as in women of childbearing potential. Since there are data showing that TNFα is involved in embryo/fetal development, administration of infliximab could impair embryo/fetal development. Furthermore, the elimination of infliximab is slow and based on the experience with cV1q, placental transfer can not be excluded. Thus, there is a possibility that infliximab could be transferred to the fetus during pregnancy and retained in the newborn child for an extended period of time, which could for instance reduce the new-born's defence against infections. Therefore, it was concluded that women of childbearing potential treated with infliximab should use adequate contraception to prevent pregnancy. Furthermore, administration of infliximab during pregnancy is not recommended. This information has been included in the SPC.

The applicant has submitted a new fertility and general reproductive toxicity study. This study was performed with an anti-mouse TNFα monoclonal antibody, chimeric V1q muG2a, which has functional characteristics similar to infliximab. In the high dose (HD) group, a reduction of the 'fertility index' and 'number of pregnant mice/ number of mice in cohabitation' was observed. Furthermore, the mean number of days in cohabituation appeared to be increased. Due to the study design, where both males and females were treated, it can not be established if these findings were male-, and/or female–mediated effects. Comparisons of systemic exposure of mice to cV1q and of humans to infliximab are uncertain. Although the relevance of these findings for humans is unknown, this information has been included in sections 4.4 and 5.3 of the SPC.

Genotoxicity and carcinogenicity
Genotoxicity tests are considered to be of limited value for this type of product. Still, a complete test battery has been performed. Infliximab did not show any genotoxic activity in these studies.

Standard carcinogenicity studies have not been performed with infliximab. A concern was expressed regarding the consequences of long-term inhibition of TNFα in relation to proliferative changes and a potential risk of tumour development. To address this concern, information was provided from TNFα knock-out mice and from studies of effects of anti-murine TNFα antibodies on tumour development. These data gave no support for the hypothesis that inhibition of TNFα is associated with an enhanced risk for tumour development.

Local tolerance
There was no indication of local irritation following intravenous administration in rabbits.

Conclusion

In vitro studies have demonstrated that infliximab binds to soluble and transmembrane human TNFα with high affinity. Furthermore, infliximab-mediated inhibition of functional activities of human TNFα has been shown in a variety of test systems. Due to the limited species reactivity of infliximab, the possibility to evaluate its toxicity profile is restricted. Data from genetically modified animals (i.e. transgenic and knock-out models) and from studies of a monoclonal antibody against mouse TNFα have provided some reassurance regarding carcinogenic potential and reproductive toxicity, although some effects on fertility were observed in mice. However, as a precautionary measure and based on other information regarding the involvement of TNFα embryo / fetal development, administration of Remicade is not recommended during pregnancy. Furthermore, women of childbearing potential should use adequate contraception to prevent pregnancy. Considering the aspects outlined above, the available preclinical data were regarded to be sufficient.

4. Part IV: Clinical aspects

The clinical trial programme that was evaluated for the initial authorisation of infliximab encompassed 14 completed studies including one study in healthy volunteers. The five Crohn's disease trials (Table 1) contained 233 patients, 199 of whom have been treated with infliximab. In addition, safety data from trials in rheumatoid arthritis (RA) and sepsis were provided.

The first extension of the indications in RA was based on data from clinical studies in 660 patients with active RA (Table 1).

Table 1 Overview of studies in support of efficacy and safety

Clinical Trial	Phase	Patient Population	Number of patients
0168T08	I	Active Crohn's disease	10
0168T11	II	Moderate to severe Crohn's disease	21
0168T16	II/III	Moderate to severe Crohn's disease	108
0168T20	II/III	Fistulising Crohn's disease	94
0168T24[1]	III	Moderate to severe Crohn's disease	40
0168T07	I	Active RA	20
0168T09	II	Active RA	73
0168T14	II	Active RA	101
0168T15/T17[2]	II	Active RA	28
0168T18	I	Active RA	16
0168T22	III	Active RA	428
0168T03	I/II	Healthy volunteers	39
0168T00	I	Compassionate use	9
0168T12	II	Ulcerative colitis	11

1: Open label study in patients earlier included in studies T 08, T11, T16 and T20.
2: These two trials had separate protocols, but included the same patients and were reported in a single study report

Further data with regard to long-term treatment of active CD (trial ACCENT I; C0168T21) and fistulising CD (ACCENT II; C0168T26) were submitted later on. ACCENT I was a multicentre, randomised, double-blind, clinical trial of maintenance infliximab treatment compared with a single dose of infliximab in 580 patients with moderately to severely active Crohn´s disease (CD). ACCENT II was a multicentre, randomised, double-blind, clinical trial of maintenance infliximab treatment compared with a 3-dose induction regimen of infliximab only in 306 patients with fistulising Crohn´s disease.

The RA indication was later extended to include methotrexate-naïve RA based on data from the ASPIRE (Active-controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset; C0168T29) trial. This is a randomised, multi-centre, double-blind, 3-arm, parallel, phase III study of Infliximab in combination with methotrexate compared with methotrexate alone, in which 1049 subjects were randomised.

A futher application for extension of the indications to include ankylosing spondylitis was based primarily upon the randomised, double-blind, placebo-controlled clinical study P01522. The table 2 shows the different studies with Infliximab in AS.

Table 2 studies with Infliximab in Ankylosing spondylitis

Study	**Design**	**Study Status**	**ITT Patients**		**Per Protocol**
			Total	**AS**	**AS**
P00420	Open-label, pilot study with a follow-up 1 year later	Completed	11	11	10 FU: 8
P01522	Double-blind, placebo-controlled with an open-label follow-up phase (2 years in total)	Ongoing (results available for one year follow-up)	70	60	27 infliximab 33 placebo
P01205	Open-label pilot study with a follow-up of 1 year	Completed	21	10	10
P02162	Double-blind, placebo-controlled, cross-over	Completed	40	19	9 infliximab 10 placebo
P01533	Open-label study with at least 6 month follow-up	Completed	50	50	48
P01227	Open-label pilot study with 1 year follow-up	Ongoing	38	29	26 infliximab
P02060	Open label	Ongoing	8	8	8 infliximab
EAP 1	Expanded access program	Ongoing	21	21	18 infiximab
EAP 2	Expanded access program	Ongoing	21	21	17 infliximab (8 pts. for 1-y-evaluation)
Total			280	239	216, thereof 173 infliximab

Psoriatic arthritis:
The pivotal trial, study P02114 (IMPACT) was an investigator-initiated, multicentre study in 104 subjects with PsA and peripheral polyarticular arthritis who had failed at least 1 DMARD. The study design included a 16-week, randomised, double-blind, placebo-controlled treatment (Stage I), followed by a 34-week, open-label treatment period (Stage II).

Study C0168T31 (SPIRIT), a randomised, double-blind, placebo-controlled Phase II Centocor-sponsored study of 249 subjects with moderate-to-severe (≥12 PASI-score) plaque-type psoriasis. provided additional safety information related to the proposed dosage of 5 mg/kg without concomitant DMARD use. Available data from 6 completed and 1 ongoing investigator-initiated studies in PsA including a total of 133 patients with PsA provided additional information about the efficacy of infliximab.

Clinical pharmacology

Pharmacodynamics in Crohn's disease
After administration of infliximab (1, 5, 10 and 20 mg/kg), serum concentrations of TNFα in Crohn's disease patients showed a consistent pattern in which low levels (5 to 25 pg/ml) of TNFα at baseline were first reduced below the level of detection (< 3 pg/ml) at one hour, followed by a rise in TNFα from 4 to 72 hours. Peak TNFα concentrations were detected at 72 hours or 2 weeks following infusion and then declined to baseline levels by 12 weeks. The peak concentrations (60 to 80 pg/ml of TNFα) were greater in the high dose groups compared with the low dose groups. The persistence of detectable TNFα was also more prolonged in the higher dose groups. The increased concentrations of TNFα observed 4 to 72 hours after administration were most likely due to the formation of infliximab/TNFα complexes as observed in studies in mice.

Immunohistochemical analyses of biopsies from patients in acute Crohn's disease (T16) showed a marked decrease in tissue TNFα after infliximab treatment. Infliximab doses of 5, 10 and 20 mg/kg demonstrated substantial declines in interleukin (IL) 6 to the normal range at 2 weeks while in the placebo group, IL-6 values increased at two and four weeks. Between baseline and two weeks, a sharp decline in C-reactive protein (CRP) was evident in all three infliximab dose groups. Total peripheral white blood cell counts were modestly lowered in infliximab-treated patients. Analyses of lamina propria mononuclear cells obtained by biopsy of the intestinal mucosa suggested that infliximab treatment caused a reduction in the numbers of cells capable of expressing TNFα and interferon gamma. Additional histological studies showed that infliximab treatment reduced inflammatory cell infiltration into affected areas of the intestine, reduced the levels of detectable TNFα and reduced the expression of other inflammatory markers at these sites. Taken together, these data support the proposed mechanism of action of infliximab, i.e. inhibition of TNFα resulting in suppression of inflammation.

Pharmacodynamics in RA
In clinical trials, serum, blood and tissue samples were analysed for the presence of markers of chronic inflammation or abnormal immune response. These studies have shown that infliximab was capable of neutralising free TNFα in a dose dependent fashion (C0168T03), and no rebound effects have been noticed after treatment discontinuation (C0168T09). In study C0168T09, where RA patients received 10 mg/kg of infliximab, serum amyloid A, acute phase reactant, VEGF, IL 8, e-selectine, ICAM-1 and VCAM-1 and matrix metalloproteinase-3 were decreased after one or a few weeks of treatment, relative to baseline levels. In study C0168T18, decreased monocyte chemoattractant protein-1 levels in the synovial tissue were observed at two weeks. Over the course of treatment, total white blood counts (WBC) remained unchanged. Eosinophils and basophils comprised minor fractions of the total counts and did not show dramatic changes over time. Increases in lymphocyte counts and accompanying decreases in neutrophil counts were evident in both 1 and 10 mg/kg treatment groups. Infliximab treatment did not exacerbate the already depressed cell-mediated immunity response seen in RA patients (Pope *et al*, 1993). These pharmacodynamic data do not indicate that infliximab has a general immunosuppressive effect during short-term. On the other hand, experimental data show that TNFα is essential for the clearing of intracellular infections. Moreover, clinical experience shows that host defence against infection is compromised in some patients treated with infliximab. No pharmacodynamic data are available on the long-term effects of infliximab on the immune system.

Pharmacokinetics
The analytical methods used for analyses of infliximab in serum, as well as analyses of antibodies to infliximab are not specific due to interference caused by free infliximab in the antibody analysis and vice versa. Thus, the interpretation of serum levels of infliximab and the analysis of antibodies to infliximab should be made with caution.

Having the limitations of the analytical methods in mind, the available pharmacokinetic data for infliximab can be summarised as follows. After administration of 5 mg/kg of infliximab, the plasma concentration of free infliximab remained in the same order as C_{max} (118 μg/ml, range: 71-283 μg/ml) for approximately 24 hours. The concentrations then declined exponentially with a half-life of 8-10 days. Detectable concentrations of free infliximab have been observed for up to 28 weeks (mean 12 weeks) after the recommended dose regimen in Crohn's disease for closure of enterocutaneous fistulae. Clearance of free infliximab was about 11 ml/h (range 3-40 ml/h). No clinically significant dose- or time dependencies have been observed in the pharmacokinetics of free infliximab. There are no specific studies regarding metabolism or excretion of infliximab in humans. Since infliximab can be expected to be eliminated in a similar manner as native antibodies, this is considered to be acceptable. Furthermore, no studies of the pharmacokinetics of infliximab have been performed in patients with impaired organ functions. Adequate warning statements have been included in the labelling.

The pharmacokinetics of infliximab in RA patients appear to be similar to the pharmacokinetics observed in patients with Crohn´s disease and under multiple dose treatment, the plasma levels were

as expected from the single-dose data. In an interaction study with methotrexate (MTX), the plasma concentrations of infliximab were slightly increased by MTX. The effect was most profound in the low dose (1 mg/kg) group. Lower frequencies of patients with antibodies to infliximab were also observed during MTX co-treatment, although these data are uncertain due to methodological limitations for the determination of antibodies to infliximab. (see above and section on Antibodies to infliximab below).

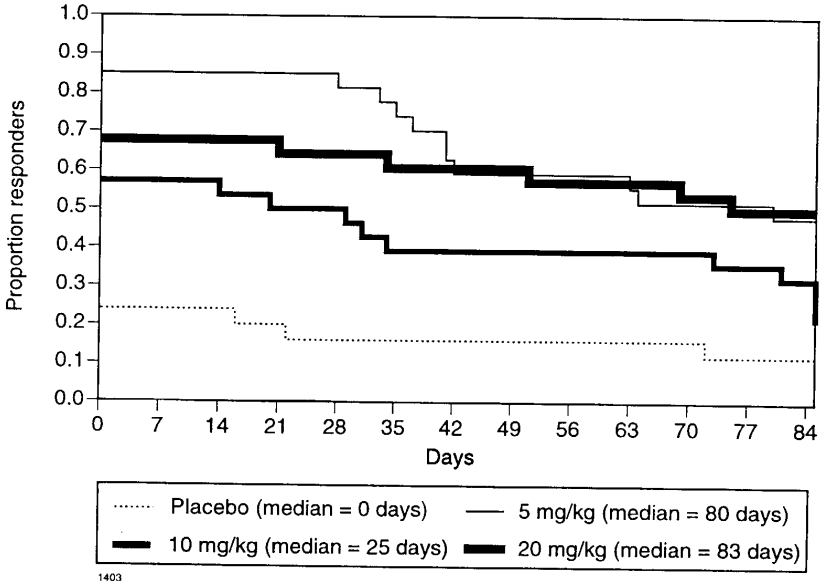
Pharmacokinetic studies indicated that most patients given one infusion of 5 mg/kg had detectable plasma concentrations of infliximab for 8 weeks. Patients who were given three infusions of 5 mg/kg had detectable plasma concentrations of infliximab for a mean of 12 weeks after the last dose administration (with a range of 4 to 28 weeks).

Clinical Efficacy

Crohn's disease
Two small non-controlled pilot studies in patients with Crohn's disease indicated that infliximab treatment induced clinical improvement in around 70 % of the patients (C0168T08 and C0168T11). Following this, one dose-response study in moderate to severe active Crohn's disease, defined as Crohn's Disease Activity Index (CDAI) between 220 and 400, was performed (C0168T16). This was a multicentre, randomised, parallel, double blind, placebo-controlled study consisting of two phases: the initial treatment phase and the repeated treatment phase. The initial treatment phase evaluated the effects of a single infusion of placebo or infliximab. At week 0, a total of 108 patients of whom approximately 76 % were non-responders to ongoing therapy with corticosteroids or other immunosuppressive medication were randomised to 5, 10 or 20 mg/kg infliximab or placebo. Patients who were not responding four weeks after the initial infusion were offered an open-label infusion of 10 mg/kg infliximab. Seventy-three patients who were responding at week eight (decrease of $\geq$ 70 CDAI scores), following the initial blinded infusion or open-label infusion (at week four), were re-randomised and participated in the repeated treatment phase. The patients were subsequently given 10 mg/kg infliximab or placebo at weeks 12, 20, 28 and 36. A last clinical and/or laboratory evaluation was performed at week 48. Clinical efficacy and safety endpoints were relevant. Patients with intraabdominal infections/abscesses were not examined. No residual benefits, *e.g.* on the need for corticosteroids or other immunosuppressants were studied.

Overall, 54 of 83 infliximab-treated patients (65%) achieved a clinical response at the week four compared to four of the 24 placebo patients (17%). The proportion of patients who responded was significantly higher in each infliximab treatment group compared with the placebo group. There was no apparent relationship between infliximab dose and the proportion of patients who responded; in fact, the 5 mg/kg dose group (27 patients) showed the highest response rate (82%, $p<0.001$ vs. placebo).

Fig 1. Kaplan-Meier curve for median time to loss of response in days – Initial treatment phase.



In the re-treatment phase, a gradual loss of efficacy was seen after each infusion. Due to the study design which allowed non-responding patients at week four to receive 10 mg of infliximab, and thus all patients had received infliximab at re-randomisation at 12 weeks, it was concluded that efficacy could only be assessed up to 12 weeks. At this time point, 13/27 (48%) of infliximab treated patients were still responding.
Subgroup analyses could not identify patient characteristics predictive of response/non-response.

In patients initially responding, results for the CDAI, quality-of-life measurement (IBDQ) and the serum marker of inflammation (CRP) showed a continued suppression of disease activity after each infliximab re-treatment and gradual return of disease activity with placebo re-treatment. Half of the infliximab-treated patients had withdrawn from the study at week 48, mostly because of side effects or lack of efficacy.

Concerns were raised during the procedure about the limited efficacy data in refractory Crohn's disease. However, due to the clear-cut response in the 5 mg dose group and the support of similar responses in the 10 and 20 mg dose groups, the data from this phase II trial was considered sufficient to give a positive view of short-term efficacy in this selected patient group.

Additional data on long-term efficacy of re-treatment of active CD were obtained from ACCENT I (C0168T21), a multicentre, randomised, double-blind, clinical trial of maintenance infliximab treatment compared with a single dose of infliximab in 580 patients with moderately to severely active Crohn´s disease (CD). The primary objective of this study was to examine whether patients responding 2 weeks after a single 5 mg/kg infusion of infliximab benefited from further treatments 2 and 6 weeks later followed by treatments every 8 weeks, compared with placebo treatment following the initial infusion. The design of the ACCENT I study was complicated and only patients with moderate disease were included. The data from single infliximab treatment can therefore only be compared to maintenance infliximab treatment within the first 10-12 weeks.

As in previous studies the rate of response to the initial infusion of infliximab was about 60%. In the responders, after the initial infusion of infliximab the remission rates at week 30 and 54 as well as time to loss of response were significantly higher in patients receiving maintenance treatment with infliximab compared with placebo infusions. However, the efficacy results mainly reflected differences in clinician interventions (change in medication, mostly corticosteroids) between the

groups and not decrease in CDAI score. Infliximab improved the quality of life (evaluated with the IBDQ SF-36).

At week 10, the proportion of patients in clinical remission/clinical response was greater in the infliximab groups compared with placebo indicating that in patients responding to an initial 5 mg/kg infusion of infliximab, induction therapy with 2 additional infusions after 2 and 6 weeks may be more efficient than a single dose. However, due to the design of the study, no conclusion could be drawn regarding the 3 dose regimen compared to a single infusion followed by treatment every 8 weeks since this comparison was not made.

For most endpoints, the infliximab 10 mg/kg group seemed to be superior to the 5 mg/kg dose. However, concerns regarding the safety of the 10 mg/kg dose outweigh its possible benefits in CD and this dose cannot be recommended for use.

As the population in the trial (moderately active disease, and few patients with documented inadequate response to standard therapy with both corticosteroids and immunomodulators) differed from the population defined in the current SPC, the CHMP did not accept a full extension of the existing indication with maintenance therapy. However, based on additional sub-group analyses showing efficacy in the restricted population defined in the SPC, and as early response status was found to be a reliable predictor of a later response, the posology section was amended in such a way to reassure that only patients who benefit from treatment will receive long-term therapy with Remicade either as maintenance or as episodic readministration after flare-up. Please refer to EPAR module 3 for the detailed wording.

Fistulising Crohn's disease was addressed in a multicentre, placebo-controlled, double-blind, 3-arm, parallel group study (C0168T20). Patients with draining enterocutaneous fistulae (approximately 50 % had one fistula) as a complication of Crohn's disease were included, of whom 93 % previously had been treated aggressively with either antibiotics or immunosuppressive drugs. A total of 96 patients were given single infusions of 5, 10 mg/kg infliximab or placebo at weeks 0, 2 and 6.

The primary efficacy response ($\geq$ 50% reduction from baseline in the number of draining fistulae for at least 2 consecutive evaluation visits , at least 1 month apart) is shown in Table 3. Also CDAI scores were reduced in the infliximab treated patients in comparison with the placebo group.

Table 3 shows the primary efficacy response in patients with Fistulising Crohn's disease

	Placebo (n= 31)	5 mg/kg (n= 31)	10 mg/kg (n= 32)	All infliximab-treated patients (n= 63)	Dose Response p-value
Pts with primary endpoint	8 (26%)	21 (68%)	18 (56%)	39 (62%)	0.017
p-value vs. placebo		0.002	0.021	0.002	

The median onset of response was 14 days. The duration of closure of the fistulae varied. In patients who met the response criteria, 7 out of 39 responded over the whole study period of 26 weeks, 7 responded over 6 visits and 5 over 5 visits. The median duration of response was 12 weeks. The number of patients with a complete response in the 5 mg/kg group at two consecutive visits was 55 %.
The long-term treatment of Crohn's disease patients with draining enterocutaneous and/or rectovaginal fistulas was studied in the ACCENT II (C0168T26) study. This was a multicentre, randomised, double-blind, clinical trial of maintenance infliximab treatment compared with a 3-dose induction regimen of infliximab only in 306 patients. Results from the ACCENT II trial did not show superiority of infliximab over placebo with regard to sustained healing of all fistulas (24% versus 16%). Infliximab did not reduce the number of new fistulas compared with placebo. Sub-group analysis further indicated that long-term treatment with infliximab was only better than placebo in patients with active fistulising CD. Symptomatic benefit for the patient has not been shown. Whether infliximab

maintenance treatment should be given on-demand or as regular treatment with 8 weeks interval remained unanswered.

In severe active Crohn's disease, available data do not support further infliximab treatment, in patients not responding within 2 weeks to the initial infusion. In fistulising Crohn's disease, data do not support further infliximab treatment, if the patient does not respond to the 3 initial infusions.

Rheumatoid arthritis
Efficacy and safety of infliximab were studied in six clinical studies in 660 patients with active RA (C0168T07, C0168T09, C0168T14, C0168T15/17, C0168T18 and C0168T22 - ATTRACT). In general, the studies were well designed. The inclusion criteria as well as the endpoints were in agreement with EULAR 28, ACR 20 and the CHMP Points to consider document on RA (CPMP/EWP/556/95). All patients included were RA patients with active erosive disease, who had failed to adequately respond to disease-modifying antirheumatic drug (DMARD) treatment. In three of the studies, infliximab was administered in conjunction with methotrexate (MTX) either at doses of 7.5 mg or ≥12.5 mg. Concurrent treatment with corticosteroids (< 10 mg/day) and nonsteroidal anti-inflammatory drugs (NSAIDs) was permitted, but these treatments were required to be stable therapeutic regimens. Concurrent treatment with a DMARD other than MTX was not permitted.

In study T09, 73 patients received either a single dose of 1 mg/kg, 10 mg/kg or placebo. Patients who initially responded but relapsed after week four and prior to the six-month evaluation, or who had not shown a response at week four, were offered a single, open-label infliximab infusion of 3, 10 or 20 mg/kg. This study indicated a dose-dependent effect with 55 % and 77 % response in the 1 mg/kg and 10 mg/kg groups, respectively compared with 12 % in the placebo group. In the open-label phase, no difference in response rates was observed between 3, 10 and 20 mg/kg. Studies T07, T15/17 and T18 provided additional support for the effect of infliximab in this population.

In study T14, a total of 101 patients were given 1, 3, 10 mg/kg or placebo either alone (MTX-) or in combination with 7.5 mg methotrexate (MTX+) at day 0 and weeks two, six, 10, and 14 and were followed for 26 weeks. Irrespective of co-administration of MTX or not, the 3 mg/kg and 10 mg/kg infliximab groups showed similar efficacy, both in terms of duration and magnitude of the response. Furthermore, the magnitude and duration of efficacy were similar for the 1 mg/kg MTX+ and the 3 mg/kg and 10 mg/kg groups. However, the duration of the clinical response was markedly shorter in the 1mg/kg MTX- group, which correlated with a decrease in detectable infliximab concentrations. Additionally, the detection of infliximab in serum following the final 14-week treatment was longer in all infliximab MTX+ groups than in groups without MTX. Data from patients who could be evaluated for antibodies to infliximab, may suggest an inverted dose-dependency of development of antibodies to infliximab. Additionally, MTX may have suppressed the development of antibodies to infliximab, at least in the 1 mg/kg group. However, the findings may also be related to the methodological limitations of the detection of antibodies to infliximab. In conclusion, MTX seemed to have little impact on the efficacy of the 3 mg/kg and 10 mg/kg doses. Additionally, there was no dose-response relationship between the 3 mg/kg and 10 mg/kg doses irrespective of MTX or not, while the 1 mg/kg MTX- regimen resulted in less efficacy than the other regimens. However, the limited number of patients in each group has hampered the interpretation of the study results.

The pivotal phase III study C0168T22 (ATTRACT), including 428 patients, is a double-blind, multi-centre, randomised clinical trial of infliximab in patients with active RA despite MTX treatment during 30-weeks with extensions to 54 and 102 weeks. Approximately 50% of patients were in functional Class III, and the median disease duration was 8.4 years. All patients were on stable MTX doses (median 15 mg/wk) for 6 months prior to enrolment and were to remain on stable doses throughout the study. Concurrent use of stable doses of oral corticosteroids (≤ 10 mg/day) and/or NSAIDs was permitted, and folate supplementation was given. All patients continued on MTX, with placebo or different dosage regimens of infliximab as add on treatment (Table 4).

Table 4 shows the treatment regimens in ATTRACT

Group	Treatment	N
1	Placebo infusions weeks 0, 2, and 6 and every 4 weeks thereafter	88
2	3 mg/kg infliximab infusions at weeks 0, 2, 6 and every 8 weeks	86
3	3mg/kg infliximab infusions at weeks 0, 2, 6 and every 4 weeks	86
4	10 mg/kg infliximab infusions at weeks 0, 2, 6 and every 8 weeks	87
5	10 mg/kg infliximab infusions at weeks 0, 2, 6 and every 4 weeks	81

After 54 weeks, while still blinded, the patients were given the opportunity to continue on randomised treatment through 102 weeks. In total 53 patients (16 on MTX alone, 8 on 3mg/kg q 8 wks, 9 on 3mg/kg q 4wks, 10 on 10 mg/kg q 4 wks and 10 on 10mg/kg q 8wks) chose not to enter the 2nd year. Patients were subsequently unblinded to whether they were receiving placebo or infliximab infusions (but not to infliximab dose regimens). Patients in the MTX alone group were given the opportunity to end their participation in the study and receive infliximab. In total 7 patients chose to receive infliximab.

The primary endpoints were the reduction of signs and symptoms as assessed by the American College of Rheumatology criteria, the prevention of structural joint damage, and the improvement in physical function. A reduction in signs and symptoms was defined to be at least a 20% improvement (ACR20) in both tender and swollen joint counts, and in 3 of the following 5 criteria: evaluator's global assessment, patient's global assessment, functional/disability measure, visual analogue pain scale and erythrocyte sedimentation rate or C-reactive protein. The Health Assessment Questionnaire (HAQ; scale 0-3) was used to measure patients' average change from baseline scores over time, in physical function. Structural joint damage (erosions and joint space narrowing) in both hands and feet was measured by the change from baseline in the total van der Heijde-modified Sharp score (0-440). X-ray data were obtained at baseline, weeks 30, 54 and 102.

Overall, the scoring systems used in the ATTRACT trial, and the evaluation procedure are considered acceptable. All four dose regimens were effective and had a greater response (ACR≥20 %) than placebo (Table 5). Some of the secondary endpoints, such as morning stiffness, fatigue, number of swollen and tender joints and patients global pain assessment indicated a somewhat better effect with 10 mg/kg compared with 3 mg/kg. This was, however, not statistically significant. This study (or any other study) has not investigated whether patients not responding on 3 mg/kg will respond on 10 mg/kg, thus this remains to be investigated. Taking the efficacy as well as the adverse event profiles into account, the 3 mg/kg q.8 week is considered the most appropriate dose recommendation.

The efficacy was sustained throughout the 30-week period and there was no difference whether Remicade was given every fourth or eighth week. Inflammatory parameters such as CRP and ESR decreased (CRP by 68 % versus 9 % with placebo at 30 weeks) during treatment, which indicated a reduced inflammatory activity. Furthermore, efficacy results for ACR and HAQ were similar at the 54 weeks evaluation and results also seemed to persist over the studied period of 102 weeks.

X-ray analyses at week 54 showed a statistically significant effect ($p<0.001$, Table 5) on van der Heijde-modified Sharp score for all Remicade dosage regimens compared to the MTX-only group ($p<0.001$, Table 5). In the combined Remicade group, 52% compared with 20% in the MTX-only group, had no deterioration in van der Heijde-modified Sharp score. There was a tendency of a better effect for the higher dosage groups. Effects were demonstrated for both components of the total score (erosions and space narrowing) and in a variety of relevant subgroups demonstrating internal consistency. However, there were a considerable number of treatment withdrawals in the trial. Therefore, a careful examination of the withdrawal pattern and the policy for handling missing data was performed. It was concluded that the number of withdrawals due to adverse events was similar in all study groups and was not expected to cause any bias. Furthermore, there was no reason to expect that the differential withdrawal due to lack of efficacy had caused any serious bias.

Table 5
Effects on ACR20, Structural Joint Damage and Physical Function at week 54

		infliximab[b]				
	Control[a]	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks	All infliximab[b]
Patients with ACR20 response/ patients evaluated (%)[c]	15/88 (17%)	36/86 (42%)	41/86 (48%)	51/87 (59%)	48/81 (59%)	176/340 (52%)
Total score[d] (van der Heijde-modified Sharp score)						
Change from baseline (Mean ± SD[c])	7.0 ± 10.3	1.3 ± 6.0	1.6 ± 8.5	0.2 ± 3.6	-0.7 ± 3.8	0.6 ± 5.9
Median[c] (Interquartile range)	4.0 (0.5,9.7)	0.5 (-1.5,3.0)	0.1 (-2.5,3.0)	0.5 (-1.5,2.0)	-0.5 (-3.0,1.5)	0.0 (-1.8,2.0)
Patients with no deterioration/patients evaluated (%)[c]	13/64 (20%)	34/71 (48%)	35/71 (49%)	37/77 (48%)	44/66 (67%)	150/285 (53%)
HAQ change from baseline over time[e] (patients evaluated)	87	86	85	87	81	339
Mean ± SD[c]	0.2 ± 0.3	0.4 ± 0.3	0.5 ± 0.4	0.5 ± 0.5	0.4 ± 0.4	0.4 ± 0.4

a: control = All patients had active RA despite treatment with stable methotrexate doses for 6 months prior to enrolment and were to remain on stable doses throughout the study. Concurrent use of stable doses of oral corticosteroids (≤ 10 mg/day) and/or non-steroidal anti-inflammatory drugs was permitted, and folate supplementation was given.
b: all infliximab doses given in combination with methotrexate and folate with some on corticosteroids and/or non-steroidal anti-inflammatory drugs
c: $p < 0.001$, for each infliximab treatment group vs. control
d: greater values indicate more joint damage.
e: HAQ = Health Assessment Questionnaire; greater values indicate less disability.

Based on additional data from ATTRACT (provided as part of a follow-up measure for evaluation of possible benefit of further treatment in initial non-responders) the CHMP concluded within the fourth annual reassessment, that available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period. This information was added to the posology section of the SPC.

The indication in RA was extended to add treatment of methotrexate-naïve subjects with early rheumatoid arthritis based on one clinical study, ASPIRE. The results of this study (see Table 6) have shown that infliximab administered as low as 3 mg/kg at week 0, 2, 6, and then every 8 weeks in combination with MTX is an efficacious treatment for patients with early RA and is better than MTX alone.

Summary of primary efficacy endpoints; randomised subjects

Table 6 Results of the ASPIRE study

		Infliximab + MTX		
	Placebo + MTX	**3 mg/kg**	**6 mg/kg**	**Combined**
Subjects randomised	282	359	363	722
Signs and Symptoms:				
Percentage ACR improvement at week 54				
Median	26.4	38.9	46.7	44.3
p-value		< 0.001	< 0.001	< 0.001
Structural Damage:				
Change from baseline in total vdH-S score at week 54				
Median	0.43	0.00	0.00	0.00
p-value		< 0.001	< 0.001	< 0.001
Physical Function:				
Improvement from baseline in HAQ averaged over time from week 30 to week 54				
Median	0.750	0.784	0.792	0.784
p-value		0.030	< 0.001	0.001

a Excludes subjects with missing week-54 erosion score.

Table 7
Secondary endpoints related to signs and symptoms

		Infliximab + MTX		
	Placebo + MTX	**3 mg/kg**	**6 mg/kg**	**Combined**
Subjects randomised	282	359	363	722
n	274	351	355	706
ACR 20 at week 54				
Subjects in response	147 (53.6%)	219 (62.4%)	235 (66.2%)	454 (64.3%)
p-value		0.028	0.001	0.002
ACR 50 at week 54				
Subjects in response	88 (32.1%)	160 (45.6%)	179 (50.4%)	339 (48%)
p-value		<0.001	<0.001	<0.001
ACR 70 at week 54				
Subjects in response	58 (21.2%)	114 (32.5%)	132 (37.2%)	246 (34.8%)
p-value		0.002	<0.001	<0.001
ACR 90 at week 54				
Subjects in response	18 (6.6%)	35 (10.0%)	60 (16.9%)	95 (13.5%)
p-value		0.130	<0.001	0.002
Percentage ACR improvement averaged over time				
n	272	348	352	700
Median	21.4	36.4	42.7	40.9
p-value		<0.001	<0.001	<0.001
at least 1 follow-up visit (n)	276	354	358	712
ACR20 response at a majority of visits (≥5) (n)	122 (44.2%)	205 (57.9%)	234 (65.4%)	439 (61.7%)
p-value		<0.001	<0.001	<0.001
Major clinical response (n)	273	348	352	700
Subjects in response	21 (7.7%)	43 (12.4%)	61 (17.3%)	104 (14.9%)
p-value		0.058	<0.001	0.003

The benefit of this combination was rapid and mostly clinically significant. The superiority over MTX alone was robust and consistent across subgroups. Signs and symptoms of the active disease could be reduced and maintained through week 54; the therapy prevented new erosions, and stopped the progression of structural damage; improvement in physical function was clinically significant.

As a result of the assessment, the CHMP requested further clarifications on the conduct of the trial and on elements of the trial analysis (such as MTX use and folic acid use in the 3 groups, baseline covariate analysis). Based on the additional data the robustness of the obtained results was confirmed. The CHMP also noted that there was a general tendency towards better efficacy with the higher 6mg/kg dose of infliximab and requested explanation on the rationale for the recommended dose of 3mg/kg. In this response the MAH referred to the ATTRACT study. Indeed, data from all dose groups in ATTRACT, which reflect this tendency, are already present in the SPC, section 5.1 Pharmacodynamics. The CHMP observed that data from an ongoing randomised, double-blind trial of the safety of infliximab in combination with MTX compared to MTX alone in patients with RA on standard DMARD background therapy are expected. One secondary objective of this trial is to assess the safety and efficacy of dose-escalation regimens above 3 mg/kg of infliximab given every 8 weeks in patients with an incomplete response to 3 mg/kg. Therefore, the submission of these data is awaited to allow a better assessment of the benefit /risk of dose escalation in RA patients. Thus, no change in the posology is proposed at the present stage.

Ankylosing spondylitis
The extension of the therapeutic indication is mainly based on one investigator-driven study including 70 subjects (protocol P01522). Efficacy for up to one year has been demonstrated in the pivotal trial, and these effects are supported by small additional studies. The pivotal study was designed as follows:

Phase A (Weeks 0–12) was a double-blind, placebo-controlled phase to assess short-term efficacy of infliximab. Subjects were to receive either 5 mg/kg infliximab i.v. (n=30) or placebo (n=30) at Weeks 0, 2 and 6.

Phase B (Week 12 to Week 54) was an open-label, non-comparative phase to assess long-term efficacy and safety of infliximab. Phase B started at Week 12, after completion of questionnaires by the subject and physician. At Week 14, an additional infusion was administered such that subjects who had received placebo in Phase A received 5 mg/kg infliximab i.v. In order to maintain the blind, subjects who had received 5 mg/kg infliximab i.v. during Phase A received a placebo infusion at Week 14. All further infusions were administered every 6 weeks (i.e., at Weeks 18, 24, 30, 36, 42 and 48). One-year efficacy was assessed at Week 54.

Long-term extension: the open-label treatment could be extended to 102 weeks with follow-up visits at 108 and 114 weeks

A per protocol population was defined; by this definition 60 patients with ankylosing spondylitis (AS) were enrolled; 27 in the infliximab arm and 33 in the placebo arm. The studied patient group was heterogeneous e.g. with respect to degree of inflammatory activity. In phase A, the primary endpoint (50% improvement in BASDAI) was reached in 22/27 infliximab patients. The open follow-up (phase B) showed similar improvement in patients who switched from placebo to infliximab.

The CHMP requested supplementary information with regard to the following issues.
Definition of a population where the benefit / risk may be positive.
Additional statistical analyses of trial P01522 indicated that patients who are HLA-B27 positive with laboratory markers of immune activation (CRP, ANA, ESR) are the subset of AS patients most likely to maximally benefit from infliximab treatment.
As patients with severe axial symptoms lack treatment options and as the additional analyses submitted support patients with increased inflammatory activity are most likely to gain benefit, the CHMP considered that a restricted AS population is relevant.

The selected dose regimen (6 weekly maintenance dosing, as monotherapy).
In the pivotal AS trial (P01522), the dose regimen of 5 mg/kg weeks 0, 2, 6 and thereafter every 6 weeks without second line therapy, was selected because a pilot trial identified a median time to relapse of about 6 weeks. The MAH concluded from available experience that a 3 mg/kg dose regimen given with or without second line therapy (generally MTX), may not be sufficiently effective. Based on data from an ongoing open study (P01227), showing that a dosing interval of 8 weeks may be sufficient in certain patients, the MAH proposed a flexible 6-8 weeks dose interval of 5 mg/kg. Thus, the CHMP accepted the following dose regimen: 5 mg/kg weeks 0, 2 and 6, and thereafter maintenance dosing every 6-8 week.

Moreover, based on data showing that patients who do not improve by 6 weeks after initiation of dosing (thus given 2 doses) are unlikely to improve later, and therefore do not warrant further exposure to infliximab, this information was also included in the SPC.

Regarding monotherapy, according to the MAH there may be some benefit of using immunosuppressive agents to delay the formation of antibodies against infliximab. But as these medicinal products have no established role in the management of AS, the CHMP decided it cannot be justified to require them for combination with infliximab therapy only for this reason.

Bridging to experience in RA and CD
Based on published experience in AS, there are few controlled trials in AS. Available data for agents with established benefit in RA such as methotrexate and sulfasalazine, indicate that they do not result in convincing benefit in AS, and lack effects on severe axial symptoms. Also oral corticosteroids are of little benefit in AS. Thus, these data show that effects of medicinal products demonstrated in RA and CD, cannot be extrapolated to AS.

Further analyses by the MAH have also indicated certain differences in the response to different dose regime of infliximab in the RA, CD and AS populations. For instance a 3 mg/kg dose regimen given with or without second line therapy (generally MTX), may not be sufficiently effective in AS. This is in contrast to RA, where the approved dose regimen of 3 mg/kg weeks 0, 2, 6 and thereafter every 8 weeks together with MTX, has shown long-term efficacy including benefit on joint damage for up to 2 years.

The discussion of the presented data resulted in a well-defined indication where the most severely ill patients, with few available treatment options, will be considered for treatment with infliximab. The CHMP accepted the 6-8 weeks dose interval. In addition, the proposed recommendation not to further administer Remicade in a patient who does not respond after 2 doses, will reassure that only patients who benefit from treatment will receive long-term therapy with Remicade. As the application was based on limited data, the MAH committed to provide further data on long-term safety and efficacy upon completion of the trials at the request from CHMP.

Psoriatic arthritis
The pivotal trial, study P02114 (IMPACT) in support of this application is a clinical study in patients with active PsA and peripheral polyarticular arthritis who had failed at least 1 DMARD. The study consisted of two stages. In stage I, subjects were randomly assigned to receive either 5 mg/kg infliximab (n=52) or placebo (n=52) infusions at weeks 0, 2, 6, and 14. In stage II, all subjects received 5 mg/kg infliximab at weeks, 22, 30, 38, and 46. Data covering 50 weeks of treatment were presented.

The dose 5mg/kg was chosen because this is the lowest dose studied in monotherapy, without concomitant MTX. The primary objective was to study efficacy (ACR20) of infliximab compared with placebo at week 16 and to determine safety of infliximab in active PsA patients who failed at least one DMARD. Secondary objective was to follow response of skin involvement, percentage ACR20 over time, and ACR50 and 70, Disease activity score (DAS), Psoriatic response criteria (PsARC). AUC percentage ACR improvement (ACRn), and change in joint scores at week 16 and week 50.

The pivotal study in PsA (IMPACT) was small and of short duration (16 weeks). Other submitted studies were open and small and can only add some support to efficacy. In the studied patient population, with moderate to severe PsA, infliximab treatment was superior in terms of clinical meaningful benefit to placebo in the double-blind placebo-controlled first stage of the pivotal trial. This benefit was maintained throughout the study period, and also achieved in the former placebo group after switching to infliximab. In addition, the benefit was confirmed by a number of secondary endpoints that add relevant efficacy data in terms of more PsA-specific clinical manifestations like enthesiopathies or dactylitis. The magnitude of efficacy of infliximab in relation to placebo was similar to data submitted in other indications and there were no signs of any different safety profile compared with the previously identified risks in other populations. Therefore, one pivotal study in PsA including a limited number of patients was considered sufficient to support efficacy. At the request from the CHMP the MAH committed to submit long-term (> 1 year) efficacy and safety data.

The definition of the patient population as initially proposed by the MAH was not fully endorsed by the CHMP, who recommended that infliximab should be primarily an option for patients with more severe disease. The claim for monotherapy was not supported sufficiently with the submitted data.
In IMPACT, the majority of patients (71%) were treated concomitantly with other DMARDs; mainly MTX. The MAH provided subgroup analyses on efficacy and safety for patients given monotherapy or

DMARD treatment, but since the monotherapy subgroup was very small (n=19 in the infliximab group), these analyses were of limited value. The CHMP agreed the following indication "*Remicade, in combination with methotrexate, for treatment of active and progressive psoriatic arthritis in patients who have responded inadequately to disease-modifying anti-rheumatic drugs"*.

Clinical Safety

In this section, a global overview of clinical safety data is presented. Based on clinical trials and current post marketing experience, the following areas have gained particular attention: fatalities, serious infections including tuberculosis (TB), worsening of heart failure and immunologically mediated phenomena such as infusion-related reactions, delayed hypersensitivity reactions, lupus-like syndromes, development of anti-nuclear antibodies (ANA), and antibodies to infliximab. Other important safety aspects concern the lack of knowledge about long-term consequences of Remicade treatment as well as whether there is an increased risk of malignancies associated with Remicade use.

Below, the data that supported the initial approvals (predominantly from clinical trials), as well as data from more recent clinical trials and current post marketing safety experience (from procedures which have been finalised before 1 October 2004) are presented.

Patient exposure
For the initial approval for Crohn's disease, data from 771 patients treated with infliximab in clinical studies were submitted. Of these, 199 were patients with Crohn's disease, of whom 40 patients were re-administered infliximab in study T24; 555 were patients with RA. Additionally, 42 patients (healthy volunteers and ulcerative colitis) had been exposed to infliximab. Four hundred sixteen of all patients received at least five infusions of infliximab. In Crohn's disease protocols, 50 % of the infliximab-treated patients had a calculated drug exposure duration of at least 14 weeks, 84% received at least 10 mg/kg infliximab and 51% received at least 20 mg/kg infliximab. In total 103 patients with Crohn's disease had received three or more infusions.

In support of safety for the first RA indication, data were presented from 913 patients including 660 patients treated for RA. In three of the six RA studies, 418 patients received concomitant MTX treatment. The largest set of safety data in RA, came from study C0168T22 (ATTRACT).

During the initial assessment for Marketing Authorisation in the EU of the Crohn's disease and RA indications, available post marketing experience was also presented and discussed. This experience comprised approximately 11,000 patients from the US with Crohn's disease (based upon Centocor licensed sales) who had received at least one dose of infliximab. Of these, approximately 2,500 patients received re-infusions at intervals of up to 12 weeks.

Since Remicade was first licensed in 1998 to the end of February 2004, approximately 509,193 patients have received it worldwide. The assessment of these post-marketing data could not be broken down by indication, as the reports cannot be separated by diagnosis. With respect to clinical trials, the main safety experience comes from RA trials, while data in Crohn's disease, ankylosing spondylitis and psoriatic arthritis trials are more limited.

Overall adverse events in clinical trials
In clinical trials, adverse reactions were reported in 57 % of infliximab treated patients compared with 36 % of placebo treated patients. There was no apparent dose-response relationship for the overall incidence of adverse reactions. The most common adverse reactions in all studies were upper respiratory infections (18.5% vs. 11.5 % in placebo treated patients), headache (20.6 vs.13 %), nausea (14.8 vs. 12.5 %), sinusitis (7.9 % vs. 2.6%), rash (8.4% vs 4.7%) and cough (8.8 % vs. 2.6%). Serious adverse reactions were observed in 3.6% of infliximab-treated patients and 2.6% of placebo-treated patients.

Fatalities
Up to 23 February 2004, in total 1285 deaths have been reported, of which 771 came from

spontaneous reporting, 514 came from studies or registries. The number of deaths relative to exposure reported during subsequent periods is stable. Patients with RA are the most commonly reported deaths. Several deaths have occurred when infliximab has been given in non-approved indications, in particular, graft-versus-host-disease, congestive heart failure (see below), and alcoholic hepatitis. Infections are by far the most common cause of death (nearly 50% of the deaths were associated with infection), where sepsis and localised infections, in particular, pneumonia accounted for about 40% of all reported deaths.

Infections
In the clinical trials, infections were reported almost twice as often in infliximab-treated patients as in placebo-treated patients (32% compared with 22%) in both Crohn's and RA patients. Non-serious infections, predominantly upper respiratory tract infections, were most common. Serious infections were observed in 5 % of both infliximab-, and placebo treated patients and the most common serious infections were pneumonia, cellulitis, and pyelonephritis. In the ATTRACT study, patients given 10 mg/kg repeatedly had a tendency of more infections than those given 3 mg/kg. One RA patient developed disseminated tuberculosis and another coccidioidomycosis beyond the 30 week study period. More patients treated with both steroids and other immunosuppressants together with infliximab experienced serious infections compared with patients treated with infliximab only (7.7 % vs 0.7 %).

In post-marketing spontaneous reporting, infections are the most common serious adverse event. These include sepsis, pneumonia, tuberculosis, and opportunistic infections such as pneumocystis carinii pneumonia, histoplasmosis, systemic candidiasis, aspergillosis, listeriosis, CMV, coccidioides, cryptococcus. Some of the cases had a fatal outcome (see fatalities above).

Given the above, Remicade is contraindicated in patients with tuberculosis or other severe infections such as sepsis, abscesses, and opportunistic infections. Patients must be monitored closely for infections including tuberculosis before, during and after treatment with Remicade. Because the elimination of infliximab may take up to six months, monitoring should be continued throughout this period. Further treatment with Remicade must not be given if a patient develops a serious infection or sepsis.

Tuberculosis (TB)
Treatment with infliximab increases the risk of activation of tuberculosis. Up to December 2000, 28 cases of active TB including miliary tuberculosis and tuberculosis with extrapulmonary location, had been reported in patients treated with Remicade One had a fatal outcome. In view of the seriousness of the TB reports available in December 2000, it was decided to revise the SPC (sections 4.3; 4.4 and 4.8) and PL for Remicade, through Urgent Safety Restricion on 14 December 2000.
This issue was closely monitored; and up to 31st October 2001, in total 129 cases of active TB had been reported in patients treated with Remicade. Of these, 19 had a fatal outcome. The majority of patients had a prior history of treatment with immunosuppressants and corticosteroids. In the majority of patients, the onset of active TB occurred within 6 months after the first infusion of Remicade, thus supporting a possible relationship with initiation of Remicade therapy. As long-term clinical experience with Remicade is still limited, the onset (or re-activation) of TB or other opportunistic infections also after a longer period of treatment cannot be ruled out. The following revised guidance was introduced into the SPC via an Urgent Safety Restriction procedure in January 2002.

"Before starting treatment with Remicade, 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 is recorded on the patient's alert card that will be provided by the local representative of the MAH. 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, Remicade treatment must not be initiated.

If inactive ('latent') tuberculosis is diagnosed, prophylactic anti-tuberculosis therapy must be started before the initiation of Remicade, and in accordance with local recommendations. In this situation, the benefit/ risk balance of Remicade therapy should be very carefully considered.

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

By February 2004 a cumulative total of 532 cases of tuberculosis were received, 445 were spontaneous and 87 trial/registry reports. Cumulatively, there were a total of 54 reports with tuberculosis as the underlying cause of death. Preventive educational programs have been initiated in the EU and in the USA. The reporting rate is stable in most countries. Tuberculosis will continue to be closely monitored. National/local recommendations should be followed to optimise diagnostic efforts and treatment/ prophylaxis.

Heart failure
During the autumn of 2001, data from a placebo-controlled clinical study aimed at evaluating the efficacy and safety of Remicade in congestive heart failure (CHF) became available. These data showed a higher incidence of mortality due to worsening of heart failure in patients treated with Remicade, especially those treated with the higher dose of 10 mg/kg (i.e. twice the maximum approved dose). In this trial, 150 patients with NYHA Class III-IV CHF (left ventricular ejection fraction </=35%) were treated with 3 infusions of Remicade 5 mg/kg, 10 mg/kg, or placebo over 6 weeks. At 38 weeks, 9 of 101 patients treated with Remicade (2 at 5 mg/kg and 7 at 10 mg/kg) died compared to one death among the 49 patients on placebo.

In October 2001, based on the initial data from the study, the EMEA issued a public statement to draw the attention of Health Care Professionals and patients to these findings. When additional data had become available from this trial, the SPC and Package Leaflet were updated, and a Patient Alert Card was added to the Product Information via an Urgent Safety Restriction procedure in January 2002.

The following recommendations have been introduced in the SPC :
"Remicade is contraindicated in patients with moderate or severe heart failure (NYHA class III/IV). Remicade should be used with caution in patients with mild heart failure (NYHA class I/II). Patients should be closely monitored and Remicade must not be continued in patients who develop new or worsening symptoms of heart failure."

Malignancies and lymphoproliferative disorders:
In clinical studies with infliximab and during long-term follow-up of three years, representing 1385 patient years, four cases of lymphoma and 10 other malignancies were detected as compared to one malignancy in placebo-treated patients followed up during 189 patient years. These observed rates and incidences were similar to those expected for the populations studied. From August 1998 to February 2004, in total 1099 cases of suspected malignancies have been reported, 185 in Crohn's disease patients, 759 in RA patients and 155 in patients with other diseases/ unknown indication.

The association between lymphoma and RA has been acknowledged and there is consensus that these patients have a two to three-fold increased risk in developing a non-Hodgkin lymphomas. Both inflammatory activity and immunosuppressive treatment have been associated with the development of this disease. However, lymphoma in Crohn's disease is rare and there is no consensus that it appears more often than in the general population. Although the number of malignancies with Remicade in general does not seem to be higher than published incidence data for this population, the findings of lymphomas in CD patients raise some concern. Considering the limited follow-up time, it is unknown if exposure to infliximab can increase the incidence of these disorders. Moreover, the long-term immunosuppressive effects of concomitant use of methotrexate and infliximab are unknown. This has been reflected in the SPC section 4.8 and is under continued monitoring.

Immunologically mediated phenomena
Remicade has been associated with immunologically mediated phenomena i.e. antibodies to infliximab, anaphylactic infusion reactions, delayed hypersensitivity (serum sickness-like) reactions, lupus-like syndromes and autoantibody formation. In addition, severe non-anaphylactic infusion reactions may occur.

Antibodies to infliximab
For the initial RA and CD protocols (excluding the ATTRACT), 289 patients were evaluable for measuring antibodies to infliximab. Of these, 80 patients (28%) were positive for antibodies to infliximab. In Crohn's disease protocols, 13% of evaluable patients were positive for antibodies to infliximab compared with 40% in the RA protocols (excluding ATTRACT). In addition, Crohn's disease patients who were positive for antibodies to infliximab tended to have lower titres than did RA patients.

A negative assay result for antibodies to infliximab does not exclude the presence of these antibodies. Thus, the impact of antibodies to infliximab on the treatment is not known, and this factor can at present not be used to predict efficacy and safety including the risk for infusion related reactions. Efforts are being made to develop a more specific assay for detection of antibodies to infliximab in the presence of infliximab.

Various data show an association between antibodies to infliximab and diminished degree of efficacy and increased incidence of infusion reactions. Results from ACCENT II also indicated that concomitant administration with immunomodulators was associated with lower titers of ATI.
The MAH has committed to monitor ATI induction during ongoing and planned studies, and will address in the analysis dose regimens to minimise antibody development and the relationship between antibody development, infusion reactions and loss of efficacy.

Acute infusion reactions including anaphylactic reactions:
In clinical trials, acute infusion reactions, which occurred during or within a few hours following the infusion, have been reported in 19 % of Crohn's disease patients and RA patients. These appeared already at the first or second infusion, but did not increase over time after the second infusion. There was no difference between doses and no relationship was observed between the initial dose of infliximab and the likelihood of any infusion-reaction. Approximately 1-4 % of the infusions were accompanied by non-specific symptoms such as fever or chills, pruritus, urticaria and cardiopulmonary reactions such as chest pain, hyper/hypotension, and dyspnoea.

Up to May 2001, 106 confirmed cases of anaphylactic infusion reactions have been included in the post-marketing database. These symptoms generally occurred 15 minutes after the start of infusion, and usually during the second or third infusion. Experience to date indicates that clinical preventive measures as outlined in the SPC, such as careful monitoring of the patient during and after infusion, pretreatment with e.g. an antihistamine, corticosteroid or paracetamol to reduce mild and transient effects) reduce the occurrence of these complications. To date, no deaths have been reported.

Suspected risk factors for anaphylactic infusion reactions include increased time intervals between infusions, a diagnosis of Crohn's disease, lack of concomitant therapy with immunosuppressive therapy, and the presence of antibodies against infliximab

In the clinical trials, patients with antibodies to infliximab at any time point were more likely to experience a reaction to an infliximab infusion than patients who were negative for antibodies to infliximab throughout the trial (36 % vs. 11 % respectively). Thus, the presence of antibodies to infliximab appears to increase the probability of an infusion reaction by a factor of 2 – 3. Furthermore, patients with antibodies to infliximab developed infusion reactions more often irrespective of concomitant MTX treatment. Most reactions were mild to moderate, but a trend towards more serious infusion reactions could be noted. In the ATTRACT study, no overall increase in infusion reactions was observed in infliximab-treated patients whose MTX doses were reduced, interrupted, or discontinued. In study T014, it was suggested that MTX may suppress the development of antibodies

to infliximab. Thus, a possible decrease of infusion reactions may justify the rational of concomitant MTX treatment.

Delayed Hypersensitivity (including Serum Sickness-Like) Reactions:
Delayed hypersensitivity reactions, possibly due to an immune response against infliximab, appeared in 10/41 (25 %) Crohn's disease patients who were re-administered infliximab after a long medicinal products holiday of two years or more. Nine of the ten patients who experienced these reactions had been treated with a liquid infliximab batch containing more protein microaggregates than the current lyophilised batches. It may be inferred that the liquid batches contributed to the occurrence of these reactions by inducing the delayed immunological response. Similar events have not been observed in RA patients, but the majority of the retreatments occurred at intervals of 14 weeks or less. Very high titres of antibodies to infliximab were detected in some of the patients with delayed hypersensitivity reactions and there was a tendency of lack of response due to the neutralising effects of antibodies to infliximab.

The appearance of delayed hypersensitivity reactions in patients readministered infliximab created problems in the assessment of the risk/benefit balance in this patient group with a life-long chronic disease. Since the delayed reactions were judged to be serious in some patients, re-treatment after a longer drug withdrawal period is of concern. It was concluded that there was enough experience to recommend re-administration of infliximab, if the treatment interval is less than 15 weeks.

Up to 30 June 2001, 58 serum sickness cases were reported during the post-marketing phase. Longer intervals between infusions with formation of antibodies to infliximab may possibly be a mechanism for this syndrome. These reports are consistent with the recommendations in the product information (SPC sections 4.2, 4.4 and 4.8) that Remicade should not be readministered to patients after a treatment interval of greater than 14 weeks.

Autoantibody Formation:
In the RA and Crohn's disease studies, the antinuclear antibody (ANA) status of infliximab-treated patients and placebo-treated patients was similar at baseline (24 % were positive for ANA). Approximately half of infliximab-treated patients in clinical studies who were ANA negative at baseline developed a positive ANA during the study compared with approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately 17% of infliximab-treated patients compared with 0% of placebo-treated patients. Risk factors for anti-dsDNA conversion include decreasing immunosuppressive therapy and baseline presence of autoantibody (such as positive ANA). However, it is not possible to predict if a patient will develop anti-dsDNA antibodies. Moreover, the consequences of development of ANA and dsDNA are unknown.

Lupus-Like Syndromes:
In the clinical trials, two of the 33 patients who became positive for anti-dsDNA at some point during follow-up, also developed clinical signs and symptoms of a lupus-like syndrome, one RA patient and one with Crohn's disease. No other autoantibodies commonly associated with SLE were detected. Up to 30 June 2001, 72 cases with lupus like syndromes were reported to the Remicade Post-marketing Database. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Remicade and is positive for antibodies against double-stranded DNA, treatment must be discontinued.

Severe Non-Anaphylactic Infusion Reactions:
Remicade is also associated with severe non-anaphylactic infusion reactions, i.e., clinically significant infusion reactions without indicators for allergic mediators. These include myocardial ischaemia, significant arrhythmia, hypotension, and dyspnoea not accompanied by urticaria and/or angioedema, and any other serious adverse reaction that occurs during or within 1 hour following Remicade infusion.

Neurological events
Concerns regarding neurological events have been raised because infliximab and other agents that inhibit TNF alpha have been associated with rare cases of exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease suggestive of multiple sclerosis or localised demyelination conditions such as optic neuritis. Based on post marketing experience, the SPC was updated regarding neurological events in 2001.

Haematological events
In clinical studies, anaemia, changes in white blood cells count and thrombocytopenia were reported as uncommon adverse reactions. In addition in the post-marketing phase pancytopenia was reported as a rare adverse reaction; this information has been added to the product information in January 2002.

Two subjects in ASPIRE and three additional subjects in previous clinical trials were reported to have pulmonary emboli. Four of the subjects had underlying cardiopulmonary disease, and the fifth subject was receiving an oral contraceptive. The conclusion of review of the postmarketing experience in PSURs (431 cases) was that thromboembolic events did not constitute a signal, but will be further monitored. The MAH has committed to study the rate of cardiolipin antibody positivity in 300 patients from ASPIRE and to explore differences amongst infliximab doses.

Gastro-intestinal events
Further to review of data from the TREAT registry, intestinal perforation and stenosis have been added to the Section on Undesirable effects in the SPC. Furthermore, based on the conclusions of PSUR 7, that treatment of patients with intestinal strictures due to Crohn`s disease is not recommended since the risk/benefit relationship in this patient population has not been established, this information has been included in the warnings section of the SPC.

Hepatobiliary disorders
Up to February 2004 in total 500 reports of hepatobiliary events were received. Abnormal hepatic function, cholecystitis, hepatitis and hepatocellular damage have been included in the SPC. Among cases of hepatic failure, the majority had an identified cause or non-sufficient information and therefore a conclusion on the cause is difficult to make.

Recent data from clinical studies suggested that subjects with AS and PsA may be more likely to develop aminotransferase elevations with infliximab treatment. After assessment of available data, the CHMP concluded that the risk/benefit for treatment of PsA and AS patients with infliximab remains positive for the following reasons. An elevated ALT has not been followed by changes in other parameters related to hepatic function and no increase in hepatic related adverse events was noted. The increase in ALT levels was mainly of low-grade (1-2 xULN). Patients with increased ALT levels >3 x ULN continued on treatment in most cases and values tended to return to normal. As expected, a tendency to a higher risk for ALT increases in those individuals, who had an increase in baseline ALT, was found.

The MAH has committed to further evaluate risks for elevated LT values and hepatobiliary events in AS, PsA and psoriasis studies. Hepatobiliary events will continue to be monitored.

Based on continued monitoring and data provided within Periodic Safety Update Reports, over time other undesirable effects such as interstitial pneumonitis/ fibrosis, vasculitis, pericardial effusion, pancreatitis have been added to the product information.

Laboratory parameters
During clinical studies, changes in creatinine and liver function parameters were observed in infliximab-treated patients. For all of these parameters, changes in individual patients were generally mild and transient; no general or dose-related trends were observed.

X-ray data
The X-ray examinations during the ATTRACT, indicated that treatment with infliximab during 54 or 102 weeks (irrespective of dose) had no deleterious effects on the cartilage.

Vaccination
The results submitted from a vaccine substudy in a subset of 100 patients from ASPIRE (patients with early RA receiving long-term infliximab therapy vaccinated with the 23-valent pneumococcal vaccine) did not allow the CHMP to draw clear conclusions or recommendations. The following information has thus been added to the SPC warnings and precautions section:
"No data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is recommended that live vaccines not be given concurrently."

Ongoing and planned studies and registries

As an outcome of the 2nd annual reassessment, which was finalised in January 2002, the MAH has regularly submitted data obtained from European patient registries in RA and Crohn's disease and from a registry in CD patients in US and Canada. Furthermore, during year 2002 educational programmes towards prescribers related to the monitoring of patients at risk for TB and treatment of patients with TB were initiated. These programs are ongoing.
There are several ongoing studies in different indications such as pediatrics (RA, Crohn), active ulcerative colitis, asthma, sarcoidosis, COPD, cancer related cachexia in pancreatic cancer and psoriasis, and follow-up studies in early RA, CD, ankylosing spondylitis and psoriatic arthritis.

5. Overall conclusions and benefit/risk assessment

The quality of the product has in all essential parts been acceptably documented. Adequate specifications have been included to control that undue aggregation of infliximab does not occur, which may impact the safety of the product. Remaining issues have been solved by commitments by the applicant to provide additional data on an ongoing basis or within defined time limits.

The preclinical safety documentation is limited. However, given the restricted availability of relevant animal models for this type of product, the information provided is considered sufficient.

With regard to the clinical documentation, it was concluded that in patients with severe, active Crohn's disease and with active fistulising disease, who have not responded to conventional treatments, short-term efficacy of Infliximab was sufficiently documented. Long-term efficacy of re-treatment has been shown in patients with severe, active Crohn`s disease who have responded within 2 weeks from the first dose. In fistulising CD, long-term maintenance treatment is only recommended in patients responding after 3 doses. Data from repeated administration suggest an acceptable safety profile when re-treatment is carried out within 16 weeks. Re-treatment after a longer interval cannot be recommended until further supporting data for safety have been provided and evaluated. When considering the clear-cut and significant efficacy response in patients who have depleted all medical treatment options and in whom surgical treatment is only palliative, the benefit/risk balance is regarded to be positive for the restricted use of Remicade as defined in the SPC.

The efficacy of infliximab in patients with active RA, despite treatment with MTX, has been demonstrated for up to 54 weeks and there are data showing maintained efficacy for up to 102 weeks. Reduction in the rate of the progression of joint damage, as measured by x-ray, has also been shown. Remicade must be given concomitantly with methotrexate since efficacy and safety have been demonstrated only in combination with MTX. Taken together, efficacy of infliximab for the treatment of signs and symptoms of RA in patients with insufficient response to MTX, has been adequately demonstrated, and the adverse reaction profile is acceptable, while respecting the revised product information. In light of this, and the severity of the disease, the risk/benefit is positive for the 3 mg/kg q. 8 week dosage in patients with concomitant MTX treatment.

The efficacy of infliximab + MTX compared to MTX alone has also been demonstrated in patients with early, moderate to severe active rheumatoid arthritis.There was a general tendency towards better efficacy with the higher 6 mg/kg dose of infliximab. However, no change in posology was recommended while awaiting further data regarding dose escalation. No new safety signals could be identified; however further monitoring (as in already ongoing studies and registries) is important when introducing infliximab to patients with RA of short duration. Therefore, although reduction of the rate of radiographic progression and convincing benefit with regard to the functional ability of the patient have been shown in patients with early moderate to severe, active RA, the CHMP decided that, due to the safety profile of infliximab, treatment with Remicade should not be given as first line treatment to patients with mild disease and with low risk for progressive disease. The CHMP considered the overall benefit / risk balance positive for the indication "*patients with severe, active and progressive rheumatoid arthritis not previously treated with methotrexate and other DMARDs".*

The efficacy of infliximab in improving clinical symptoms and signs of ankylosing spondylitis in the patient population with severe axial symptoms, who have elevated serological markers of inflammatory activity and have reponded inadequately to conventional therapy has been demonstrated for up to one year.

The efficacy of infliximab in combination with methotrexate in the treatment of patients with active, progressive psoriatic arthritis who have responded inadequately to disease-modifying anti-rheumatic drugs was demonstrated in one pivotal study (data covering 50 weeks).

Although data on the AS and PsA population are limited, the safety profile of infliximab in AS and PsA was similar to that observed in patients with RA or CD. Infliximab may offer a new therapeutic option for adult patients with AS and PsA when the response to previous therapy has been inadequate. Based on the review of data on safety and efficacy and the commitments agreed to by the Marketing Authorisation Holder, the benefit/risk profile of Remicade in the treatment of ankylosing spondylitis patients and psoriatic arthritis (as specified above) and used according to the recommendations in the product information is favourable.

The main safety concerns with Remicade, which apply for patients with Crohn's disease, RA, ankylosing spondylitis and psoriatic arthritis are:

- serious infections including TB
- infusion-related reactions including anaphylactic/toid reactions and if there is a possible increase in severity or frequency of these related to the number of infusions,
- antibody development
- worsening of heart failure
- haematological reactions
- neurological disorders
- possible increased risk of malignancies
- the fact that long-term consequences of Remicade treatment are unknown.

Thus, it is highly important that the provisions stated in the SPC are strictly adhered to.

Benefit/risk assessment

The CHMP concluded in its July 2004 meeting that Remicade continues to have a positive benefit/risk balance in Crohn`s disease, Rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis provided that the latest Product Information is adhered to.
This conclusion is based on the CHMP review of data on quality, safety and efficacy within 4 annual reassessment procedures, PSURs, variation procedures and the first 5-year renewal.
The marketing authorisation was renewed with a commitment from the MAH regarding the outstanding follow-up measures and the yearly submission of PSURs.