Informasi produk untuk pasien

INFLIX

Infliximab 100 mg/vial

Serbuk terliofilisasi untuk konsentrat untuk Injeksi IV

Baca Panduan Pengobatan yang disertakan dengan INFLIX sebelum Anda menerima pengobatan pertama, dan sebelum setiap kali Anda mendapatkan pengobatan INFLIX. Panduan Pengobatan ini tidak menggantikan konsultasi dengan dokter Anda tentang kondisi medis atau pengobatan Anda.

Apa itu INFLIX?

INFLIX adalah obat yang digunakan untuk mengobati orang dewasa dengan reumatoid artritis aktif derajat sedang hingga berat, penyakit Crohn, kolitis ulserativa dan psoriasis plak. Pada penyakit Crohn, dan kolitis ulserativa, INFLIX diperuntukkan bagi orang yang belum respons dengan cukup baik terhadap obat-obatan lain. INFLIX juga digunakan untuk mengobati ankylosing spondylitis aktif, artritis psoriatik.

Pemerian Obat / Penampakan Obat ini:

Produk ini adalah serbuk berwarna putih. Setelah menambahkan 10ml WFI, harus dilarutkan dalam 2 menit dan larutannya harus tidak berwarna, kuning pucat, dan tidak ada benda asing.

Apa informasi terpenting yang harus saya ketahui tentang INFLIX?

INFLIX dapat menyebabkan efek samping yang serius, termasuk:

1. **Risiko Infeksi**

INFLIX adalah obat yang mempengaruhi sistem kekebalan tubuh Anda. INFLIX dapat menurunkan kemampuan sistem kekebalan tubuh Anda untuk melawan infeksi. Infeksi serius telah terjadi pada pasien yang menerima INFLIX. Infeksi ini termasuk tuberkulosis (TB) dan infeksi yang disebabkan oleh virus, jamur atau bakteri yang telah menyebar ke seluruh tubuh. Beberapa pasien telah meninggal dunia karena infeksi ini.

- Dokter Anda harus melakukan tes TB sebelum memulai INFLIX
- Dokter Anda harus memantau Anda dengan ketat untuk tanda dan gejala TB selama pengobatan dengan INFLIX

Sebelum memulai INFLIX, beri tahu dokter Anda jika Anda:

- Merasa Anda memiliki infeksi. Anda harusnya tidak mulai memakai INFLIX jika Anda memiliki jenis infeksi apapun
- Sedang diterapi karena infeksi
- Memiliki tanda-tanda infeksi, seperti demam, batuk, *flu-like symptoms*
- Memiliki luka atau koreng terbuka di tubuh Anda
- Mengalami banyak infeksi atau memiliki infeksi yang kambuh-kambuhan
- Memiliki diabetes atau masalah sistem kekebalan tubuh. Orang dengan kondisi ini memiliki peluang lebih tinggi untuk infeksi
- Memiliki TB, atau pernah melakukan kontak erat dengan penderita TB
- Tinggal atau pernah tinggal di area tertentu dari negara di mana ada peningkatan risiko untuk mengalami jenis infeksi jamur tertentu (*histoplasmosis*, *coccidiodomycosis*, atau *blastomycosis*). Infeksi ini dapat berkembang atau menjadi lebih berat jika Anda memakai INFLIX. Jika Anda tidak

tahu apakah Anda pernah tinggal di daerah yang umum ditemukan *histoplasmosis*, *coccidiodomycosis*, atau *blastomycosisis*, tanyakan kepada dokter Anda.
- Menderita atau pernah menderita hepatitis B
- Menggunakan obat Kineret (anakinra)

Setelah memulai INFLIX, jika Anda memiliki infeksi, tanda-tanda infeksi termasuk demam, batuk, *flu-like symptoms* atau memiliki luka atau koreng terbuka di tubuh Anda, segera hubungi dokter Anda. INFLIX dapat membuat Anda lebih mungkin terkena infeksi atau membuat infeksi yang Anda miliki menjadi lebih berat.

2. Risiko Kanker
- Ada kasus kanker yang tidak biasa pada pasien anak-anak dan remaja yang memakai TNF-blocking agents.
- Untuk orang dewasa yang menggunakan obat-obatan TNF-blocker, termasuk INFLIX, kemungkinan terkena limfoma atau kanker lainnya dapat meningkat
- Orang yang telah dirawat karena artritis reumatoid, penyakit Crohn, ankylosing spondylitis, artritis psoriatik dan psoriasis plak untuk waktu yang lama mungkin lebih mungkin mengalami limfoma. Ini terutama berlaku untuk orang dengan penyakit yang sangat aktif
- Beberapa pasien dengan penyakit Crohn atau kolitis ulserativa yang telah menerima INFLIX telah mengalami jenis kanker langka yang disebut Limfoma sel-T Hepatosplenik. Kebanyakan dari pasien ini adalah remaja atau laki-laki dewasa muda. Jenis kanker ini mengakibatkan kematian. Semua pasien ini juga telah menerima obat yang dikenal sebagai azathioprine atau 6-mercaptopurine bersama dengan INFLIX
- Pasien dengan PPOK (jenis penyakit paru yang spesifik) mungkin memiliki peningkatan risiko terkena kanker saat sedang diterapi dengan INFLIX
- Beri tahu dokter Anda jika Anda pernah menderita jenis kanker apapun. Diskusikan dengan dokter Anda setiap kebutuhan untuk menyesuaikan obat-obatan yang mungkin Anda pakai

Apa yang harus saya katakan kepada dokter saya sebelum memulai pengobatan dengan INFLIX
Dokter Anda akan menilai kesehatan Anda sebelum setiap pengobatan
Beritahu dokter Anda tentang semua kondisi medis Anda, termasuk jika Anda:
- Memiliki infeksi (lihat **"Apa informasi terpenting yang harus saya ketahui tentang INFLIX?"**)
- Memiliki masalah liver lainnya termasuk gagal hati
- Mengalami gagal jantung atau kondisi jantung lainnya. Jika Anda mengalami gagal jantung, penyakit ini mungkin menjadi lebih berat saat Anda memakai INFLIX
- Menderita atau pernah menderita kanker jenis apapun
- Pernah menjalani fototerapi (pengobatan dengan sinar ultraviolet atau sinar matahari bersama dengan obat untuk membuat kulit Anda sensitif terhadap cahaya) untuk psoriasis. Anda mungkin memiliki peluang lebih tinggi terkena kanker kulit saat menerima INFLIX
- Memiliki PPOK (Penyakit Paru Obstruktif Kronik), jenis penyakit paru yang spesifik. Pasien dengan PPOK mungkin memiliki peningkatan risiko terkena kanker saat memakai INFLIX
- Mengalami atau pernah mengalami kondisi yang mempengaruhi sistem saraf Anda seperti
  - *Multiple sclerosis*, atau sindrom *Guillain-Barré*, atau
  - Jika Anda mengalami kebas atau kesemutan, atau
  - Jika Anda mengalami kejang
- Baru saja menerima atau dijadwalkan menerima vaksin. Anda tidak boleh menerima vaksin hidup saat memakai INFLIX

- Sedang hamil atau berencana untuk hamil. Tidak diketahui apakah INFLIX membahayakan bayi Anda yang belum lahir. INFLIX harus diberikan kepada wanita hamil hanya jika jelas diperlukan. Konsultasikan dengan dokter Anda tentang menghentikan INFLIX jika Anda sedang hamil atau berencana untuk hamil
- Sedang menyusui atau berencana untuk menyusui. Tidak diketahui apakah INFLIX masuk ke dalam ASI Anda. Konsultasikan dengan dokter Anda tentang cara memberi makan bayi Anda saat memakai INFLIX. Anda tidak boleh menyusui saat memakai INFLIX

Apa yang harus saya hindari saat menerima INFLIX?
Jangan menggunakan INFLIX dan obat KINERET (Anakinra) bersama-sama

Bisakah saya menggunakan INFLIX saat saya menggunakan obat lain?
Beritahu dokter Anda jika Anda memakai obat-obatan lain termasuk obat-obatan *over the counter*, suplemen atau produk herbal sebelum Anda diobati dengan INFLIX. Jika Anda mulai menggunakan atau berencana untuk mulai menggunakan obat baru saat Anda menggunakan INFLIX, beri tahu dokter Anda.

Apa kemungkinan efek samping dari INFLIX?
INFLIX dapat menyebabkan efek samping yang serius, termasuk:
Lihat **"Apa informasi terpenting yang harus saya ketahui tentang INFLIX?"**
INFLIX, seperti obat-obatan lain yang memengaruhi sistem kekebalan tubuh Anda, adalah obat kuat yang dapat menyebabkan efek samping yang serius. Kemungkinan efek samping yang serius termasuk:
Infeksi Serius:

- Beberapa pasien mengalami infeksi serius saat menerima INFLIX. Infeksi serius ini termasuk TB dan infeksi yang disebabkan oleh virus, jamur atau bakteri yang telah menyebar ke seluruh tubuh. Beberapa pasien meninggal dunia karena infeksi ini. Jika Anda mengalami infeksi saat menerima pengobatan dengan INFLIX, dokter Anda akan mengobati infeksi Anda dan mungkin perlu menghentikan pengobatan INFLIX Anda.
- Beritahu dokter Anda segera jika Anda memiliki salah satu dari tanda-tanda infeksi berikut saat atau setelah memakai INFLIX:
  - Demam
  - Merasa sangat lelah
  - Batuk
  - Memiliki *flu-like symptoms*
  - Kulit hangat, merah, atau nyeri
- Dokter Anda akan memeriksa Anda untuk TB dan melakukan tes untuk melihat apakah Anda memiliki TB. Jika dokter Anda merasa bahwa Anda berisiko terkena TB, Anda mungkin akan diobati dengan obat untuk TB sebelum Anda memulai pengobatan dengan INFLIX dan selama pengobatan dengan INFLIX
- Bahkan jika tes TB Anda negatif, dokter Anda harus hati-hati memantau Anda untuk infeksi TB saat Anda memakai INFLIX. Pasien yang memiliki tes kulit TB negatif sebelum menerima INFLIX juga dapat mengalami TB aktif
- Jika Anda adalah carrier kronis virus hepatitis B, virus dapat menjadi aktif saat Anda sedang diobati dengan INFLIX. Dalam beberapa kasus, pasien meninggal dunia akibat reaktivasi virus hepatitis B. Dokter Anda dapat melakukan tes darah sebelum Anda memulai pengobatan dengan INFLIX dan kadang-kadang saat Anda sedang diterapi. Beritahu dokter Anda jika Anda memiliki salah satu dari gejala berikut:
  - Merasa tidak enak badan

- Nafsu makan menurun
- Kelelahan (fatigue)
- Demam, ruam kulit dan/atau nyeri sendi

Gagal Jantung:
Jika Anda memiliki masalah jantung yang disebut gagal jantung kongestif, dokter Anda harus memeriksa Anda dengan cermat saat Anda menggunakan INFLIX. Gagal jantung kongestif Anda mungkin menjadi lebih buruk saat Anda menggunakan INFLIX. Pastikan untuk memberi tahu dokter Anda tentang gejala baru atau yang lebih buruk termasuk:
- Sesak napas
- Pembengkakan pergelangan tumit atau kaki
- Kenaikan berat badan mendadak

Pengobatan dengan INFLIX mungkin perlu dihentikan jika Anda mendapatkan gagal jantung kongestif baru atau yang lebih buruk

Penyakit Liver:
Pada kasus yang jarang terjadi, beberapa pasien yang menggunakan INFLIX telah mengalami masalah liver yang serius. Beritahu dokter Anda jika Anda memiliki:
- Penyakit kuning (kulit dan mata menguning)
- Urin berwarna coklat tua
- Nyeri di sisi kanan area perut Anda (sakit perut sisi kanan)
- Demam
- Kelelahan ekstrim (kelelahan parah)

Masalah Darah:
Pada beberapa pasien yang menggunakan INFLIX, tubuh mungkin tidak membuat cukup sel darah yang membantu melawan infeksi atau membantu menghentikan pendarahan. Beritahu dokter Anda jika Anda
- Mengalami demam yang tidak kunjung hilang
- Memar atau berdarah dengan sangat mudah
- Terlihat sangat pucat

Reaksi alergi:
Beberapa pasien memiliki reaksi alergi terhadap INFLIX. Beberapa dari reaksi ini sangat berat. Reaksi-reaksi ini dapat terjadi saat Anda mendapatkan pengobatan INFLIX Anda segera setelahnya. Dokter Anda mungkin perlu menghentikan atau menjeda pengobatan Anda dengan INFLIX dan mungkin memberi Anda obat-obatan untuk mengobati reaksi alergi. Tanda-tanda reaksi alergi dapat meliputi:
- Gatal-gatal (bercak kulit merah, menebal, gatal)
- Kesulitan bernapas
- Nyeri dada
- Tekanan darah tinggi atau rendah
- Demam
- Menggigil

Beberapa pasien yang diobati dengan INFLIX telah mengalami reaksi alergi yang tertunda. Reaksi tertunda terjadi 3 hingga 12 hari setelah menerima pengobatan dengan INFLIX. Beritahu dokter Anda segera jika Anda memiliki salah satu dari tanda-tanda reaksi alergi tertunda untuk INFLIX:
- Demam
- Ruam

- Sakit kepala
- Sakit tenggorokan
- Nyeri otot atau sendi
- Pembengkakan di wajah dan tangan
- Kesulitan menelan

Gangguan Sistem Saraf:
Dalam kasus yang jarang terjadi, pasien yang menggunakan INFLIX mengalami masalah dengan sistem saraf mereka. Beritahu dokter Anda jika Anda memiliki:
- Perubahan dalam penglihatan Anda
- Kelemahan pada lengan dan/atau kaki Anda
- Mati rasa atau kesemutan di bagian tubuh mana pun
- Kejang

Kanker:
Laporan terkait jenis kanker darah yang disebut limfoma pada pasien INFLIX atau penghambat TNF lainnya jarang terjadi tetapi lebih diperkirakan untuk terjadi pada orang secara umum. Orang yang telah diterapi karena rheumatoid artritis, penyakit Crohn, *ankylosing spondylitis* atau *psoriatic arthritis* untuk waktu yang lama, terutama mereka yang memiliki penyakit yang sangat aktif mungkin lebih rentan untuk mengalami limfoma. Anak-anak dan dewasa muda yang telah diobati karena penyakit Crohn dengan INFLIX mengalami jenis limfoma langka yang sering mengakibatkan kematian. Pasien-pasien ini juga menerima obat-obatan yang dikenal sebagai *azathioprine* atau *6-mercaptopurine*. Kanker, selain limfoma, juga telah dilaporkan. Jika Anda mengambil INFLIX atau TNF blocker lainnya, risiko Anda untuk mengalami limfoma atau kanker lain dapat meningkat. Anda juga harus memberi tahu dokter Anda jika Anda pernah menderita atau mengalami limfoma atau kanker lain saat Anda menggunakan INFLIX. Pasien dengan jenis kanker yang spesifik dengan pengobatan INFLIX. Jika Anda menderita PPOK Anda harus mendiskusikan dengan dokter Anda apakah INFLIX sesuai untuk Anda.

Lupus-Like Syndrome:
Beberapa pasien mengalami gejala yang mirip gejala Lupus. Jika Anda mengalami salah satu dari gejala berikut, dokter Anda dapat memutuskan untuk menghentikan pengobatan Anda dengan INFLIX.
- Ketidaknyamanan dada atau rasa sakit yang tidak hilang
- Sesak napas
- Nyeri sendi
- Ruam di pipi atau lengan yang semakin parah di bawah sinar matahari

Psoriasis:
Beberapa orang yang menggunakan INFLIX memiliki psoriasis baru atau perburukan psoriasis yang sudah mereka miliki. Beri tahu dokter Anda jika Anda mengalami bercak bersisik merah atau benjolan di kulit yang berisi nanah. Dokter Anda mungkin memutuskan untuk menghentikan pengobatan Anda dengan INFLIX.

Apa efek samping yang lebih umum dari INFLIX?
- Infeksi saluran pernapasan, seperti infeksi sinus dan nyeri tenggorokan
- Sakit kepala
- Ruam
- Batuk
- Nyeri perut

Beritahu dokter Anda tentang efek samping yang mengganggu Anda atau yang tidak kunjung membaik. Penjelasan ini tidak mencakup semua efek samping dengan INFLIX. Tanyakan kepada dokter atau apoteker Anda untuk informasi lebih lanjut.

Anda juga dapat melaporkan efek samping melalui:
Pharmaceutical Industry Reporting Contacts
PT ETANA BIOTECHNOLOGIES INDONESIA
Kawasan Industri Pulogadung, Jl. Rawa Gelam V, Blok. L, Kav. 11-13, Jakarta
Email : pv@id.etanabiotech.com dan Indonesia-MESO-BadanPOM@hotmail.com
Web-site : https://ebi-pharmacovigilance.azurewebsites.net/

Seberapa sering saya akan menerima INFLIX?
Reumatoid Artritis
Jika Anda menerima INFLIX untuk reumatoid artritis, Anda akan menerima dosis pertama Anda diikuti dengan dosis tambahan pada 2 dan 6 minggu setelah dosis pertama. Anda kemudian akan menerima dosis setiap 8 minggu. Dokter Anda akan memantau respons Anda terhadap INFLIX dan dapat mengubah dosis Anda atau mengobati Anda lebih sering (sesering setiap 4 minggu).

Penyakit Crohn atau *Fistulizing Crohn's Disease*
Jika Anda menerima INFLIX untuk penyakit Crohn aktif atau *fistulizing Crohn's disease*, Anda akan menerima dosis pertama Anda diikuti dengan dosis tambahan pada 2 dan 6 minggu setelah dosis pertama. Anda kemudian akan menerima dosis setiap 8 minggu. Dokter Anda akan memantau respons Anda terhadap INFLIX dan dapat mengubah dosis Anda.

Kolitis Ulserativa
Jika Anda menerima INFLIX untuk kolitis ulserativa, Anda akan menerima dosis pertama Anda diikuti dengan dosis tambahan pada 2 dan 6 minggu setelah dosis pertama. Anda kemudian akan menerima dosis setiap 8 minggu dan dokter Anda akan memantau respons Anda terhadap INFLIX.

Ankylosing Spondylitis
Jika Anda menerima INFLIX untuk *ankylosing spondylitis* Anda akan menerima dosis pertama Anda diikuti dengan dosis tambahan pada 2 dan 6 minggu setelah dosis pertama. Anda kemudian akan menerima dosis setiap 6 minggu.

Psoriatic Arthritis
Jika Anda menerima INFLIX untuk psoriatic arthritis Anda akan menerima dosis pertama Anda diikuti dengan dosis tambahan pada 2 dan 6 minggu setelah dosis pertama. Anda kemudian akan menerima dosis setiap 8 minggu.

Psoriasis Plak
Jika Anda menerima INFLIX untuk psoriasis Anda akan menerima dosis pertama Anda diikuti dengan dosis tambahan pada 2 dan 6 minggu setelah dosis pertama. Anda kemudian akan menerima dosis setiap 8 minggu.

Siapa yang tidak boleh menerima INFLIX?
Anda tidak boleh menerima INFLIX jika Anda memiliki:

- Gagal jantung, kecuali dokter Anda telah memeriksa Anda dan memutuskan bahwa Anda dapat memakai INFLIX. Konsultasikan dengan dokter Anda tentang gagal jantung Anda
- Memiliki reaksi alergi terhadap INFLIX, atau bahan lain dalam INFLIX. Lihat akhir dari Panduan Pengobatan ini untuk daftar lengkap bahan-bahan dalam INFLIX

Bagaimana INFLIX akan diberikan kepada saya?
INFLIX akan diberikan kepada Anda oleh seorang profesional kesehatan. INFLIX akan diberikan kepada Anda melalui infus. Ini berarti bahwa obat akan diberikan kepada Anda melalui jarum yang ditempatkan di pembuluh darah di lengan Anda. Biasanya akan memakan waktu sekitar 2 jam untuk memberi Anda dosis penuh obat. Selama waktu itu dan untuk jangka waktu setelah Anda menerima INFLIX, Anda akan dipantau oleh profesional kesehatan. Dokter Anda mungkin meminta Anda untuk memakai obat-obatan lain bersama dengan INFLIX.
Hanya seorang profesional kesehatan yang harus menyiapkan obat dan memberikannya kepada Anda.

Bagaimana jika saya menggunakan lebih banyak INFLIX daripada yang seharusnya?
Dosis tunggal hingga 20 mg/kg telah diujikan tanpa efek toksik langsung. Dalam kasus overdosis, dianjurkan untuk pemantauan terhadap tanda-tanda atau gejala efek samping maupun efek dan pengobatan simtomatik yang tepat dapat segera diberikan.

Bagaimana jika saya masih memiliki pertanyaan?
Jika Anda memiliki pertanyaan, atau masalah, selalu bicarakan terlebih dahulu dengan dokter Anda.

Bagaimana cara menyimpan INFLIX?
2-8 °C, hindari dari paparan cahaya. Larutan rekonstitusi: infus harus dimulai dalam waktu 3 jam setelah rekonstitusi dan pengenceran pada suhu ruang (25°C).

Isi kemasan dan informasi lainnya
Bahan aktif farmasi (API) dari Inflix adalah infliximab dan eksipien lainnya adalah sukrosa, tween 80, natrium dihidrogen fosfat monohidrat, disodium hidrogen fosfat dihidrat, dan air untuk injeksi. Produk ini adalah serbuk putih yang tidak berwarna hingga seperti cairan kuning pucat dengan opalesen setelah pelarutan. Tidak ada benda asing.
Dus, 1 vial @100mg Reg. No. XXXXXXXXXXXXXX

HARUS DENGAN RESEP DOKTER

Diproduksi oleh:
Taizhou Mabtech Pharmaceuticals Co., Ltd.
Jiangsu – China

Didaftarkan oleh:
PT Etana Biotechnologies Indonesia
Jakarta – Indonesia

Tanggal disetujui pertama kali
DD/MM/YY

INFLIX

Infliximab 100 mg/vial

Lyophilized powder for concentrate for IV Injection

SUMMARY OF PRODUCT CHARACTERISTICS

WARNINGS

SERIOUS INFECTIONS

Patients treated with Infliximab are at increased risk for developing serious infections that may lead to hospitalization or death (*See warnings and Precaution and Adverse Reactions*) Most Patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Infliximab should be discontinued if a patient develops a serious infections or sepsis.
Reported infections include:

- Active tuberculosis including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before Infliximab use and during therapy. Treatment for latent infection should be initiated prior to Infliximab use
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infections. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral and other infections due to opportunistic pathogens The risks and benefits or treatment with Infliximab should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection Patients should be closely monitored for the development of sign and symptoms of infection during and after treatment with Infliximab, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including Infliximab (*see Warning and Precautions*)
Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including Infliximab. These cases have had a very aggressive disease course and have been fatal. All reported Infliximab cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. All of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with Infliximab at or prior to diagnosis

INFLIX

General name: Infliximab for injection

FORMULA

API: Infliximab
Excipients: sucrose, tween 80, sodium dihydrogen phosphate, disodium hydrogen phosphate

DESCRIPTION

This Product is a white loose powder. After adding 10ml WFI, the solution should be colorless to pale yellow. No foreign matter.

INDICATIONS AND USAGE

Rheumatoid Arthritis

Infliximab, in combination with methotrexate, is indicated for reducing signs as well as the improvement in physical function in:

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

In these patient population, a reduction in the rate of progression of joint damage, as measured by X-ray, has been demonstrated.

Crohn's Disease

Infliximab is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.

Infliximab is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in patients with fistulizing Crohn's disease.

Ankylosing Spondylitis

Infliximab is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Psoriatic Arthritis

Infliximab is indicated for reducing signs and symptoms in patients with active arthritis in patients with psoriatic arthritis who have had inadequate response to conventional therapy.

Ulcerative Colitis

Infliximab is indicated for reducing signs and symptoms, achieving clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to severely active ulcerative colitis who have had inadequate response to conventional therapy.

Plaque Psoriasis

Infliximab is indicated for the treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, Infliximab should be used after phototherapy has been shown to be ineffective or inappropriate.

STRENGTH

100mg/vial

DOSAGE AND ADMINISTRATION

Infliximab is for intravenous use in adults and has not been studied in children (0-17 years). Infliximab treatment is to be administered under the supervision and monitoring of specialized physicians experienced in the diagnosis and treatment of rheumatoid arthritis, inflammatory bowel diseases, or ankylosing spondylitis. Patients treated with Infliximab should be given the package leaflet and the special Alert card. Prior to initiating Infliximab and periodically during therapy, patients should be evaluated for active tuberculosis and tested for latent infection (See Warnings and Precautions). The recommended infusion time is 2 hours. All patients administered Infliximab are to be observed for at least 1-2 hours post infusion for acute infusion related reactions. Emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway must be available.

Patients may be pretreated with e.g., an antihistamine, hydrocortisone and/or paracetamol and infusion rate may be slowed in order to decrease the risk of infusion related reactions especially if infusion related reactions have occurred previously.
During Infliximab treatment, other concomitant therapies, e.g., corticosteroids and immunosuppressant should be optimized.

Rheumatoid Arthritis
The recommended dose of Infliximab is 3 mg/kg given as an intravenous infusion followed with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. Infliximab should be given in combination with methotrexate. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every 4 weeks bearing in mind that risk of serious infections is increased at higher doses (see ADVERSE REACTIONS, Infections). Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Severe, active Crohn's disease
5 mg/kg given as an intravenous infusion over a 2-hour period. Available data do not support further Infliximab treatment, in patients not responding within 2 weeks to the initial infusion. In responding patients, the alternative strategies for continued treatment are:

- Maintenance: Additional infusion of 5 mg/kg at 2 and 6 weeks after initial dose, followed by infusion every 8 weeks
- Re-administration: Infusion of 5 mg/kg if signs and symptoms of the disease recur.

Fistulizing, active Crohn's Disease
An initial 5 mg/kg infusion over 2-hour period is to be followed with additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion. If a patient does not respond after these 3 doses, no additional treatment with Infliximab should be given. In responding patients, the strategies for continued treatment are:

- Additional infusions of 5 mg/kg every 8 weeks
- Re-administration if signs and symptoms of the disease recur followed by infusion of 5 mg/kg every 8 weeks

In Crohn's disease, experience with re-administration if signs and symptoms of disease recur is limited and comparative data on the benefit / risk of the alternative strategies for continued treatment are lacking.

Ankylosing Spondylitis
The recommended dose of Infliximab is 5 mg/kg given as an intravenous infusion followed with additional similar doses at 2 and 6 weeks after the first infusion, then every 6 weeks thereafter. If a patients does not respond by 6 weeks (i.e. after 2 doses), no additional treatment with infliximab should be given.

Psoriatic Arthritis
The recommended dose of Infliximab is 5 mg/kg given as an intravenous infusion followed with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. Infliximab can be used with or without methotrexate.

Ulcerative Colitis
The recommended dose of Infliximab is 5 mg/kg given as an induction regimen at 0,2,6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active ulcerative colitis.

Plaque Psoriasis

The recommended dose of Infliximab is 5 mg/kg given as an intravenous induction regimen at 0, 2, and 6 weeks followed by maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of chronic severe (i.e., extensive and/or disabling) plaque psoriasis.

Re-administration for Crohn's disease and Rheumatoid arthritis

If the signs and symptoms of disease recur, Infliximab can be readministered within 16 weeks following the last infusion. In clinical studies, delayed hypersensitivity reactions have been uncommon and have occurred after drug free interval of less than 1 year. The safety and efficacy of re-administration after a drug free interval of more than 16 weeks has not been established. This applies to both Crohn's disease patients and rheumatoid arthritis patients.

Re-administration for Ankylosing spondylitis

The safety and efficacy of re-administration, other than every 6 to 8 weeks, has not been established.

Re-administration for Psoriatic arthritis

The safety and efficacy of re-administration, other than every 8 weeks, has not been established.

Re-administration for Psoriasis

Limited experience from retreatment with one single Infliximab dose in psoriasis after and interval of 20 weeks suggest reduced efficacy and a higher incidence of mild to moderate infusion reactions when compared to the initial induction regimen.

Preparation and Administration Instructions

Use aseptic technique.

Infliximab vials do not contain antibacterial preservatives. Therefore, the vials after reconstitution should be used immediately, not re-entered or stored. The diluent to be used for reconstitution is 10 mL of Sterile Water for Injection, USP. The total dose of the reconstituted product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP. The infusion concentration should range between 0.4 mg/mL and 4 mg/mL. The Infliximab infusion should begin within 3 hours of preparation.

1. Calculate the dose and the number of Infliximab vials needed. Each Infliximab vial contains 100 mg of infliximab. Calculate the total volume of reconstituted Infliximab solution required.
2. Reconstitute each Infliximab vial with 10 mL of Sterile Water for Injection, USP, using a syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the centre of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to light yellow and opalescent, and the solution may develop a few translucent particles as infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign particles are present.
3. Dilute the total volume of the reconstituted Infliximab solution dose to 250 mL with 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of reconstituted Infliximab from the 0.9% Sodium Chloride Injection, USP, 250 mL bottle or bag. Slowly add the total volume of reconstituted Infliximab solution to the 250 mL infusion bottle or bag. Gently mix.
4. The infusion solution must be administered over a period of not less than 2 hours and must use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2µm or less). Any unused portion of the infusion solution should not be stored for reuse.
5. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of Infliximab with other agents. Infliximab should not be infused concomitantly in the same intravenous line with other agents.
6. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particulates are observed, the solution should not be used.

ADVERSE REACTIONS

From the Innovator study (Remicade), the data described herein reflect exposure to Infliximab in 4779 adult patients (1304 patients with rheumatoid arthritis, 1106 patients with Crohn's disease, 202 with ankylosing spondylitis, 293 with psoriatic arthritis, 484 with ulcerative colitis, 1373 with plaque psoriasis, and 17 patients with other conditions), including 2625 patients exposed beyond 30 weeks and 374 exposed beyond one year. The most common reasons for discontinuation of treatment was infusion-related reactions (e.g., dyspnea, flushing, headache and rash). Adverse events have been reported in a higher proportion of rheumatoid arthritis patients receiving the 10 mg/kg dose than the 3 mg/kg dose, however, no differences were observed in the frequency of adverse events between the 5 mg/kg dose and 10 mg/kg dose in patients with Crohn's disease. The detail of adverse reactions can be referred in the following chapter.

From the manufacturer study (INFLIX), as a biosimilar product, the clinical data and post-marketing data are both limited. In the single-dose phase I study, no adverse event (AEs) was observed in the infliximab (3 mg/kg) group. In the repeat-dose phase I study (Study ID: C008RAI), only 2 subjects had mild laboratory test abnormalities with a good prognosis. In the phase II/III efficacy study (Study ID: C008RAII/III), the respiratory disorders had the highest incidence and were mainly manifested by upper respiratory tract infections with an incidence of 10.61% (35/330), 11.82% (13/110), and 11.82% (13/110) in the infliximab (4-dose) group, the placebo group, and the infliximab (3-dose) group, respectively, with no significant inter-group difference. In the phase III comparison study (Study ID: C008RAIII), infections and infestations had the highest incidence. The incidence of the upper respiratory tract infections was highest: 33.3% (64/192) in the infliximab group. In the phase I bioequivalence study (Study ID: INFLIXHV-I), investigations had the highest incidence: 45.5% (20/44) in the infliximab group. Most AEs were Grade 1. 2 important AEs were observed: 2 cases (inflammation in the superior lobe of the left lung and otitis externa of the left ear) in the infliximab group.

Infusion-related Reactions

Acute infusion reactions

An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 to 2 hours after an infusion. Approximately 20% of Infliximab-treated patients in all clinical studies experienced an infusion reaction compared to approximately 10% of placebo-treated patients. Among all Infliximab infusions, 3% were accompanied by nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Serious infusion reactions occurred in<1% of patients and included anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients discontinued Infliximab because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion. Infliximab infusions beyond the initial infusion were not associated with a higher incidence of reactions. The infusion reaction rates remained stable in psoriasis through 1 year in psoriasis Study I. In psoriasis Study II, the rates were variable over time and somewhat higher following the final infusion than after the initial infusion. Across the 3 psoriasis studies, the percent of total infusions resulting in infusion reactions (i.e. an adverse event occurring within 1 to 2 hours) was 7% in the 3 mg/kg group, 4% in the 5 mg/kg group, and 1% in the placebo group

Patients who became positive for antibodies to infliximab were more likely (approximately 2- to 3-fold) to have an infusion reaction than were those who were negative. Use of concomitant immunosuppressant agents appeared to reduce the frequency of antibodies to infliximab and infusion reactions (see ADVERSE REACTIONS, Immunogenicity and PRECAUTIONS, Drug Interactions).

In post-marketing experience, cases of anaphylactic-like reactions, including laryngeal/pharyngeal edema and severe bronchospasm, and seizure have been associated with Infliximab administration.

Delayed Reactions/Reactions following re-administration

Plaque Psoriasis
In psoriasis, studies, approximately 1% of Infliximab-treated patients experienced a possible delayed hypersensitivity reaction, generally reported as serum sickness or a combination of arthralgia and/or myalgia with fever and/or rash. These reactions generally occurred within two weeks after repeat infusion.

Crohn's disease
In a study where 37 of 41 patients with Crohn's disease were retreated with infliximab following a 2 to 4 year period without infliximab treatment, 10 patients experienced adverse events manifesting 3 to 12 days following infusion of which 6 were considered serious. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients also experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat, and headache. Patients experiencing these adverse events had not experienced infusion-related adverse events associated with their initial infliximab therapy. These adverse events occurred in 39% (9/23) of patients who had received liquid formulation which is no longer in use and 7% (1/14) of patients who received lyophilized formulation. The clinical data are not adequate to determine if occurrence of these reactions is due to differences in formulation. Patients' signs and symptoms improved substantially or resolved with treatment in all cases.
There are insufficient data on the incidence of these events after drug-free intervals of 1 to 2 years. These events have been observed only infrequently in clinical studies and post-marketing surveillance with retreatment intervals up to 1 year.

Infections
In Infliximab clinical studies, treated infections were reported in 36% of Infliximab-treated patients (average of 51 weeks of follow-up) and in 25% of placebo-treated patients (average of 37 weeks of follow-up). The infections most frequently reported were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Among Infliximab-treated patients, serious infections included pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection. In all clinical trials, 7 opportunistic infections were reported; 2 cases each of coccidioidomycosis (1 case was fatal) and histoplasmosis (1 case was fatal), and 1 case each of pneumocystosis, nocardiosis and cytomegalovirus. Tuberculosis was reported in 14 patients, four of whom died due to military tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported post-marketing. Most of these cases of tuberculosis occurred within the first 2 months after initiation of therapy with Infliximab and may reflect recrudescence of latent disease (see WARNINGS, RISK OF INFECTIONS). In the 1 year placebo-controlled studies RA I and RA II, 5.3% of patients receiving Infliximab every 8 weeks with MTX developed serious infections as compared to 3.4% of placebo patients receiving MTX. Of 924 patients receiving Infliximab, 1.7% developed pneumonia and 0.4% developed TB, when compared to 0.3% and 0.0% in the placebo arm respectively. In a shorter (22-week) placebo-controlled study of 1082 RA patients randomized to receive placebo, 3 mg/kg or 10 mg/kg Infliximab infusions at 0, 2, and 6 weeks, followed by every 8 weeks with MTX, serious infections were more frequent in the 10 mg/kg Infliximab group (5.3%) than the 3 mg/kg or placebo groups (1.7% in both). During the 54 weeks Crohn's II Study, 15% of patients with fistulizing Crohn's disease developed a new fistula-related abscess.
In Infliximab clinical studies in patients with ulcerative colitis, infections treated with antimicrobials were reported in 27 % of Infliximab-treated patients (average of 41 weeks of follow-up) and 18% of placebo-treated patients (average 32 weeks of follow-up). The types of infections, including serious infections, reported in patients with ulcerative colitis were similar to those reported in other clinical studies. In post-marketing experience, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving Infliximab alone or in combination with immunosuppressive agents. The onset of serious infections may be preceded by constitutional symptoms such as fever, chills,

weight loss, and fatigue. The majority of serious infections, however, may also preceded by signs or symptoms localized to the site of the infection

Autoantibodies/Lupus-like Syndrome
Approximately half of Infliximab-treated patients in clinical trials who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial compared with approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately one-fifth of Infliximab-treated patients compared with 0% of placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon.

Malignancies
In controlled-trials, more Infliximab-treated patients developed malignancies than placebo-treated patients. (See Warnings and Precautions). In a randomized controlled clinical trial exploring the use of Infliximab in patients with moderate to severe COPD who were either current smokers or ex-smokers, 157 patients were treated with Infliximab at doses similar to those used in rheumatoid arthritis and Crohn's disease. Of these Infliximab-treated patients, 9 developed a malignancy, including 1 lymphoma, for a rate of 7.67 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 3.51-14.56). There was 1 reported malignancy among 77 control patients for a rate of 1.63 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 0.04-9.10). The majority of the malignancies developed in the lung or head and neck. Malignancies, including non-Hodgkin's lymphoma and Hodgkin's disease, have also been reported in patients receiving Infliximab during post-approval use.

Patients with Heart Failure
In a randomized study evaluating Infliximab in moderate to severe heart failure (NYHA Class III/IV; left ventricular ejection fraction ≤35%), 150 patients were randomized to receive treatment with 3 infusions of Infliximab 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks. Higher incidences of mortality and hospitalization due to worsening heart failure were observed in patients receiving the 10 mg/kg Infliximab dose. At 1 year, 8 patients in the 10 mg/kg Infliximab group had died compared with 4 deaths each in the 5 mg/kg Infliximab and the placebo groups. There were trends towards increased dyspnea, hypotension, angina, and dizziness in both the 10 mg/kg and 5 mg/kg Infliximab treatment groups, versus placebo. Infliximab has not been studied in patients with mild heart failure (NYHA Class I/II). (See Contraindications and Warnings and Precautions Patients with Heart Failure.)

Immunogenicity
Treatment with Infliximab can be associated with the development of antibodies to infliximab. The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through one to two years of Infliximab treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease patients receiving Infliximab after drug free intervals >16 weeks. The majority of antibody-positive patients had low titers. Patients who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy and to experience an infusion reaction (see ADVERSE REACTIONS, Infusion-related Reactions) than were patients who were antibody negative. Antibody development was lower among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX.
In the psoriasis Study II, which included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 36% of patients treated with 5 mg/kg every 8 weeks for 1 year, and in 51% of patients treated with 3 mg/kg every 8 weeks for 1 year. In the psoriasis Study III, which also include both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 20% of patients treated with 5 mg/kg induction (week 0,2 and 6), and in 27% of patients treated with 3 mg/kg induction. Despite the increase in antibody formation, the infusion reaction rates in Studies I and II in patients treated with 5 mg/kg induction

followed by every 8 week maintenance for 1 year and in Study III in patients treated with 5 mg/kg induction (14.1%-23.0%) and serious infusion reaction rates (<1%) were similar to those observed in other country populations. The clinical significance of apparent increased immunogenicity on efficacy and infusion reactions in psoriasis patients as compared to patients with other diseases treated with Infliximab over the long term is not known.
The data reflect the percentage of patients whose test results were positive for antibodies to infliximab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to infliximab with the incidence of antibodies to other products may be misleading.

Hepatotoxicity
Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported rarely in patients receiving Infliximab (see WARNINGS, Hepatotoxicity). Reactivation of hepatitis B has occurred in patients receiving Infliximab who are chronic carriers of this virus (i.e., surface antigen positive) (see WARNINGS, Hepatotoxicity). In clinical trials in rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis, elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving Infliximab than in controls (Table 1), both when Infliximab was given as monotherapy and when it was used in combination with other immunosuppressive agents. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of Infliximab, or modification of concomitant medications.

Table 1
Proportion of Patients with elevated ALT in Clinical Trials

	Proportion of patients with elevated ALT					
	>1 to <3 x ULN		≥ 3 x ULN		≥ 5 x ULN	
	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab
Rheumatoid arthritis[1]	24%	34%	3%	4%	<1%	<1%
Chron's disease[2]	34%	39%	4%	5%	0%	2%
Ulcerative colitis[3]	12%	15%	1%	2%	<1%	<1%
Ankylosing spondylitis[4]	13%	40%	0%	6%	0%	2%
Psoriatic arthritis[5]	16%	42%	0%	5%	0%	2%
Plaque psoriasis[6]	24%	49%	<1%	8%	0%	3%

[1] Placebo patients received methotrexate while Infliximab patients received both Infliximab and methotrexate. Median follow-up was 58 weeks.
[2] Placebo patients in the 2 Phase III trials in Crohn's disease, received an initial dose of 5 mg/kg infl iximab at study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo maintenance group and then later crossed over to Infliximab are included in the Infliximab group in the ALT analysis. Median follow-up was 54 weeks.
[3] Median follow-up was 54 weeks.
[4] Median follow-up was 30 weeks.
[5] Median follow-up was 24 weeks for Infliximab group and 18 weeks for placebo group.
[6] ALT values are obtained in 2 Phase 3 psoriasis studies with median follow-up of 50 weeks for Infliximab and 18 weeks for placebo.

Adverse Reactions in Psoriasis Study

During the placebo-controlled portion across the 3 clinical trials up to week 16, the proportion of patients who experienced at least 1 SAE (defined as resulting in death, life threatening, requires hospitalization, or persistent or significant disability/incapacity) was 1.7% in the 3 mg/kg Infliximab group, 3.2% in the placebo group, and 3.9% in the 5 mg/kg Infliximab group.
Among patients in the 2 Phase 3 studies, 12.4% of patients receiving Infliximab 5 mg/kg every 8 weeks through 1 year of maintenance treatment experienced at least 1 SAE in Study I. In Study II, 4.1% and 4.7% of patients receiving Infliximab 3 mg/kg and 5 mg/kg every 8 weeks, respectively, through 1 year of maintenance treatment experienced at least 1 SAE.
One death due to bacterial sepsis occurred 25 days after the second infusion of 5 mg/kg Infliximab. Serious infections included sepsis, and abscesses. In Study I, 2.7% of patients receiving Infliximab 5 mg/kg every 8 weeks through 1 year of maintenance treatment experienced at least 1 serious infection. In Study II, 1.0% and 1.3% of patients receiving Infliximab 3 mg/kg and 5 mg/kg, respectively, through 1 year of treatment experienced at least 1 serious infection. The most common serious infection (requiring hospitalization) was abscess (skin, throat, and peri-rectal) reported by 5 (0.7%) patients in the 5 mg/kg Infliximab group. Two active cases of tuberculosis were reported: 6 weeks and 34 weeks after starting Infliximab.
In the placebo-controlled portion of the psoriasis studies, 7 of 1123 patients who received Infliximab at any dose were diagnosed with at least one NMSC compared to 0 of 334 patients who received placebo.
In the psoriasis studies, 1% (15/1373) of patients experienced serum sickness or a combination of arthralgia and/or myalgia with fever, and/or rash, usually early in the treatment course. Of these patients, 6 required hospitalization due to fever, severe myalgia, arthralgia, swollen joints, and immobility.

Other Adverse Reactions
Safety data are available from 4779 Infliximab-treated adult patients, including 1304 with rheumatoid arthritis, 1106 with Crohn's disease, 484 with ulcerative colitis, 202 with ankylosing spondylitis, 293 with psoriatic arthritis, 1373 with plaque psoriasis and 17 with other conditions. Adverse events reported in ≥5% of all patients with rheumatoid arthritis receiving 4 or more infusions are in Table 2. The types and frequencies of adverse reactions observed were similar in Infliximab-treated rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis and Crohn's disease patients except for abdominal pain, which occurred in 26% of Infliximab-treated patients with Crohn's disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-up for patients who never received Infliximab to provide meaningful comparisons.

Table 2
ADVERSE EVENTS OCCURRING IN 5% OR MORE OF PATIENTS RECEIVING 4 OR MORE INFUSIONS FOR RHEUMATOID ARTHRITIS

	Placebo (n=350)	Infliximab (n=1129)
Average weeks of follow-up	59	66
Gastrointestinal		
Nausea	20%	21%
Abdominal Pain	8%	12%
Diarrhea	12%	12%
Dyspepsia	7%	10%
Respiratory		
Upper respiratory tract infection	25%	32%
Sinusitis	8%	14%
Pharyngitis	8%	12%
Coughing	8%	12%

Bronchitis	9%	10%
Rhinitis	5%	8%
Skin and appendages disorders		
Rash	5%	10%
Pruritus	2%	7%
Body as a whole-general disorders		
Fatigue	7%	9%
Pain	7%	8%
Resistance mechanism disorders		
Fever	4%	7%
Moniliasis	3%	5%
Central and peripheral nervous system disorders		
Headache	14%	18%
Musculoskeletal system disorders		
Back pain	5%	8%
Arthralgia	7%	8%
Urinary system disorders		
Urinary tract infection	6%	8%
Cardiovascular disorders, general		
Hypertension	5%	7%

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not predict the rates observed in broader patient populations in clinical practice.
The most common serious adverse events observed in clinical trials were infections (see ADVERSE REACTIONS). Other serious, medically relevant adverse events ≥0.2% or clinically significant adverse events by body system were as follows:

Body as a whole: allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequela
Blood: pancytopenia
Cardiovascular: circulatory failure, hypotension, syncope
Gastrointestinal: constipation, gastrointestinal hemorrhage, ileus, intestinal obstruction, intestinal perforation, intestinal stenosis, pancreatitis, peritonitis, proctalgia
Central & Peripheral Nervous: meningitis, neuritis, peripheral neuropathy, dizziness
Heart Rate and Rhythm: arrhythmia, bradycardia, cardiac arrest, tachycardia
Liver and Biliary: biliary pain, cholecystitis, cholelithiasis, hepatitis
Metabolic and Nutritional: dehydration
Musculoskeletal: intervertebral disk herniation, tendon disorder
Myo-, Endo-, Pericardial and Coronary Valve: myocardial infarction
Platelet, Bleeding and Clotting: thrombocytopenia
Neoplasms: basal cell, breast, lymphoma
Psychiatric: confusion, suicide attempt
Red Blood Cell: anemia, hemolytic anemia
Reproductive: menstrual irregularity
Resistance Mechanism: cellulitis, sepsis, serum sickness
Respiratory: adult respiratory distress syndrome, lower respiratory tract infection (including pneumonia), pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency
Skin and Appendages: increased sweating, ulceration
Urinary: renal calculus, renal failure
Vascular (Extracardiac): brain infarction, pulmonary embolism, thrombophlebitis
White Cell and Reticuloendothelial: leukopenia, lymphadenopathy

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medical product is important. It allows continued monitoring of the benefit / risk balance of the medical product. Healthcare professional are asked to report any suspected adverse reaction.

Pharmaceutical Industry Reporting Contacts

PT ETANA BIOTECHNOLOGIES INDONESIA

Kawasan Industri Pulogadung, Jl. Rawa Gelam V, Blok. L, Kav. 11-13, Jakarta

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Post-marketing Experience

From the Innovator study (Remicade), the following adverse reactions, some with fatal outcome, have been reported during post-approval use of Infliximab: neutropenia (see Warnings and Precautions), interstitial lung disease (including pulmonary fibrosis / interstitial pneumonitis and very rare rapidly progressive disease), idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic and cutaneous vasculitis, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, peripheral demyelinating disoreders (such as Guillain-Barré syndrome, chronic infl amatory demyelinating polyneuropathy, and multifical motor neuropathy) , new onset and worsening psoriasis (all subtypes including pustular, primarily palmoplantar), transverse myelitis, and neuropathies (additional neurologic events have also been observed) [see Warnings and Precautions] and acute liver failure, jaundice, hepatitis, and cholestatis [see Warnings and Precautions]. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Infliximab exposure.

Table 3
Undesirable Effects in Clinical Studies and from Post-Marketing experience

Infections and infestations	
Common:	Viral infection (e.g. influenza, herpes infections)
Uncommon:	Tuberculosis, bacterial infections (e.g. sepsis, cellulites, abscess), fungal infections (e.g.candidiasis).
Not known:	Opportunistic infections (such as invasive fungal infections [pneumocystosis, histoplasmosis,

	aspergillosis, coccidioidomycosis, cryptococcosis, blastomycosis], bacterial infections [atypical mycobacterial, listeriosis, salmonellosis], and viral infections [cytomegalovirus]), parasitic infections, hepatitis B reactivation.
Neoplasms benign, malignant and unspecified (including cysts and polyps) Rare: Not known:	 Lymphoma. Hepatosplenic T-cell lymphoma (primarily in adolescents and young adults with Crohn's disease and ulcerative colitis), non-Hodgkin's lymphoma, Hodgkin's disease, leukaemia.
Blood and lympathic system disorders Uncommon: Not known:	 Neutropenia, leucopenia thrombocytopenia, anaemia, lymphopenia, lymphadenopathy, lymphocytosis. Agranulocytosis, thrombotic thrombocytopenic purpura, pancytopenia, haemolytic anaemia, idiopathic thrombocytopenic purpura.
Immune system disorders Common: Uncommon: Not known:	 Serum sickness-like reaction Anaphylactic reactions, lupus-like syndrome, allergic respiratory symptom. Anaphylactic shock, serum sickness, vasculitis
Psychiatris disorders Uncommon:	 Depression, amnesia, agitation, confusion, insomnia, somnolence, nervousness, apathy
Nervous systems disorders Common: Uncommon: Rare: Not known:	 Headache, vertigo, dizziness Central nervous system demyelinating disorders (multiple sclerosis-like disease). Meningitis Peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy), central nervous system demyelinating disorders (such as optic neuritis), transverse myelitis, seizure, neuropathy, hypoaesthesia, paraesthesia,
Eye disorders Uncommon: Not known	 Endophtalmitis, keratitis, conjunctivitis periorbital oedema, hordeolum Transient visual loss occurring during or within two hours of infusion.
Cardiac disorders Uncommon: Rare: Not known:	 Cardiac failure aggravated, arrhythmia, syncope, bradycardia, cyanosis, palpitation. Tachycardia Myocardial ischaemia/myocardial infarction occurring during or within two hours of infusion, cardiac failure, pericardial effusion.
Vascular disorders	

Common: Uncommon: Rare:	Flushing Hypotension, peripheral ischaemia, hypertension, thrombophlebitis, haematoma, ecchymosis, petechia, vasospasm, hot flush Circulatory failure
Respiratory, thoracic and mediastinal disorders Common: Uncommon: Rare: Not known:	 Lower respiratory tract infection (e.g. bronchitis, pneumonia), Upper respiratory tract infection, sinusitis, dyspnoea, Pulmonary oedema, bronchospasm, pleurisy, epitaxis, Pleural effusion Interstitial lung disease (including rapidly progressive disease, lung flbrosis and pneumonitis)
Gastrointestinal disorders Common: Uncommon: Rare: Not known:	 Abdominal pain, diarrhoea, nausea, dyspepsia. Diverticulitis, gastroesophageal reflux, constipation, cheilitis, Intestinal perforation, gastrointestinal haemorrhage, intestinal stenosis, Pancreatitis.
Hepatobiliary disorders Common: Uncommon: Rare: Not known:	 Transaminases increased. Cholecystitis, hepatic function abnormal. Hepatitis Liver failure, autoimmune hepatitis, hepatocellular damage, jaundice
Skin and subcutaneous tissue disorders Common: Uncommon: Not known:	 Urticaria, rash, pruritus, hyperhidrosis, dry skin Bullous eruption, furunculosis, fungal dermatitis, onychomycosis, eczema, seborrhoea, rosacea, skin papilloma, hyperkeratosis, alopecia, abnormal skin pigmentation, Toxic epidermal necrolysis, Stevens-Johnson-Syndrome, new onset or worsening psoriasis, including pustular psoriasis (primarily palm & soles), erythema multiforme.
Musculoskeletal and connective tissue disorders Uncommon:	 Arthralgia, myalgia, back pain
Renal and urinary disorders Uncommon:	 Pyelonephritis, urinary tract infection
Reproductive system and breast disorders Uncommon:	 Vaginitis
General disorders and administration site conditions Common: Uncommon: Rare:	 Infusion-related reactions, chest pain, fatigue, fever. Impaired healing, injections site reactions, chills, oedema, pain. Granulomatous lesion

Investigations Uncommon:	Autoantibody positive, complement factor abnormality

(Common >1/100, <1/10; uncommon >1/1000, <1/100; rare >1/10,000, <1/1000; very rare <1/10,000, including isolated reports)

From the manufacturer study (INFLIX), as a biosimilar product, the post-marketing data is limited since it is firstly approved in July, 2021 (China). Until the end of 2023, about 2530 patients (reckoned) use the product and totally 86 adverse drug reaction (ADR) are collected in China. In these ADR, two new and severe are found: ADR (facial edema; intestinal tract bleeding+invalid treatment) and ADR (pale; skin swell; erythema; nervous pain+jerk; skin swell+ erythema+ desquamation; chest uncomfortable; chest uncomfortable+throat stimulation; invalid treatment). There is no safety signal related to large population. From these ADR, there is no new safety signal found and all ADR have been included in above table.

CONTRAINDICATIONS

From the Innovator study (Remicade), Infliximab at doses >5 mg/kg should not be administered to patients with moderate to severe heart failure. In a randomized study evaluating Infliximab in patients with moderate to severe heart failure (New York Heart Association [NYHA] Functional Class III/IV), Infliximab treatment at 10 mg/kg was associated with an increased incidence of death and hospitalization due to worsening heart failure (see WARNINGS and ADVERSE REACTIONS, Patients with Heart Failure). Infliximab should not be administered to patients with known hypersensitivity to any murine proteins or other component of the product and patients with tuberculosis or other severe infections such as sepsis, abscesses, and opportunistic infections.

WARNINGS AND PRECAUTIONS

Serious Infection (See boxed WARNING)

From the Innovator study (Remicade), serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral or other opportunistic pathogens, including sepsis have been reported in patients receiving TNF-blocking agents. Among opportunistic infections, tuberculosis, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, and pneumocystosis were the most commonly reported. Patients have frequently presented with disseminated rather than localized disease, and are often taking concomitant immunosuppressants such as methotrexate or corticosteroids with Infliximab.

Treatment with Infliximab should not be initiated in patients with an active infection, including clinically important localized infections. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

- With chronic or recurrent infection;
- Who have been exposed with tuberculosis;
- Who have resided or travelled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis;
- With underlying conditions that may predispose them to infection

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving Infliximab, including patients who have previously received treatment for latent or active tuberculosis. Patients should be evaluated tuberculosis risk factors and tested for latent infection prior to initiating Infliximab and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis

is needed prior to initiating Infliximab, even for patients previously vaccinated with Bacille Calmette-Guerin (**BCG**).
Anti-tuberculosis therapy should also be considered to initiation of Infliximab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether anti-tuberculosis therapy is appropriate for an individual patient.
Tuberculosis should be strongly considered in patients who develop a new infection during Infliximab treatment, especially in patients who have previously or recently travelled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.
Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Infliximab, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with Infliximab.
Infliximab should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with Infliximab should be closely monitored, undergo a prompt and complete diagnosis workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.
For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnosis workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy.

Malignancies
From the Innovator study (Remicade), malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF-blocking agents (initiation of therapy <18 years of age), including Infliximab. Approximately half of these cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF blocker therapy. Most of the patients were receiving concomitant immunosuppresants. These cases were reported post-marketing and are derived from a variety of sources, including registries and spontaneous post-marketing reports.
Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including Infliximab. These cases have had a very aggressive disease course and have been fatal. All reported Infliximab cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were in adolescent and young adult males. All of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with Infliximab at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to Infliximab or Infliximab in combination with these other immunosuppressants.
In the controlled portions of clinical trials of some TNF-blocking agents including Infliximab, more malignancies (excluding lymphoma and nonmelanoma skin cancer [NMSC] have been observed in patients receiving those TNF-blockers compared with control patients. During the controlled portions of Infliximab trials in patients with moderately to severely active rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis,14 patients were diagnosed with malignancies (excluding lymphoma and NMSC) among 4019 Infliximab treated patients vs 1 among 1597 control patients (at a rate of 0.52/100 patient-years among Infliximab treated patients vs a rate of 0.11/100 patient-years among control patients), with median duration of follow-up

0.5 years for Infliximab-treated patients and 0.4 years for control patients. Of these, the most common malignancies were breast colorectal, and melanoma. The rate of malignancies among Infliximab-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected.

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. In the controlled and open-label portions of Infliximab clinical trials, 5 patients developed lymphomas, among 5707 patients treated with Infliximab (median duration of follow-up 1.0 years) vs 0 lymphomas in 1600 control patients (median duration of follow-up 0.4 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow up, which is approximately three-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis. Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 5 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow up, which is approximately four-fold higher than expected in the general population. Patient with Crohn's disease, rheumatoid arthritis or plaque psoriasis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for development of lymphoma, even in the absence of TNF blocker therapy. Cases of acute and chronic leukemia have been reported with post-marketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF blocker therapy, patients with rheumatoid arthritis may be at higher risk (approximately 2-fold) than the general population for the development of leukemia.

In a clinical trial exploring the use of Infliximab in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and neck origin, were reported in Infliximab-treated patients compared with control patients. All patients had a history of heavy smoking (see Adverse reaction). Prescribers should exercise caution when considering the use of Infliximab in patients with moderate to severe COPD.

Psoriasis patients should be monitored for nonmelanoma skin cancers (NMSCs), particularly those patients who have had prior prolonged phototherapy treatment. In the maintenance portion of clinical trials for Infliximab, NMSCs were more common in patients with previous phototherapy (see Adverse reaction). The potential role of TNF-blocking in the development of malignancies is not known [see Adverse reaction] Rates in clinical trials for cannot be compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering Infliximab treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving Infliximab.

Hepatitis B Virus Reactivation

From the Innovator study (Remicade), use of TNF blockers, including Infliximab has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers, including Infliximab, for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, TNF blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is

controlled is no known. Therefore, prescribers should exercise when considering resumption of TNF blocker therapy in this situation and monitor patients closely.

Hepatotoxicity
From the Innovator study (Remicade), severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis have been reported rarely in post-marketing data in patients receiving Infliximab. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between two weeks to more than a year after initiation of Infliximab; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., ≥ 5 times the upper limit of normal) develops, Infliximab should be discontinued, and a through investigation of the abnormality should be undertaken. As with other immunosuppressive drugs, use of Infliximab has been associated with reactivation of hepatitis B in patients who are chronic carriers of this virus (i.e., surface antigen positive). Chronic carriers of hepatitis B should be appropriately evaluated and monitored prior to the initiation of and during treatment with Infliximab. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving Infliximab without progression to severe hepatic injury (see Adverse Reaction).

Patients with Heart Failure
From the Innovator study (Remicade), infliximab has been associated with adverse outcomes in patients with heart failure, and should be used in patients with heart failure only after consideration of other treatment options. The results of a randomized study evaluating the use of Infliximab in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg Infliximab, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking Infliximab. There have also been rare post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer Infliximab to patients with heart failure, they should be closely monitored during therapy, and Infliximab should be discontinued if new or worsening symptoms of heart failure appear. (See CONTRAINDICATIONS and ADVERSE REACTIONS, Patients with Heart Failure.)

Hematologic Events
From the Innovator study (Remicade), cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving Infliximab. The causal relationship to Infliximab therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with Infliximab who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever) while on Infliximab. Discontinuation of Infliximab therapy should be considered in patients who develop significant hematologic abnormalities.

Hypersensitivity
From the Innovator study (Remicade), infliximab has been associated with hypersensitivity reactions that vary in their time of onset. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of Infliximab infusion. However, in some cases, serum sickness-like reactions have been observed in Crohn's disease patients 3 to 12 days after Infliximab therapy was reinstituted following an extended period without Infliximab treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias,

polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with marked increase in antibodies to infliximab, loss of detectable serum concentrations of infliximab, and possible loss of drug efficacy. Infliximab should be discontinued for severe reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction (see ADVERSE REACTIONS, Infusion-related Reactions).

Neurologic Events

From the Innovator study (Remicade), infliximab and other agents that inhibit TNF have been associated in rare cases with optic neuritis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis, and CNS manifestation of systemic vasculitis. Prescribers should exercise caution in considering the use of Infliximab in patients with pre-existing or recent onset of central nervous system demyelinating or seizure disorders. Discontinuation of Infliximab should be considered in patients who develop significant central nervous system adverse reactions.

PRECAUTIONS

Autoimmunity

From the Innovator study (Remicade), treatment with Infliximab may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Infliximab, treatment should be discontinued (see ADVERSE REACTIONS, Autoantibodies/Lupus-like Syndrome).

Vaccinations

From the Innovator study (Remicade), no data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is recommended that live vaccines not be given concurrently.

Use with Anakinra

From the Innovator study (Remicade), serious infections were seen in clinical studies with concurrent use of anakinra and another TNFα-blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of nature of the adverse event seen with combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNFα-blocking agent. Therefore, the combination of Infliximab and anakinra is not recommended.

USE IN SPECIFIC POPULATIONS

Pregnancy Category B

From the Innovator study (Remicade), it is not known whether Infliximab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Infliximab should be given to a pregnant woman only if clearly needed, Because infliximab does not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with Infliximab. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies.

Nursing Mothers

From the Innovator study (Remicade), it is not known whether Infliximab is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from Infliximab. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
From the Innovator study (Remicade), safety and effectiveness of Infliximab in patients with juvenile rheumatoid arthritis, and in pediatric patients with Crohn's disease, Ulcerative Colitis and plaque psoriasis have not been established.

Geriatric Use
From the Innovator study (Remicade), in rheumatoid arthritis and plaque psoriasis clinical trials, no overall differences were observed in effectiveness or safety in 181 patients with rheumatoid arthritis and 75 patients with plaque psoriasis aged 65 or older who received Infliximab compared to younger patients although the incidence of serious adverse events in patients aged 65 or older was higher in both Infliximab and control groups compared to younger patients. In Crohn's disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis studies, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly (see ADVERSE REACTIONS, Infections).

DRUG INTERACTIONS

Anakinra
From the Innovator study (Remicade), serious infections were seen in clinical studies with concurrent use of anakinra and another TNFα-blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with combination of etanercept and anakinra, similar toxicities may also result from the combination of anakinra and other TNFα-blocking agents. Therefore, the combination of Infliximab and anakinra is not recommended (See Warnings and Precautions)

Methotrexate (MTX) and Other Concomitant Medications
From the Innovator study (Remicade), specific drug interaction studies, including interactions with MTX, have not been conducted. The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one or more concomitant medications. In rheumatoid arthritis, concomitant medications besides MTX were nonsteroidal anti-inflammatory agents (NSAIDs), folic acid, corticosteroids and/or narcotics. Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA and aminosalicylates. In psoriatic arthritis clinical trials, concomitant medications included MTX in approximately half of the patients as well as nonsteroidal anti-inflammatory agents (NSAIDs), folic acid and corticosteroids. Concomitant MTX use may decrease the incidence of anti-infliximab antibody production and increase infliximab concentrations.

Immunosuppresants
From the Innovator study (Remicade), patients with Crohn's disease who received immunosuppressants tended to experience fewer infusion reactions compared to patients on no immunosuppressants (see Adverse Reactions). Serum infliximab concentrations appeared to be unaffected by baseline use of medications for the treatment of Crohn's disease including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and aminosalicylates.

OVERDOSAGE

Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

CLINICAL STUDIES

Rheumatoid Arthritis

From the Innovator study (Remicade), the safety and efficacy of Infliximab were assessed in two multicenter, randomized, double-blind, pivotal trials: ATTRACT (Study RA I) and ASPIRE (Study RA II). Concurrent use of stable doses of folic acid, oral corticosteroids (≤10 mg/day) and/or non-steroidal anti-inflammatory drugs was permitted. Study RA I was a placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with MTX. Patients enrolled had a median age of 54 years, median disease duration of 8.4 years, median swollen and tender joint count of 20 and 31 respectively, and were on a median dose of 15 mg/wk of MTX. Patients received either placebo + MTX or one of 4 doses/schedules of Infliximab + MTX: 3 mg/kg or 10 mg/kg of Infliximab by IV infusion at weeks 0, 2 and 6 followed by additional infusions every 4 or 8 weeks in combination with MTX.

Study RA II was a placebo-controlled study of three active treatment arms in 1004 MTX naive patients of 3 or fewer years duration active rheumatoid arthritis. Patients enrolled had a median age of 51 years with a median disease duration of 0.6 years, median swollen and tender joint count of 19 and 31, respectively, and >80% of patients had baseline joint erosions. At randomization, all patients received MTX (optimized to 20 mg/wk by week 8) and either placebo, 3mg/kg or 6 mg/kg Infliximab at weeks 0, 2, and 6 and every 8 weeks thereafter.

Data on use of Infliximab without concurrent MTX are limited (see ADVERSE REACTIONS, Immunogenicity).

Clinical response

In Study RA I, all doses/schedules of Infliximab + MTX resulted in improvement in signs and symptoms as measured by the American College of Rheumatology response criteria (ACR 20) with a higher percentage of patients achieving an ACR 20, 50 and 70 compared to placebo + MTX (Table 4). This improvement was observed at week 2 and maintained through week 102. Greater effects on each component of the ACR 20 were observed in all patients treated with Infliximab +MTX compared to placebo + MTX (Table 5). More patients treated with Infliximab reached a major clinical response than placebo-treated patients (Table 4). In Study RA II, after 54 weeks of treatment, both doses of Infliximab + MTX resulted in statistically significantly greater response in signs and symptoms compared to MTX alone as measured by the proportion of patients achieving ACR 20, 50 and 70 responses (Table 4). More patients treated with Infliximab reached a major clinical response than placebo-treated patients.

Table 4
ACR RESPONSE (PERCENT OF PATIENTS)

	Study RA I					Study RA II		
		Infliximab + MTX					Infliximab + MTX	
		3 mg/kg		10 mg/kg			3 mg/kg	6 mg/kg
Response	Placebo + MTX (n=88)	q 8 wks (n=86)	q 4 wks (n=86)	q 8 wks (n=87)	q 4 wks (n=81)	Placebo + MTX (n=274)	q 8 wks (n=351)	q 8 wks (n=355)
ACR 20								
Week 30	20%	50%[a]	50%[a]	52%[a]	58%[a]	N/A	N/A	N/A
Week 54	17%	42%[a]	48%[a]	59%[a]	59%[a]	54%	62%[c]	66%[a]
ACR 50								
Week 30	5%	27%[a]	29%[a]	31%[a]	26%[a]	N/A	N/A	N/A
Week 54	9%	21%[c]	34%[a]	40%[a]	38%[a]	32%	46%[a]	50%[a]
ACR 70								
Week 30	0%	8%[b]	11%[b]	18%[a]	11%[a]	N/A	N/A	N/A
Week 54	2%	11%[c]	18%[a]	26%[a]	19%[a]	21%	33%[b]	37%[a]
Major clinical response [#]	0%	7%[c]	8%[b]	15%[a]	6%[c]	8%	12%	17%[a]

A major clinical response was defined as a 70% ACR response for 6 consecutive months (consecutive visits spanning at least 26 weeks) through week 102 for Study RA I and week 54 for Study RA II.

[a] $p \leqslant 0.001$

[b] $p < 0.01$

[c] $p < 0.05$

Table 5
COMPONENTS OF ACR 20
AT BASELINE AND 54 WEEKS (Study RA I)

Parameter (medians)	Placebo + MTX (n=88)		Infliximab + MTX [a] (n=340)	
	Baseline	Week 54	Baseline	Week 54
No. of Tender Joints	24	16	32	8
No. of Swollen Joints	19	13	20	7
Pain[b]	6.7	6.1	6.8	3.3
Physician's Global Assessment[b]	6.5	5.2	6.2	2.1
Patient's Global Assessment[b]	6.2	6.2	6.3	3.2
Disability Index (HAQ-DI) [c]	1.8	1.5	1.8	1.3
CRP (mg/dL)	3.0	2.3	2.4	0.6

[a] All doses/schedules of Infliximab + MTX
[b] Visual Analog Scale (0=best, 10=worst)
[c] Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3=worst)

Radiographic response

Structural damage in both hands and feet was assessed radiographically at week 54 by the change from baseline in the van der Heijde-modified Sharp (vdH-S) score, a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet.[7]

In Study RA I, approximately 80% of patients had paired x-ray data at 54 weeks and approximately 70% at 102 weeks. The inhibition of progression of structural damage was observed at 54 weeks (Table 6) and maintained through 102 weeks.

In Study RA II, >90% of patients had at least two evaluable x-rays. Inhibition of progression of structural damage was observed at weeks 30 and 54 (Table 6) in the Infliximab + MTX groups compared to MTX alone. In an exploratory analysis of Study RA II, patients treated with Infliximab +MTX demonstrated less progression of structural damage compared to MTX alone, whether baseline acute phase reactants (ESR and CRP) were normal or elevated: patients with elevated baseline acute phase reactants treated with MTX alone demonstrated a mean progression in vdH-S score of 4.2 units compared to patients treated with Infliximab + MTX who demonstrated 0.5 units of progression; patients with normal baseline acute phase reactants treated with MTX alone demonstrated a mean progression in vdH-S score of 1.8 units compared to Infliximab + MTX who demonstrated 0.2 units of progression. Of patients receiving Infliximab + MTX, 59% had no progression (vdH-S score≤ 0 unit) of structural damage compared to 45% patients receiving MTX alone. In a subset of patients who began the study without erosions, Infliximab + MTX maintained an erosion free state at 1 year in a greater proportion of patients than MTX alone, 79% (77/98) vs. 58% (23/40), respectively ($p<0.01$). Fewer patients in the Infliximab + MTX groups (47%) developed erosions in uninvolved joints compared to MTX alone (59%).

Table 6
RADIOGRAPHIC CHANGE FROM BASELINE TO WEEK 54

	Study RA I			Study RA II		
		Infliximab + MTX			Infliximab + MTX	
	Placebo + MTX (n=64)	3 mg/kg q 8 wks (n=71)	10 mg/kg q 8 wks (n=77)	Placebo + MTX (n=282)	3 mg/kg q 8 wks (n=359)	6 mg/kg q 8 wks (n=363)
Total Score						
Baseline						
Mean	79	78	65	11.3	11.6	11.2
Median	55	57	56	5.1	5.2	5.3
Change from baseline						
Mean	6.9	1.3[a]	0.2[a]	3.7	0.4[a]	0.5[a]
Median	4.0	0.5	0.5	0.4	0.0	0.0
Erosion Score						
Baseline						
Mean	44	44	33	8.3	8.8	8.3
Median	25	29	22	3.0	3.8	3.8
Change from baseline						
Mean	4.1	0.2[a]	0.2[a]	3.0	0.3[a]	0.1[a]
Median	2.0	0.0	0.5	0.3	0.0	0.0
JSN Score						
Baseline						
Mean	36	34	31	3.0	2.9	2.9
Median	26	29	24	1.0	1.0	1.0
Change from baseline						
Mean	2.9	1.1[a]	0.0[a]	0.6	0.1[a]	0.2
Median	1.5	0.0	0.0	0.0	0.0	0.0

[a] P < 0.001 for each outcome against placebo.

Physical function response

Physical function and disability were assessed using the Health Assessment Questionnaire (HAQ-DI) and the general health-related quality of life questionnaire SF-36.

In Study RA I, all doses/schedules of Infliximab + MTX showed significantly greater improvement from baseline in HAQ-DI and SF-36 physical component summary score averaged over time through week 54 compared to placebo + MTX, and no worsening in the SF-36 mental component summary score. The median (interquartile range) improvement from baseline to week 54 in HAQ-DI was 0.1(-0.1, 0.5) for the placebo + MTX group and 0.4 (0.1, 0.9) for Infliximab + MTX ($p<0.001$). Both HAQ-DI and SF-36 effects were maintained through week 102. Approximately 80% of patients in all doses/schedules of Infliximab + MTX remained in the trial through 102 weeks.

In Study RA II, both Infliximab treatment groups showed greater improvement in HAQ-DI from baseline averaged over time through week 54 compared to MTX alone; 0.7 for Infliximab + MTX vs. 0.6 for MTX alone ($p<0.001$). No worsening in the SF-36 mental component summary score was observed.

From the manufacturer study (INFLIX), as a biosimilar product, Rheumatoid Arthritis is chosen as indication in clinical study. A 30-week, multi-center, randomized, double-blind, Remicade®-control, parallel-group, phase III clinical study of the product in combination with MTX (study C008RAIII) was completed to confirm the similar efficacy for INFLIX and Remicade.

Clinical response

A total of 390 subjects were included in the FAS dataset, and 349 in the PPS dataset. Primary efficacy index: The ratio of subjects reaching ACR20 at week 30 in the INFLIX group and Remicade® group in the FAS dataset was 57.6% (110 subjects) and 62.2% (120 subjects), with an inter-group difference of

–4.6%. The lower limit of one-sided 97.5% CI was –14.29%, which was not lower than the threshold for non-inferiority (–15%). Thus, INFLIX could be considered non-inferior to Remicade®. The analysis showed that, in the FAS set, the ACR20 response in the INFLIX group and the Remicade® group was 57.6% and 62.2%, respectively, with a difference of –4.6%. The two-sided 95% CI was (–14.29, 5.12), which was within the equivalence range of (–15% to +15%). In which, the test statistics, P value, was 2.10 (0.018) and –3.95 (< 0.001) for the comparison with the lower and upper limit, respectively, indicating an inter-group equivalence. In the PPS set, the ACR20 response in the INFLIX group and the Remicade® group was 64.0% and 67.2%, respectively, with a difference of –3.3%. The two-sided 95% CI was (–13.18, 6.62), which was within the equivalence range of (–15% to +15%). In which, the test statistics, P value, was 2.32 (0.010) and –3.62 (< 0.001) for the comparison with the lower and upper limit, respectively, indicating an inter-group equivalence.
The ACR20 response may be affected by different baseline characteristics of the subjects and the immunogenicity (ADAs and neutralizing antibodies) of the monoclonal antibody, so the primary efficacy index was analysed by subgroups based on "weight", "age", "ADAs", and "neutralizing antibodies".
In the FAS dataset, the product and Remicade® showed high similarity in the primary efficacy index, without inter-group significant difference. The 20 elderly subjects enrolled in the study reported good efficacy, with no difference from the efficacy in subjects < 65 years old. The production of ADAs may affect the efficacy of monoclonal antibodies. For ADA-positive subjects in the study, the efficacy of the product was not significantly affected by the production of ADAs and was highly similar to that of Remicade®. For subjects with neutralizing antibodies, the inter-group comparison showed that the efficacy of the product was highly similar to that of Remicade®. The PPS-based results were consistent with the FAS-based conclusions.
In summary, the efficacy of the product was highly similar to that of Remicade®, as shown by efficacy index analysis and subgroup analysis. The combined therapy of the product with MTX can act rapidly and persistently to relieve moderate to severe active RA in a comprehensive, profound, and effective manner in adult patients, thereby improving their quality of life.

Active Crohn's Disease
From the Innovator study (Remicade), the safety and efficacy of single and multiple doses of Infliximab were assessed in two randomized, double-blind, placebo-controlled clinical studies in 653 patients with moderate to severely active Crohn's disease [Crohn's Disease Activity Index (CDAI) ≥220 and ≤400] with an inadequate response to prior conventional therapies. Concomitant stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents were permitted and 92% of patients continued to receive at least one of these medications.
In the single-dose trial[8] of 108 patients, 16% (4/25) of placebo patients achieved a clinical response (decrease in CDAI ≥70 points) at week 4 vs. 81% (22/27) of patients receiving 5 mg/kg Infliximab (p<0.001, two-sided, Fisher's Exact test). Additionally, 4% (1/25) of placebo patients and 48% (13/27) of patients receiving 5 mg/kg Infliximab achieved clinical remission (CDAI<150) at week 4.
In a multidose trial (ACCENT I [Study Crohn's I])[9], 545 patients received 5 mg/kg at week 0 and were then randomized to one of three treatment groups; the placebo maintenance group received placebo at weeks 2 and 6, and then every 8 weeks; the 5 mg/kg maintenance group received 5 mg/kg at weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance group received 5 mg/kg at weeks 2 and 6, and then 10 mg/kg every 8 weeks. Patients in response at week 2 were randomized and analysed separately from those not in response at week 2. Corticosteroid taper was permitted after week 6.
At week 2, 57% (311/545) of patients were in clinical response. At week 30, a significantly greater proportion of these patients in the 5 mg/kg and 10 mg/kg maintenance groups achieved clinical remission compared to patients in the placebo maintenance group (Table 7).
Additionally, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg Infliximab maintenance groups were in clinical remission and were able to discontinue corticosteroid use compared to patients in the placebo maintenance group at week 54 (Table 7).

Table 7
CLINICAL REMISSION AND STEROID WITHDRAWAL

	Single 5 mg/kg Dose[a] Placebo Maintenance	Three Dose Induction[b] Infliximab Maintenance q 8 wks 5 mg/kg	10 mg/kg
Week 30	25/102	41/104	48/105
Clinical remission	25%	39%	46%
p-value[c]		0.022	0.001
Week 54			
Patients in remission able to discontinue corticosteroid use[d]	6/54	14/56	18/53
	11%	25%	34%
p-value[c]		0.059	0.005

[a] Infliximab at week 0
[b] Infliximab 5 mg/kg administered at weeks 0, 2 and 6
[c] p-values represent pairwise comparisons to placebo
[d] Of those receiving corticosteroids at baseline

Patients in the Infliximab maintenance groups (5 mg/kg and 10 mg/kg) had a longer time to loss of response than patients in the placebo maintenance group (Figure 1). At weeks 30 and 54, significant improvement from baseline was seen among the 5 mg/kg and 10 mg/kg Infliximab-treated groups compared to the placebo group in the disease specific inflammatory bowel disease questionnaire (IBDQ), particularly the bowel and systemic components, and in the physical component summary score of the general health-related quality of life questionnaire SF-36.

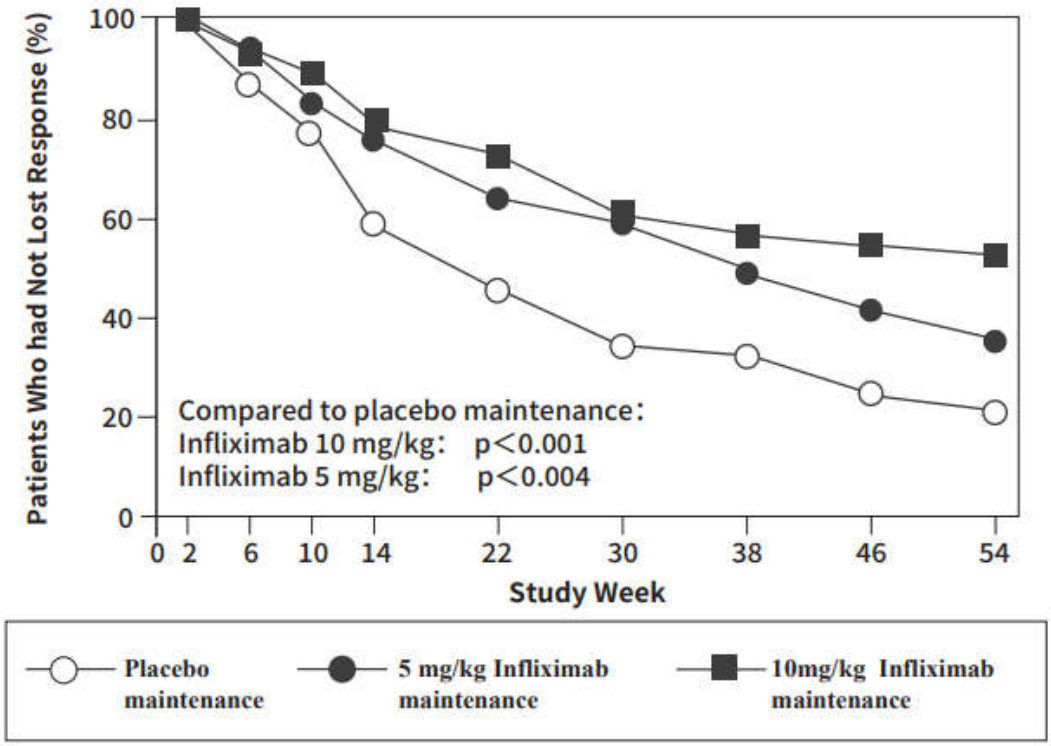


Figure 1
Kaplan-Meier estimate of the proportion of patients who had not lost response through week 54

In a subset of 78 patients who had mucosal ulceration at baseline and who participated in an endoscopic sub-study, 13 of 43 patients in the Infliximab maintenance group had endoscopic evidence of mucosal healing compared to 1 of 28 patients in the placebo group at week 10. Of the Infliximab-treated patients showing mucosal healing at week 10, 9 of 12 patients also showed mucosal healing at week 54. Patients who achieved a response and subsequently lost response were eligible to receive Infliximab on an episodic basis at a dose that was 5 mg/kg higher than the dose to which they were randomized. The majority of such patients responded to the higher dose. Among patients who were not in response at week 2, 59% (92/157) of Infliximab maintenance patients responded by week 14 compared to 51% (39/77) of placebo maintenance patients. Among patients who did not respond by week 14, additional therapy did not result in significantly more responses (see DOSAGE AND ADMINISTRATION).

Fistulizing Crohn's Disease

From the Innovator study (Remicade), the safety and efficacy of Infliximab were assessed in 2 randomized, double-blind, placebocontrolled studies in patients with fistulizing Crohn's disease with fistula(s) that were of at least 3 months duration. Concurrent use of stable doses of corticosteroids, 5-aminosalicylates, antibiotics, MTX, 6-mercaptopurine (6-MP) and/or azathioprine (AZA) was permitted.

In the first trial,[10] 94 patients received three doses of either placebo or Infliximab at weeks 0, 2 and 6. Fistula response (≥ 50% reduction in number of enterocutaneous fistulas draining upon gentle compression on at least two consecutive visits without an increase in medication or surgery for Crohn's disease) was seen in 68% (21/31) of patients in the 5 mg/kg Infliximab group (p=0.002) and 56% (18/32) of patients in the 10 mg/kg Infliximab group (p=0.021) vs. 26% (8/31) of patients in the placebo arm. The median time to onset of response and median duration of response in Infliximab treated patients was 2 and 12 weeks, respectively. Closure of all fistula was achieved in 52% of Infliximab-treated patients compared with 13% of placebo-treated patients ($p < 0.001$).

In the second trial (ACCENT II [Study Crohn's II]), patients who were enrolled had to have at least one draining enterocutaneous (perianal, abdominal) fistula. All patients received 5 mg/kg Infliximab at weeks 0, 2 and 6. Patients were randomized to placebo or 5 mg/kg Infliximab maintenance at week 14. Patients received maintenance doses at week 14 and then every eight weeks through week 46. Patients who were in fistula response (fistula response was defined the same as in the first trial) at both weeks 10 and 14 were randomized separately from those not in response. The primary endpoint was time from randomization to loss of response among those patients who were in fistula response.

Among the randomized patients (273 of the 296 initially enrolled), 87% had perianal fistulas and 14% had abdominal fistulas. Eight percent also had rectovaginal fistulas. Greater than 90% of the patients had received previous immunosuppressive and antibiotic therapy.

At week 14, 65% (177/273) of patients were in fistula response. Patients randomized to Infliximab maintenance had a longer time to loss of fistula response compared to the placebo maintenance group (Figure 2). At week 54, 38% (33/87) of Infliximab-treated patients had no draining fistulas compared with 22% (20/90) of placebo-treated patients (p=0.02). Compared to placebo maintenance, patients on Infliximab maintenance had a trend toward fewer hospitalizations.

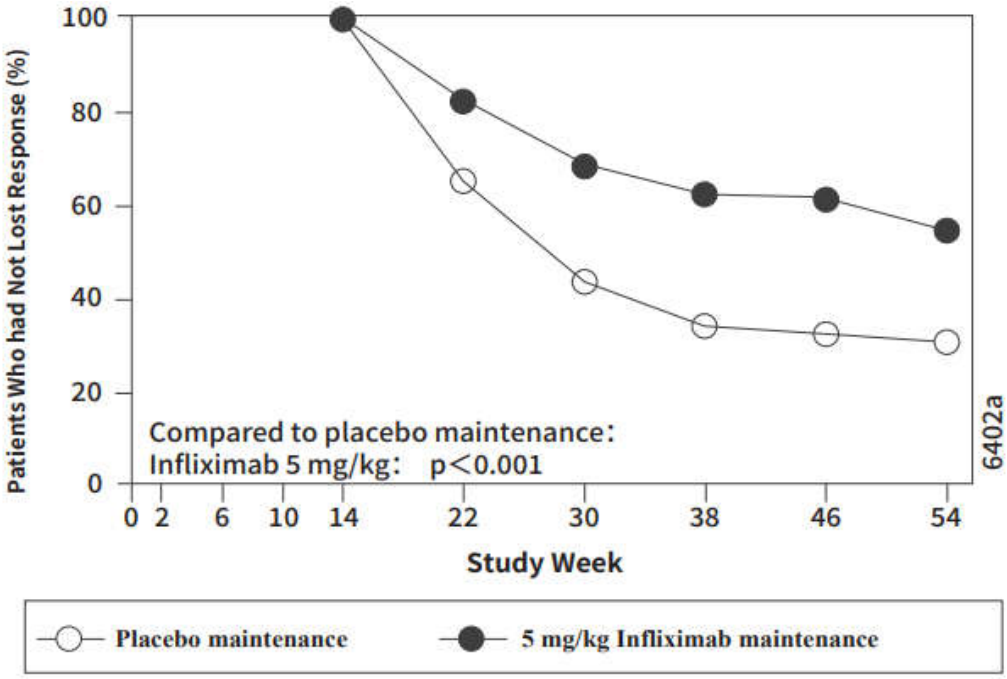


Figure 2
Life table estimates of the proportion of patients who had not lost fistula response through week 54

Patients who achieved a fistula response and subsequently lost response were eligible to receive Infliximab maintenance therapy at a dose that was 5 mg/kg higher than the dose to which they were randomized. Of the placebo maintenance patients, 66% (25/38) responded to 5 mg/kg Infliximab, and 57% (12/21) of Infliximab maintenance patients responded to 10 mg/kg.
Patients who had not achieved a response by week 14 were unlikely to respond to additional doses of Infliximab.
Similar proportions of patients in either group developed new fistulas (17% overall) and similar numbers developed abscesses (15% overall).

Ankylosing Spondylitis
From the Innovator study (Remicade), the safety and efficacy of Infliximab were assessed in a randomized, multi-center, double-blind, placebo-controlled study in 279 patients with active ankylosing spondylitis. Patients were between 18 and 74 years of age, and had ankylosing spondylitis as defined by the modified New York criteria for Ankylosing Spondylitis.11 Patients were to have had active disease as evidenced by both a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score >4 (possible range 0-10) and spinal pain >4 (on a Visual Analog Scale [VAS] of 0-10). Patients with complete ankylosis of the spine were excluded from study participation, and the use of Disease Modifying Anti-Rheumatic Drugs (DMARDs) and systemic corticosteroids were prohibited. Doses of Infliximab 5 mg/kg or placebo were administered intravenously at Weeks 0, 2, 6, 12 and 18. At 24 weeks, improvement in the signs and symptoms of ankylosing spondylitis, as measured by the proportion of patients achieving a 20% improvement in ASAS response criteria (ASAS 20), was seen in 60% of patients in the Infliximab-treated group vs. 18% of patients in the placebo group($p<0.001$). Improvement was observed at week 2 and maintained through week 24 (Figure 3 and Table 8).

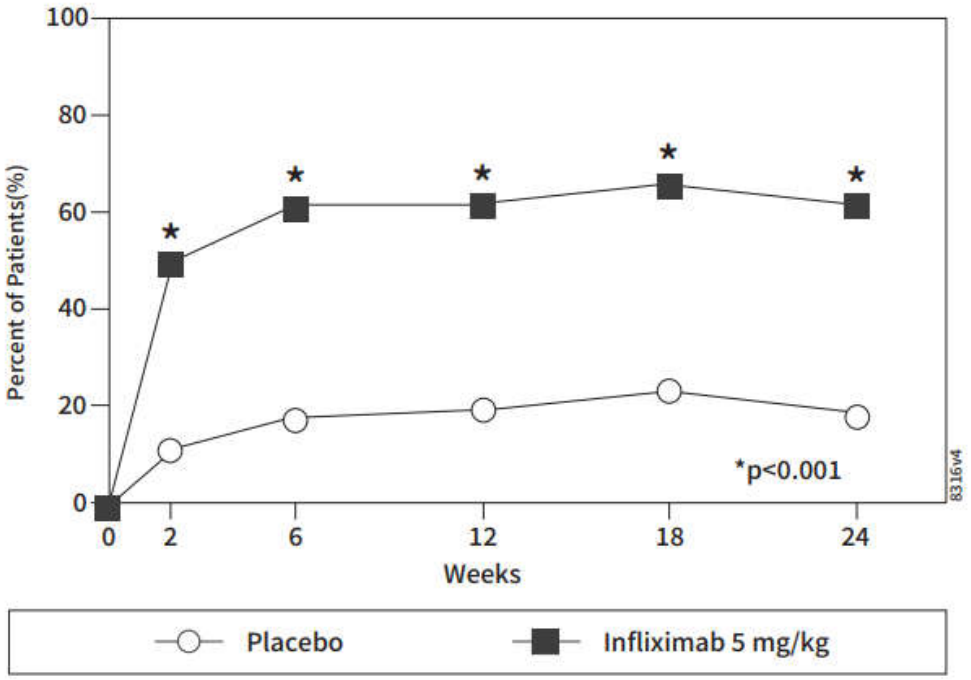


Figure 3
Proportion of patients achieving ASAS 20 response

At 24 weeks, the proportions of patients achieving a 50% and a 70% improvement in the signs and symptoms of ankylosing spondylitis, as measured by ASAS response criteria (ASAS 50 and ASAS 70, respectively), were 44% and 28%, respectively, for patients receiving Infliximab, compared to 9% and 4%, respectively, for patients receiving placebo ($p<0.001$, Infliximab vs. placebo). A low level of disease activity (defined as a value <20 [on a scale of 0-100 mm] in each of the four ASAS response parameters) was achieved in 22% of Infliximab-treated patients vs. 1% in placebo-treated patients($p<0.001$).

Table 8
COMPONENTS OF ANKYLOSING SPONDYLITIS DISEASE ACTIVITY

	Placebo (n=78)		Infliximab 5mg/kg (n=201)		
	Baseline	24 Weeks	Baseline	24 Weeks	p-value
ASAS 20 response Criteria (Mean)					
Patient global assessment [a]	6.6	6.0	6.8	3.8	<0.001
Spinal pain [a]	7.3	6.5	7.6	4.0	<0.001
BASFI [b]	5.8	5.6	5.7	3.6	<0.001
Inflammation [c]	6.9	5.8	6.9	3.4	<0.001
Acute Phase Reactants					
Median CRP [d] (mg/dL)	1.7	1.5	1.5	0.4	<0.001
Spinal Mobility (cm, Mean)					
Modified Schober' s test [e]	4.0	5.0	4.3	4.4	0.75
Chest expansion [e]	3.6	3.7	3.3	3.9	0.04
Tragus to wall [e]	17.3	17.4	16.9	15.7	0.02
Lateral spinal flexion [e]	10.6	11.0	11.4	12.9	0.03

[a] measured on a VAS with 0=" none" and 10=" severe"
[b] Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions
[c] Inflammation, average of last 2 questions on the 6 question BASDAI
[d] CRP normal range 0-1.0 mg/dL
[e] Spinal mobility normal values: modified Schober' s test: >4 cm; chest expansion:>6 cm; tragus to wall: <15 cm; lateral spinal flexion exion: >10 cm

[a] measured on a VAS with 0= "none" and 10= "severe"
[b] Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions
[c] Infl ammation, average of last 2 questions on the 6 question BASDAI
[d] CRP normal range 0-1.0 mg/dL
[e] Spinal mobility normal values: modifi ed Schober' s test: >4 cm; chest expansion:>6 cm; tragus to wall: <15 cm; lateral spinal fl exion: >10 cm

The median improvement from baseline in the general health-related quality of life questionnaire SF-36 physical component summary score at week 24 was 10.2 for the Infliximab group vs. 0.8 for the placebo group ($p < 0.001$). There was no change in the SF-36 mental component summary score in either the Infliximab group or the placebo group. Results of this study were similar to those seen in a multicenter double-blind, placebo-controlled study of 70 patients with ankylosing spondylitis.

Psoriatic Arthritis
From the Innovator study (Remicade), safety and efficacy of Infliximab were assessed in a multicenter, double-blind, placebo-controlled study in 200 adult patients with active psoriatic arthritis despite DMARD or NSAID therapy (≥ 5 swollen joints and ≥ 5 tender joints) with one or more of the following subtypes: arthritis involving DIP joints(n = 49), arthritis mutilans (n = 3), asymmetric peripheral arthritis (n = 40), polyarticular arthritis(n = 100), and spondylitis with peripheral arthritis (n = 8). Patients also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Forty-six percent of patients continued on stable doses of methotrexate (≤ 25 mg/week). During the 24-week double-blind phase, patients received either 5 mg/kg Infliximab or placebo at weeks 0, 2, 6, 14, and 22 (100 patients in each group). At week 16, placebo patients with < 10% improvement from baseline in both swollen and tender joint counts were switched to Infliximab induction (early escape).
Treatment with Infliximab resulted in improvement in signs and symptoms, as assessed by the ACR criteria, with 58% of Infliximab-treated patients achieving ACR 20 at week 14, compared with 11% of placebo-treated patients ($p < 0.001$). The response was similar regardless of concomitant use of methotrexate. Improvement was observed as early as week 2. At 6 months, the ACR 20/50/70 responses were achieved by 54%, 41%, and 27%, respectively, of patients receiving Infliximab compared to 16%,

4%, and 2%, respectively, of patients receiving placebo. Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and spondylitis with peripheral arthritis subtypes.
Compared to placebo, treatment with Infliximab resulted in improvements in the components of the ACR response criteria, as well as in dactylitis and enthesopathy (Table 9). The results of this study were similar to those seen in an earlier multicenter, randomized, placebo-controlled study of 104 patients with psoriatic arthritis.

Table 9
COMPONENTS OF ACR 20 AND PERCENTAGE OF PATIENTS WITH 1 OR MORE JOINTS WITH DACTYLITIS AND PERCENTAGE OF PATIENTS WITH ENTHESOPATHY AT BASELINE AND WEEK 24

	Placebo (n=100)		Infliximab 5mg/kg [a] (n=100)	
Parameter (medians)	Baseline	Week 24	Baseline	Week 24
No of Tender Joints [b]	24	20	20	6
No. of Swollen Joints [c]	12	9	12	3
Pain [d]	6.4	5.6	5.9	2.6
Physician's Global Assessment [d]	6.0	4.5	5.6	1.5
Patient's Global Assessment [d]	6.1	5.0	5.9	2.5
Disability Index (HAQ-DI) [e]	1.1	1.1	1.1	0.5
CRP (mg/dL) [f]	1.2	0.9	1.0	0.4
% Patients with 1 or more digits with dactylitis	41	33	40	15
% Patients with enthesopathy	35	36	42	22

[a] p<0.001 for percent change from baseline in all components of ACR 20 at week 24, p<0.05 for % of patients with dactylitis, and p=0.004 for % of patients with enthesopathy at week 24
[b] Scale 0-68
[c] Scale 0-66
[d] Visual Analog Scale (0=best, 10=worst)
[e] Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3=worst)
[f] Normal range 0-0.6 mg/dL

Improvement in PASI in patients with baseline body surface area (BSA) ≥ 3% (n=87 placebo, n=83 Infliximab) was achieved at week 14, regardless of concomitant methotrexate use, with 64% of Infliximab-treated patients achieving at least 75% improvement from baseline vs. 2% of placebo treated patients; improvement was observed as early as week 2. At 6 months, the PASI 75 and PASI 90 responses were achieved by 60% and 39%, respectively, of patients receiving Infliximab compared to 1% and 0%, respectively, of patients receiving placebo. Ulcerative Colitis The safety and efficacy of Infliximab were assessed in two randomized, double-blind, placebo controlled studies in 728 patients with moderately to severely active ulcerative colitis (UC) (Mayoscore12 6 to 12 [of possible range 0-12], Endoscopy subscore ≥ 2) with an inadequate response to conventional oral therapies (Studies UC I and UC II). Concomitant treatment with stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents was permitted. Corticosteroids taper was permitted after week 8. In both studies, patients were randomized to receive either placebo, 5 mg/kg Infliximab or 10 mg/kg Infliximab at weeks 0,2,6,14 and 22. Patients in Study UC I had failed to respond or were intolerant to oral corticosteroids, 6-mercaptopurine (6-MP), or azathioprine (AZA). Patients in Study UC II had failure to respond or were intolerant to the above treatments and/or aminosalycilates. Similar proportions of patients in Studies UC I and UC II were receiving corticosteroids (61% and 51%, respectively), 6-MP/azathioprine (49% and 43%) and aminosalycylates (70% and 75%) at baseline. More patients in

Study UC II than UC I were taking solely aminosalycilates for UC (26% vs. 11%, respectively). Clinical response was defi ned as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1. In both studies, greater percentages of patients in both Infliximab groups achieved a clinical response, a sustained clinical response (response at both weeks 8 and 30), clinical remission and other assessed clinical outcomes than in placebo group (Table 10). Of patients on corticosteroids at baseline, greater proportions of patients in the Infliximab treatment groups were in clinical remission and able to discontinue corticosteroids at week 30 compared with the patients in the placebo treatment groups (22% in Infliximab treatment groups vs 10% in placebo groups in Study UC I; 23% in Infliximab treatment groups vs 3% in placebo group in Study UC II). The Infliximab associated response was generally similar in the 5 mg/kg and 10 mg/kg dose groups.

Table 10
Response, Remission, and Mucosal Healing in Ulcerative Colitis Studies

	Study UC I			Study UC II		
	Placebo	5mg/kg Infliximab	10mg/kg Infliximab	Placebo	5 mg/kg Infliximab	10 mg/kg Infliximab
Patients randomized	121	121	121	123	121	120
Clinical Response[1]						
Week 8	37%	69%*	62%*	29%	65%*	69%*
Week 30	30%	52%*	51%*	26%	47%*	60%*
Sustained Response (both Week 8 and 30)	23%	49%*	46%*	15%	41%*	53%*
Clinical Remission[2]						
Week 8	15%	39%*	32%*	6%	34%*	28%*
Week 30	16%	34%*	37%*	11%	26%**	36%*
Sustained Remission (both Week 8 and 30)	8%	23%*	26%*	2%	15%*	23%*
Mucosal Healing[3]						
Week 8	34%	62%*	59%*	31%	60%*	62%*
Week 30	25%	50%	49%*	30%	46%*	57%*

* P < 0.001, ** P < 0.01

[1] Defi ned as a decrease from baseline in the Mayo score by ⩾ 30% and ⩾ 3 points, accompanied by a decrease in the rectal bleeding subscore of ⩾ 1 or rectal bleeding subscore of 0 or 1. (The Mayo score consists of the sum of four subscore; stool frequency, rectal bleeding, physician' s global assessment and endoscopy fi ndings).

[2] Defi ned as a Mayo score ⩽ 2 points, no individual subscore > 1.

[3] Defi ned as a 0 or 1 on the endoscopy subscore of the Mayo score.

The improvement with Infliximab was consistent across all Mayo subscores thorugh week 30 (study UC I shown in Table 11; Study UC II was similar).

Table 11
Proportion of patients in Study UC I with Mayo subscores indicating inactive or mild disease through week 30

	Placebo (n=121)	Study UC I Infliximab 5 mg/kg (n=121)	10 mg/kg (n=122)
Stool frequency			
Baseline	17%	17%	10%
Week 8	35%	60%	58%
Week 30	35%	51%	53%
Rectal Bleeding			
Baseline	54%	40%	48%
Week 8	74%	86%	80%
Week 30	65%	74%	71%
Physician' s global assessment			
Baseline	4%	6%	3%
Week 8	44%	74%	64%
Week 30	36%	57%	55%
Endoscopy findings			
Baseline	0%	0%	0%
Week 8	34%	62%	59%
Week 30	26%	51%	52%

Plaque psoriasis

From the Innovator study (Remicade), the safety and efficacy of Infliximab were assessed in three randomized, double-blind, placebo controlled studies in patients 18 years of age and older with chronic, stable plaque psoriasis involving≥10% BSA, a minimum PASI score of 12, and who were candidates for systemic anti-psoriatic therapy or phototherapy. Patients with guttate, pustular, or erythrodermic psoriasis were excluded from these studies. No concomitant anti-psoriatic therapies were allowed during the study, with the exception of low-potency topical corticosteroids on the face and groin after week 10 of study initiation.

Study I (EXPRESS) evaluated 378 patients who received placebo or Infliximab at a dose of 5 mg/kg at weeks 0,2, and 6 (induction therapy), followed by maintenance therapy every 8 weeks. At week 24, the placebo group crossed over to Infliximab induction therapy (5mg/kg), followed by maintenance therapy every 8 weeks. Patients originally randomized to Infliximab continued to receive Infliximab 5mg/kg every 8 weeks through week 46. Across all treatment groups, the median baseline PASI score was 21 and the baseline Static Physician Global Assessment (sPGA) score ranged from moderate (52% of patients) to marked (36%) to severe (2%). In addition, 75% of patients had a BSA >20%. Seventy-one percent of patients previously received therapy and 82% received phototherapy.

Study II (EXPRESS II) evaluated 835 patients who received placebo or Infliximab at doses of 3 mg/kg or 5mg/kg at weeks 0,2, and 6 (induction therapy). At week 14, within each Infliximab dose group, patients were randomized to either scheduled (every 8 weeks) or as needed (PRN) maintenance treatment through week 46. At week 16, the placebo group crossed over to Infliximab induction therapy (5mg/kg), followed by maintenance therapy every 8 weeks. Across all treatment groups, the median baseline PASI score was 18 and 63% of patients had a BSA >20%. Fifty-five percent of patients previously received systemic therapy and 64% received a phototherapy.

Study III (SPIRIT) evaluated 249 patients who had previously received either psoralen plus ultraviolet A treatment (PUVA) or other systemic therapy for their psoriasis. These patients were randomized to receive either placebo or Infliximab at doses of 3 mg/kg or 5 mg/kg at weeks 0,2, and 6. At week 26, patients with a sPGA score of moderate or worse (greater than or equal to 3 on a scale of 0 to 5) received an additional dose of the randomized treatment. Across all treatment groups, the median baseline PASI score was 19 and the baseline sPGA score ranged from moderate (62% of patients) to marked (22%) to severe (3%). In addition, 75% of patients had a BSA >20%. Of the enrolled patients 114 (46%) received the week 26 additional dose.

In Studies I, II and III, the primary endpoint was the proportion of patients who achieved a reduction in score of at least 75% from baseline at week 10 by the PASI (PASI 75). In Study I and Study III, another evaluated outcome included the proportion of patients who achieved a score of "cleared" or "minimal" by the sPGA. The sPGA is a 6 category scale ranging from "5 = severe" to "0 = cleared" indicating the physician's overall assessment of the psoriasis severity focusing on induration, erythema, and scaling. Treatment success, defined as "cleared" or "minimal", consisted of none or minimal elevation in plaque, up to faint red coloration in erythema, and none or minimal fine scale over < 5% of the plaque. Study II also evaluated the proportion of patients who achieved a score of "clear" or "excellent" by the relative Physician's Global Assessment (rPGA). The r PGA is a 6 category scale ranging from "6 =worse" to "1 = clear" that was assessed relative to baseline. Overall lesions were graded with consideration to the percent of body involvement as well as overall induration, scaling and erythema. Treatment success, defined as "clear" or "excellent", consisted of some residual pinkness or pigmentation to marked improvement (nearly normal skin texture; some erythema may be present). The results of these studies are presented in Table 12.

Table 12
Psoriasis Studies I, II, and III, Week 10 percentage of patients who achieved PASI 75 and Percentage Who Achieved Treatment "Success" with Physician's Global Assessment

	Placebo	Infliximab	
		3 mg/kg	5 mg/kg
Psoriasis Study I – patients randomized[a]	77	---	301
PASI 75	2 (3%)	---	242 (80%)*
sPGA	3 (4%)	---	242 (80%)*
Psoriasis Study II – patients randomized[a]	208	313	314
PASI 75	4 (2%)	220 (70%)*	237 (75%)*
rPGA	2 (1%)	217 (69%)*	234 (75%)*
Psoriasis Study III – patients randomized[b]	51	99	99
PASI 75	3 (6%)	71 (72%)*	87 (88%)*
sPGA	5 (10%)	71 (72%)*	89 (90%)*

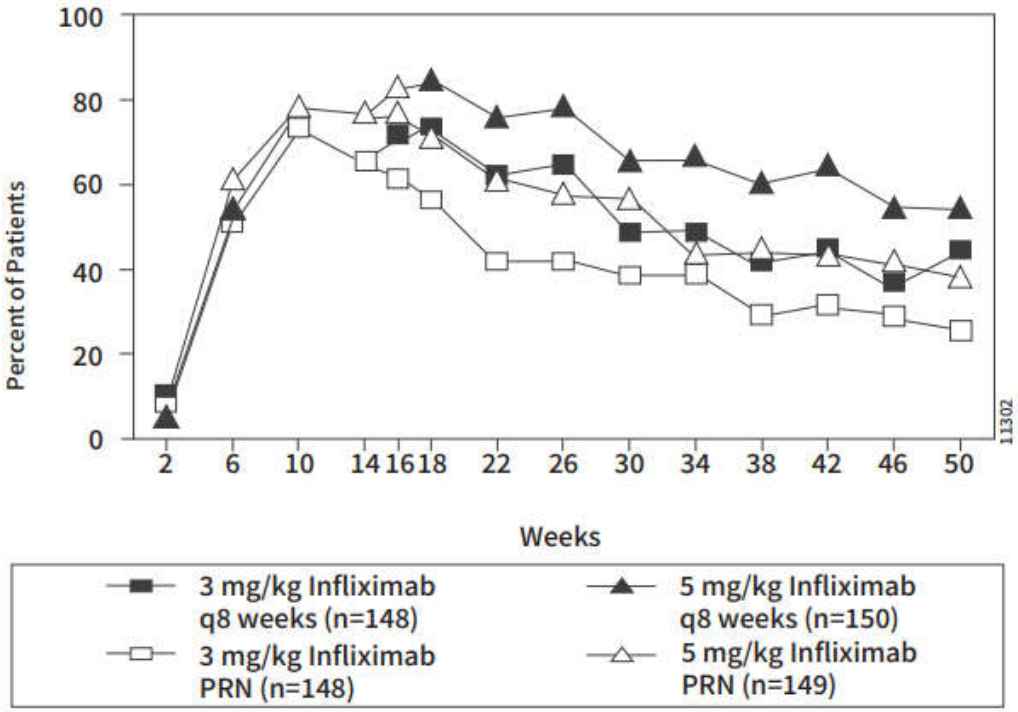
* $p < 0.001$ compared with placebo
a Patients with missing data at week 10 were considered as nonresponders.
b Patients with missing data at week 10 were imputed by last observations.

In Study I, in the subgroup of patients with more extensive psoriasis who had previously received phototherapy, 85% of patients on 5 mg/kg Infliximab achieved a PASI 75 at week 10 compared with 4% of patients on placebo.

In Study II, in the subgroups of patients with more extensive psoriasis who had previously received phototherapy, 72% and 77% of patients on 3 mg/kg and 5mg/kg Infliximab achieved a PASI 75 at week 10 respectively compared with 1% on placebo. In Study II, among patients with more extensive

psoriasis who had failed or were intolerant to phototherapy, 70% and 78% of patients on 3 mg/kg and 5 mg/kg Infliximab achieved PASI 75 at week 10 respectively, compared with 2% on placebo.
Maintenance of responses was studied in a subset of 292 and 297 Infliximab treated patients in the 3 mg/kg and 5 mg/kg groups; respectively, in Study II. Stratified by PASI response at week 10 and investigational site, patients in the active treatment groups were re-randomized to either a scheduled or as needed maintenance (PRN) therapy, beginning on week 14.
The groups that received a maintenance dose every 8 weeks appear to have a greater percentage of patients maintaining a PASI 75 through week 50 as compared to patients who received the as needed or PRN doses and the best response was maintained with the 5 mg/kg every 8 week dose. These results are shown in Figure 4. At week 46, when Infliximab serum concentrations were at through level, in the every 8 week dose group, 54% of patients in the 5 mg/kg group compared to 36% in the 3 mg/kg group achieved PASI 75. The lower percentage of PASI 75 responders in the 3 mg/kg every 8 week dose group compared to the 5 mg/kg group was associated with a lower percentage of patients with detectable trough serum Infliximab levels. This may be related in part to higher antibody rates. In addition, in a subset of patients who had achieved a response at week 10, maintenance of response appears to be greater in patients who received Infliximab every weeks at the 5 mg/kg dose. Regardless of whether the maintenance doses are PRN or every 8 weeks, there is a decline in response in a subpopulation of patients in each group over time. The results of Study I through Week 50 in the 5 mg/kg every 8 weeks maintenance dose group were similar to the result from Study II.

Figure 4
Proportion of Patients Achieved ≥75% Imprvement in PASI from Baseline through Week 50; patients randomized at Week 14



Efficacy and safety of Infliximab treatment beyond 50 weeks have not been evaluated in patients with plaque psoriasis.

CLINICAL PHARMACOLOGY

General

Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors.[2,3] Infliximab does not neutralize TNFα (lymphotoxin α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab can be lysed in vitro[3] or in vivo.[4] Infliximab inhibits the functional activity of TNFα in a wide variety of in vitro bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes and epithelial cells. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab prevents disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allows eroded joints to heal.

Pharmacodynamics

From the Innovator study (Remicade), elevated concentrations of TNFα have been found in involved tissues and fluids of patients with rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. In rheumatoid arthritis, treatment with Infliximab reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion [E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)], chemoattraction [IL-8 and monocyte chemotactic protein (MCP-1)] and tissue degradation [matrix metalloproteinase (MMP) 1 and 3]. In Crohn's disease, treatment with Infliximab reduced infiltration of inflammatory cells and TNFαproduction in inflamed areas of the intestine, and reduced the proportion of mononuclear cells from the lamina propria able to express TNFα and interferon. After treatment with Infliximab, patients with rheumatoid arthritis or Crohn's disease exhibited decreased levels of serum IL-6 and C-reactive protein (CRP) compared to baseline. Peripheral blood lymphocytes from Infliximab-treated patients showed no significant decrease in number or in proliferative responses to in vitro mitogenic stimulation when compared to cells from untreated patients. In psoriatic arthritis, treatment with Infliximab resulted in a reduction in the number of T-cells and blood vessels in the synovium and psoriatic skin lesions as well as a reduction of macrophages in the synovium. In plaque psoriasis, Infliximab treatment may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamics activities and the mechanism(s) by which Infliximab exerts its clinical effect is unknown.

Pharmacokinetics

From the Innovator study (Remicade), in adults, single intravenous (IV) infusions of 3 mg/kg to 20 mg/kg showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Pharmacokinetic results for doses of 3 mg/kg to 10 mg/kg in rheumatoid arthritis, 5 mg/kg in Crohn's disease and 3mg/kg to 5 mg/kg in plaque psoriasis indicate that the median terminal half-life of infliximab is 7.7 to 9.5 days. Following an initial dose of Infliximab, repeated infusions at 2 and 6 weeks resulted in predictable concentration-time profiles following each treatment. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8-week intervals. Development of antibodies to infliximab increased infliximab clearance. At 8 weeks after a maintenance dose of 3 to 10 mg/kg of Infliximab, median infliximab serum concentrations ranged from approximately 0.5 to 6 mcg/mL; however, infliximab concentrations were not detectable (<0.1 mcg/mL) in patients who

became positive for antibodies to infliximab. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight, or gender. It is not known if there are differences in clearance or volume of distribution in patients with marked impairment of hepatic or renal function. A pediatric Crohn's disease pharmacokinetic study was conducted in 21 patients aged 11 to 17 years old. No notable differences in single-dose pharmacokinetic parameters were observed between pediatric and adult Crohn's disease patients

From the manufacturer study (INFLIX), as a biosimilar product, PK study (study CMAB008HV-I) is conducted in health subject to compare the PK character between INFLIX and Remicade. A total of 90 healthy male subjects were enrolled in the study, with 45 subjects each in the INFLIX and Remicade® groups. After a single dose of INFLIX or Remicade (5 mg/kg), the mean Cmax was 109 μg/mL (13%) [arithmetic mean (arithmetic CV%), the data below are expressed in the same way] vs. 105 μg/mL (12%), the median Tmax was 4.00 h (2.12–12.00 h) [median (min–max)] vs. 4.00 h (2.10–12.00 h), the mean AUC0-t was 24,500 μg*h/mL (24%) vs. 24,700 μg*h/mL (23%), the mean AUC0-∞ was 25,500 μg*h/mL (23%) vs. 25,500 μg*h/mL (25%), the mean T1/2 was 301 h (25%) vs. 312 h (29%), the mean Vd was 5.51 L (20%) vs. 5.54 L (18%), and the mean CL was 0.0132 L/h (22%) vs. 0.0130 L/h (23%). According to the data, the PK parameters of CMAB008 and Remicade® are similar.

PRECLINICAL SAFETY DATA

From the Innovator study (Remicade), infliximab does not react with TNFα from species other than human and chimpanzees. Therefore, conventional preclinical safety data with infliximab are limited. In a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. In a fertility and general reproductive function study, the number of pregnant mice was reduced following administration of the same analogous antibody. It is not known whether this finding was due to effects on the males and/or the females. In a 6-month repeated dose toxicity study in mice, using the same analogous antibody against mouse TNFα, crystalline deposits were observed on the lens capsule of some of the treated male mice. No specific ophthalmologic examinations have been performed in patients to investigate the relevance of this findings for humans. Long-term studies have not been performed to evaluate the carcinogenic potential of infliximab. Studies in mice deficient in TNFα demonstrated no increase in tumours when challenged with known tumour initiators and/or promoters.

From the manufacturer study (INFLIX), as a biosimilar product, the preclinical safety data with infliximab are limited. In a single dose (2.0g/kg) toxicity study (mice), the results showed that the maximum tolerated dose (MTD) was > 2.0 g/kg for tail vein injection of infliximab. In a repeated dose toxicity study (monkey), the results show there was no obvious toxicity when cynomolgus monkeys were intravenously injected with infliximab at 10–100 mg/kg for 30 days, infliximab had no irritation to the blood vessels of cynomolgus monkeys and no antibodies (monkey anti-rc TNF mAb) were detected in all animals after administration which means immunotoxicity is limited. In a in vitro study with rabbit red blood cells, no hemolysis or agglutination was observed.

Carcinogenesis, Mutagenesis and Impairment of Fertility

From the Innovator study (Remicade), the significance of the results of nonclinical studies for human risk is unknown. A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNFα to evaluate tumorigenicity. cV1q is an analogous antibody that inhibits the function of TNFα in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the in vivo mouse micronucleus test or the Salmonella-Escherichia coli (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. It is not known whether infliximab can

impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study.

STORAGE
Store at temperature 2ºC–8ºC, protect from light.
Reconstituted solutions: the infusion shall begin within 3 hours after reconstitution and dilution at room temperature (25ºC).

PACKAGE
Box, 1 vial @ 100 mg Reg. No. XXXXXXXXXXXXXXX

MANUFACTURED BY:
Taizhou Mabtech Pharmaceuticals Co., Ltd.
Jiangsu - China

REGISTERED BY:
PT Etana Biotechnologies Indonesia
Jakarta – Indonesia

First Date of Approval
DD/MM/YY

HARUS DENGAN RESEP DOKTER