age of the neonate and the following doses have been suggested based upon the age at the first dose:

- less than 48 hours old: 200 micrograms/kg initially followed by two further doses of 100 micrograms/kg each
- 2 to 7 days old: three doses of 200 micrograms/kg each
- over 7 days old: 200 micrograms/kg initially followed by two further doses of 250 micrograms/kg each

If, 48 hours after this course of therapy the ductus remains open or re-opens, a second course may be used, but if this produces no response (which may be the case in 25% of infants treated[4,9]) surgery may be necessary.

Indometacin has been given orally where the injection is unavailable, but absorption of oral indometacin is poor and incomplete in premature neonates.

A decreased need for surgical closure and reduced recurrences were seen in neonates in whom standard intravenous indometacin therapy was then followed by maintenance therapy (intravenous indometacin 200 micrograms/kg daily for an additional 5 days).[10] Prolonged therapy using high doses of up to 1 mg/kg as a single dose every 12 hours has also been used with some success in a few infants who have not responded to standard regimens.[11] Similar beneficial findings were reported[12] in infants given prolonged low-dose indometacin therapy (100 micrograms/kg daily for 6 days). An additional benefit was a lower incidence of adverse effects; fewer infants had a rise in serum creatinine or urea concentrations. However, a systematic review[13] has suggested that such regimens are no more effective than the shorter standard regimens, and found an increased rather than decreased incidence of adverse effects (including a trend towards increased risk of necrotising enterocolitis[1,6]). Prolonged treatment with indometacin could not be recommended.[13] Prophylactic treatment or treatment of asymptomatic ductus with indometacin has been tried in premature infants, and there is good evidence to suggest that this is effective in reducing the risk of symptomatic patent ductus arteriosus and intraventricular haemorrhage (see above) in such patients;[7,14,15] however, prophylactic treatment has not been shown to significantly reduce the risk of short-term pulmonary complications such as bronchopulmonary dysplasia. Systematic reviews[14,15] have also found no evidence of either benefit or harm in neurological development or other longer term outcomes.

Some other NSAIDs have also been tried in the treatment of patent ductus arteriosus. Ibuprofen appears to be effective in closing a patent ductus arteriosus,[16] and it has been suggested that ibuprofen might be a better choice than indometacin as, unlike indometacin, it does not have adverse effects on renal, mesenteric, and cerebral haemodynamics. However, a recent systematic review[16] found no significant difference in the effectiveness of ibuprofen compared to indometacin and, although the risk of oliguria was reduced with ibuprofen, the risk for chronic lung disease may be increased. Ibuprofen is also effective when used prophylactically; however, there have been reports of pulmonary hypertension with such use and ibuprofen is not recommended.[17]

Oral therapy with ibuprofen has also been tried.[18]

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9. Gersony WM, *et al.* Effects of indomethacin in premature infants with patent ductus arteriosus: results of a national collaborative study. *J Pediatr* 1983; **102:** 895–906.
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12. Rennie JM, Cooke RWI. Prolonged low dose indomethacin for persistent ductus arteriosus of prematurity. *Arch Dis Child* 1991; **66:** 55–8.
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18. Heyman E, *et al.* Closure of patent ductus arteriosus with oral ibuprofen suspension in premature newborns: a pilot study. *Pediatrics* 2003; **112:** 1170. Full version: http://pediatrics.aappublications.org/cgi/reprint/112/5/e354.pdf (accessed 07/11/07)

Polyhydramnios. Reports[1-3] of the beneficial effects of indometacin in the management of polyhydramnios (an excessive accumulation of amniotic fluid). Polyhydramnios is a feature of the neonatal variant of Bartter's syndrome (see also above).

1. Cabrol D, *et al.* Treatment of symptomatic polyhydramnios with indomethacin. *Eur J Obstet Gynecol Reprod Biol* 1996; **66:** 11–15.
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Premature labour. The most common approach to postponing premature labour (p.2003) with drugs has historically been with a selective $beta_2$ agonist. However, as prostaglandins have a role in uterine contraction and cervical ripening and dilatation, prostaglandin synthetase inhibitors such as indometacin have also been used. Comparative studies[1,2] have shown that indometacin and ritodrine are equally effective in inhibiting uterine contractions and delaying delivery in patients in preterm labour who have intact membranes and in whom the gestational age is less than or equal to 34 weeks. In one study[2] an initial oral loading dose of indometacin 50 mg was given, followed by 25 to 50 mg orally every 4 hours until contractions stopped and then by a maintenance dose of 25 mg every 4 to 6 hours. In the other comparative study[1] indometacin was given as a 100-mg rectal suppository followed by 25 mg orally every 4 hours for 48 hours; if regular uterine contractions persisted 1 to 2 hours after the initial suppository, an additional 100-mg suppository was given before beginning oral therapy. Terbutaline was given for maintenance therapy.

Unfortunately indometacin can constrict the ductus arteriosus,[3-5] which may lead to pulmonary hypertension,[2] and has also been associated with bronchopulmonary dysplasia,[6] reduced volume of amniotic fluid (oligohydramnios)[2,4] and possible renal damage (see Effects on the Kidneys, above) in the fetus. Another complication is that prenatal indometacin exposure may increase both the incidence and severity of patent ductus arteriosus in premature infants,[7,8] as shown by the increased need for post-natal indometacin therapy and surgical ligation in such infants. However, there is evidence to suggest that there is no significant increase in the risk of neonatal complications in infants exposed to indometacin tocolysis when compared with control groups of infants who received either no treatment or tocolysis with drugs other than indometacin.[9,10]

The evidence for any overall benefit of indometacin in delaying labour is equivocal,[11-13] and it is generally reserved as a second-line tocolytic or for use with an intravenous tocolytic when an additive effect is required.

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4. Hallak M, *et al.* Indomethacin for preterm labor: fetal toxicity in a dizygotic twin gestation. *Obstet Gynecol* 1991; **78:** 911–13.
5. Vermillion ST, *et al.* The effect of indomethacin tocolysis on fetal ductus arteriosus constriction with advancing gestational age. *Am J Obstet Gynecol* 1997; **177:** 256–61.
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7. Norton ME, *et al.* Neonatal complications after the administration of indomethacin for preterm labor. *N Engl J Med* 1993; **329:** 1602–7.
8. Hammerman C, *et al.* Indomethacin tocolysis increases post-natal patent ductus arteriosus severity. Abstract: *Pediatrics* 1998; **102:** 1202–3. Full version: http://pediatrics.aappublications.org/cgi/content/full/102/5/e56 (accessed 07/11/07)
9. Vermillion ST, Newman RB. Recent indomethacin tocolysis is not associated with neonatal complications in preterm infants. *Am J Obstet Gynecol* 1999; **181:** 1083–6.
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Preparations

BP 2008: Indometacin Capsules; Indometacin Suppositories;
USP 31: Indomethacin Capsules; Indomethacin Extended-release Capsules; Indomethacin for Injection; Indomethacin Oral Suspension; Indomethacin Suppositories; Indomethacin Topical Gel.

Proprietary Preparations (details are given in Part 3)
Arg.: Agilex; IM 75; Indotex; Klonametacina; ***Austral.:*** Arthrexin; Indocid; Indocid PDA; ***Austria:*** Flexidin; Indo; Indobene; Indocid; Indocollyre; Indohexal; Indomelan; Indoptol; Liometacen; Luiflex; Ralicid; ***Belg.:*** Dolcidium; Indocid; Indocollyre; Luiflex; ***Braz.:*** Agilisin; Indocid; Indocid Colirio†; Metacidil†; ***Canad.:*** Indocid PDA; Indocid†; Indotec†; Novo-Methacin; Nu-Indo; Rhodacine; ***Chile:*** Flexono; Moviflex; ***Cz.:*** Bonidon†; Elmetacin; Indobene; Indocollyre; Vonum Cutan; ***Denm.:*** Confortid; Indocid†; ***Fin.:*** Confortid; Indocid; Indometin; ***Fr.:*** Chrono-Indocid; Indocid; Indocollyre; ***Ger.:*** Confortid; Elmetacin; Indo; Indo Top; Indo-paed; Indo-Phlogont†; Indocolir; Indocontin†; Indomet-ratiopharm; Indomet-ratiopharm m†; Indomet†; Indomisal†; Inflam; Mobilat Akut Indo; Rheubalmin Indo; Sigadoc†; ***Gr.:*** Begincalm†; Dolcispray; Fortathrine; Hastel; Indocid; Indomethol; Itapredin; Reumacid; Reumadolor; ***Hong Kong:*** Indocid; Indocin PDA; Indocollyre; Indogesic†; Indomet†; ***Hung.:*** Elmetacin; Indobene; Indocollyre; ***India:*** Idicin†; Indocap; Indocid; ***Indon.:*** Dialon; ***Irl.:*** Cidomel†; Flexin Continus; Indocid PDA; Indocid†; ***Israel:*** Indocollyre; Indomed; Indoptic†; Indotard; Indovis; ***Ital.:*** Imet†; Indocid; Indocollirio; Indom; Indoxen; Liometacen; Metacen; ***Jpn:*** Catlep; Idomethine; Infree; ***Malaysia:*** Arthrexin†; Domicap†; Indo; Indocid†; Indomen; ***Mex.:*** Antalgin; Artaxol; Biometacin; Draxil; Grindocin†; Indaflex; Indocarsil; Indocid; Indoman; Indotrin; Italon; Labymetacyn†; Malival; Mefazil; Soltacina; Stratasin; ***Neth.:*** Dometin†; Indocid; Indocid PDA; Indocollyre; Indoptol†; ***Norw.:*** Confortid; Indocid; ***NZ:*** Arthrexin; Elmetacin†; Indocid PDA; Rheumacin; ***Philipp.:*** Infree; Vi-Gel; ***Pol.:*** Elmetacin; Indocollyre; Metindol; ***Port.:*** Autritis; Dolovin; Elmetacin; Indocid; Indocollyre; Indogel; Indospray; Reumacide; ***Rus.:*** Indomin (Индомин); Indotard (Индотард)†; Indovis (Индовис)†; Metindol (Метиндол); ***S.Afr.:*** Acuflex; Adco-Indogel; Aflamin; Arthrexin; Betacin; Elmetacin; Flamaret; Flamecid; Indocid; Mediflex†; Methocaps; Nisaid; Restameth-SR†; ***Singapore:*** Indo; Indocollyre; Indomen; ***Spain:*** Aliviosin; Artrinovo; Flogoter; Inacid; Indocaf; Indolgina; Indonilo; Mederreumol†; Neo Decabutin; Reumo†; Reusin; ***Swed.:*** Confortid; Indomee; ***Switz.:*** Bonidon; Elmetacin; Indo-Mepha†; Indocid; Indophtal; ***Thai.:*** Ammi-Indocin; Bucin†; Docin; Elmego; Elmetacin; Idc; Indocid; Indocin; Indocollyre; Indomed; Indono; Inflamate; Inthacine; Liometacen; Metindo; Satogesic; ***Turk.:*** Endol; Endosetin; Indocolir; Inomet; ***UAE:*** Rothacin; ***UK:*** Flexin Continus†; Indocid PDA; Indocid†; Indolar SR; Indomax†; Indomod†; Pardelprin; Rimacid; Slo-Indo; ***USA:*** Indocin; ***Venez.:*** Cevimin; Elmetacin; Indocid; Melior†; Romazulan†.

Multi-ingredient: ***Austria:*** Vonum; ***Fin.:*** Indalgin; ***Fr.:*** Indobiotic; ***Ger.:*** Inflam†; ***Ital.:*** Difmetre; ***Jpn:*** Vantelin; ***Mex.:*** Artindol; Malival Compuesto; Morlan; Reupat; ***Port.:*** Indobiotic; ***Rus.:*** Indovasin (Индовазин); ***Spain:*** Artri; Fiacin; ***Switz.:*** Indobiotic†; Ralur†; ***Turk.:*** Indobiotic.

Infliximab *(BAN, rINN)*

cA2; CenTNF; Infliksimab; Infliksimabi; Infliximabum. Immunoglobulin G (human-mouse monoclonal cA2 heavy chain anti-human tumor necrosis factor), disulfide with human-mouse monoclonal cA2 light chain, dimer.

Инфликсимаб
CAS — 170277-31-3.
ATC — L04AB02.
ATC Vet — QL04AB02.

Adverse Effects, Treatment, and Precautions

Acute infusion reactions during or within 1 to 2 hours of infusion are common with infliximab, and other TNF inhibitors, particularly with the first or second dose. Symptoms include fever, chills, pruritus, urticaria, dyspnoea, chest pain, and hypertension or hypotension. Mild reactions may respond to a reduced rate of infusion or a temporary interruption. If reactions are more severe, therapy should be stopped. Pretreatment with paracetamol, corticosteroids, and antihistamines may be considered. TNF inhibitors should only be given where facilities for resuscitation are available. Delayed reactions have occurred 3 to 12 days after infliximab treatment; symptoms include myalgia, arthralgia, fever, and rash. Similar delayed reactions may also be seen when infliximab has been restarted after an extended period without treatment (see below).

Other, common, adverse effects include nausea and vomiting, abdominal pain, diarrhoea, fatigue, dizziness, headache, and back pain. Antibodies to infliximab (human antichimeric antibodies) may develop, and are associated with an increased incidence of hypersensitivity reactions. Antinuclear antibodies and anti-double-stranded-DNA antibodies have also developed with TNF inhibitor therapy. A lupus-like syndrome has occurred rarely; treatment should be stopped if it develops.

Infections are common in patients treated with infliximab or other drugs that inhibit TNF, and most often affect the upper respiratory tract and the urinary tract. TNF inhibitors have also been associated rarely with the development of serious opportunistic infections, sepsis, pneumonia, and onset or reactivation of tuber-

culosis (see below), particularly in patients with underlying conditions predisposing them to infections; in some cases death has resulted. TNF inhibitors should not be given to patients with severe infection, including active tuberculosis, abscesses, and opportunistic infections, and should be stopped if these develop. Patients should be evaluated for latent and active tuberculosis before beginning therapy; if evidence of latent tuberculosis is found, the risks and benefits of treatment should be considered carefully and chemoprophylaxis should be started before giving a TNF inhibitor. They should also be used with care in those with chronic infections, a history of recurrent infections, or with underlying conditions that may predispose to infections. Patients with fistulising Crohn's disease with suppurative fistulas should not be given infliximab until possible infection sources such as abscesses have been ruled out. Patients should be instructed to seek medical advice if symptoms suggestive of tuberculosis (such as persistent cough, weight loss, or low grade fever) occur. Patients should be monitored for signs of infection after stopping treatment: for adalimumab and infliximab, which both have long half-lives, monitoring should continue for 5 or 6 months, respectively; because of its relatively shorter half-life, the elimination of etanercept may be quicker.

There have been rare reports of severe hepatic reactions such as acute liver failure, jaundice, hepatitis, and cholestasis with infliximab; some cases have been fatal or required transplantation. Patients with signs or symptoms of hepatotoxicity should be evaluated and infliximab should be stopped in those patients with jaundice or marked elevations in liver enzyme values. Infliximab and other TNF inhibitors have also been associated with the reactivation of hepatitis B in chronic carriers, which has resulted in fatalities in some cases. Patients at risk of hepatitis B infection should be screened before starting treatment; it is recommended that carriers treated with a TNF inhibitor are closely monitored during, and for several months after stopping, treatment.

Blood dyscrasias, including leucopenia, thrombocytopenia, pancytopenia, and aplastic anaemia, have been reported rarely with TNF inhibitors; in some cases the outcome was fatal. They should be used with caution in patients with a history of blood dyscrasias.

Rare, and sometimes fatal, cases of interstitial lung disease including pulmonary fibrosis and pneumonitis have been reported with TNF inhibitors.

Infliximab and other TNF inhibitors are also associated with an increased incidence of malignancies including lymphoma (see also Carcinogenicity, below), although occurrences are rare. Some groups of patients treated with TNF inhibitors may already have an increased background risk of developing malignancies, regardless of drug treatment. Care has been advocated in patients with a history of malignancy.

Anaphylactic reactions have been reported rarely with TNF inhibitors. Infliximab should be avoided in patients with a history of hypersensitivity to the drug or other murine proteins.

TNF inhibitors have been associated in rare cases with seizures and clinical or radiological worsening of demyelinating disorders such as multiple sclerosis or optic neuritis; care is required in prescribing it to patients with such disorders or symptoms suggestive of their onset.

Worsening and, in some cases, new-onset heart failure has been reported with TNF inhibitors (see Effects on the Heart, below). (NYHA class III or IV). In the UK, infliximab is contra-indicated in patients with moderate to severe heart failure; however, US licensed product information advises that doses up to 5 mg/kg may be used in such patients. It should be used with caution in patients with mild heart failure (NYHA class I or II). All patients with heart failure should be closely monitored and infliximab stopped in those who develop new or worsening symptoms of heart failure. Similar recommendations are given for the TNF inhibitors adalimumab and etanercept, although UK licensed information for etanercept only advises caution in patients with heart failure.

◊ General references.

1. Hansen RA, *et al.* Serious adverse events with infliximab: analysis of spontaneously reported adverse events. *Clin Gastroenterol Hepatol* 2007; **5:** 729–35.

Carcinogenicity. Malignancies, especially lymphomas, have been seen in patients treated with TNF inhibitors for rheumatoid arthritis and Crohn's disease;[1] however, the suggestion of a causal relationship is controversial. A meta-analysis[2] in 2006 identified 24 published reports of malignancies in 3493 study patients with rheumatoid arthritis who had received at least one dose of a TNF inhibitor (adalimumab or infliximab) along with 2 cases in 1512 control patients; further, unpublished, cases were also found using FDA data to give 29 malignancies in the treatment groups and 3 in the control groups. Based on these figures, there was a 3.3-fold increase in the risk of malignancy in patients receiving TNF inhibitors when compared with controls. These results have, however, been criticised[3] on a number of points including the difficulty in applying them to current practice because etanercept was not included in the analysis, and, in particular, the unexpectedly low rate of malignancies in the control groups. Other studies in patients with rheumatoid arthritis[4,5] and Crohn's disease[6] have generally concluded that the overall risk of malignancies is not significantly increased in patients taking TNF inhibitors when compared with patients who have not taken these drugs. Some studies[4,7] in patients with rheumatoid arthritis have, however, shown a possible increased risk of lymphoma with TNF inhibitor treatment, but caution in interpreting these results was recommended as they were based on a small number of cases; in addition, the background risk of lymphoma is increased in rheumatoid arthritis regardless of treatment. The risk of malignancies with TNF inhibitors requires further study.

Rare cases of hepatosplenic T-cell lymphoma have been seen in adolescents and young adults given infliximab for the treatment of Crohn's disease. In July 2006, the manufacturer was aware of 6 cases of this type of lymphoma in 5 adolescents aged 12 to 19 years and one 31-year-old adult;[8] 4 of the 6 cases occurred in males. The treatment duration ranged from 1 or 2 infusions to over 4 years of therapy; in all cases, patients were also taking or had taken azathioprine or 6-mercaptopurine. This type of lymphoma is aggressive and 5 of the above patients died. A causal relationship was not clearly established although it could neither be excluded. Further cases have since been reported.[9]

1. Brown SL, *et al.* Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. *Arthritis Rheum* 2002; **46:** 3151–8.
2. Bongartz T, *et al.* Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006; **295:** 2275–85. Correction. *ibid.*; 2482.
3. Dixon W, Silman A. Is there an association between anti-TNF monoclonal antibody therapy in rheumatoid arthritis and risk of malignancy and serious infection? Commentary on the meta-analysis by Bongartz et al. *Arthritis Res Ther* 2006; **8:** 111.
4. Geborek P, *et al.* Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. *Ann Rheum Dis* 2005; **64:** 699–703.
5. Setoguchi S, *et al.* Tumor necrosis factor α antagonist use and cancer in patients with rheumatoid arthritis. *Arthritis Rheum* 2006; **54:** 2757–64. Correction. *ibid.*; 3134.
6. Biancone L, *et al.* Infliximab and newly diagnosed neoplasia in Crohn's disease: a multicentre matched pair study. *Gut* 2006; **55:** 228–33.
7. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. *Arthritis Rheum* 2004; **50:** 1740–51.
8. Schering, Canada. Health Canada endorsed important safety information on Remicade (infliximab) (issued 24th July, 2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/remicade_3_hpc-cps-eng.pdf (accessed 29/08/08)
9. Mackey AC, *et al.* Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2007; **44:** 265–7.

Delayed reactions. Ten of 37 patients with Crohn's disease retreated with infliximab after a 2 to 4 year period without treatment had delayed hypersensitivity reactions, of which 6 were considered serious. None of the patients had had infusion-related adverse effects with their original infliximab therapy. Adverse reactions developed in 9 of the 23 patients originally treated with a discontinued liquid formulation, and in 1 of the 14 patients who previously received the marketed formulation, leading to speculation that the formulation may have been a contributing factor.

Effects on blood lipids. A 35-year-old man with psoriatic arthritis and psoriasis developed markedly elevated triglyceride levels and a mildly increased total cholesterol level after a single infusion of infliximab;[1] tests prior to therapy had shown a mild hypertriglyceridaemia for which he had received no treatment. No further doses of infliximab were given and his triglyceride levels subsequently improved.

1. Antoniou C, *et al.* Elevated triglyceride and cholesterol levels after intravenous antitumour necrosis factor-α therapy in a patient with psoriatic arthritis and psoriasis vulgaris. *Br J Dermatol* 2007; **156:** 1090–1.

Effects on the CNS. Aseptic meningitis developed in a patient after his fifth injection of infliximab for rheumatoid arthritis.[1] Similar symptoms also occurred after a sixth injection.

Two patients with inflammatory bowel disease developed acute motor neuropathy with multiple conduction blocks following infliximab treatment; both patients improved after infliximab was stopped.[2] Similar adverse effects were reported in 2 further patients:[3] one was taking etanercept for rheumatoid arthritis and the other infliximab for ankylosing spondylitis. Three cases of bilateral optic neuropathy associated with infliximab therapy have also been reported.[4] Other neuropathies have been associated with TNF inhibitor treatment, including Guillain-Barré syndrome.[5]

1. Marotte H, *et al.* Infliximab-induced aseptic meningitis. *Lancet* 2001; **358:** 1784.
2. Singer OC, *et al.* Acute neuropathy with multiple conduction blocks after TNFα monoclonal antibody therapy. *Neurology* 2004; **63:** 1754.
3. Richez C, *et al.* Neuropathy resembling CIDP in patients receiving tumor necrosis factor-α blockers. *Neurology* 2005; **64:** 1468–70.
4. ten Tusscher MPM, *et al.* Bilateral anterior toxic optic neuropathy and the use of infliximab. *BMJ* 2003; **326:** 579.
5. Stübgen J-P. Tumor necrosis factor-α antagonists and neuropathy. *Muscle Nerve* 2008; **37:** 281–92.

Effects on the heart. The FDA has reported[1] on 47 patients who developed heart failure during long-term therapy with TNF antibodies (etanercept and infliximab) for arthritic conditions or Crohn's disease. Of these, 38 developed new-onset heart failure, 19 having documented risk factors for heart failure, and 9 had exacerbation of existing heart failure. The median time to new-onset heart failure was 3.5 months. However, studies[2-4] investigating a possible association between TNF inhibitors and the development of heart failure have been equivocal and further investigation is warranted.

Preliminary investigations on the use of infliximab in the treatment of moderate to severe heart failure failed to show any clinical improvement in patients given infliximab 5 mg/kg or 10 mg/kg when compared with placebo;[5] in addition, those given the higher dose had an increased risk of death or hospitalisation due to worsening heart failure.

1. Kwon HJ, *et al.* Case reports of heart failure after therapy with a tumor necrosis factor antagonist. *Ann Intern Med* 2003; **138:** 807–11.
2. Jacobsson LTH, *et al.* Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. *J Rheumatol* 2005; **32:** 1213–18.
3. Curtis JR, *et al.* Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-α antagonists. *Rheumatology (Oxford)* 2007; **46:** 1688–93.
4. Listing J, *et al.* Does tumor necrosis factor α inhibition promote or prevent heart failure in patients with rheumatoid arthritis? *Arthritis Rheum* 2008; **58:** 667–77.
5. Chung ES, *et al.* Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-α, in patients with moderate-to-severe heart failure: results of the Anti-TNF Therapy Against Congestive Heart failure (ATTACH) trial. *Circulation* 2003; **107:** 3133–40.

Effects on the lungs. Infliximab treatment has been associated with a fatal exacerbation of previously asymptomatic fibrosing alveolitis in 3 patients with chronic rheumatoid arthritis;[1] all 3 patients were also taking azathioprine and prednisolone. There was no evidence of infection or other underlying causes for the decline in respiratory function.

1. Ostor AJK, *et al.* Fatal exacerbation of rheumatoid arthritis associated fibrosing alveolitis in patients given infliximab. *BMJ* 2004; **329:** 1266.

Effects on the skin. Patients with rheumatoid arthritis receiving TNF inhibitor therapy are more likely to develop adverse skin reactions than those who are not.[1] Of 289 patients taking TNF inhibitors (infliximab, etanercept, adalimumab, and lenercept), 72 (25%) reported 128 dermatological events including skin infections, eczema, drug-related eruptions, and malignancies such as actinic keratosis; of the 289 patients not taking TNF inhibitors, 37 (13%) reported dermatological events.

In another review,[2] cutaneous adverse effects were seen in 35 out of 150 patients receiving TNF inhibitors (adalimumab, etanercept, or infliximab) for rheumatic disorders; cases included dermatitis herpetiformis and leucocytoclastic vasculitis although eczematous and skin infections were more common or infectious. Perhaps unexpectedly, psoriasis-like lesions were seen in 8 patients, 6 of whom had no history of psoriasis; similar effects have also been noted in other patients with rheumatoid arthritis[3] or Crohn's disease.[4]

Rare cases of serious skin reactions have been associated with TNF inhibitor treatment.[5] Since approval in 1998, the FDA has received 15 cases of erythema multiforme, 5 cases of Stevens-Johnson syndrome, and 1 case of toxic epidermal necrolysis associated with infliximab; cases for etanercept, approved in the same year, included 13 reports of erythema multiforme, and 4 reports each of Stevens-Johnson syndrome and toxic epidermal necrolysis. For adalimumab, which was marketed late in 2002, there have been 4 cases of erythema multiforme and 2 of Stevens-Johnson syndrome.

1. Flendrie M, *et al.* Dermatological conditions during TNF-α-blocking therapy in patients with rheumatoid arthritis: a prospective study. *Arthritis Res Ther* 2005; **7:** R666–R676.

2. Lee H-H, *et al.* Cutaneous side-effects in patients with rheumatic diseases during application of tumour necrosis factor-α antagonists. *Br J Dermatol* 2007; **156:** 486–91.
3. Dereure O, *et al.* Psoriatic lesions induced by antitumour necrosis factor-α treatment: two cases. *Br J Dermatol* 2004; **151:** 506–7.
4. Verea MM, *et al.* Psoriasiform eruption induced by infliximab. *Ann Pharmacother* 2004; **38:** 54–7.
5. FDA. Tumor necrosis factor alpha (TNF-α) antagonists: serious skin reactions. *FDA Drug Safety Newsletter* 2007; **1:** 18–20. Available at: http://www.fda.gov/cder/dsn/2008_winter/2008_winter.pdf (accessed 17/06/08)

Infection. There have been spontaneous reports of onset or reactivation of *tuberculosis* in patients treated with infliximab, including cases of miliary tuberculosis and unusual extrapulmonary disease.[1] The UK CSM noted in February 2001 that there had been 28 such reports worldwide. The US manufacturers subsequently reported[2] (in October 2001) that other serious opportunistic infections, including *histoplasmosis*, *listeriosis*, and *pneumocystosis* had occurred, and had led to some deaths; the number of reported cases of tuberculosis had risen to 84. Further opportunistic infections also continued to be reported; FDA data up to August 2002 included reports of *candidiasis*, *coccidioidomycosis*, *nocardiosis*, *aspergillosis*, and infections due to non-tuberculous mycobacteria.[3] Health Canada reported[4] in October 2004 that it had received 188 and 109 reports of infections associated with infliximab and etanercept, respectively, from January 2000 to May 2004. Of these, 10 and 2 reports were of tuberculosis associated with infliximab and etanercept, respectively. The FDA also received 25 reports of tuberculosis associated with etanercept between November 1998 and March 2002.[5] Although the majority of patients also had a history of treatment with immunosuppressants including corticosteroids, the inhibition of TNF may affect normal immune responses and predispose patients to opportunistic infections.

Guidelines[6] have been issued by the British Thoracic Society to quantify the risks of reactivation of tuberculosis with TNF inhibitors and to advise on the treatment of such infection in patients being assessed for TNF inhibitor therapy.

1. CSM/MCA. Infliximab (Remicade) and tuberculosis. *Current Problems* 2001; **27:** 7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 13/06/08)
2. Schaible TF [Centocor, Inc.]. Important drug warning (issued 5th October, 2001). Available at: http://www.fda.gov/medwatch/safety/2001/remicadeTB_deardoc.pdf (accessed 13/06/08)
3. Wallis RS, *et al.* Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis* 2004; **38:** 1261–5. Correction. *ibid.*; **39:** 1254–5.
4. Health Canada. Infliximab (Remicade) and etanercept (Enbrel): serious infections and tuberculosis. *Can Adverse React News* 2004; **14** (4): 2–3. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n4-eng.pdf (accessed 29/08/08)
5. Mohan AK, *et al.* Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. *Clin Infect Dis* 2004; **39:** 295–9.
6. British Thoracic Society Standards of Care Committee. BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-α treatment. *Thorax* 2005; **60:** 800–5. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Anti%20TNF%20Treatment/Guidelines/antitnf_treatment.pdf (accessed 13/06/08)

Interactions

Live vaccines should not be given with infliximab or other drugs that inhibit TNF as the effect of such drugs on vaccine efficacy or the risk of infection transmission is unknown. The use of TNF inhibitors with the interleukin-1 receptor antagonist anakinra may increase the risk of serious infections and neutropenia; such combinations are not recommended. A similar interaction has been seen with TNF inhibitors and the co-stimulation blocker abatacept.

Abatacept. Use of the TNF inhibitor etanercept with abatacept has resulted in an increase in the incidence of serious adverse effects including serious infections; in addition, there was no increase in clinical benefit.[1] Combinations of abatacept with TNF inhibitors are not recommended by UK licensed product information.

1. Weinblatt M, *et al.* Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. *Ann Rheum Dis* 2007; **66:** 228–34.

Anakinra. The incidence of serious infections, injection site reactions, and neutropenia is increased when anakinra is given with the TNF inhibitor etanercept.[1] In addition, the combination did not provide any further clinical benefit when compared to etanercept alone. Similar findings may be expected if anakinra is given with other TNF inhibitors.

1. Genovese MC, *et al.* Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis Rheum* 2004; **50:** 1412–19.

Pharmacokinetics

Infliximab shows linear pharmacokinetics. It is distributed primarily in the vascular compartment and, after single doses, has a terminal elimination half-life of 8 to 9.5 days. After repeated doses, infliximab has been detected in serum for at least 8 weeks.

◊ References.

1. Klotz U, *et al.* Clinical pharmacokinetics and use of infliximab. *Clin Pharmacokinet* 2007; **46:** 645–60.

Uses and Administration

Infliximab is a chimeric monoclonal antibody to tumour necrosis factor α (TNF), a pro-inflammatory mediator. Elevated levels of TNF have been found in the affected tissues and fluids of patients with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis, and Crohn's disease and ulcerative colitis. Elevated TNF levels are also found in psoriatic plaques.

Infliximab is given by intravenous infusion over a usual period of not less than 2 hours; shorter infusion times have been used in some patients with rheumatoid arthritis (see below for further details).

Infliximab is used with methotrexate in the management of moderate to severe, active **rheumatoid arthritis** to reduce the signs and symptoms of the disease, delay structural damage, and improve physical function; in the UK it is licensed for use in patients who have had an inadequate response to standard disease-modifying antirheumatic drugs (DMARDs) although, in severe progressive cases, it may be used in patients not previously treated with methotrexate or other DMARDs; in the USA it may be used for treating early rheumatoid arthritis. Infliximab is given in a dose of 3 mg/kg, repeated at 2 and 6 weeks, then every 8 weeks thereafter. For the first 3 doses infliximab should be infused for at least 2 hours; however, UK licensed product information suggests that subsequent infusion times may be reduced to a minimum period of 1 hour in those who tolerate the initial infusions. A clinical response is usually achieved within 12 weeks of starting treatment. Patients with an inadequate response during this period or who later relapse may benefit by increasing the dose: in the UK, a maximum dose of 7.5 mg/kg every 8 weeks (with increases made in steps of 1.5 mg/kg) is recommended whereas, in the USA, a maximum dose of 10 mg/kg is allowed. Alternatively, a dose of 3 mg/kg may be given as often as every 4 weeks in such patients. Continuing therapy in those who show no response within the first 12 weeks of treatment or after dose adjustment should be carefully reconsidered: in the UK NICE recommends that infliximab be withdrawn if there is no adequate response within 6 months of starting treatment.

Patients with moderate to severe, active **Crohn's disease** unresponsive to conventional treatment may be given a single infliximab dose of 5 mg/kg. This may be followed by a maintenance regimen of additional infusions of 5 mg/kg at 2 and 6 weeks after the initial infusion and then every 8 weeks, or the drug may be readministered when signs and symptoms of the disease recur (but see below). UK licensed product information does not recommend further doses in patients who are unresponsive after the first 2 doses; in the USA, a patient is not considered to be unresponsive until 3 doses have been given. A similar regimen is used in patients with fistulising Crohn's disease although therapy should not be considered ineffective until after the third dose of infliximab. US product information suggests that doses of up to 10 mg/kg may be used in patients who relapse after an initial response. Infliximab is also used in the treatment of moderate to severe, active **ulcerative colitis** in patients unresponsive to conventional therapy; the recommended dose is 5 mg/kg given as a regimen similar to that used for Crohn's disease (see above). Therapy should not be considered ineffective until after the third dose of infliximab.

In the treatment of **ankylosing spondylitis**, UK licensed product information recommends that infliximab should only be used in patients with severe disease who have had an inadequate response to conventional treatment; however, in the USA it may be used in early treatment, to reduce the signs and symptoms. The initial dose is 5 mg/kg, repeated at 2 and 6 weeks and then every 6 to 8 weeks; if there is no response after 2 doses no further treatment should be given.

Infliximab is also used in the treatment of active and progressive **psoriatic arthritis**; in the UK, its use is limited to patients who have had an inadequate response to standard DMARD but, as before, US licensed product information allows earlier use. In the USA, it may be given with or without methotrexate; however, UK product information only recommends use without methotrexate in those patients who are intolerant of or have contra-indications to such treatment. It is given in a single dose of 5 mg/kg, repeated at 2 and 6 weeks and then every 8 weeks thereafter. Guidance issued by NICE in the UK recommends that treatment with infliximab is stopped after 12 weeks in those who show an inadequate response.

Infliximab is used in the treatment of moderate to severe plaque **psoriasis**. Its use is usually limited to patients in whom other treatments are not suitable. Infliximab is given in a dose of 5 mg/kg, repeated at 2 and 6 weeks, then every 8 weeks thereafter. Treatment should be stopped after 14 weeks (4 doses) in patients who show no response.

If the signs and symptoms of rheumatoid arthritis or Crohn's disease recur infliximab may be readministered if within 16 weeks of the last infusion. **Readministration** after a drug-free interval of more than 16 weeks may be associated with an increased risk of delayed hypersensitivity (see Delayed Reactions, above) and consequently is not recommended. Recommendations regarding the readministration of infliximab for other indications (other than those detailed above) have not been established. Limited data from readministration with a single dose of infliximab in psoriasis after an interval of 20 weeks suggest reduced efficacy and a higher incidence of mild to moderate infusion reactions when compared with the initial regimen.

For details of infliximab use in children, see below.

Administration in children. Infliximab is licensed for use in moderate to severe, active Crohn's disease in children aged 6 years and over who have not responded to conventional therapy, or who have contraindication for or are intolerant of such treatments; doses are the same as those used in adults (see above). UK licensed product information suggests that the dosage interval may be adjusted to maintain any benefits; however, further treatment is unlikely to be of use in patients not responding within the first 10 weeks.

Although unlicensed for such use in the UK, infliximab has also been used in children with fistulising Crohn's disease; the *BNFC* recommends that those aged 6 to 18 years may be treated with the same dosage regimen that is used for this indication in adults (see above).

Asthma. TNF inhibitors such as infliximab have been investigated in the treatment of refractory asthma (p.1108).[1,2] There is some evidence that only a minority of patients will respond to such therapy, and that the benefits and risks must therefore be carefully assessed.[2]

1. Erin EM, *et al.* The effects of a monoclonal antibody directed against tumor necrosis factor-α in asthma. *Am J Respir Crit Care Med* 2006; **174:** 753–62.
2. Brightling C, *et al.* Targeting TNF-alpha: a novel therapeutic approach for asthma. *J Allergy Clin Immunol* 2008; **121:** 5–10.

Inflammatory bowel disease. Infliximab is used in adults for the treatment of Crohn's disease[1-11] and ulcerative colitis[8,12-16] (see Inflammatory Bowel Disease, p.1697); it has also been used in children in the treatment of inflammatory bowel disease,[17-20] particularly Crohn's disease.

In the treatment of Crohn's disease, guidance issued in the UK by NICE recommends that infliximab is used in patients with severe disease when treatment with immunomodulators and corticosteroids has failed or is not tolerated, and when surgery is inappropriate.[21]

In the treatment of ulcerative colitis, guidance issued by NICE recommends against the use of infliximab in subacute manifestations of moderately to severely active disease (defined as that which would normally be managed in an outpatient setting, and does not require hospitalisation or the consideration of urgent surgical intervention).[22] The use of infliximab in acute manifes-

tations of moderately to severely active ulcerative colitis is under review by NICE.

1. Present DH, *et al.* Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999; **340:** 1398–405.
2. Rutgeerts P, *et al.* Efficacy and safety of retreatment with antitumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology* 1999; **117:** 761–9.
3. Hanauer SB, *et al.* ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359:** 1541–9.
4. Rutgeerts P, *et al.* Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* 2004; **126:** 402–13.
5. Sands BE, *et al.* Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004; **350:** 876–85.
6. Panaccione R, *et al.* Canadian Association of Gastroenterology Clinical Practice Guidelines: the use of infliximab in Crohn's disease. *Can J Gastroenterol* 2004; **18:** 503–8. Also available at: http://www.cag-acg.org/uploads/guidelines/Infliximab%20guidelines%202004.pdf (accessed 13/06/08)
7. Siddiqui MAA, Scott LJ. Infliximab: a review of its use in Crohn's disease and rheumatoid arthritis. *Drugs* 2005; **65:** 2179–2208. Correction. *ibid.* 2006; **66:** 1359.
8. Rutgeerts P, *et al.* Review article: infliximab therapy for inflammatory bowel disease — seven years on. *Aliment Pharmacol Ther* 2006; **23:** 451–63.
9. Rutgeerts P, *et al.* Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc* 2006; **63:** 433–42.
10. Lémann M, *et al.* Groupe d'Etude Therapeutique des Affections Inflammatoires du Tube Digestif (GETAID). Infliximab plus azathioprine for steroid-dependent Crohn's disease patients: a randomized placebo-controlled trial. *Gastroenterology* 2006; **130:** 1054–61.
11. Osterman MT, Lichtenstein GR. Infliximab in fistulizing Crohn's disease. *Gastroenterol Clin North Am* 2006; **35:** 795–820.
12. Probert CS, *et al.* Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial. *Gut* 2003; **52:** 998–1002.
13. Rutgeerts P, *et al.* Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353:** 2462–76. Correction. *ibid.* 2006; **354:** 2200.
14. Lawson MM, *et al.* Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 13/06/08).
15. Aberra FN, Lichtenstein GR. Infliximab in ulcerative colitis. *Gastroenterol Clin North Am* 2006; **35:** 821–36.
16. Gisbert JP, *et al.* Systematic review: Infliximab therapy in ulcerative colitis. *Aliment Pharmacol Ther* 2007; **25:** 19–37.
17. Baldassano R, *et al.* Infliximab (REMICADE) therapy in the treatment of pediatric Crohn's disease. *Am J Gastroenterol* 2003; **98:** 833–8.
18. Hyams J, *et al.* REACH Study Group. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology* 2007; **132:** 863–73.
19. de Ridder L, *et al.* Infliximab use in children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2007; **45:** 3–14.
20. Veres G, *et al.* Infliximab therapy in children and adolescents with inflammatory bowel disease. *Drugs* 2007; **67:** 1703–23.
21. NICE. Guidance on the use of infliximab for Crohn's disease: Technology Appraisal Guidance 40 (issued April 2002). Available at: http://www.nice.org.uk/nicemedia/pdf/NiceCROHNS40GUIDANCE.pdf (accessed 13/06/08)
22. NICE. Infliximab for subacute manifestations of ulcerative colitis: Technology Appraisal Guidance 140 (issued April 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA140Guidance.pdf (accessed 28/07/08)

Leprosy. Infliximab has been used[1] in the treatment of recurrent type 2 (erythema nodosum leprosum) lepra reactions (see Leprosy, p.176). However, 2 cases of rapidly progressive leprosy developing in patients given infliximab for rheumatoid arthritis have also been described;[2] reversal (type 1) reactions occurred in both when infliximab was stopped.

1. Faber WR, *et al.* Treatment of recurrent erythema nodosum leprosum with infliximab. *N Engl J Med* 2006; **355:** 739.
2. Scollard DM, *et al.* Development of leprosy and type 1 leprosy reactions after treatment with infliximab: a report of 2 cases. *Clin Infect Dis* 2006; **43:** e19–e22.

Psoriasis. Infliximab is used in the treatment of moderate to severe plaque psoriasis (p.1583).[1-8] In the UK, NICE recommends[8] that it be reserved for severe cases, unresponsive to standard therapies (including ciclosporin, methotrexate, and PUVA) or where such therapies cannot be used.

1. Benoit S, *et al.* Treatment of recalcitrant pustular psoriasis with infliximab: effective reduction of chemokine expression. *Br J Dermatol* 2004; **150:** 1009–12.
2. Gottlieb AB, *et al.* Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2004; **51:** 534–42.
3. Reich K, *et al.* EXPRESS study investigators. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005; **366:** 1367–74.
4. Reich K, *et al.* Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2006; **154:** 1161–8.
5. Smith CH, *et al.* Infliximab for severe, treatment-resistant psoriasis: a prospective, open-label study. *Br J Dermatol* 2006; **155:** 160–9.
6. Menter A, *et al.* A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol* 2006; **56:** 31.e1–15.
7. Poulalhon N, *et al.* A follow-up study in 28 patients treated with infliximab for severe recalcitrant psoriasis: evidence for efficacy and high incidence of biological autoimmunity. *Br J Dermatol* 2007; **156:** 329–36.
8. NICE. Infliximab for the treatment of adults with psoriasis: Technology Appraisal Guidance 134 (issued January 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA134Guidance.pdf (accessed 22/08/08)

Rheumatoid arthritis. TNF inhibitors play an increasingly important role in the management of rheumatoid arthritis; they tend to be reserved for patients who are unresponsive to more conventional disease-modifying drugs, although some favour use earlier in management.

Some references to the use of infliximab in rheumatoid arthritis (p.11) and juvenile idiopathic arthritis (p.10).

1. Maini R, *et al.* ATTRACT Study Group. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. *Lancet* 1999; **354:** 1932–9.
2. Lipsky PE, *et al.* Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000; **343:** 1594–1602.
3. Maini RN, *et al.* Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum* 2004; **50:** 1051–65.
4. Quinn MA, *et al.* Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005; **52:** 27–35.
5. Voulgari PV, *et al.* Infliximab therapy in established rheumatoid arthritis: an observational study. *Am J Med* 2005; **118:** 515–20.
6. Ruperto N, *et al.* Paediatric Rheumatology International Trials Organisation. Pediatric Rheumatology Collaborative Study Group. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum* 2007; **56:** 3096–3106.
7. NICE. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis: Technology Appraisal Guidance 130 (issued October 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA130guidance.pdf (accessed 13/06/08)

Sarcoidosis. For a mention of possible benefit from infliximab in sarcoidosis, see p.1512.

Spondyloarthropathies. References to the use of infliximab in the treatment of ankylosing spondylitis and psoriatic arthritis (p.13). In the UK, NICE considers that TNF inhibitors should be reserved for severe active psoriatic arthritis unresponsive to at least 2 standard disease-modifying drugs; etanercept or adalimumab are preferred to infliximab.

1. Brandt J, *et al.* Infliximab in the treatment of active and severe ankylosing spondylitis. *Clin Exp Rheumatol* 2002; **20** (Suppl 28): S106–S110.
2. Brandt J, *et al.* Successful short term treatment of severe undifferentiated spondyloarthropathy with the anti-tumor necrosis factor-alpha monoclonal antibody infliximab. *J Rheumatol* 2002; **29:** 118–22.
3. Collantes-Estévez E, *et al.* Infliximab in refractory spondyloarthropathies: a multicentre 38 week open study. *Ann Rheum Dis* 2003; **62:** 1239–40.
4. Robinson DM, Keating GM. Infliximab: in ankylosing spondylitis. *Drugs* 2005; **65:** 1283–91.
5. NICE. Etanercept and infliximab for the treatment of adults with psoriatic arthritis: Technology Appraisal Guidance 104 (issued July 2006). Available at: http://www.nice.org.uk/nicemedia/pdf/TA104guidance.pdf (accessed 13/06/08)
6. Rott S, *et al.* Successful treatment of severe psoriatic arthritis with infliximab in an 11-year-old child suffering from linear psoriasis along lines of Blaschko. *Br J Dermatol* 2007; **157:** 191–2.

Uveitis. Infliximab has been tried with some success in the treatment of uveitis (p.1515) including that associated with Behçet's syndrome (p.1499). Uveitis can also develop as a complication of other inflammatory disorders such as rheumatoid arthritis; treatment with infliximab may improve ocular symptoms in addition to its effect on the primary disorder.

References.

1. Murphy CC, *et al.* Tumor necrosis factor alpha blockade with infliximab for refractory uveitis and scleritis. *Ophthalmology* 2004; **111:** 352–6.
2. Bodaghi B, *et al.* Therapeutic use of infliximab in sight threatening uveitis: retrospective analysis of efficacy, safety, and limiting factors. *Ann Rheum Dis* 2005; **64:** 962–4.
3. Braun J, *et al.* Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the anti-tumor necrosis factor agents infliximab and etanercept. *Arthritis Rheum* 2005; **52:** 2447–51.
4. Richards JC, *et al.* Infliximab for juvenile idiopathic arthritis-associated uveitis. *Clin Experiment Ophthalmol* 2005; **33:** 461–8.
5. Lindstedt EW, *et al.* Anti-TNF-α therapy for sight threatening uveitis. *Br J Ophthalmol* 2005; **89:** 533–6.
6. Saurenmann RK, *et al.* Tumour necrosis factor alpha inhibitors in the treatment of childhood uveitis. *Rheumatology (Oxford)* 2006; **45:** 982–9.
7. Kahn P, *et al.* Favorable response to high-dose infliximab for refractory childhood uveitis. *Ophthalmology* 2006; **113:** 860–4.e2.
8. Guignard S, *et al.* Efficacy of tumour necrosis factor blockers in reducing uveitis flares in patients with spondylarthropathy: a retrospective study. *Ann Rheum Dis* 2006; **65:** 1631–4.
9. Tynjälä P, *et al.* Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. *Ann Rheum Dis* 2007; **66:** 548–50.
10. Ardoin SP, *et al.* Infliximab to treat chronic noninfectious uveitis in children: retrospective case series with long-term follow-up. *Am J Ophthalmol* 2007; **144:** 844–849.
11. Pipitone N, *et al.* Infliximab for the treatment of Neuro-Behçet's disease: a case series and review of the literature. *Arthritis Rheum* 2008; **59:** 285–90.

Vasculitic syndromes. For a preliminary report on the use of infliximab in Takayasu's arteritis, see p.1514. Infliximab has also been investigated in the management of Kawasaki disease (p.2228) in patients who are unresponsive to standard treatment.[1-3]

1. Burns JC, *et al.* Infliximab treatment for refractory Kawasaki syndrome. *J Pediatr* 2005; **146:** 662–7.
2. Saji T, Kemmotsu Y. Infliximab for Kawasaki syndrome. *J Pediatr* 2006; **149:** 426.
3. O'Connor MJ, Saulsbury FT. Incomplete and atypical Kawasaki disease in a young infant: severe, recalcitrant disease responsive to infliximab. *Clin Pediatr (Phila)* 2007; **46:** 345–8.

Preparations

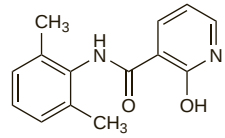
Proprietary Preparations (details are given in Part 3)
Arg.: Remicade†; Revellex†; ***Austral.:*** Remicade; ***Belg.:*** Remicade; ***Braz.:*** Remicade; ***Canad.:*** Remicade; ***Chile:*** Remicade; ***Cz.:*** Remicade; ***Denm.:*** Remicade; ***Fin.:*** Remicade; ***Fr.:*** Remicade; ***Ger.:*** Remicade; ***Gr.:*** Remicade; ***Hong Kong:*** Remicade; ***Hung.:*** Remicade; ***Indon.:*** Remicade; ***Irl.:*** Remicade; ***Israel:*** Remicade; ***Ital.:*** Remicade; ***Jpn:*** Remicade; ***Malaysia:*** Remicade; ***Mex.:*** Remicade; ***Neth.:*** Remicade; ***Norw.:*** Remicade; ***NZ:*** Remicade; ***Philipp.:*** Remicade; ***Pol.:*** Remicade; ***Port.:*** Remicade; ***Rus.:*** Remicade (Ремикейд); ***S.Afr.:*** Revellex; ***Singapore:*** Remicade; ***Spain:*** Remicade; ***Swed.:*** Remicade; ***Switz.:*** Remicade; ***Thai.:*** Remicade; ***Turk.:*** Remicade; ***UK:*** Remicade; ***USA:*** Remicade; ***Venez.:*** Remicade.

Isonixin *(rINN)*

Isonixine; Isonixino; Isonixinum. 2-Hydroxy-*N*-(2,6-dimethylphenyl)nicotinamide.

Изониксин

$C_{14}H_{14}N_2O_2$ = 242.3.
CAS — 57021-61-1.



Profile
Isonixin is an NSAID (p.96) that has been used in the management of pain and inflammation associated with musculoskeletal and joint disorders. It has been used in doses of 400 mg two to four times daily by mouth or by rectal suppository. It has also been applied topically as a 2.5% cream.

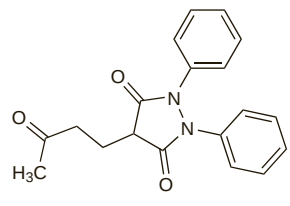
Preparations
Proprietary Preparations (details are given in Part 3)
Spain: Nixyn.
Multi-ingredient: ***Spain:*** Nixyn.

Kebuzone *(rINN)*

Kebuzona; Kébuzone; Kebuzonum; Ketophenylbutazone. 4-(3-Oxobutyl)-1,2-diphenylpyrazolidine-3,5-dione.

Кебузон

$C_{19}H_{18}N_2O_3$ = 322.4.
CAS — 853-34-9.
ATC — M01AA06.
ATC Vet — QM01AA06.



Profile
Kebuzone, a phenylbutazone derivative, is an NSAID (p.96). It has been given for musculoskeletal, joint, and soft-tissue disorders in oral doses of up to 1.5 g daily in divided doses. Kebuzone has also been given as the sodium salt by intramuscular injection in doses equivalent to 1 g of base once or twice daily.

Porphyria. Kebuzone is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals* or *in-vitro* systems.