NIHS 2128

9th February 2001

To the Director-General of Pharmaceutical and Medical Safety Bureau, Ministry of Health, Labour and Welfare

Director-General of National Institute of Health Sciences

Evaluation Report

This is to report the outcome of the evaluation of the approval application of the drug described below by the Pharmaceuticals and Medical Devices Evaluation Centre.

[Product Name] Remicade IV Infusion 100

[Non-propriety Name] Infliximab (recombinant)

[Applicant] Tanabe Seiyaku Co., Ltd.

[Submission Date] 27th September 1999

[Classification] 1-(1) Drugs containing a new active ingredient

[Chemical Structure]

Molecular Weight: ca 149,000

Structural Formula: Figure 1 and Figure 2

Chemical Name:

(Japanese) *Omitted.*

(English) Glycoprotein (molecular weight; ca 149,000) consisting of two molecules of light chain each containing 214 amino acid residues ($C_{1028}H_{1587}N_{279}O_{337}S_6$: molecular weight 23,438.67) and two molecules of heavy chains each containing 450 amino acid residues ($C_{2203}H_{3411}N_{585}O_{682}S_{16}$: molecular weight 49,516.25), produced in mouse myeloma cells transfected with genomic DNA encoding human/mouse chimeric monoclonal anti-human TNFα antibody consisting of a variable region derived from mouse monoclonal anti-human TNFα antibody and a constant region from human IgG1.

[Remark] Orphan drug (designated on 1st April 1996)

[Evaluated by] Evaluation Division I

Figure 1

cA2 H Chain Amino Acid Sequence

Omitted, as the original print is illegible.

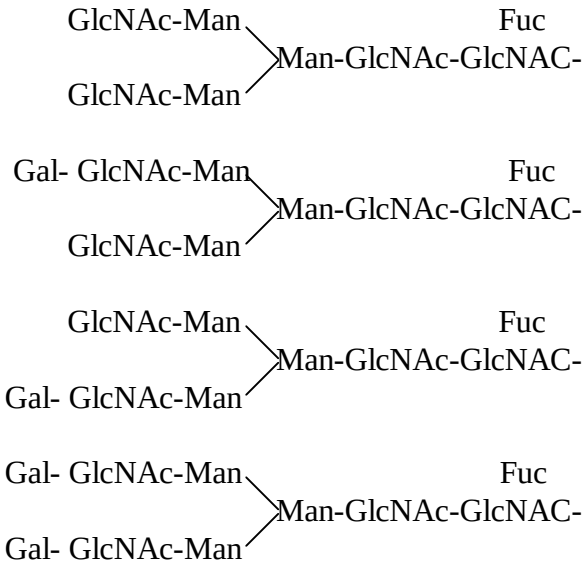
cA2 L Chain Amino Acid Sequence

Omitted, as the original print is illegible.

Infliximab's Amino Acid Sequences (to show the details, a single letter represents an amino acid.)

Figure 2

Estimated carbohydrate chain structure of infliximab



Fuc: Fucose, Man: Mantose, Gal: Galactose, GlcNAc: N-acetylglucosamine

Outcome of Evaluation

9th February 2001

[Product name] Remicade IV Infusion 100

[Non-propriety name] Infliximab (recombinant)

[Applicant] Tanabe Seiyaku Co., Ltd.

[Submission date] 27th September 1999

[Outcome of Evaluation]

<Efficacy>

In a double-blind, placebo-controlled, comparative study that targeted Western patients with moderately to severely active Crohn's disease who had had an inadequate response to prior conventional therapies, a single dose of 5 mg/kg or over significantly reduced Crohn's Disease Activity Indexes at 12 weeks after dosing. A similar trend was also observed in a phase II clinical study implemented in Japan. In a Western placebo-controlled, double-blinded comparative study in patients with external fistula, a significantly higher proportion of patients showed more than 50% closure of external fistulas after 3 infusions.

<Safety>

Occurrences of infections, including serious cases, which were thought to be attributed to the infliximab's immune suppressing action, were observed. As there is a concern that the same action may also be associated with incidents of malignant tumours, we believe a follow-up investigation is necessary. As infliximab is mouse/human chimeric antibody, incidents of allergic reactions (including rare serious reactions) were observed at the second or subsequent administrations. Therefore, we believe that adequate care should be taken when re-administering infliximab.

<Overall Assessment>

As a result of evaluation at the Pharmaceuticals and Medical Devices Evaluation Centre, we judge that Remicade is approvable with the following Indication and Dosage and Administration, bearing in mind that the disease in question is an intractable rare disease

and considering the efficacy of Remicade, although long-term safety of Remicade has not been fully confirmed.

[Indication]

Treatment of Crohn's disease with any of the following conditions (only when the patients have had an inadequate response to prior conventional therapies)

Patients with moderately to severely active diseases

Patients with external fistula

<Precautions for Use Concerning Indication>

Remicade should be administered if a clear clinical symptom attributed to Crohn's disease persists after appropriate therapies, such as nutritional interventions and drug treatments (e.g., 5-aminosalicylic acid preparations).

[Dosage and Administration]

For patients with moderately to severely active disease:

Intravenously infuse 1 dose of 5 mg per 1 kg of body weight.

For patients with external fistulas:

Intravenously infuse 3 doses (the initial dose, 2 weeks later and 6 weeks later) of 5 mg per 1 kg of body weight.

When administering Remicade, use an in-line filter with the membrane filter pore size of 1.2μm or less.

<Precautions for Use Concerning Dosage and Administration>

1) Retreatment

It has been demonstrated that the effect of Remicade appears by 2 weeks after dosing and the response is maintained for several weeks. Therefore, observe the patient for at least 2 weeks from a treatment and if the patient responds and then redevelops a symptom of Crohn's disease, the patient maybe retreated with Remicade. Long-term efficacy of a retreatment has not been demonstrated. When retreating a patient with Remicade, observe the patients carefully, preparing for an occurrence of delayed hypersensitivity.

2) Administration method

Remicade should be intravenously infused gradually, taking more than 2 hours, through an independent infusion line.

17th November 2000

Evaluation Report (1)

1. Filed Article

[Product Name]	Remicade IV Infusion 100
[Non-propriety Name]	Infliximab
[Applicant]	Tanabe Seiyaku Co., Ltd.
[Submission Date]	27th September 1999 (import approval)
[Dosage Form]	A freeze-dried formulation for intravenous infusion, containing 100 mg of infliximab (recombinant) in one vial
[Indication at Filing]	* Reducing symptoms of patients with moderately to severely active Crohn's disease who have had an inadequate response to prior conventional therapies * Reduction in the number of draining external fistulas of patients with fistulising Crohn's disease.
[Dosage and Administration at Filing]	* For patients with moderately to severely active Crohn's disease who have had an inadequate response to prior conventional therapies, a single dose of 5 mg/kg should be administered as an intravenous infusion. * For Crohn's disease patients with draining external fistulas, 5mg/kg doses should be administered as intravenous infusions at 2 and 6 weeks after the initial infusion.
[Remark]	Orphan drug (designated on 1st April 1996)

2. Outline of Submitted Data and Evaluation

A. Origin, details of discovery and history of development

As TNFα was first reported as a soluble factor that was induced in the mouse serum after BCG-sensitisation and caused necrosis of tumour cells, a hope was raised as an

anti-tumour agent specific to tumour cells. However, it has become clear that it is a kind of cytokine and it plays an important role in the immunological reactions, inflammation reactions, antibacterial reactions, endotoxin shocks and cachexia. As for involvement of TNFα with diseases, it has been known to be associated with activities of inflammatory diseases, such as Crohn's disease and chronic rheumatoid arthritis, and other autoimmune diseases since its discovery. The scientific rationale for effectiveness of a TNFα suppression in treatment of Crohn's disease has been supported by a correlation between the amount of TNFα in patients' faeces and the disease activity, and increased production of inflammatory cytokines including INFα in enteric lesions. In animal models of various inflammatory bowel diseases, treatment effects have also been confirmed when Th1 cell's hyperactivity was suppressed by anti-mouse TNFα antibody, etc.

Infliximab is mouse/human chimeric monoclonal antibody consisting of a variable region derived from mouse monoclonal antibody with binding capacity specific to human TNFα antibody, and a constant region of human IgG1, κ isotype antibody, and it exerts its effect by neutralising TNFα. By making the antibody chimeric, antigenicity in humans was reduced, and reductions in the dose amount and the frequency of treatments and a possibility of long-term repeated treatment of patients with chronic diseases were anticipated.

As the cause of Crohn's disease is unknown and the treatment method has not been established, it has been appointed as a special disease in Japan. The estimated number of patients is around 17,000. In overseas countries, infliximab was designated as an orphan drug for Crohn's disease in 1996, Japanese clinical studies were implemented and then the approval application was filed. Abroad, it was approved in the USA in 1998, and already more than 20,000 patients have received the treatment. In 1999, the European Agency for the Evaluation of Medicinal Products recommended the approval and it has been approved in 15 European countries.

B. Data concerning physical and chemical characteristics and specifications and test methods

Infliximab is anti-human TNFα chimeric monoclonal antibody obtained through gene

recombination, and it consists of a variable region of mouse monoclonal antibody that specifically recognises human TNFα and a constant region of human IgG1. Infliximab is manufactured in the following way. From mouse anti-human TNFα producing hybridoma, clone genes for the light and heavy chains of the variable region (antigen binding region) of anti-human TNFα antibody and link them with respective genes for the light and heavy chains of the constant region of human antibody to produce expression constructs of the light and heavy chains. Transfer those expression constructs to host cells, xxxx. From the resulting seed cells, prepare the master cell bank (MCB) and from MCB, prepare the manufacturer's working cell bank (MWCB). By cultivating a large amount of MWCB, the culture supernatant containing infliximab is obtained. With regard to these processes, the preparation processes and maintenance procedures of MCB and MWCB are established.

With the culture supernatant containing infliximab, perform affinity chromatography, ion exchange chromatography, xxxx treatment, xxx treatment, ultrafilteration to remove viruses and dialysis by ultrafiltration to prepare an infliximab bulk solution. The infliximab bulk solution is stored under a deep freeze condition (xx °C). A viral validation is performed here, and process management tests for the purification process have been set.

After defrosting the infliximab bulk solution in a deep freeze, measure xxxxxxxx, add refined white sugar and polysorbate 80 and produce Remicade IV Infusion 100 in accordance with the freeze dry method.

As specifications of the bulk solutions, contents, pH, bioactivity, xxxx purity tests [SDS-PAGE method, charge heterogeneity (isoelectric focusing), xxxxxxxxxxxxxxxxxxxxxxx], bacterial endotoxins test, xxxxxx and assays have been established.

For the formulated products, contents, descriptions (appearance), identifications, xxxxxxxxxx, pH, bioactivity, xxxxx, purity tests [xxx, SDS-PAGE method, charge heterogeneity (isoelectric focusing), xxxxxxxxxxxxxxxxxx], water content, particle test, bacterial endotoxins test, weight variation test, sterility test and assays have been established.

The Pharmaceutical and Medical Devices Evaluation Centre (hereinafter referred to as Evaluation Centre) has asked the applicant to provide their account for the manufacturing method and the specifications and test methods, by requesting them to

submit results of MCB and MWCB management tests, to establish necessary tests, etc., and has instructed a reorganisation of the application form.

C. Data concerning stability

The stability of the bulk solutions is investigated in a long-term storage study [polycarbonate containers (sealed), xx °C or xx °C] with test items of bioactivity, the SDS-PAGE method, charge heterogeneity xxxxxxxxxxxxxxxxx and assays. Results showed that the bulk solutions in deep freeze (xx °C) and liquid state (xx °C) were stable after 12 months, any of the batches showing no time changes in any of the measurements. This study is still on-going.
The formulated products are investigated in an accelerated study (colourless glass vials, 30 °C), a stress study [temperature (colourless glass vials, 45 °C), light (colourless glass vials or colourless grass vials shaded by aluminium)] and a long-term storage study (colourless glass vials, 5 °C) with test items of descriptions (appearance), xxxx pH, bioactivity, purity tests (xxxxx SDS-PAGE method, charge heterogeneity, xxxxxxx), water content, particle test, insoluble particulate matter and assays. In the long-term storage study, no batches showed time changes and they were stable after 36 months.

D. Data concerning acute toxicity, subacute toxicity, chronic toxicity, reproductive toxicity and other toxicities.

Infliximab is chimeral (mouse/human) monoclonal antibody that has a variable region of mouse monoclonal antibody with specificity to human TNFα and a constant region of human IgG1, and it has a strong reactivity to human's and chimpanzee's TNFα. It shows very weak reactivity to the dog, but it does not show crossreactivity to TNFα of any other experimental animals. Therefore, toxicity studies are mainly carried out in chimpanzees. For reproductive and developmental toxicity studies, anti-mouse TNFα xxxxxx monoclonal antibody was prepared and the reproductive and developmental toxicity studies were conducted in mice.
A single dose toxicity study was carried out in rats with intravenous administration and the approximate lethal dose was considered to be over 90 mg/kg. As changes in general

signs, changes associated with administration of heteroprotein, such as anaemia and proliferation of kupffer cells, were observed.

As a repeated dose toxicity study program, a rat 7-day repeated intravenous administration study, and chimpanzee 3 day and 5 day repeated intravenous administration studies were conducted. In the rat 7-day study, anaemia and proliferation of kupffer cells similar to the single dose study, and also liver weight increases, hypertrophy/hyperplasy of liver cells, and GOT and GPT increases were observed. Some of these findings were persistent even in the group which had a 2-week recovery period. However, these were considered to be changes caused by administration of heteroprotein (Pharmacometrics 27, 23, 1894). In the chimpanzee studies, abnormalities in general signs and other test items were not observed. In one animal in the control group that received a small amount (7.3μg/mL) of infliximab by mistake, anti-infliximab antibody was detected, suggesting a possibility of antibody production with infliximab administration. The no toxicity dose is estimated to be below 30 mg/kg/day in rats and not less than 30 mg/kg/day in chimpanzees.

For reproductive and developmental toxicity studies, anti-mouse TNFα antibody was produced and a fertility study and an organogenesis study were conducted in mice. The result showed that infliximab administrations did not affect the reproductive function of male and female parent animals, and teratogenicity, embryo-lethality and developmental inhibitions in foetuses were not observed either. The no toxicity dose was estimated as 40 mg/kg/day or more in all studies.

As genotoxicity studies, a bacterial reverse mutation test, a chromosome aberration test with mammalian cultured cells and a mouse micronucleus test were implemented and all tests showed negative results.

Local irritation studies were carried out in rabbits that received a single dose intravenously, subcutaneously or intramuscularly. In all studies, it was considered to be a weak irritant.

Carcinogenicity studies were not conducted, as infliximab was not crossreactive to rat and mouse TNFα, therefore, it was considered impossible to assess effects of long-term suppression of TNFα, even if infliximab was administered to rats or mice.

An antigenicity study and a dependency study were not conducted.

As 2 types of infliximab that were produced from different producer cell lines xxxxxxx

were used in these toxicity studies, comparative investigations in rat single and repeated dose toxicity studies and a chimpanzee repeated dose study were carried out to see if there were differences in toxicity through the producer cell lines. Based on the results, the applicant judged that the 2 types of infliximab from the different producer cell lines were equivalent in toxicity assessments.

The Evaluation Centre asked the applicant to explain the reason for the delay in conducting the reproductive and developmental toxicity studies in view of the overall development process. The applicant responded that they had known that the infliximab did not bind with TNFα of animals other than humans and chimpanzees and they were unable to assess infliximab using rats or rabbits, which were usually employed in reproductive and developmental toxicity studies. However, they did not think investigation of effects of TNFα suppressions on reproduction and development unnecessary and, if they were able to produce alternative antibody that suppressed TNFα in the same way as infliximab, that would provide useful information. Therefore, they created new anti-mouse TNFα xxxxx antibody and then implemented reproductive and developmental toxicity studies, which caused the slight delay. The Evaluation Centre accepted the response.

The Evaluation Centre asked the applicant to provide a discussion on human safety, including an example on a similar drug, because the clinical dose in human (5 mg/kg) was close to the approximate lethal dose in rats (90 mg/kg or over), which was 18 times the human clinical dose, and the no toxicity doses in the repeated dose toxicity studies and reproductive and developmental toxicity studies (about 30 to 40 mg/kg), which were roughly between 6 and 8 times. The applicant stated that the dosages used in these studies were equivalent to the maximum doses they could technically administer and even at these maximum doses, no changes other than various changes attributed to administration of heteroprotein in rats were observed. Comparing the exposures, they were sufficiently exposed; the exposure to the chimpanzees was 15 to 25 times, the parent animals in reproduction and developmental toxicity studies had about two-fold exposures and the foetal exposure was almost equal to the clinical dose; and infliximab administration to humans was unlikely to cause serious toxicity reaction at the clinical dose level. The applicant responded that rituximab, which was chimeric monoclonal antibody of CD20 antigen on B-cells, did not show serious toxicities (Japanese

Pharmacology & Therapeutics 27, 1903, 1999), and they judged that the exposure was similar to that of infliximab. The Evaluation Centre accepted the response.
In the reproductive and developmental toxicity study program, infliximab was administered intermittently, once a week in Seg.I, and twice in Seg.II, on day 6 and day 12 of pregnancy. The Evaluation Centre asked the applicant to account for appropriateness of intermittent doses, as reproductive and developmental toxicity studies generally use repeated doses because of their uniqueness. The applicant responded that sufficient levels of anti-mouse TNFα antibody for it to exerts its effects were detected in the serum of male and female parent animals in Seg.I and the serum of female animals and foetal extracts in Seg.II, showing satisfactory exposures, and they believed that infliximab was administered at an appropriate dose and regime for assessing the effects on reproductive functions. The Evaluation Centre accepted the response.
The Evaluation Centre asked the applicant's opinion on not conducting carcinogenicity studies, as mouse/human chimeric monoclonal antibody that specifically binds with human TNFα had some unknown factors. The applicant considered implementation of carcinogenicity studies with rats and mice inappropriate, as infliximab did not show crossreactivity with rat and mouse's TNFα. They stated that a six-month repeated-dose toxicity study with mouse anti-TNFα antibody, which investigated the effects of a long-term suppression of mouse TNFα activities, was currently implemented, and in an interim report (at end of 13-week treatment: 16th March 2000), no changes associated with infliximab administration were observed. The Evaluation Centre believes that it is necessary to conduct carcinogenicity studies, because when it was designated as an orphan drug, the subcommittee expressed the opinion that infliximab should be developed paying attention to the reproductive and developmental toxicity studies and possibilities of tumour development, which had not been investigated, and the indication is likely to be expanded to include Behchet's disease and malignant rheumatoid arthritis.

E. Data concerning pharmacological actions

As the pharmacological program supporting the efficacy of infliximab, a study investigated binding characteristics of infliximab and TNFα, a study on *in vitro* TNF α neutralising effects, and *in vivo* studies using human TNFα transgenic mice and a human

TNFα administered mouse lethal model have been implemented. As infliximab only showed crossreactivities with human and chimpanzee's TNFα, general pharmacology studies were not conducted.

The Scatchard Plot Analysis of solid phase radioimmunoassay showed that infliximab bound to soluble human TNFα (binding constant $1 \times 10^{10}\,M^{-1}$). TNFα was expressed on the cell surface membrane as membrane-bound protein, was cleaved by a proteolytic enzyme, and the free extracellular portions (monomers) self-associated to form bioactive trimeric TNFα. Therefore, the binding capacity of infliximab with trimeric, monomeric and membrane-bound TNFα was investigated. The result showed that infliximab bound to any of the monomeric trimeric and membrane-bound TNFα, the binding constant to natural membrane-bound TNFα was $1.1 \times 10^{9}\,M^{-1}$ according to a study using xxxx cells, and infliximab was divalent antibody, one molecule of which bound to two molecules of trimeric TNFα.

Results of an investigation of interactions with TNFα receptor showed that infliximab inhibited binding of TNFα and TNFα receptor and it had a concentration dependent dissociation effect on TNFα bound with membrane TNFα receptor. Infliximab only showed high specificities towards human and chimpanzee's TNFα and showed no crossreaction with TNFα receptors of other animal species.

An *in vitro* study showed that infliximab possessed neutralising effects on TNFα bioactivities. In the study, neutralising effects were investigated using IL-6 production and cell proliferation of human fibroblasts, increases in coagulation factor production in endothelial cells, appearance of adhesion molecules in endothelial cells and induction of neutrophil superoxide production with TNFα stimulus as indexes. It was confirmed that infliximab neutralised these TNFα bioactivities. In contrast, infliximab showed cytotoxicity towards cells expressing membrane-bound TNFα through human IgG_1-Fc mediating complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC).

Infliximab significantly improved the survival rate and hepatic lesions of galactosamine treated mice that received human TNFα, when it was intravenously administered at 0.4 mg/kg and 1.2 mg/kg, respectively. Infliximab also significantly improved the survival rate of xxxxx transgenic mice (overexpression of human TNFα and xxxxxxxxx), when

0.5 mg/kg was intraperitoneally administered twice a week. Intraperitoneal administration (5mg/kg, twice weekly) of infliximab significantly improved pathological changes in the joints (enlargement of the joint width) and suppressions of bodyweight gains in xxx transgenic mice (mice introduced with human TNFα gene) and xxxx transgenic mice (overexpression of human TNFα and developed xxxxx). As well as reducing serum TNFα concentrations in both types of mice, IL-6 concentrations and TNFα activities were significantly reduced in xxxxx mice.

Based on those results, it was concluded that infliximab had remedial effects on pathology attributed to human bioactivities through 1) neutralisation of TNFα's bioactivities, 2) dissociation of receptor-bound TNFα, and 3) cytotoxicity towards cells expressing membrane-bound TNFα, which were results of its mechanism of action, i.e., the high specificity and affinity with human TNFα.

As TNFα occurs as membrane-bound and free TNFα and it exists as a trimer, the Evaluation Centre requested the applicant to discuss effects on hormonal immunity and cell-mediated immunity, which were expected from the binding characteristics of infliximab and INFα, and review the points to be considered when treating patients with infliximab. In response, the applicant rearranged the mechanism of action of infliximab and stated that although cells expressing membrane-bound TNFα received cytotoxicity though CDC or ADCC in patients who received infliximab, it was shown that infliximab only bound to TNFα expressing cells in human tissues and they did not believe that it had non-specific cytotoxicity to cells that were not expressing membrane-bound TNFα. Furthermore, the applicant replied that they have contraindicated infliximab to patients who had a history of hypersensitivity to mice originating proteins, as infliximab consisted of protein parts derived from a mouse, antibody of infliximab was produced in some cases and there was a tendency that the patients who had produced antibody to develop more hypersensitivities when they were re-treated with infliximab. The Evaluation Centre judged those responses adequate.

The Evaluation Centre asked the applicant to examine the infliximab concentration at which dissociation of TNFα binding to a TNFα receptor expressing cell xxxx was observed, in terms of the relationship with the clinical dose. The applicant replied that the maximal blood concentration after an intravenous infusion at the clinical dose, 95.5μg/mL, was comparative to the concentrations set in the *in vitro* study (50 to 200

μg/mL) and the dissociation of the TNFα-TNFα receptor complex by infliximab was clinically significant. In response, the Evaluation Centre requested the applicant to re-submit the discussion, taking into the account that the complex dissociation by infliximab was not potent even at higher concentrations and considering the results of a study with endothelial cells from human umbilical code vessels. The applicant replied that involvement of CDC or ADCC was possible *in vivo* and the degree of the contribution of the complex dissociation to the clinical effect was not clear. The Evaluation Centre judged this response was acceptable.

F. Data on Absorption, Distribution, Metabolism and Elimination

Metabolism of infliximab was investigated using chimpanzees, xxx mice, wild-type mice of the same strain and C3H/HeN mice.

When one male chimpanzee received a single dose of intravenous infliximab (30 mg/kg), the serum unchanged infliximab concentration at 5 minutes after dosing was 825μg/mL and the plasma half-life ($T_{1/2}$) was 139.7 hours. When the same amount was repeatedly dosed intravenously once daily for 3 days, the serum unchanged infliximab concentration at 5 minutes after the third administration (an average taken from 1 male and 1 female) was 1,563μg/mL, being 1.56 times the concentration after the initial administration. When 15 mg/kg was administered, the serum unchanged infliximab concentration at 5 minutes after dosing (an average taken from 3 animals in total; 1 male and 2 females) was 443μg/mL. Based on these study results with 15 mg and 30 mg doses, the applicant concluded that there was a correlation between the dosed amount and the serum unchanged infliximab concentration. (According to the attached data xxxx, these studies were carried out using blood samples collected from chimpanzees in safety studies and these studies were not planned as pharmacokinetic studies. The applicant has been instructed to amend the descriptions in the Summary Document in line with the attached data.)

The maximal concentration (C_{max}) of serum unchanged infliximab and $T_{1/2}$ when xxxx mice or wild-type mice of the same strain received 10 mg/kg of infliximab intraperitoneally were, respectively, 94.8μg/mL and 74.6 hours and 165μg/mL and 274 hours. (The pharmacokinetic parameters were calculated combining study results shown

in the two attached data and only written in the Summary Document. The applicant has been asked if it was possible to describe the calculation of the pharmacokinetic parameters in the attached data.) Elimination of radioactivity from the blood after intravenous administration of 10 mg/kg of [^{35}S]-labelled infliximab to xxx or wild-type mice of the same strain was compared with the results obtained from xxx mice that received [^{35}S]-labelled control antibody. The elimination of the radioactivity was the fastest from the blood of xxxx mice that received [^{35}S]-labelled infliximab. The applicant concluded that faster elimination of unchanged infliximab from the blood of the human TNFα transgenic xxx mice compared with the wild-type mice was due to a formation of immune complex in xxx mice through neutralisation of human TNFα by infliximab and processing of the immune complex by the reticuloendothelial system, etc.

When a xxx and a wild-type mouse of the same strain received an intravenous administration of 10mg/kg of [^{35}S] rebelled infliximab, tissue radioactivity was high in the heart, lung and pancreas and no significant distribution difference was observed between the xxx mouse and the wild-type mouse of the same strain. In a xxxxxxxxxxxxxxxx analysis of serum samples collected from a xxxx mouse at 1 hour, 72 hours and 1 week after an administration described above, only unchanged infliximab was detected and no radioactivity that was thought to be attributed to metabolites was detected. In an enzyme immunoassay of TNFα, the infliximab-TNFα complex was detected in the serum of xxx mice that received infliximab, reaching the maximum (2ng/mL) on 3 days after the administration. Furthermore, as the constant region of infliximab was identical to human IgG_1, the applicant argued that infliximab was metabolised by the same passway as IgG_1.

The urinary and faecal excretion rates of an intravenous administration of 10 mg/kg of [^{35}S] labelled infliximab up to 14 days after administration in xxx mice were 11.5% and 12.2%, and the total excretion rate was 23.7%.

When Japanese Crohn's disease patients received a single continuous intravenous administration of 1 to 10 mg/kg of infliximab, the serum concentration decreased after dosing at $T_{1/2}$ of 151 to 246 hours and $T_{1/2}$ showed a tendency of an increase with a dose increase. The C_{max} and area under the blood concentration-time curve (AUC) increased in proportion to the dosed amount. Neutralising antibody (HACA) was found in 2 patients out of 17 assessable patients (11.8%), and all positive cases were in the 1 mg group (2 out of 3 in the group). The HACA production rate for Japanese and

Westerners in the groups receiving 5 mg or more was low, and the applicant considered that there were few or no ethnic differences in the immunogenicity of infliximab.
Effects of the sex, age, bodyweight, liver and kidney functions and concurrent medications on pharmacokinetic parameters were reviewed in studies implemented abroad. As a result, no clear effects other than concurrent medications were observed. With regard to the concurrent medications, patients who used concurrent adrenocortical hormones showed a significant increase in the volume of distribution at steady state (Vdss).
When pharmacokinetic parameters of Westerners and Japanese that were calculated under the same condition were compared, 90% confidence intervals of the ratio of ethnic groups regarding the serum infliximab concentration at 2 hours after dosing (C_{2H}), AUC, total clearance (CL) and $T_{1/2}$ included 1. When 5 mg was administered, the Vdss and the mean retention time in Japanese were between 0.5 and 0.6 times that of these in Westerners, but when 10 mg was administered, they were between 1.1 and 1.2 times. The applicant concluded that there was no large ethnic difference in pharmacokinetics of infliximab in Westerners and Japanese.
The Evaluation Centre requested the applicant to discuss the probable mode of metabolism of infliximab-TNFα complex. The applicant replied that they believed that the infliximab complexes were opsonized in the same way as other general immune complexes were expected to, up-taken by reticuloendothelial cells via their Fc and C3 receptors, and degenerated. The Evaluation Centre accepted the response and instructed the applicant to add this to the Summary Document.
When investigating the ethnic differences in pharmacokinetics of Westerners and Japanese, the applicant compared the kinetics by extracting a group of patients who did not use adrenocortical hormones concurrently. Therefore, the Evaluation Centre asked the applicant to discuss the effect of concurrent adrenocortical hormones on the patient background in an American study. The applicant compiled the response rates, the incidences of adverse events and the incidences of adverse drug reactions by presence and absence of concurrent adrenocortical hormones, and based on the result, they considered that the presence/absence of concurrent adrenocortical hormones did not result in a large difference in the patient background, etc., thus it was appropriate to compare the ethnic differences in the group of patients who did not use concurrent

adrenocorticdal hormones. The Evaluation Centre replied that this response was appropriate.

G. Data on Results of Clinical Trials

(1) Overview of submitted data

Based on 14 clinical studies implemented in Europe and America and 2 phase II studies implemented in Japan, the efficacy and safety of infliximab was investigated.
Overseas clinical studies of infliximab were as follows. The phase I study was implemented in the United Kingdom targeting healthy volunteers (one phase I/II study in healthy volunteers). Following this, to investigate efficacy and safety of infliximab for Crohn's disease in Europe and America, 4 clinical studies in Crohn's disease (1 phase I study, 1 phase II study, 1 phase II/III study, and 1 phase III study) were implemented. Furthermore, 9 clinical studies targeting diseases other than Crohn's disease (1 phase I study, 1 phase I/II study and 3 phase II studies in chronic rheumatoid arthritis patients; 1 phase II study in ulcerative colitis patients, 1 phase I study in xxxxxxxx compassionate use; 1 phase I/II study and 1 phase II/III study in xxxxxxxxxxx patients) were conducted. Results of these studies were used for safety investigation of infliximab. Data from the clinical studies in xxxxx patients and the clinical study in xxxxxxx compassionate use were submitted as reference data.
As Japanese clinical studies, phase II studies were conducted targeting Crohn's disease. Similar to clinical trials in Europe and America, blood concentration profiles, efficacy and safety of an administration of 1 to 10 mg/kg infliximab to active Crohn's disease patients were investigated. In malignant rheumatoid arthritis patients, safety of 1 mg/kg or 5 mg/kg infliximab administrations was investigated. The efficacy of infliximab was assessed basing on clinical study results in Crohn's disease and the safety was assessed including studies in malignant rheumatoid arthritis.
The number of subjects in Japanese and overseas clinical studies was 258 with Crohn's disease (233 in overseas countries, 25 in Japan), and it was 551 including other diseases (excluding xxx) (524 in overseas countries, 27 in Japan). When patients with xxx were included, it was 664 (637 in overseas countries, 27 in Japan).
In overseas countries, three studies in Crohn's disease (a xxxx study, a re-administration

study in Crohn's disease patients who had participated a trial before [the study was completed] and a maintenance therapy study after remission) and a phase III study in chronic rheumatoid arthritis, and in Japan, a phase II study in chronic rheumatoid arthritis and a phase II study in Behchet's disease are currently on-going or in a process of study report production.

In the re-administration study in Crohn's disease patients who had participated in a trial before (xxxxxxxx), serious delayed hypersensitivity symptoms were observed. Outside of clinical trials, Centocore supplied clinical samples of infliximab on request from medical institutes xxxxxxxxxxx and xxxxxxxxxxxx and they were given to xxxxx patients and chronic rheumatoid arthritis patients. They were not included in the attached data, but one malignant lymphoma was found in a study in xxxxxxx patients abroad. As post-marketing safety data, all serious adverse events occurred up to *year/month/date* were investigated.

I. Phase I Study (xxxxxxxxxxx)

In a phase I study of infliximab in healthy volunteers, 3 each of healthy volunteers in the UK received a single dose of 0.1, 1 and 5 mg/kg infliximab. No adverse drug reactions were observed and no clinically significant abnormal changes in clinical lab data were seen. To evaluate *in vivo* TNFα neutralising effects, the blood TNFα concentrations were measured after endotoxin was administered following 0.01, 0.1, 1 or 10 mg/kg of infliximab (to 5 subjects each). The result showed that with a dose over 1 mg/kg, TNFα increases were suppressed and with 10 mg/kg, no TNFα was detected. In all groups that received infliximab, adverse drug reactions were not observed, demonstrating its tolerability (phase I/II study [healthy volunteers] (Study Number: xxxxx); Data Number xxx).

The first dose to a Crohn's disease patient was carried out in a compassionate use study (Study Number: xxxx; Data Number xxx) to a one-year old, Dutch girl with Crohn's disease and improvements of the Crohn's disease symptoms, including fever and diarrhoea, were seen. Following that, in the Netherlands, 8 patients and 2 patients with steroid resistant active Crohn's disease received a single dose of 10 and 20 mg/kg of infliximab, respectively (phase I study [Crohn's disease] (Study Number: xxxxx); Data

Number xxxx). One patient who developed a sigmoid perforation (a relevancy to the study was ruled out) during the study was excluded from the assessment, and the Crohn's Disease Activity Index (CDAI) of all assessable 9 patients fell below 150 and achieved the remission level. The median CDAI of the 9 patients, which was 233 before dosing, was 32 after 4 weeks and 33 after 8 weeks, showing clear improvements and the response was maintained for 8 weeks. No adverse drug reaction was observed, demonstrating tolerability. HACA was not observed in all 7 patients who were tested.

II. Moderately to severely active Crohn's disease patients who have had an inadequate response to prior conventional therapies

An open label investigation of efficacy and safety of a single dose of 1, 5, 10 and 20 mg/kg infliximab (5 subjects per group) in patients with active Crohn's disease who had had an inadequate response to prior conventional therapies was conducted in Europe and America (phase II study [Crohn's disease] (Study Number: xxxx); Data Number xxx). The CDAI improvement was used for efficacy assessment, which was defined as a reduction of CDAI by 70 from baseline without starting a new drug therapy or other treatments for Crohn's disease. With the primary efficacy endpoint, which was the CDAI improvement within 4 weeks of the treatment, all groups achieved a high improvement rate, over 80%, that was 100% (5/5), 80.0% (4/5), 100% (5/5) and 80.0% (4/5) in 1, 5, 10 and 20 mg/kg groups, respectively. Ninety percent of all patients (18/20) showed the CDAI improvement at some assessment time points within 12 weeks of treatment. At week 12, the CDAI improvement rates in 1, 5, 10 and 20 mg/kg groups were 20.0% (1/5), 66.7% (2/3), 80.0% (4/5) and 50.0% (2/4), respectively, and all groups that received more than 5 mg/kg maintained the improvement in CDAI better than the 1 mg/kg group. The 1 mg/kg group showed no improvement in the Visual Analogue Scale (VAS) with endoscopies, but 5 to 20 mg/kg groups showed improvements at week 4, which were maintained until week 8. All dose groups showed improvement in the IBDQ (inflammatory bowel disease questionnaire) up until week 12. Adverse drug reactions were observed in 38.1% (8/21), which were dizziness, tiredness and abnormal vision, but none were serious. The incidences by dosed amount were 60% (3/5) in the 1 mg/kg group, 80% (4/5) in the 5 mg/kg group, 0% (0/5) in the 10

mg/kg group and 20% (1/5) in the 20 mg/kg group, showing no correlation to the dose. HACA was found in 5 out of 15 evaluated patients (33.3%) and 3 of them were in the 1 mg/kg group. From the above, they estimated that the effective dose was 5 mg/kg or above.

In the phase II/III double-blind study [Crohn's disease] (Study Number: xxxxx), patients with moderately to severely active Crohn's disease who had had an inadequate response to prior conventional therapies received an initial dose of 5, 10 or 20 mg/kg infliximab using placebo as a control in a double-blind fashion [induction phase (the first infusion)], then at week 4, patients who did not show CDAI improvement received an open label administration of 10 mg/kg [induction phase (open label infusion)]. At 8 weeks after the first infusion or the open label infusion, patients who showed CDAI improvement were then randomised to groups, which either received 4 infusions of placebo or 10 mg/kg at week 12 and every 8 weeks subsequently [repeated infusion phase] (Data Number xxxx). The CDAI improvement rate at week 4 after the first infusion, which was the primary endpoint, was 16.7% (4/24) in the placebo group, where as 81.5% (22/27), 50.0% (14/28) and 64.7% (18/28) in the 5, 10 and 20 mg/kg groups, respectively, and the combined rate for the groups received infliximab was 65.1% (54/83), showing a significantly higher CDAI improvement rate than the placebo group ($P<0.001$, Cochran-Mantel-Haenszel χ^2 test). At week 12, it was 12.0% (3/25) in the placebo group, where as 48.1% (13/27), 28.6% (8/28) and 46.4% (13/28) in the 5, 10 and 20 mg/kg groups, respectively, showing a significantly higher CDAI improvement rate than the placebo group ($P=0.024$, Cochran-Mantel-Haenszel χ^2 test). As above, all groups that received infliximab (5 to 20 mg/kg) maintained higher CDAI improvement rates after an infusion until week 12 than the placebo group and also all infliximab groups showed improvements in Crohn's Disease Endoscopic Index of Severity (CDEIS) and IBDQ. The incidence of adverse drug reactions in the placebo group was 24.0% (6/25) at week 6.9, which was the average duration of the observation in the placebo group, and that in the infliximab groups was higher, 34.9% (29/83) at week 10.1, which was the average duration of the observation in the infliximab groups, but there was no difference in incidences of adverse drug reactions at around the observation period. Although no event was found to have a clear difference in the incidence compared with the placebo group, hypersensitive symptoms such as rash/eruption, increased sweating and hypotension were found more in the infliximab groups. No serious adverse drug reaction

was observed after the first infusion. In the assessment up to 48 weeks in patients who responded to the first infusion or the open label infusion and then received 10 mg/kg for 4 times every 8 weeks, the infliximab group showed no bigger decrease in the response than the placebo group in term of CDAI improvement and the remission rate, but it was not possible to confirm significant improvement maintenance effects. The incidences of adverse drug reactions in the placebo group and the infliximab group were similar, 36.1% (13/36) in the average duration of observation in the placebo group, week 30.7, where as 54.1% (20/37) in the average duration of observation in the infliximab group, week 32.5. The events with high incidences were hypersensitive symptoms, such as rash/eruptions. Serious adverse drug reactions were observed in 8 patients during the open label infusion phase and the repeated infusion phase. They were infections including pneumonia (3 cases), changes in blood pressure and dyspnoea during infusions (3 cases), malignant lymphoma (1 case) and lupus arthritis (1 case). Throughout the phases, HACA was expressed in 16% (10/62).

As the above clinical study results confirmed that 1 mg/kg shows efficacy for a while, but continuation of the response was inadequate, there was no difference in efficacy of doses above 5 mg/kg and there was no specific dose correlation in safety between 1 mg/kg and 20 mg/kg, 5 mg/kg was considered to be appropriate as the dose amount. The efficacy of a single dose of 5 mg/kg infliximab to patients with moderately to severely active Crohn's disease who had had an inadequate response to prior conventional therapy was demonstrated.

III. Patients with Crohn's disease with draining external fistula(s) (xxxxxxx)

In the double-blind phase III study [Crohn's disease] (Study Number: xxx), patients with Crohn's disease with draining external fistula(s) (including fistulas in the perianal area) received 3 infusions of placebo, 5 mg/kg or 10 mg/kg of infliximab at week 0, week 2 and week 6 to investigate the efficacy, safety and pharmacokinetics (Data Number xxx). The efficacy primary endpoint was the proportion of patients who showed closure of more than 50% of draining fistulas compared with baseline for at least 1 month after the infusion (50% closure rate). The 50% closure rate was 25.8% (8/32) in the placebo group, whereas it was 67.7% (21/31) and 56.3% (18/32) in the 5 mg/kg group and the 10 mg/kg group, respectively, which were significantly higher in the groups received

infliximab (p=0.002 and 0.021, two-tailed, Fisher's exact test). The proportion of patients who showed closure of all fistulas was 12.9% (4/31) in the placebo group, whereas it was 54.8% (17/31) and 37.5% (12/32) in the 5 and 10 mg/kg groups, which were significantly higher in the groups receiving infliximab (P=0.001 and 0.041, two-tailed, Fisher's exact test). Both the 50% closure rate and the total closure rate were slightly higher in the 5 mg/kg group compared with the 10 m/kg group, but they were considered to have no substantial difference. The incidence of adverse drug reactions in the placebo group was 45.2% (14/31) at week 19.8, which was the average duration of the observation for in the placebo group, and that in the infliximab groups was similar, 50.8% (32/63) at week 21.2, which was the average duration of the observation in the infliximab groups. No clear difference in incidences of adverse drug reactions by dosed amount was seen. Events seen at a higher incidence than in the placebo group were tiredness, nausea, eczema and purities. Serious adverse drug reactions were observed in 3 patients in the 10mg/kg group (pneumonia, furunculosis and anal ulcer). The HACA expression was seen in 6.0% (3/50).

As the groups that received infliximab showed significantly higher efficacy than the placebo group, there was no difference between the 5 mg/kg group and the 10 mg/kg group and there was no difference in the incidences of adverse drug reactions by dosed mount, 3 doses of 5 mg/kg at weeks 0, 2 and 6 were considered to be appropriate.

IV. Summary of overseas safety in all diseases including Crohn's disease

To assess the safety, of the studies implemented in Europe and America, 4 clinical studies in patients with Crohn's disease and 7 clinical studies in patients with diseases other than Crohn's disease, excluding a study (chronic rheumatoid arthritis xxxxxx) which was excluded from the NDA for the USA because the study report was under production when the NDA was filed for Crohn's disease in the USA (*date/month/year*) and 2 studies in patients with xxxx (xxxxxxxxxx), were pooled. The safety data of studies that were not included in the pooled analysis were compiled separately by study. In 11 studies in the pool analysis, 453 patients received 1207 doses of infliximab in total. The cumulative dose was up to 60 mg/kg and the most widely distributed cumulative dose was 10 mg/kg or over and less than 20 mg/kg, which was received by 140 patients (30.9%). In all studies other than xxxxxx, patients were followed-up for up to 3 years

after administration for safety investigation. One hundred and ninety seven patients were followed for at least 2 years, and 30 of them were patients with Crohn's disease.
In a double-blind study in patients with Crohn's disease (Study Number: xxxxxx), when the incidence of adverse drug reactions was compared with the placebo group, it was similar considering the average duration of the observation. A specific trend in incidences of adverse drug reactions in the infliximab groups depending on the dosed amount was not observed. There were no events that showed clear differences in the incidence compared with the placebo group, but hypersensitivity symptoms, such as rash/eruption, increased sweating and hypotension, were seen more often in the infliximab group. In the studies targeting patients with Crohn's disease, about 5 % of patients discontinued an infliximab infusion because of adverse events. The common reasons for discontinuations were infusion reactions (adverse events occurred during or within 2 hours of an infusion) and infections. In double-blind studies in chronic rheumatoid arthritis (xxxxxxxxxxxxx), the incidence of adverse drug reactions in patients with diseases other than Crohn's disease was compared with the placebo groups. The incidence of adverse drug reactions was about 2 times higher than the placebo groups in all studies. The reactions that occurred at higher incidences than the placebo group were infections such as pneumonia, herpes simplex, abscess and bronchitis, and hypersensitive symptoms such as rash/eruption and pruritus. The adverse events to be noted when using infliximab are as follows.

(1) Adverse events during an infusion or shortly after an infusion (infusion reactions)

An infusion reaction was defined as any adverse event that occurred during or up to 2 hours after an infusion. Only 6.5% (9/139) of patients who received placebo developed infusion reactions, where as 15.9% (72/453) of patients who received infliximab developed infusion reactions. Of 1207 doses of infliximab, non-specific symptoms, such as fever and malaise, occurred in 4.8% (58 doses), pruritus or urticaria occurred in 1.2% (14 doses), cardiopulmonary reactions (mainly chest pain, reduced blood pressure, increased blood pressure or dyspnoea) in 1.5% (18 doses) and concurrent pruritus/urticaria and cardiopulmonary reactions occurred in 0.2% (2 doses). Nine out of 72 patients

who showed infusion reactions discontinued the infliximab infusion. All of them recovered with treatments for the infusion reaction and/or the discontinuation of the infusion. Seven point one percent (32/453) of patients showed infusion reactions at the first infusion and 10.2% (31/304) of patients showed infusion reactions at the second infusion. No increase in incidences of infusion reactions was observed beyond the third infusion. The incidence of infusion reactions was higher in HACA positive patients (36.3% [29/80]) than in HACA negative patients (10.8% [22/203]). The incidence of infusion reactions in patients who used concomitant immunosuppressant agents was lower.

(2) Infection

Twenty-one point zero percent (95/453; average of 22.3 week follow up) of patients that received infliximab and 11.0% (12/109; average of 12.2 week follow up) of patients that received placebo developed infection. Fifteen patients (3.3%) who received infliximab developed serious infections, i.e., suspected pneumonia, cellulites, infections at the carthererised area of the central vain, sepsis, cholecystitis, endophthalmitis and abscesses. Two patients who received placebo (1.8%) developed serious infections. Eleven point one percent (7/63) of patients with fistulising Crohn's disease developed a new abscess at 8 to 16 weeks after the last infusion of infliximab.

(3) Autoantibodies/lupus-like syndrome

In patients treated with infliximab who were tested for antinuclear antibodies (ANA), the rate of patients who were ANA-positive was 23.8% (85/357) before the treatment, but it increased to 35.9% (128/357) by the last evaluation. Anti-dsDNA antibodies developed in 8.6% (14/162) of Crohn's disease patients treated with infliximab. Notably, in Crohn's disease patients who used a concomitant immunosuppressant, production of anti-dsDNA antibodies was reduced (3.5% [4/115] in patients received immunosuppressant compared with 20.8% [10/48] in patients not receiving any immunosuppressant). Crohn's disease patients were approximately 2 times more likely to develop anti-dsDNA

antibodies if they were ANA-positive at study entry.

Two patients (anti-dsDNA antibody positive) developed signs consistent with the lupus-like syndrome. One of them who had rheumatoid arthritis developed dyspnoea and pleuropericarditis, which disappeared in 6 to 8 weeks from starting an oral steroid treatment. Another patient had Crohn's disease and developed lupus arthritis. It responded to a steroid and disappeared within 6 months from the last infliximab infusion. The patients were followed up for xx months to xx years after the last infliximab infusions, but no other autoimmune abnormalities were observed.

(4) Lymphoproliferative disease

As a result of the follow-up of clinical studies up to *day/month/year*, 1 patient with Crohn's disease and 2 patients with chronic rheumatoid arthritis developed malignant lymphoma, and 1 patient with chronic rheumatoid arthritis developed myeloma, out of 394 patients who were followed for x month to x years after the final infliximab infusions. Furthermore, between *date/month/year,* and *date/month/year*, malignant lymphoma was found in 1 patient with chronic rheumatoid arthritis. Malignant lymphoma was found in a patient with non-Crohn's disease xxxxx in a short follow-up period. In studies that are currently conducted (as of *date/month/year*), 1 patient in a clinical trial in chronic rheumatoid arthritis was found to have malignant lymphoma. These malignant lymphoma were found in patients with long duration of the diseases and chronic exposure to immunosuppressant therapies. Such patients were reported to be more at a risk of developing a malignant tumour. There was insufficient data to determine relationships of the development of the malignant lymphomas and the dosed amount or duration of infliximab treatment.

At the request of centres that participated in clinical studies of Crohn's disease patients, a re-administration study is currently conducted, in which patients with active Crohn's disease who have previously received infliximab in a Crohn's disease clinical study are allowed to receive up to 5 infusions of 5 mg/kg. Of 40 patients who retreated with infliximab after a 2 to 4-year interval from the previous infusion, 10 patients (25%) developed latent adverse drug reactions

such as muscle ache, rash, fever and joint pain, and 6 of them had serious adverse drug reactions involving hospitalisation. HACA was assessable in 6 out of those 10 patients, and all 6 patients were negative prior to the infusion, but turned positive after infusions.

In the early studies before the current freeze-dried formulation had become available, liquid formulation was used. Of patients who received the liquid formulation in the previous treatment, 37.5% (9/24) developed latent adverse drug reactions, which was higher than 6.3% (1/16) of patients who received the freeze-dried formulation in the previous treatment. However, it is not clear if this difference is due to the difference in the formulations.

V. Japanese Clinical Studies

In a phase II study [Crohn's disease] (Study Number: xxxxxx), 25 patients with active Crohn's disease received a single dose of 1, 3, 5 or 10 mg/kg. As well as the International Organization for the Study of Inflammatory Bowl Disease (IOIBD) Scale, which is the most widely used in Japan, CDAI and X-ray/endoscopic examinations were chosen as the efficacy primary endpoints. The improvement rate of the IOIBD score showed that, at week 4, a high proportion of patients were improved, 66.7% (2/3), 71.4% (5/7), 80.0% (4/5) and 85.7% (6/7) with 1, 3, 5 and 10 mg/kg, respectively. At week 12, it was 33.3% (1/3), 0% (0/7), 40.0% (2/5) and 42.9% (3/7), respectively, and the response was maintained at a dose above 5 mg/kg. In terms of CDAI remission rate, the response was also maintained at a dose above 5 mg/kg. The improvement rate after 4 weeks according to X-ray/endoscopic examinations was 63.6% (7/11) for all infliximab groups combined, demonstrating the morphological response. The incidences of adverse drug reactions (excluding abnormal changes in lab test results) were 0% (0/3), 50.0% (3/6), 71.4% (5/7) and 12.5% (1/8) with 1, 3, 5 and 10 mg/kg. The incidences of abnormal changes in lab test results of which relevancy to infliximab cannot be ruled out were 33.3% (1/3), 16.7% (1/6), 14.3% (1/7) and 37.5% (3/8), respectively. None of them had a correlation with the dosed amounts and no serious adverse drug reaction was found. Two out of 17 patients (11.8%) who were assessable for HACA expression

turned positive and both of them were in the 1 mg/kg group.
In the on-going phase II clinical study in chronic rheumatoid arthritis (Study umber: xxxx), administration of 3 doses of 1, 3, 5 or 7 mg/kg on weeks 0, 2 and 6 has been planned and up to now (as of *date/month/year*), 30 patients completed the 1 mg/kg dosing regimen and 31 patients completed the 3 mg/kg dosing regimen (61 patients in total). One patient in the 1 mg/kg group (fever) and 2 patients in the 3 mg/kg group (fever/nausea/vomiting, infectious arthritis) developed serious adverse events, but they were improved after administration of an antibacterial agent, etc. During a follow-up after the assessments, breast cancer was found in 1 patient.
When efficacy and safety assessments in overseas and Japanese clinical studies were compared, their patient backgrounds and concurrently used medications were similar. The results of the efficacy assessments in Japan and abroad were similar and no Japanese-specific serious adverse drug reactions were observed in the safety assessment.
Based on the results of clinical studies in Japan and abroad as described above, a single dose of 5 mg/kg infliximab infusion showed a high efficacy in providing symptomatic relief in patients with moderately to severely active Crohn's disease who had had an inadequate response to prior conventional therapies. Three infusions of 5 mg/kg also demonstrated a high efficacy in a treatment aiming at reduction of the number of draining external fistulas in patients with fistulasing Crohn's disease. With regard to the safety, it was considered that infusion reactions and late-onset hypersensitivities, infections, lupus-like symptoms and lymphoproliferative diseases should be noted.
As Crohn's disease is highly likely to recur or relapse after a surgical operation, an operation is avoided as far as possible, in principle, but an operation is indicated for medical treatment non-responders who repeatedly develop fistulas, intestinal blockages and perforations. It has been reported that the proportion of patients receiving an operation after developing Crohn's disease is 16.2% in 5 years and 39.1% in 10 years. It has also been reported that the proportion of patients receiving a reoperation after an operation is 39% in 5 years and 56% in 10 years, and the proportion of patients receiving a reoperation after an initial operation for perforating complications, such as fistulas, is 57% in 5 years and 68% in 10 years, which is higher than that of patients who had non-perforating complications. The clinical studies of infliximab targeted patients with moderately to severely active Crohn's disease who had had inadequate response to prior conventional therapies or those with a complication of draining external fistula(s), and

the applicant believes that there is an urgent need for a therapeutic agent. Therefore, the manufacturing approval application was made using the overseas clinical study results as a core.

(2) Details of Evaluation at the Evaluation Centre

The Evaluation Centre mainly reviewed the following points.

[Clinical positioning of infliximab]

The Evaluation Centre asked the applicant about the therapeutic positioning of infliximab. The applicant replied that infliximab would be prescribed to the moderately to severely active patients who had had an inadequate response to these therapies, that the prescription would be concurrently with or in place of nutritional interventions or medicinal therapies such as steroids and immunosuppressants, and the applicant believes that it will not be the first choice on the initial diagnosis. The applicant stated that they were currently conducting a clinical trial in view of a need for a maintenance therapy with long-term administration, and steroid sparing may be possible depending on the result. The Evaluation Centre accepted the responses.

[Comparability of overseas data and Japanese data]

The Evaluation Centre instructed the applicant to carry out comparisons of pathologies, diagnostic criteria, treatment policies and prognoses of Crohn's disease in Japan and the West, in terms of assessment of the overseas data. The applicant's replies were as follows. Pathologies, diagnostic criteria and prognoses of Crohn's disease are considered to be roughly the same. With regard to differences in the first choice of the Crohn's disease treatments, a drug therapy, such as a steroid, an aminosallicylic acid preparation and an immunosuppressant, is often chosen abroad, but a nutritional intervention is often the first choice in Japan and an aminosallicylic acid preparation is the most popular drug therapy in Japan. These differences are not due to an ethnic difference in a response to treatments, but because nutritional interventions are not preferred choices abroad as the compliance cannot be maintained due to poor QOL associated with the limited diet and a high cost of nutritional interventions (in the USA, it costs about 240,000 yen per month). However, reports showing efficacy of nutritional interventions are found abroad as well as in Japan. A therapeutic guideline in the USA

(Management of Crohn's Disease in Adults, the American Journal of Gasteroenterology 92:559-566, 1997) lists predonzolone (40 to 60 mg) as the first choice for moderate to severe patients (including patients with mild-to-moderate symptoms who did not respond to treatment), but it also mentions nutritional interventions as alternative and effective therapies. Therefore, the applicant believed that the difference in the choice of drug treatments or nutritional interventions were not due to differences in response to the treatments but due to the differences in the healthcare environment. The Evaluation Centre accepted the reply.

When background factors of overseas patients and Japanese patients were compared, 60% of the overseas patients were using a steroid compared with 27% in the Japanese patients. The Evaluation Centre instructed the applicant to review a possibility that more severe patients were recruited abroad. The applicant stated that in 8 reports which compared nutritional interventions and steroid therapies abroad, 6 reported that a higher improvement was seen with steroid therapies, therefore, steroids were widely used abroad. In addition, when comparing severe patients, 11 out of 25 patients (44%) received a nutritional intervention of over 1,200 kcal/day concurrently with a steroid in the Japanese study and 60% of patients in the overseas xxxx study used a concomitant steroid, therefore there was not a big difference in concomitant treatments. Furthermore, when background factors of CDAI and C responsive protein (CRP), which indicate the severity, measured at baseline were compared, they were 280 and 4.0, respectively, in the Japanese study and 307 and 2.0, respectively, in the xxxx study, thus CDAI was similar and CRP was higher in the Japanese patients who used less steroids. The applicant argued that these results did not agree with a statement that there were more severe cases among the overseas patients, and the Evaluation Centre accepted the reply.

The Evaluation Centre requested the applicant to explain the relationship of Endoscopic Improvement used in the Japanese study and Crohn's Disease Endoscopic Index of Severity (CDEIS) used in the overseas studies. In the xxx study, CDEIS was used as a secondary efficacy endpoint, but it was assessed only in the European centres not in the American centres, and only 27 patients (out of 108 patients in total) were evaluated. CDEIS correlated with the severity assessments of diseased areas made by investigators who carried out endscopic examinations, and that was validated, but endoscopic examinations were essential and the calculation was complicated. In the xxx study, the results before an infliximab infusion and 4 weeks after the infusion were compared. On

the other hand, in the Japanese phase II study, X-ray or endoscpic examinations were carried out at baseline and week 4 for morphological evaluations and the images were assessed in an interpretation meeting attended by 6 Crohn's disease specialists. The assessment procedure was that, to start with, findings on the major lesions in the large and small intestines, such as cobblestone appearances, longitudinal ulcers, apthours ulcers and other ulcers, were scored using 4 categories, and longitudinal ulcers and cobblestone appearances, which were the main parameters, were compared with baseline and scored for the morphological improvements using a 6 category scale. The applicant stated that although the assessment procedures were different as described above, both CDEIS and Japanese morphological assessment criteria were objective ways of making an assessment and it was possible to compare the efficacy assessments made by two sets of criteria. The Evaluation Centre accepted the reply as these assessment criteria were based on objective findings, although no evaluation was made on direct comparison of the two criteria.

Pharmacokinetics of the Japanese and Westerners were compared in 6 Japanese that received 5 mg/kg and 7 Japanese that received 10 mg/kg, and 9 Westerners that received 5 mg/kg and 6 Westerners that received 10 mg/kg. Comparisons of data including C_{2H}, AUC, $T_{1/2}$ and CL were presented. The applicant stated that although the number of cases was small, they believed that their pharmacokinetics did not have a large difference considering the variation. The Evaluation Centre accepted the reply.

[Appropriateness of infliximab dose selection]

In the overseas study xxx, CDAI improvement was superior with 5 mg/kg than with 10 mg/kg at any time-point, but in Japanese studies, there was a trend that 10 mg/kg was superior, so the Evaluation Centre asked the applicant to explain the appropriateness of the dose selection. Although in the study xxx, a significant difference from the placebo group was observed in CDAI improvement, no clear dose response between the infliximab groups was observed and it was considered to have reached a level at doses above 5 mg/kg (clinical response/CDAI improvement within 4 weeks: 24.0% in the placebo group, 85.2% in the 5 mg/kg group, 57.1% in the 10 mg/kg group and 67.9% in the 20 mg/kg group). In the Japanese study, CDAI improvement was 83.3% (5/6) in the 10 mg/kg group and 75.0% (3/4) in the 5 mg/kg group, but they were within a range of variation as the number of patients was small. The 3 mg/kg group was considered to

have inadequate improvement after week 8. In the fistula study xxx, 67.7% and 56.3% in the 5 mg/kg group and the 10 mg/kg group had closure of fistulas (50% closure), respectively, showing similar rates. In the dose-response study in chronic rheumatoid arthritis, the response rate at 3 mg/kg and 10 mg/kg was also similar. From the above, the applicant replied that, efficacy of infliximab was considered to reach a level at above 5 mg/kg and the recommended dose was set the same as the overseas recommended dose, 5 mg/kg. The Evaluation Centre accepted the reply.

[Indication for treatment of Crohn's disease with external fistulas]

As no clinical study was conducted in Crohn's disease with external fistulas in Japan, the Evaluation Centre asked for the rationale for claiming the usefulness of infliximab to Japanese patients. According to the report from the Intractable Inflammatory Bowl Disease Study Group of 1993, a survey of long-term prognosis of 501 patients with Crohn's disease in Japan, of 408 patients who answered to the survey, 188 were receiving a treatment or under observation and of those, 28 patients (14.8%) had fistula(s). The number of the certificates issued for Crohn's disease specified medical care receivers in 1998 was 16,891 and based on this, the number of patients with a complication of fistula(s) in Japan was estimated at around 2,500. In the Japanese studies, patients with "significant fistula(s) and anal lesions" were excluded, but this exclusion was set referring to clinical studies of a similar drug. Therefore, no clinical study was conducted in Japan. However, in the phase III placebo controlled study in patients with fistulising Crohn's disease abroad, the rate of 50% closure after 3 infusions of 5 mg/kg or 10 mg/kg of infliximab was 25.8% (8/31) in the placebo group and 61.9% (39/63) in the infliximab groups. Furthermore, 11 out of 12 patients (91.7%) whose baseline CDAI was over 220 showed remission (an improvement of CDAI to below 150) and closure of fistulas was observed. Three out of 8 patients (37.5%) who did not show remission showed closure of fistulas. Therefore, the applicant considered that remission of symptoms of Crohn's disease measured by CDAI and closure of fistulas in patients that received infliximab were correlated. Based on this, although the applicant did not implement clinical assessment in patients with fistulasing Crohn's disease in Japan, the clinical study results in patients with moderately to severely active Crohn's disease who had had an insufficient response to prior conventional therapies suggested infliximab's efficacy in fistulising patients. The applicant also added that fistulas were serious

conditions and unpleasant to patients, and they were reported not to respond well with conventional medical therapies and reoperations were often required after a surgical operation, therefore, fistulising Crohn's disease was included in the indication, considering the high efficacy of infliximab in placebo controlled clinical studies abroad. The Evaluation Centre understands that Crohn's disease with external fistulas is refractory to treatments and the clinical symptoms present large problems, efficacy was confirmed in studies in overseas patients with external fistulas and a correlation of CDAI improvement and closure of fistulas is predicted. However, for this indication, 3 infusions are required, as the patients who are refractory to other therapies are targeted and we cannot deny that there are insufficient data available on efficacy and safety of multiple infusions in Japanese patients at the time of the approval evaluation. Keeping these points in mind, considering clinical needs for the indication as a priority and referring to overseas safety data, the Evaluation Centre would like to accept the reply which stated that the efficacy for this indication was suggested. In this instance, it is essential to instruct the applicant to gather sufficient safety information regarding this indication after the launch. The Evaluation Centre is planning to make the final decision on the Indication and Approval Conditions after to consulting with the experts.

[Safety of infliximab]

The Evaluation Centre requested the applicant to review the possibility of an increased incidence of malignant tumours with long-term use of infliximab based on clinical study data. Reported malignant tumours that were developed during clinical studies or during follow-up were; 1 case of B cell lymphoma, which developed during the study period of an overseas Crohn's disease study and 4 cases in total of thyroid papillary carcinoma, prostate cancer, intestine signet-ring cell carcinoma and skin cancer which were found during follow-up. In an overseas chronic rheumatoid arthritis study, 2 cases of B-cell lymphoma, 2 cases of melanoma, 1 case each of Hodgkin's lymphoma, gastric adenocarcinoma, colon cancer, myeloma and skin basal cell carcinoma, which make 9 in total, and in ATTRACT xxxxx in an overseas chronic rheumatoid arthritis study, 3 cases in total of lymphoma, concurrent squamous cancer and malignant melanoma and rectal adenoma, in a Japanese chronic rheumatoid arthritis study, 1 case each of breast cancer and lung cancer and in a overseas xxxxxx study in xx patients, 1 case of B-cell lymphoma were reported (total number of subjects received administration: 771 aboard and 118 in

Japan). The applicant replied that the relationship of infliximab and development of malignant tumours was currently unclear, and it has been reported that the incidence of malignant tumours in patients with chronic rheumatoid arthritis and Crohn's disease was high, in patients with chronic rheumatoid arthritis, the duration of illness and the incidence showed a correlation and the incidence of malignant tumours in patients using an immunosuppressant was high. In 3-year follow-up of a clinical study in overseas patient with Crohn's disease, 1 case out of 199 patients developed malignant lymphoma (0.5%). According to literature, the incidence of malignant lymphoma in patients with Crohn's disease receiving treatments including an immunosuppressant was 0% to 0.64%. Data up to week 54 of the overseas phase III study in chronic rheumatoid arthritis (ATTRACT) were compared with the NIH SEER database, but no significant difference was found. Furthermore, in the USA, between *month/year* and *month/year*, about 34,000 patients with Crohn's disease received infliximab and in November 1999, chronic rheumatoid arthritis was added to the Indication. Serious post-marketing adverse events so far reported were 14 cases of malignant tumours (2 cases of small intestinal adenocarcinoma, 1 case each of Hodgkin's lymphoma, myeloid leukaemia M5, mucinous adenoma, seminoma, sequamous cancer, bladder cancer, laryngeal cancer, prostate cancer, cancer with adenosis, cervical cancer, adenocarcinoma and pancreatic cancer), 8 cases of lupus, 4 cases of multiple neuropathy (3 not recovered), and 17 cases of anaphylactic or anaphylactoid reactions.

Although the relevancy of infliximab on incidents of serious adverse events including malignant tumours was thought to be unclear so far, the Evaluation Centre judged that the fact that they occurred needed to be described in the prescribing information to alert people.

The Evaluation Centre instructed the applicant to review a relationship between HACA expression and infusion reactions, in view of multiple infusions in patients with external fistulas. In all studies and Crohn's disease studies, the incidence of infusion reactions was 10.8% (all studies: 22/203) and 13.8% (Crohn's disease studies: 16/116) in HACA negative patients, respectively; and 36.3% (29/80) and 38.9% (7/18) in HACA positive patients, respectively; thus the incidence was higher in the positive patients. The incidence by the number of infusions was increased to 10.2% (31/304) by the second infusion and of those, 4 cases developed serious infusion reactions (3 in the Crohn's disease study xxxx and 1 in the chronic rheumatoid arthritis study xxxx) and the infusion

was discontinued. HACA production was confirmed in 3 patients, but all of them recovered with discontinuation or medical interventions, showing reversibility. In the overseas phase III study in chronic rheumatoid arthritis, in which multiple doses of 15 infusions were administered in 54 weeks (xxx), no increase in infusion reactions with repeated doses was observed and no serious infusion reactions developed. From above, the applicant responded that they believed that there was a relevancy between HACA expression and irreversible reactions such as an anaphylactic shock.

As the incidence of infusion reactions was increased with HACA expression and patients were discontinued because of that, the Evaluation Centre judged that the prescribing information needed to state that HACA was expressed with infliximab infusions, the incidence of infusion reactions increased and if a patient was receiving multiple repeated infliximab infusions, the infusion should be carried out under full observation; and instructed the applicant to add these to the Important Basic Precautions of the prescribing information.

[Endpoints of infliximab clinical assessment]

As clinical studies of infliximab employed several evaluation methods, the Evaluation Centre asked for the rationales and the details.

As a rationale for setting more than a 70-point reduction of CDAI from baseline as CDAI improvement, the applicant replied as follows: A review of a correlation of a 4-levelled overall assessments by physicians and CDAI showed that it was appropriate to draw a line between the active phase and the inactive phase at CDAI 150 and a line between the active phase and extremely severe cases at 450. They decided to use 'more than 70-point reduction', because 70 was a difference of 220 which was the lowest CDAI for the inclusion criteria used in overseas studies and 150 which was the lowest value of CDAI for the active phase. The Evaluation Centre accepted the response.

IOIBD, CPR and Erythrocyte Sedimentation Rate (ESR) used in inclusion criteria in Japanese studies were used in a definition of remission in the draft amendment of Crohn's disease treatment guideline in Japan and were widely used in Japan. The applicant also added that they used these in the inclusion criteria of infliximab clinical studies, as they were employed in clinical studies of a similar drug, mesalazine. For comparisons with overseas studies, CDAI, which was used commonly, was used.

A correlation between CDEIS and CDAI was investigated, and the correlation coefficient was r=0.561, and also IBDQ, which was used for QOL assessment, was negatively correlated with CDAI, at r=-0/67. The applicant replied that, therefore, it was appropriate to use them as endpoints.

The Evaluation Centre suspected that differences in the way studies were carried out in Japan and abroad had an influence on the different assessment methods used in Japan and abroad. However, as CDAI for evaluating the activity of Crohn's disease was often used abroad and known to be reliable, the Evaluation Centre judged the clinical assessments in the submission were appropriate.

[Concerning Indication and Dosage and Administration]

The applicant was instructed to review consistency of the description of Indication with the overseas indication. The Evaluation Centre judged the following description appropriate.

The Indication in the submission was "for reducing symptoms of patients with moderately to severely active Crohn's disease who have had an inadequate response to prior conventional therapy, reduction in the number of draining external fistulas of patients with fistulising Crohn's disease", but it was changed to "Treatment of the following Crohn's disease patients who have had an inadequate response to prior conventional therapies: (1) patients with moderately to severely active diseases, (2) patients with draining external fistula."

Originally, Dosage and Administration was "For patients with moderately to severely active Crohn's disease who have had an inadequate response to prior conventional therapy, a single dose of 5 mg/kg should be administered as intravenous infusion. For Crohn's disease patients with draining external fistulas, 5mg/kg doses should be administered as intravenous infusion at 2 and 6 weeks after the initial infusion", but they agree to change it to "1. Patients with moderately to severely active disease: administer an intravenous infusion of 5 mg/kg, taking more than 2 hours. 2. Patients with external fistulas: administer intravenous infusions of 5 mg/kg 2 and 6 weeks after the initial dose, taking more than 2 hours." Precautions for Use Concerning Dosage and Administration was changed from "Re-treatment: If a symptom recurs, re-administer infliximab within 14 weeks from the initial treatment. Long-term efficacy of a re-treatment has not been established." to "Re-treatment: It has been reported that serious delayed adverse drug

reactions occurred with re-administration of infliximab after long drug-free intervals. Therefore, if symptoms of Crohn's disease recur, re-administer infliximab within 14 weeks from the initial treatment. Long-term efficacy of a re-treatment has not been established" to raise a caution for delayed adverse drug reactions with a re-administration. Furthermore, the details of previous conventional therapies, "Infliximab should only be administered if clear clinical symptoms attributed to Crohn's disease persist after appropriate therapies, including a nutritional intervention and drug treatment (a 5-acetylsalicylic acid preparation and/or an adrenocortical hormone)" were added.

3. Compliance Review Reports by OPSR and Evaluation Centre's Decision

1) Evaluation Centre's Decision on Document Compliance Inspection

As the outcome of a document compliance inspection of Remicade I.V. Infusion 100, the OPSR pointed out some protocol violations. The protocol violations that may affect safety were also reviewed during the approval evaluation.

After full review of protocol violations that may affect efficacy and safety, the Evaluation Centre judged that the handling of the cases was appropriate and inclusion of them in the approval evaluation data would cause no problem.

2) Evaluation Centre's Decision on GCP on-site Inspection

Use of concomitant medications in one case was not described in the CRF, but as a result of a GCP Assessment Meeting, it was not considered to be GCP incompliant. The Evaluation Centre judged that there was no problem in carrying out evaluation based on the approval evaluation data.

4. Overall Assessment

As a result of the review of the submitted data as described above, the Evaluation Centre believes that infliximab could be approved after amending Indication and Dosage and Administration as follows. However, as there is a pharmacological possibility of developing tumours with administration of infliximab and HACA expression was observed with multiple infusions, we need to pay full attention to a long-term use of infliximab. We will make a decision on the approval of infliximab after discussion

especially of the safety issues of infliximab with the expert council members, including a necessity to conduct a carcinogenicity study.

[Indication]

Treatment of the following Crohn's disease patients who have had an inadequate response to prior conventional therapies:

(1) patients with moderately to severely active diseases

(2) patients with draining external fistula

[Dosage and Administration]

1. Patients with moderately to severely active disease: administer an intravenous infusion of 5 mg/kg, taking more than 2 hours.
2. Patients with external fistulas: administer intravenous infusions of 5 mg/kg 2 and 6 weeks after the initial dose, taking more than 2 hours.

9th February 2001

Evaluation Report (2)

1. Application

Product Name	Remicade IV Infusion 100
Non-Propriety Name	Infliximab (recombinant)
Applicant	Tanabe Seiyaku Co., Ltd.
Submission Date	27th September 1999

2. Summary of Evaluation

With the Evaluation Report (1), the Evaluation Centre asked expert members for their opinions. This report is the outcome of the evaluation on the basis of consultations with the expert council members.

1) Concerning specifications and test methods and data on stability

(1) Concerning specifications and test methods

(i) Insoluble particulate matter test

The Evaluation Centre believed that a specification on insoluble particulate matter was essential, since Remicade was an injection that required reconstitution before use, and the Evaluation Centre asked for the reason for not establishing the Insoluble Particulate Matter Test. The applicant explained that because of the characteristics of protein particulates produced when Remicade was reconstituted with Water for Injection, values that were measured using the automated method of the Light Obstruction Particle Count Test would be very likely to vary widely. They also explained, based on actual measurements, that particles that would be detected by the Insoluble Particulate Matter Test were removed, as a 1.2 μm in-line filter was used when infusing. They replied that the specification for the alternative test, the Particle Test, was established appropriately compared with the Insoluble Particulate Matter

Test. The Evaluation Centre judged the established specification was acceptable, providing that the Dosage and Administration column stated that an in-line filter must be used when infusing.

(ii) SDS-PAGE Test Method of the Purity Tests

The Evaluation Centre judged that there was a danger that the SDS-PAGE Test Method for the formulated product did not assure the quality of infusions received by patients, as the test used a solution passed through a xx μm filter, but patients would receive the formulated product after removal of insoluble matters with a 1.2μm in-line filter in medical practice. Therefore, the applicant was instructed to perform SAS-PAGE using solutions that were obtained by passing Remicade through a xx μm filter and a 1.2μm filter, either to demonstrate no difference between them, or, if there was a difference, the test method should be changed to use a 1.2μm filter. The applicant agreed to this and is currently carrying out the test. The test result will be reported to the Evaluation Centre by *date/month/year*. The applicant stated that they would re-set the test method without delay, if there was a difference between the filters. The Evaluation Centre accepted the reply.

(iii) Heterogeneity of carbohydrate chains

To one molecule of infliximab, two strands of N-linked, double strand, complex carbohydrate chains are linked, but xxxxxxxxx confirmed the existence of xxx types of molecule species. The abundance ratio of each molecule species on the basis of this heterogeneity of carbohydrate chains was not set as a specification, but the Evaluation Centre believed that the heterogeneity of carbohydrate chains should be established in the Specifications and Test Methods, as the evaluations should be based on the current scientific standard, and requested the applicant to establish a test method. In response, the applicant stated that they would establish a molecule weight distribution test using mass spectroscopy as an in-process management test. However, the Evaluation Centre requested the applicant to establish a quantitative test method on heterogeneity of carbohydrate chains, considering the molecule weight distribution test insufficient, as it

would provide qualitative information but not quantitative information. The applicant replied that they decided to establish a quantitative method for carbohydrate chain analysis by xxxxxx with xxxxx and to manage heterogeneity of the carbohydrate chains within a certain range by establishing a standard for the abundance ratio. The Evaluation Centre accepted this reply.

(iv) Clarity and colour of solution

As the colour of the actual solution did not agree with the colour of the solution established as a part of the purity tests for the formulated product, the Evaluation Centre requested an amendment to the specification. The Applicant replied that they would amend the specification on the colour of the solution and the Evaluation Centre accepted the response.

The expert council members supported the above applicant's responses and the Evaluation Centre's judgements on the specifications and test methods.

(2) Concerning reconstitution and diluent

As Remicade is freeze-dried formulation, it is prepared by reconstituting with Water for Injection then diluting with JP Physiological Saline. The Evaluation Centre asked if it was possible to use Physiological Saline for reconstitution and to dilute with other infusions. The applicant answered that the quality would not be affected if Physiological Saline were used for reconstitution. They stated, however, injectable solutions other than Physiological Saline should not be used for dilution because the electrophoresis pattern created by isoelectric focusing showed a change after 24-hour standing when it was dissolved in with a 5% glucose solution, which was a common use in medical practice, and also insoluble matters were found when a trace amount of Zn^{2+} or Fe^{3+} was present. Following this, the Evaluation Centre instructed the applicant to amend the Precautions for Application in the Prescribing Information, including the precaution given for reconstitution of Remicade.

(3) Concerning descriptions on the import approval application form

The Evaluation Centre instructed the applicant that the column for the Manufacturing Method in the import approval application form needed to describe all processes that assured the quality and specifications of infliximab. The applicant amended the descriptions on various processes and procedures, including processes for MCB and MWCB preparation and maintenance, cell culture and isolation/purification, so that they were more detailed. The Evaluation Centre and the expert council members accepted these.

(4) Concerning stability

The result of the accelerated study (30°C, 24 months) of the formulated product showed that it was stable apart from slight time-changes in the Particle Test and the Insoluble Foreign Matter Test. In the Stress Study (light), it was stable, showing no change with exposure of 1,200,000 Lux·hr and total near-ultraviolet radiant energy of 200W·hr/m^2.
Based on the above and long-term storage study results, the applicant stated that the formulated product in colourless glass vials that was stored between 2 and 8 °C would be stable for 3 years.

2) Concerning data on toxicity

In an expert consultation, a necessity of implementing a carcinogencity study was pointed out, as there was a concern over a reduction in immune actions due to the TNFα inhibition. To this, the applicant replied that they believed implementation of a carcinogenicity study was unnecessary at the moment for the following reasons.
Infliximab is a chimeric (mouse/human) monoclonal antibody specific to human TNFα. It shows a strong anti-TNFα action towards human and chimpanzee's TNFα, but is not crossreactive towards experimental animals, such as mice, rats and rhesus monkeys and it has been confirmed that infliximab does not inhibit the TNFα activities of those animals. Therefore, toxicity studies in common experimental animals are considered to

be inappropriate as a validation method that would demonstrate the toxicity profile of infliximab on the basis of its pharmacological actions. Furthermore, in a rat repeated dose toxicity study, a strong immune reaction to heteroprotein was developed, which made toxicity assessment of repeated-doses difficult. Therefore, the applicant created a new anti-mouse TNFα xxxxx antibody, thinking that if they produced an alternative antibody that suppressed TNFα in a similar way as infliximab did, it would provide useful information. With this antibody, the effect of a suppression of mice's TNFα activity was assessed in a mouse reproductive toxicity study, and also a 6-month chronic toxicity study is currently underway. No toxicological findings were obtained in the reproductive toxicity study and an interim result after 3 months of the 6-month chronic toxicity study also showed no toxicological findings.

At the same time, the applicant collected data on TNFα defective mice. There was no more increase in spontaneous tumours in TNFα defective mice compared with wild-type mice and a carcinogenicity study in TNFα defective mice with known carcinogens showed no more increase in oncogenesis than in wild-type mice (USA, BLA Supplement for Rheumatoid Arthritis, reference).

As above, the applicant replied that implementation of carcinogenicity studies in experimental animals with infliximab or alternative antibodies was not very meaningful, as no toxicological findings were obtained in the long-term toxicity study of infliximab, no genotoxicity of infliximab was observed, no toxicological findings were seen in the study using the alternative antibody to infliximab and the studies using TNFα defective mice did not show effects on oncogenesis or increases in tumours. Furthermore, they explained that xxx study (assessing events, QOL, disease conditions, etc., xxxxxxxxxxxxx in xx Crohn's disease patients for xx years) was started in the USA from *month/year*, and infliximab's effects on neoplasia in humans should be able to assess in the study.

As this approval application was made with an assumption that use of infliximab was for a limited period, i.e., in the acute phase of Crohn's disease for inducing remission, the expert council members and the Evaluation Centre judged that results of the toxicological studies did not suggest serious safety issues for use in this period and accepted the response of the applicant in essence.

However, they think that safety of long-term use of infliximab for remission

maintenance therapy in Crohn's disease and treatment of chronic rheumatoid arthritis, which are under development, require a fresh examination.

3) Concerning data on pharmacology

The expert council members asked for an explanation of the relationship between pharmacological actions observed in various human TNFα transgenic mice and the human pathology. The applicant replied as follows.

TNFα transgenic mice that are hyperexpressing human TNFα are not completely consistent with all aspects of the human pathosis said to involve TNFα, for example, different characteristics (pathology) are expressed depending on the strain because of differences in the gene expressing cells, etc., and a strain that presents intestinal pathological changes has not been established. However, pathophysiological and pathological changes seen in these transgenic mice, such as exhaustions and polyarthritis, are suggestive of similarities to the human pathology thought to involve TNFα. The reason for transgenic mice showing similar pathology to human's may lie in manifestation of inflammatory bioactivities through binding of human TNFα with mouse's TNFR I, since TNFR I, which is a type of TNFα receptor in mice, has almost the same affinity as human TNFR I. As infliximab improved the pathology of those transgenic mice, an inhibition of the binding of human TNFα with TNFR I is inferred. Furthermore, the TNFα's bioactivity neutralising effect in those mice models suggests that infliximab could improve pathology of Crohn's disease because of an association of human TNFα and Crohn's disease activities. The Evaluation Centre judged the studies with these model animals appropriate for showing the pharmacological actions of infliximab, and the expert council members agreed to this.

4) Concerning clinical data

The Evaluation Centre instructed the applicant to provide responses on safety and post-marketing surveillance after a consultation with the expert council members on major issues relating to efficacy and safety of infliximab, and then examined the clinical data.

(1) Was the clinical assessment of the efficacy of infliximab in Crohn's disease conducted appropriately? (Including extrapolation of overseas study results)

(2) Concerning appropriateness of the dose selection

With regard to those two points, the expert council members agreed to the Evaluation Centre's opinion that the drug was approvable with a reference to overseas dosage and administration, despite the small number of patients in Japanese clinical studies, because Crohn's disease was a retractable and rare disease with a strong need for clinical application of a new therapy. With regard to extrapolation of the data, the expert council members judged that it was acceptable, because the rationales for appropriateness of CDAI used in overseas clinical studies and setting of an increase of more than 70-points as an improvement were logical. However, the expert council members advanced a view that the clinical positioning of infliximab as a drug to be used in patients who were resistant to other therapies that were confirmed to be efficacious for this disease (drug treatments, such as steroids, mesalazine and salazosulfapyridine and elemental enteral alimentation), should be clearly stated.

(3) Concerning indication for treatment of patients with external fistulas

The expert council members advanced a view that administration to patients with external fistulas should be approved, considering current unavailability of any other effective treatments for this condition. They stated that the clinical usefulness was great, if operations could be avoided or recurrences after operations could be suppressed, considering that the outcome of operative therapies for the disease were not necessarily favourable. However, although more than 50% of patients achieving 100% closure of external fistulas in Crohn's disease patients sufficiently suggests usefulness of infliximab, persistence of the effect is still unclear and we need to wait for results of clinical studies on remission maintenance therapy for Crohn's disease. Furthermore, there was an opinion that it was unclear if infliximab could be the first choice, as no study was conducted directly comparing the efficacy of infliximab with

an immunosuppressant or nutritional intervention. Based on the above consultation, although only overseas data from clinical studies in patients with external fistulas were submitted, the Evaluation Centre judged that it was appropriate to include Crohn's disease patients with external fistulas (if a response to prior conventional therapies was inadequate) in the indication for infliximab, considering currently available therapies for the disease. The Evaluation Centre thinks that a post-marketing survey for confirming efficacy and safety in patients with external fistulas and long-term data (efficacy, safety, HACA, etc.,) is required after the launch, to which the expert council members agreed. With regard to the description of the indication in the column, "Indication", the expert council members advanced a view that the word "draining" was not needed as external fistulas were draining without an exception. The Evaluation Centre agreed to this and instructed the applicant to amend the description of "Indication".

(4) Concerning safety of multiple infusions

This submission concerns the indication in the remission induction phase. However, if one considers the clinical course of this disease, it is fully expected that maintenance therapy with infliximab is necessary after remission induction, in order to maintain the alleviation of the symptoms achieved through the induction. In this setting, because of the characteristics of infliximab, appearance of HACA and the associated reduction in the efficacy, and reduced safety are expected. Clinical results concerning multiple infusions shown in this submission are limited and we cannot see that the safety has been assured. The point most stressed in the consultation with the expert council members also concerned safety of infliximab multiple infusions. Currently, clinical studies on remission maintenance therapies have been conducted in Japan and abroad, but no final reports have been produced. The expert council members, therefore, advanced a view that there was a need to instruct the applicant to gather sufficient information in a post-marketing survey. Furthermore, they pointed out that it was necessary to investigate concurrent use with nutritional interventions or immunosuppressants, which was expected to happen in clinical practice, and sufficient post-marketing information gathering on the possibilities of developing malignant tumours or infections with multiple doses of infliximab.

From above, the Evaluation Centre judged that the applicant needed to gather sufficient information in a post-marketing survey and the Prescribing Information should be amended appropriately, as insufficient clinical data on multiple doses of infliximab were currently available, and decreases in responses and safety through appearance of HACA and development of malignant tumours and infections through immunosuppression of infliximab were expected. The expert council members also pointed out that the Prescribing Information needed to clearly state, "the indication for Remicade is limited to induction of remission, and efficacy and safety of the remission maintenance therapy has not been confirmed". Considering the merit of the infliximab treatment in treatment-resistant Crohn's disease patients and the associated safety, the Evaluation Centre judged that administrations of infliximab should be limited to the above indication, because sufficient amounts of information on safety of multiple doses of infliximab were not available.

With regard to durability of the effect with multiple doses, the Evaluation Centre said that the improvement maintenance effect of infliximab was not clearly shown quoting page 22, line 22 of the Evaluation Report (1), "In the assessment up to 48 weeks in patients who responded to the first infusion or the open label infusion and then received 10 mg/kg for 4 times every 8 weeks, the infliximab group showed no bigger decrease in the response than the placebo group in terms of CDAI improvement and the remission rate, but it was not possible to confirm significant improvement maintenance effects". To this, the expert council members presented their opinion that there was a problem in the timing of starting multiple doses in this trial and no significant difference was found because effects of previous infliximab treatment in the placebo group were unexpectedly persistent, therefore, the existence of a group of patients who showed continued response with repeated doses could be predicted from the result of this study. The Evaluation Centre agrees to the view, but believes that it is not possible to consider that a remission maintenance effect has been fully demonstrated in this study at the moment.

(5) Concerning safety statements in Prescribing Information of infliximab

The Evaluation Centre and the expert council members judged that the Prescribing

Information of infliximab described currently available safety data from overseas and Japanese clinical trials that were pooled and analysed and it provides the necessary information. However, further attention should be drawn to susceptibility to infections, development of malignant tumours, infusion reactions, etc. Therefore, they instructed the applicant to include more detailed descriptions advising not to carry out an infusion for remission maintenance therapy, usefulness of which has not been proven at the moment, and on an increased possibility of developing latent hypersensitivity with re-administrations after a more than 14-week interval from the previous infusion. The applicant submitted a revised draft, which added these points in "Important Basic Cautions" and "Careful Administration". The Evaluation Centre accepted this.

(6) Major issues on safety of infliximab

(i) On occurrences of malignant tumours and infections and the countermeasures

Follow-up surveillance data on occurrences of malignant tumours for xx years after completion of treatment in Japanese patients up to *day/month/year* were reported. In a follow-up of 25 patients with Crohn's disease, 91 patients with chronic rheumatoid arthritis, 2 patients with malignant rheumatoid arthritis and 4 patients with Behcet's disease, occurrences of 1 breast cancer, 2 lung cancer and 1 tongue tumour were found as malignant tumours and of those, the breast cancer was seen in a Crohn's disease patient. From overseas, malignant lymphoma, myeloma, malignant melanoma, squamous cell carcinoma and rectal adenocarcinoma, etc., were reported. With regard to infections, tuberculosis described below and 2 cases (abroad) with exacerbation of hepatitis B, to which relationships of infliximab were uncertain but suspected, were reported. With regard to tuberculosis, on 20th December 2000, the EMEA reported 28 cases of tuberculosis (9 in north America and 19 in Europe) found in the post-marketing surveillance (from August 1998 till December 2000) of patients who received infliximab and added statements to the SPC (Summary of Product Characteristics) and Package Leaflet, including not to administer infliximab to patients

suspected with tuberculosis unless the suspicion was cleared, patients should always be evaluated for active or latent tuberculosis prior to the treatment and if the symptoms of tuberculosis appears during therapy, notify the doctor immediately. The Evaluation Centre obtained details of all cases on *day/month/year* from the applicant and reviewed the cases. Ten out of 28 cases had been diagnosed with Crohn's disease and the rest were with chronic rheumatoid arthritis and many of them used concurrent medications including steroids, azachioprine, 6-metocaptoprin and mesaladie. The number of times infliximab infusion were received by the patients was once by 5 patients, twice by 5, 3 times by 14, 4 times by 1, 6 times by 2 and times unknown by 1. One patient with chronic rheumatoid arthritis died and another patient with Crohn's disease died from gastrointestinal haemorrhage and advanced renal failure, but the patient's doctors ruled out involvement of tuberculosis. As a result of the review, the Evaluation Centre decided that there was a need to "Contraindicate" infliximab to patients with serious infectious diseases including tuberculosis, "Careful Administration" was required to patients with a history of tuberculosis and "Warnings" on occurrences of serious infections were required, and instructed the applicant to add the necessary descriptions to the Prescribing Information.

(ii) Concerning a relationship of HACA and infusion reactions

To date, HACA production with administration of infliximab has been reported. As production of HACA might be related to infusion reactions, the applicant was asked to provide the method of the HACA test and to illustrate available data on causal relationships of HACA and infusion reactions in order to examine a need for HACA testing before re-administration.

As the Sandwich ELISA method that uses infliximab as a ligand is employed for the HACA test, it is not possible to measure HACA while infliximab is present in blood. Therefore, measurements could only be taken on at least 12 weeks from administration of infliximab (it has been demonstrated that the elimination half-life of one dose of 5 mg/kg infliximab to patients with Crohn's disease is about 8 days and it takes about 12 weeks or more to be eliminated from the blood after dosing). Therefore, a presence of HACA could be confirmed, if a test is positive after 12 weeks, but it is not detectable

before that. Currently, methods to test for HACA in the presence of infliximab are being investigated, but none are established.

The applicant explained the relationship of HACA and infusion reactions, presenting the results of a study implemented abroad. In a study, in which patients who had participated in previous clinical trials of Crohn's disease received re-administrations (up to 5 doses), 10 out of 40 patients developed latent adverse drug reactions including muscle pains, rash and fevers, on 3 to 12 days after a re-administration, but all of them showed negative HACA immediately before the re-administration and only 1 out of 10 patients had a history of positive HACA in the previous clinical trial. HACA was tested in 6 out of 10 patients who showed the latent adverse drug reactions, and all of them were turned HACA positive. Seven patients were HACA positive, but did not show latent hypersensitivity reactions. Based on these, the applicant responded that HACA could be detected after development of a latent hypersensitivity reaction, but it was not possible to predict a risk of developing latent hypersensitivity reactions from a test before re-administration. At the same time, when incidences of infusion reactions in patients who turned HACA positive during any studies (HACA positive patients) and HACA negative patients were compared, in the Crohn's disease studies, they were 38.9% (7/18) in HACA positive patients and 13.8% (16/116) in HACA negative patients, showing a higher incidence in HACA positive patients. Similarly, in a pooled analysis of studies in chronic rheumatoid arthritis, the incidence in HACA positive patients was higher, 36.3% (29/80) in positive patients and 10.8% (22/203) in negative patients. Three out of 4 patients with serious infusion reactions and 5 out of 9 patients who had to discontinue the infusion due to infusion reactions were HACA positive patients. The applicant stated that the above suggested higher incidences of infusion reactions in HACA positive patients, but as stated before, infusion reactions and latent hypersensitivity could not be predicted by testing before re-administration with the existing HACA test method. The Evaluation Centre understood problems with the currently available test method, however, noted that the incidence of adverse drug reactions in HACA positive patients was high and decided that improvement on the test method and a continuous accumulation of data from patients who received treatment were necessary, therefore the Centre requested the applicant to take measures. The applicant replied that they would test HACA as a part

of routine visits to clinics with request of medical facilities after launch, so the Evaluation Centre accepted the reply. The Evaluation Centre believes that it is necessary to establish a method of measuring HACA in patients receiving infliximab treatment, and that patients should be asked if they have received infliximab treatment before, and re-treatment of any patients should be carried out with a caution, as there is no certain way to predict infusion reactions after re-administration at the moment. With regard to this issue, the Prescribing Information has a description under "Careful Administration" to the effect that infliximab should be re-administered to a patient with caution.

With regard to the rationale for the "Warning" on occurrences of hypersensitivity when re-administering after an interval of 14 weeks or more, the applicant stated that re-analysis of cases who received re-administration of infliximab in Crohn's disease clinical studies showed latent hypersensitivities in 12 patients out of 39 patients who received 39 doses, although the number of the patients had an interval of over 14 weeks was small. At the same time, none of the 212 patients who received 309 doses and were re-treated within 14 weeks showed latent hypersensitivities. The applicant stated that based on these analyses, they added a statement, "if re-administering after an interval of 14 weeks or more, observe fully, preparing for an occurrence of latent hypersensitivity", to the Prescribing Information.

(7) Concerning an outline of a post-marketing clinical study and currently on-going clinical studies of infliximab

The Evaluation Centre asked the applicant to submit an outline (draft) of the post-marketing survey considering the above evaluation.

As the outlined plan for the post-marketing survey for the filed indication for treatment of the acute phase, they replied that they were planning to investigate patient background, concomitant medications, efficacy and adverse events (including events at re-infusions) in xxx patients with moderately to severely active Crohn's disease and Crohn's disease patients with external fistulas. They also said that they were going to focus on safety information and step-up the gathering of spontaneous reports and analyse adverse events reported from medical facilities where infliximab was delivered.

Currently, 2 studies of infliximab are underway abroad investigating remission maintenance therapy. In xxxxxxxxxxxxxxx study, xxxxx moderately to severely active patients were divided into xxx groups, receiving xxx doses for xxx weeks xxxxxxxx weeks and in xxxxxx study, xxxxx patients with closed fistula who were divided into xxxx groups, receiving xx doses for xxxx weeks xxxxxx week. A Japanese remission maintenance therapy study in Crohn's disease targeted xx patients with xxxxxxxxx who received infliximab at xxxxxxxx weeks xxxxxxxxxxxxxxxxxx. It was started in *month/year,* and treatment of xxxth patients has started in *month/year*. In addition, long-term studies targeting chronic rheumatoid arthritis and Behcet's disease are also in progress. The applicant stated that with these post-marketing survey, post-marketing safety up-date and clinical studies in Japan and abroad, they could collect and analyse information on infections, incidences of malignant tumours, incidences of infusion reactions and HACA, relationships of adverse drug reactions and responses, and relationships with concurrent medications, etc.

The Evaluation Centre believes that it is important to collect and analyse sufficient information in the post-marketing surveillance following the outline of the plan.

5) Concerning Indication and Dosage and Administration of infliximab

As a result of evaluation based on the deliberation on the above points with the expert council members, the applicant was instructed to amend "Indication" and "Dosage and Administration" of infliximab as follows. With regard to "Indication", in order to clarify that infliximab is not the first choice for Crohn's disease, it was changed to "for treatment of Crohn's disease with the one of the following conditions (only when the patients have had an inadequate response to prior conventional therapies)" and then simply stated "patients with external fistulas" considering conditions of patients with external fistulas. Furthermore, the applicant was instructed to change the description illustrating 'prior conventional therapies' in the section of "<Precautions for Use Concerning Indication>", considering the way Crohn's disease was medically treated now, so that it read "Remicade should be administered if a clear clinical symptom attributed to Crohn's disease persists after appropriate therapies, such as nutritional interventions and drug treatments (e.g. 5-aminosalicylic acid preparations)". With

regard to “Dosage and Administration”, because the use of an in-line filter during infusion was considered essential as a prerequisite for accepting the Particle Test as an alternative to an Insoluble Particulate Matter Test in the Specifications and Test Method of the formulated product, the applicant was instructed to add “when administering Remicade, use an in-line filter with the membrane filter pore size of 1.2μm or less”.

3. Amendments to the Evaluation Report (1)

1) p.10, line 15: replace “dialysis by ultrafiltration” with “condensation and dialysis by ultrafiltration”.
2) p.10, line 16: replace “viral validation” with “process validation”.
3) p.17, line 19: replace “(an average taken from 3 animals in total; 1 male and 2 females)” with “(an average taken from 3 animals in total; 2 males and 1 female)”.
4) p.17, 2nd line from the bottom: replace: replace “respectively, 94.8μg/mL and 74.6 hours and 165μg/mL and 274 hours” with “respectively, 129.7μg/mL and 78.5 hours and 188.6μg/mL and 266.2 hours”, following the applicant’s report of errors on figures in the document.
5) p.29, line 6: replace “Of patients who received the liquid formulation in the previous treatment, 37.5% (9/24) developed latent adverse drug reactions which was higher than 6.3% (1/16) of patients who received the freeze-dried formulation in the previous treatment” with “Of patients who received the liquid formulation in the previous treatment, 39.1% (9/23) developed latent adverse drug reactions which was higher than 5.9% (1/17) of patients who received the freeze-dried formulation in the previous treatment”, following the applicant’s report of errors on figures in the document.
6) p.32, line 15: replace “11 out of 25 patients (44%) received a nutiritinal intervention of over 1,200 kcal/day concurrently with a steroid in the Japanese study” with “11 out of 25 patients (44%) received a nutritional intervention of over 1,200 kcal/day or a steroid concurrently in the Japanese study”.
7) p.39, line 8: replace “a 5-acetylsalicylic acid preparation” with “ a 5-aminosalicylic acid preparation”.
The above amendments do not affect the evaluation result.

4. Overall Judgement

Based on the above evaluation result, we have judged that the product is approvable providing that amendments to the Indication and the Dosage and Administration and additions of the Precaution for Use Concerning Indication and the Precaution for Use Concerning Dosage and Administration are made as follows, and the product should be discussed by the 1st Committee on Drugs. As infliximab is an orphan drug, we consider the re-examination period of 10 years is appropriate. Considering its acute toxicity and the Dosage and Administration, the drug substance should be classified as a powerful medicine. As this product is a mouse/human chimeric anti-TNFα monoclonal antibody, which is new as a chimeric antibody, and it is not a salt, derivative or substitution product of an approved product with a similar pharmacological action to the approved product, it should be discussed in a Pharmaceutical Affairs Sectional Meeting.

[Indication]

Treatment of Crohn's disease with any of the following conditions (only when the patients have had an inadequate response to prior conventional therapies)

Patients with moderately to severely active diseases

Patients with external fistula

<Precautions for Use Concerning Indication>

Remicade should be administered if a clear clinical symptom attributed to Crohn's disease persists after appropriate therapies, such as nutritional interventions and drug treatments (e.g. 5-aminosalicylic acid preparations).

[Dosage and Administration]

- For patients with moderately to severely active disease:
  Intravenously infuse 1 dose of 5 mg per 1 kg of body weight.
- For patients with external fistulas:
  Intravenously infuse 3 doses (the initial dose, 2 weeks later and 6 weeks later)

of 5 mg per 1 kg of body weight.

When administering Remicade, use an in-line filter with the membrane filter pore size of 1.2μm or less.

<Precautions for Use Concerning Dosage and Administration>

1) Retreatment

It has been demonstrated that the effect of Remicade appears by 2 weeks after dosing and the response is maintained for several weeks. Therefore, observe the patient for at least 2 weeks from a treatment and if the patient responds and then redevelops a symptom of Crohn's disease, the patient may be retreated with Remicade. Long-term efficacy of a retreatment has not been demonstrated. When re-treating a patient with Remicade, observe the patient carefully, preparing for an occurrence of delayed hypersensitivity.

2) Administration method

Remicade should be intravenously infused gradually, taking more than 2 hours, through an independent infusion line.

NIHS 3730

1st November 2001

To the Director-General of Pharmaceutical and Medical Safety Bureau, Ministry of Health, Labour and Welfare

Director-General of National Institute of Health Sciences

Evaluation Report (2)

This is to report the outcome of the additional evaluation, which was carried out by the Pharmaceuticals and Medical Devices Evaluation Centre, concerning a medicinal product, Remicade IV Infusion 100, of which the outcome of the evaluation has been reported in NHIS 2128 on 9th February 2001.

Outcome of the Evaluation

Produced on 1st November 2001

[Product name] Remicade IV Infusion 100

[Non-propriety name] Infliximab (recombinant)

[Applicant] Tanabe Seiyaku Co., Ltd.

[Submission date] 27th September 1999

[Outcome of evaluation]

<Overall Assessment>

As a result of the evaluation by the Pharmaceuticals and Medical Devices Evaluation Centre, we judged Remicade approvable under the following Indication and Dosage and Administration.

Indication

Treatment of Crohn's disease with any of the following conditions (only when the patients have had an inadequate response to prior conventional therapies)

Patients with moderately to severely active diseases

Patients with external fistula

<Precautions for Use Concerning Indication>

Remicade should be administered if a clear clinical symptom attributed to Crohn's disease persists after appropriate therapies, such as nutritional interventions and drug treatments (e.g., 5-aminosalicylic acid preparations).

Dosage and Administration

For patients with moderately to severely active disease:

Intravenously infuse 1 dose of 5 mg per 1 kg of body weight.

For patients with external fistulas:

Intravenously infuse 3 doses (the initial dose, 2 weeks later and 6 weeks later) of 5 mg per 1 kg of body weight.

When administering Remicade, use an in-line filter with the membrane filter pore size of 1.2μm or less.

<Precautions for Use Concerning Dosage and Administration>

1) Retreatment

It has been demonstrated that the effect of Remicade appears by 2 weeks after dosing and the response is maintained for several weeks. Therefore, the patient should have a minimum of 2-weeks follow-up after a treatment and if the patient responds and then redevelops a symptom of Crohn's disease, the patient may be re-treated with Remicade. Long-term efficacy of retreatment has not been demonstrated. When re-treating a patient with Remicade, observe the patient carefully, preparing for an occurrence of delayed hypersensitivity.

2) Method of reconstitution and dilution of Remicade

One vial of Remicade should be reconstituted with 10 mL of JP Water for Injection. A necessary amount of Remicade solution determined from body weight of the patient should be diluted in about 250 mL of JP Physiological Saline. It should not be mixed with other injections, infusion fluids, etc.

3) Administration method

Remicade should be intravenously infused gradually, taking more than 2 hours, through an independent infusion line.

Evaluation Report

1st November 2001

[Product name]	Remicade IV Infusion 100
[Non-propriety name]	Infliximab (recombinant)
[Applicant]	Tanabe Seiyaku Co., Ltd.
[Submission date]	27th September 1999 (submission for an approval to import the formulated product)

1. Details of Evaluation

As the culture medium used in a production process of infliximab contains a material derived from cattle that is against a director-general's notification that prohibits use of the material as a raw ingredient of a medicine because of a potential risk of Transmittable Spongiform Encephalopathies (TSEs), the Evaluation Centre reviewed the safety of this material derived from cattle. Safety data on infliximab that were reported since the production of the evaluation report (NHIS 2128 on 9th February 2001, hereinafter referred to as Evaluation Report (1)) were also reviewed and described in the following report.

(1) Concerning safety of the material derived from cattle used in the infliximab production

In production of infliximab, a material derived from the cattle spleen is used as an ingredient of a cell culture medium (product name:xxxxxxxxxx), but the cattle spleen is one of the ingredients that are prohibited for use as raw materials of medicines in the director-general's notification, issued on 12th December 2000 (PAB1226 "Concerning Quality and Safety Assurance of Medicines, etc., Manufactured Using Bovine-Derived Materials as an Ingredient"). The Evaluation Centre, recognising safety of xxxxxxxx as an important issue on the quality of infliximab, had two consultations with expert council members on this issue and assessed safety of infliximab.

1) Concerning xxxxxxxxx

xxxxxxxx is a type of peptone and a mixture of amino acids and peptides obtained by hydrolysis of the cattle spleen and blood by xxxxxxxx enzyme. TSEs, including Bovine Spongiform Encephalopathy (BSE), are said to be transmitted by infectious prions (PrP^{SC}) which are glycoproteins with a molecular weight of between 30,000 to 35,000, and they are transmitted through a consumption of tissues from an infected animal that contain PrP^{sc}. According to the risk assessment on BSE infection made by the European Union Pharmaceutical Committee, the cattle spleen is classified into Category II along with the dura maters, intestines, etc., which are the most dangerous organs after the brain, spinal code, etc. (Category I)

The Evaluation Centre asked the applicant's view on a potential risk of BSE infection with infliximab through a use of xxxxxxxxxx in the production process. The applicant responded with their view that it did not pose a risk for the following reasons.

(i) xxxxxxx was made from materials that were derived from cattle in a region where BSE has never been seen.

(ii) Molecular weight distribution of xxxxxxxxxxxxxxx was measured and no molecule was over xxxxxxx, so it is considered unlikely to be contaminated with PrP^{sc}.

(iii) Even if xxxxxxxx was contaminated with PrP^{sc}, it receives ultrafiltration with a membrane with a molecular cut-off point of xxxxx before it is added to the medium, which will prevent contaminations with PrP^{sc} in the manufacturing process.

(iv) The purification process of infliximab could prevent contamination of the bulk solution and the formulated product with PrPsc.

The Evaluation Centre considered that a replacement is necessary, for example replacing the ingredient of the medium with peptones that were not originated from the cattle spleen or replacing the medium with another medium containing amino acids, as even if BSE had not been seen in the country of origin at the moment, BSE might be found in future. Therefore, the Centre asked the applicant to consider a review of the manufacturing method. The applicant replied that it was impossible to address this immediately, as culture process validations, etc., for making an alternation to the medium will take several years.

2) Concerning safety assessment on the medium for infliximab production

The Evaluation Centre consulted expert council members regarding safety of xxxxxxxxxxx as an ingredient of the medium with the safety data submitted by the applicant.

(i) Possibility of removal of PrP^{sc} contamination in the raw material

Expert council members advanced an opinion that, xxxxxxxxx treatment in a production process of xxxxxxx would not affect the infectiousness, as PrP^{sc} is xxxxxxxx. In their opinion, ultrafiltration before it was added to the medium would be effective in removing PrP^{sc}. They made a suggestion to repeat ultrafiltration twice with different cut-off values. It has been reported that a contamination of the culture solution with PrP^{sc} could cause abnormalities in normal prions (PrP^{c}), when cultured cells in a cell culture system produced a large amount of PrP^{c} (J.Virol., 74:320, 2000), therefore, if the medium is contaminated with PrP^{sc}, they need to give consideration to a build-up of PrP^{sc} in the culture process. The expert council members advanced an opinion that if a process, for example a bioassay of the final product to rule out PrP^{sc} contamination, was added, safety of infliximab would be enhanced further.
The applicant referred to a report on scrapie prions (Golker c. F., et.al., Biologicals, 1996; 24, 103) and used it as a rationale for removal of PrP^{sc} with ultrafiltration, but the expert council members advanced an opinion that the capacity needed to be assessed on the model of the real-life manufacturing process.
On the applicant's claim that even if PrP^{sc} contaminated the culture supernatant, several types of column chromatography in the purification process of infliximab, which were carried out after infliximab production by cell culture, would remove PrP^{sc}, the expert council members pointed out that it was not established, as the behaviour of PrP^{sc} in chromatography has not been defined.
Furthermore, they concluded that the above discussion was on an assumption that the raw material, i.e., the cattle spleen, did not contain PrP^{sc}, and they could not say that it was safe because of the removal process with ultrafiltration, even if a material with

PrP^{sc} was used.

(ii) Concerning detection of PrP^{sc}

The expert council members advanced an opinion that it maybe possible to check the final safety of the formulated product in an assay for PrP^{sc}. The expert council members provided information that, although no assay system that was sensitive enough to be put into practical use as a test method for medicines has been established up to now, highly sensitive detection methods other than bioassays have been under development.

(iii) Possible alternatives for the medium ingredient

The expert council members supported the Evaluation Centre's view that the peptone added to the medium needed to be replaced with a peptone not derived from the cattle spleen on the assumption that the currently BSE free regions became BSE positive. Another opinion was presented, which was, even if cattle did not show a symptom of BSE, one could not say with a certainty that PrP^{sc} did not exist in the spleen or lymph nodes, as PrP^{sc} was thought to accumulate in the spleen or lymph nodes at the early stage of PrP^{sc} infection in cattle, in general. As it was understandable that time would be required for switching the source of the ingredient of the medium in order to review the quality assurance throughout the manufacturing process, the expert council members forwarded an opinion that it was necessary to ask the applicant to report progresses of the switch-over.

(iv) Concerning safety issues raised on infliximab

Based on the consultation with the expert council members, the Evaluation Centre requested the applicant to provide their opinions on the following points.

- A possibility of implementing a PrP^{sc} clearance study that confirms efficiency of ultrafiltration in removing PrP^{sc}.

- A strategy for calling attention to the risk associated with the currently available product in the column for Important Basic Precautions in the Prescribing Information.

3) Concerning assessment of the ultrafiltration process and infliximab safety assessment

In response to the outcome of the first expert consultation on safety of the material derived from cattle, Centcore US, the producer of infliximab, implemented a PrPsc clearance study on the ultrafiltration process, which was placed before adding xxxxxxxx to the medium for infliximab production, and the applicant submitted the result.

The study was conducted using a homogenate of the brain of hamsters infected with scrapie (xxxx strain) as a sample containing PrP^{sc}, which was ultrafiltrated with a membrane with a molecule cut-off point of xxx kDa, and the removal rate of PrP^{sc} was obtained using the highly sensitive Western blotting. As a result of the tests under various conditions, the level of PrP^{sc} in any of the solutions after filtration was below the detection limit and the clearance factor (xxxxxxxxxxxxxxxxx) was xxx or over, on average.

Based on this result, the applicant claimed safety of xxxxxxxxxx from the following points.

(i) BSE has not been found in the North America, where the cattle that were used as sources of xxxxx were originated.
(ii) There has been no report of infection by the spleen of BSE infected cattle.
(iii) The cattle spleen used as a raw material has been broken down to xxxxxxxx molecule weight xxxx or less.
(iv) The result of the validation showed that even if PrP^{sc} was present in xxxxxxxxx, it could be removed efficiently.

The Evaluation Centre made the following assessments on the result of the clearance study on the ultrafiltration process submitted.

(i) On a point that xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxx, as the important step of PrP^{sc} removal is this ultrafiltration process, it was considered appropriate as a method of the process validation.

(ii) The investigation was carried out under conditions which contained far greater levels of the brain homogenate than that expected from the actual system, and the concentration, processing pressure and processing speed were varied, in order to account for some degrees of changes in the process.

(iii) A biochemical method was used for detection of PrP^{sc}. The chosen method was validated for specificity, linearity, reproducibility, etc., and thought to be reliable in detecting proteins within an extent of PrP^{sc} concentrations set in the study, out of various methods of determination, including biological test methods, that have been developed currently.

With regard to the findings of the clearance study, the Evaluation Centre felt that the PrP^{sc} clearance study was implemented appropriately considering the current scientific level, although the rationale given for the validity of the model and the detection sensitivity were not completely satisfactory.

Based on these data, the second expert consultation on safety of the material derived from cattle was held concerning the PrP^{sc} clearance study and safety of infliximab.

The expert council members agreed to the Evaluation Centre's judgement on appropriateness of the clearance study. They presented a view that the sensitivity of the detection method was an issue and false-negative results might be given. They said, to assure negative infectivity for future, implementation of a bioassay, which detects infectivity rather than proteins, would be needed. They added that, it would take xxx years to be able to implement a highly sensitive bioassay. However, considering the assumption that the spleen from a herd of cattle from BSE free regions was used, the Evaluation Centre judged that they had to accept the assessment based on this study at the moment.

The expert council members indicated the need to keep on collecting information actively and pay attention, as it has been pointed out that prion protein with molecular weight of about 8,000 was found in the brain of patients with Gerstmann-Sträussler-

Scheinker disease, which was a human prion disease (Proc. Natl. Acad. Sci. USA, 1998: 95, 8322, etc.,), although infectivity of this protein or presence in cattle, etc., have not been reported so far.

4) Concerning risk/benefit of infliximab

With the findings of the expert consultation, the Evaluation Centre assessed a risk/benefit assessment of infliximab on the basis of the quality.
Those who are targeted in this submission of infliximab are patients with moderately to severely active Crohn's disease who have had an inadequate response to prior conventional therapies or patients with a complication of draining external fistulas.
Crohn's disease is an inflammatory bowel disease with an unknown cause with its favourite site at the terminal ileum. As no treatment has been established, it was designated as a specified disease and the estimated number of patients is around 17,000. In Japan, the ratio of male and female patients is 1.7 to 2.3 vs 1, more prominent in males. It is more often found in young people and the age of both onset and diagnosis is peaked at between late teens and early twenties and 75% of all patients are between 15 and 29 years old.
Four main characteristic symptoms are abdominal pain, diarrhoea, fever and weight loss. More than 40% show anal lesions (periproctal ulcerations, burrows, fistulas, anal fissures, etc.)
Its clinical course is gradual deterioration repeating remission and deterioration and complete cure is rare. Even if a temporary remission is achieved with a medical treatment, it progresses presenting bowel passage disorders, internal and external fistulas, haemorrhage, etc., in due course, which require surgical operations. A high percentage of patients experience a recurrence after an operation, often requiring re-operations. A cumulative rate to receive operations is said to be 16% at 5 yeas from the onset and 40% at 10 years from the onset. Medical treatment for the active phase is hospitalisation and complete rest, while ingestion is prohibited, the patients receive total parenteral nutrition or enteral alimentation. The treatment is distressing, especially for young patients. Corticosteroids, salazosulfapyrudine and mesalazine are also administered, but they are only effective in relieving the symptoms. No drug is

found effective for remission maintenance at the moment, but continued administration of steroids or immunosuppressants are often carried out. In Japan, no difference in the cumulative survival rate and the expected survival rate is shown.

Although this disease does not shorten life expectancy significantly, it often occurs in employable young people and presents huge limitations to every-day life throughout their life. Considering this and the current situation with the limitations to the effectiveness and choices of treatment, the Evaluation team and the expert consultation members judged that providing a treatment for patients who have an inadequate response to existing therapies would be a great benefit.

On the other hand, the Evaluation Centre and the council members who are experts on this matter judged the risk associated with xxxxxx used for manufacturing of infliximab was rather small as; (i) the cattle spleen from a BSE free country is used, (ii) ultrafiltration with a membrane with a molecular cut-off point of xxxxx is performed, and (iii) the clearance study confirmed the removal efficiency of the ultrafiltration process. The applicant was asked about assurance of safety of the cattle spleen used as a raw material, and they replied that the current risk was thought to be small, considering the history of the BSE surveillance (observation of animal health, periodical tests on samples using the immunohistological staining method, etc,) and a legal measure (prohibiting animal proteins in feed) in the US, where the material was sourced, and a high possibility of specifying the producer of the cattle used. However, they added, they were preparing for a system of informing regulatory authorities in various countries, including Japan, and asking their advice on a response, in case BSE was found in the US in future.

In order to make an assurance of safety for the future, the Evaluation Centre asked the applicant to implement a PrP^{sc} clearance study on ultrafiltration using a bioassay for detection and to review changing the ingredient of the culture medium to one without the cattle spleen. The applicant replied that they were going to deal with both. Regarding information provision to healthcare professionals, they replied that they would provide information by putting in statements concerning the use of the cattle spleen in infliximab production and the measures taken for a prevention of unlikely PrP^{sc} contamination in the Prescribing Information (Draft), so that the healthcare professionals could consider the risk and benefit at the scene of medical care.

From the above, the Evaluation Centre judged that the benefit of infliximab to the patients out-weighed the risk of PrP^{sc} contamination, considering the severity of the patients who would receive infliximab.

As a result of those assessments, the Evaluation Centre judged that it was possible to apply infliximab to the exceptive clauses under 3. (2) of the notification from the director of the Evaluation and Licensing Division on 16th October 2001 (Notification PFSB/ELD 1434, "concerning handling of approval applications, etc., regarding further assurance of quality and safety of medicinal products, medical devices, etc., produced from materials derived from cattle, etc.")

(2) Concerning Safety of Infliximab

1) Concerning deterioration of demyelinating disease

The European Agency for the Evaluation of Medicinal Products (EMEA) has issued a public statement on etanercept (a soluble human TNF-α receptor modifying protein), which has similar pharmacological actions to infliximab on 3rd October 2000, pointing out that it may cause demyeliating disease, such as multiple sclerosis (MS) (http://www.emea.eu.int/pdfs/human/press/pus/3087100en.pdf). Therefore, the Evaluation Centre asked the applicant if there has been a case without previous history of MS who newly developed MS in the infliximab's adverse drug reaction database. The applicant replied that 5 cases were reported so far (note: 7 cases, if patients who experienced exercitation of MS were included). These cases gave rise to a suspicion that infliximab treatment initiated MS and there ought to be an important safety issue, the Evaluation Centre judged that they needed to have an expert consultation on this matter.

In the expert consultation, the following four points were discussed, i.e., (i) concerning a relationship of drugs with a TNF inhibiting effect and MS, (ii) concerning a relationship of 5 cases that developed MS and infliximab treatment, (iii) concerning safety of infliximab and (iv) concerning necessary preventative measures, if infliximab's potential to cause MS was suspected.

They stated on (i) that, as there has been a report that MS was exacerbated rather than

improved when infliximab was used in a clinical trial to treat MS (Neurology, 1996; 47, 1531-1534), infliximab was likely to have the potential to activate underlying or existing MS.

On (ii), they stated that, as it was reported that 1% of patients with inflammatory bowl disease, including Crohn's disease, had concurrent MS and this was 4 times higher than the normal population (Mayo clin. proc., 2000; 75 802-806) and that MS and Crohn's disease shared similar disease susceptibility genes (Proc. Natl. Acad. Sci., 1998; 95:9979-9984), a possible manifestation of demyelinating disease with an effect of infliximab used to treat Crohn's disease or induction of symptoms was suggested.

On (iii), they presented an opinion that, considering that Crohn's disease could not be fully controlled with existing therapies in many patients (especially fistulas) and surgical treatments could not be curative therapies as with ulcerative colitis, and with a presumption that efficacy of infliximab for intractable Crohn's disease had been demonstrated, the usefulness in patients with severe Crohn's disease should be recognised, providing that both patients and physicians would fully understand the potential of developing a new condition, i.e., MS. However, they stated, as the prevalence of demyelinating disease in Japan was lower than in the West and other serious adverse events, such as hypersensitivity, were reported with infliximab, data on infliximab safety in the Japanese population needed to be collected and it was best to survey all treated patients once launched, if possible.

On (iv), they stated that, it was appropriate to contraindicate infliximab to patients with a history of MS and it was best to determine presence of MS in remaining patients before initiating infliximab treatment with sufficient tests, including examinations by a neurologist and head MRI. They added that infliximab should be used after both the physician and the patient understood the benefit and the risk fully.

Based on the above discussion, the Evaluation Centre requested the applicant to review a statement on demyelinating disease in the Prescribing Information. The applicant responded that they were going to contraindicate patients with, or with a history of, demyelinating disease (e.g. MS). They were going to add patients who showed a suspicious sign of demyelinating disease, or patients with a family history of demyelinating disease under Administer with Care and state that a decision to initiate infliximab treatment should only be made after sufficient tests. In Warnings, they were

going to state that infliximab should be administered only when the benefit of treatment is considered to outweigh the risk.
The Evaluation Centre accepted the response.

2) Concerning risk of tuberculosis

This product has already been marketed in the West with indications for Crohn's disease and chronic rheumatoid arthritis, and out of 170, 000 patients who received infliximab treatment in clinical trials and post-marketing stages, 84 cases of tuberculosis were reported (as of end June, 2001). In response, the EMEA issued a public statement warning of tuberculosis on 20th December 2000 (http://www.emea.eu.int/pdfs/human/press/pus/444500en.pdf). and following that, the Prescribing Information was amended in the US on 8th August 2001 adding episodes of tuberculosis (including disseminated and extrapulmonary tuberculosis) in the Warnings. Considering these circumstances, the expert council members were consulted on the risk of tuberculosis in infliximab treatment again. As Crohn's disease is sometimes treated differently from Japan, for example an immunosuppressant is concurrently used abroad, it is difficult to predict whether a similar situation to abroad arises in Japan. However, the expert said that sufficient attention should be raised in the Prescribing Information and in other ways, as risk of tuberculosis infection in Japan was no lower than abroad, for example, an increase in the incidence of tuberculosis in the younger Japanese population was becoming an object of public concern. In response, the applicant stated that they were going to amend cautions on tuberculosis in the Prescribing Information (Draft) so that implementation of a chest x-ray examination was mentioned. The Evaluation Centre accepted the response.
After the expert consultation, an analysis result of 70 cases extracted from MedWatch spontaneous reporting concerning cases of tuberculosis with infliximab treatment by the US FDA was reported (N.Engl. J. Med., 2001; 345: 1098-1104). The report pointed out that the onsets after 1 to 3 doses of infliximab were common and many had extrapulmonary diseases including disseminated tuberculosis. On 5th October 2001, the US Centcore added statements in the Warnings in the Prescribing Information to the effect that "these infections, including tuberculosis, have been fatal" and "patients

should be evaluated for latent tuberculosis, and tuberculosis must be treated before starting infliximab treatment". The Evaluation Centre considered that methods of preventing an onset of tuberculosis with infliximab treatment or detecting tuberculosis early should be described in the Prescribing Information adequately, taking the above information and handling of tuberculosis in Japan into account, and the centre asked the applicant to review. The applicant replied that they were going to set up patient groups for Contraindication and Careful Administration with regard to tuberculosis, and to improve the way of calling for attention and providing information further. The Evaluation Centre checked the Prescribing Information (Draft) and accepted the response.

3) Concerning worsening congestive heart failure

A finding of a placebo-controlled, double-blind study in congestive heart failure patients with infliximab showed that higher rates of mortality and hospitalisations for worsening of congestive heart failure in patients treated with infliximab prompted the EMEA to issue a public statement on 18th October 2001 (http://www.emea.eu.int/pdfs/human/press/pus/325701en.pdf). On the same day, the US Centcore published an Important Drug Warning to the effect that "do not initiate infliximab treatment in patients with congestive heart failure" when considering infliximab treatment, and if patients with congestive heart failure have already receiving infliximab treatment, "treatment should be discontinued if congestive heart failure is worsening" and "even if congestive heart failure is not worsening, discontinuation of infliximab should be considered and if a decision is made to continue treatment, the condition of the congestive heart failure should be closely monitored". The Evaluation Centre asked the applicant to supply the details of the clinical study and asked about measures on congestive heart failure in the Japanese Prescribing Information (Draft). The applicant submitted data insisting that the study report of the clinical study had not been produced and the data were from a preliminary analysis. According to that, 150 patients with stable congestive heart failure in NYHA class III-IV (EF≤0.35) were randomly allocated to 3 groups that received intravenous infusions of either placebo, 5 mg/kg of infliximab or 10 mg/kg of infliximab on weeks 0, 2 and 6. Assessments on

the primary endpoints, i.e., NYHA function classification, global assessment, hospitalisations due to worsening of congestive heart failure and mortality, were made on week 14. The proportion of patients who were hospitalised or died due to worsening of congestive heart failure on week 14 was 4.2% in the placebo group, 4.0% in the 5 mg/kg group and 20.9% in the 10 mg/kg group (no breakdown of the patient numbers stated). According to the result of 28-week monitoring, 0 out of 49 in the placebo group, 2 out of 50 (0 up to week 14) in the 5 mg/kg group and 5 out of 51 (1 up to week 15) in the 10 mg/kg group have died. The applicant stated that they were going to contraindicate infliximab to patients with severe congestive heart failure and put remaining patients with congestive heart failure under the Administer with Care category in the Japanese Prescribing Information (Draft) as a countermeasure. The Evaluation Centre accepted this reply, but instructed the applicant to reflect the result of this clinical trial to the Prescribing Information (Draft) as much as possible and to try to provide information. The Evaluation Centre believes that the contents of the Prescribing Information need to be reviewed again when they can make a final assessment on this clinical study.

4) Concerning incidences of malignant tumours

As the Evaluation Centre was notified that, in an annual meeting of the American College of Gastroenterology on 22nd October 2001, the result of a clinical study (a placebo-controlled double-blind study) in patients with Crohn's disease who received continuous infliximab treatment for 1 year was published and it reported 6 incidences of malignant tumour, the Evaluation Centre requested the details from the applicant. The applicant stated that the clinical trial in question is the Crohn's disease maintenance therapy clinical study abroad (xxxxxxxxxx) and submitted details of 5 cases apart from 1 case with breast cancer that developed it after *day/month/year*. The applicant replied on the causal relationship of infliximab and occurrences of malignant tumours stating that the US Centcore viewed the relationship unclear and the applicant had the same opinion. Furthermore, based on 27 cases of malignant lymphoma and other malignant tumours reported in infliximab clinical studies and during 3-year follow-up of clinical studies, the expected numbers of malignant tumour patients in

patients who received placebo and patients who received infliximab were calculated and they were compared with the actual numbers of cases with malignant tumour. According to that, the observed number and the expected number of patients with malignant tumours in all studies in Crohn's disease were 2 and 0.18 in patients that received placebo and 6 and 2.66 in patients that received infliximab. The numbers in all studies in chronic rheumatoid arthritis were 0 and 1.37 in patients that received placebo and 12 and 9.93 in patients that received infliximab. The numbers in all studies regardless of the targeted disease were 2 and 1.57 in patients that received placebo and 18 and 12.66 in patients that received infliximab (note: non-melanoma skin cancer seen in 9 patients that received infliximab was excluded from this pooled comparison, because it was impossible to calculate the estimated number, as its incidence was not available on data bases). The Evaluation Centre believes that although those data are limited, they do not rule out a relationship between infliximab and occurrences of malignant tumours at the moment and investigations on occurrences of malignant tumours need to be continued further. As stated earlier, since it is important for both the physician and the patient to fully understand risk and benefit of infliximab when starting infliximab treatment, it is essential to provide information for making a risk assessment for individual cases. Therefore, the Evaluation Centre considered that the applicant needed to provide the current status of occurrences of malignant tumours specifically and in detail in the Japanese Prescribing Information, although the causal relationship was unknown, and instructed the applicant to do so. The applicant replied that they were going to describe the observed number and the estimated number of malignant tumour cases in the Japanese Prescribing Information (Draft) and the Evaluation Centre accepted the reply.
The Evaluation Centre also asked the applicant to carry out a post-marketing survey of all patients, as far as possible. The applicant submitted an outline of a planned safety and efficacy survey, which targeted all infliximab treated patients, as far as possible, focused on occurrences of infections, malignant tumours, etc., and covered all instructions.

2. Overall Assessment

It has been demonstrated that infliximab is highly effective in achieving a remission in patients with active Crohn's disease and with external fistulas compared with placebo, but serious issues on safety have been pointed out, for example, it has been confirmed to cause serious adverse drug reactions such as infections, including tuberculosis, and hypersensitivity, and relationships with demylinating disease and worsening of congestive heart failure have been suggested. The Indication column of infliximab have already stated "only for patients who have an inadequate response to prior conventional therapies", and when the safety issues stated in this report are considered together, infliximab needs to be used with a consideration to risk and benefit. Therefore, it is necessary to provide appropriate information to healthcare scene, so that physicians and patients can consider the usefulness when initiating treatment.
In conclusion, the Evaluation Centre considers Remicade approvable, providing appropriate information is provided in the Prescribing Information, etc., and a post-marketing survey on safety is conducted in all patients who receive infliximab. As a result of re-assessment of toxicity of infliximab, the Evaluation Centre judges that both the drug substance and the formulated product should be designated as a powerful drug. Also, the Centre believes that infliximab should be discussed by the 1st Committee on Drugs and in a Pharmaceutical Affairs Council Sectional Meeting. There is no change to the re-examination period in the assessment in Evaluation Report (1), set as 10 years.

20th November 2001

Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau

Evaluation Report (3)

Product Name	Remicade IV Infusion 100
Non-Propriety Name	Infliximab (recombinant)
Applicant	Tanabe Seiyaku Co., Ltd.
Submission Date	27th September 1999

[Evaluation Findings]

The Evaluation Report (2) (NHIS 3730 on 1st November 2001) is amended as follows.

Page 15, line 34 “27 cases of malignant lymphoma and other malignant tumours reported” is replaced with “27 malignant lymphomas and other malignant tumours reported in 26 patients”.

This amendment does not affect the evaluation outcome.