REMICADE® (100 MG POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION) PRESCRIBING INFORMATION

ACTIVE INGREDIENT: infliximab

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

INDICATIONS:
Rheumatoid arthritis: Remicade, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate; and adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.
Adult Crohn's disease: Remicade is indicated for treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies; and treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).
Paediatric Crohn's disease: Remicade is indicated for treatment of severe, active Crohn's disease, in children and adolescents aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies. Remicade has been studied only in combination with conventional immunosuppressive therapy.
Ulcerative colitis: Remicade is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.
Paediatric ulcerative colitis: Remicade is indicated for treatment of severely active ulcerative colitis, in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.
Ankylosing spondylitis: Remicade is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.
Psoriatic arthritis: Remicade is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Remicade should be administered in combination with methotrexate, or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated.
Psoriasis: Remicade is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA.

DOSAGE & ADMINISTRATION: Remicade treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of rheumatoid arthritis, inflammatory bowel diseases, ankylosing spondylitis, psoriatic arthritis or psoriasis. Remicade should be administered intravenously. Remicade infusions should be administered by qualified healthcare professionals trained to detect any infusion-related issues. Patients treated with Remicade should be given the package leaflet and the patient reminder card. During Remicade treatment other concomitant therapies, e.g., corticosteroids and immunosuppressants should be optimised.
Adults:
Rheumatoid arthritis: 3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Remicade

must be given concomitantly with methotrexate. Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. If a patient has an inadequate response or loses response after this period, consideration may be given to increase the dose step-wise by approximately 1.5 mg/kg, up to a maximum of 7.5 mg/kg every 8 weeks. Alternatively, administration of 3 mg/kg as often as every 4 weeks may be considered. If adequate response is achieved, patients should be continued on the selected dose or dose frequency. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment or after dose adjustment.

Moderately to severely active Crohn's disease: 5 mg/kg given as an intravenous infusion followed by an additional 5 mg/kg infusion 2 weeks after the first infusion. If a patient does not respond after 2 doses, no additional treatment with infliximab should be given. Available data do not support further infliximab treatment, in patients not responding within 6 weeks of the initial infusion. In responding patients, the alternative strategies for continued treatment are; Maintenance: Additional infusion of 5 mg/kg at 6 weeks after the initial dose, followed by infusions every 8 weeks or; Re-administration: Infusion of 5 mg/kg if signs and symptoms of the disease recur. Although comparative data are lacking, limited data in patients who initially responded to 5 mg/kg but who lost response indicate that some patients may regain response with dose escalation. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment.

Fistulising, active Crohn's disease: 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusions at 2 and 6 weeks after the first infusion. If a patient does not respond after 3 doses, no additional treatment with infliximab should be given. In responding patients, the alternative strategies for continued treatment are; Maintenance: Additional infusions of 5 mg/kg every 8 weeks or; Re-administration: Infusion of 5 mg/kg if signs and symptoms of the disease recur followed by infusions of 5 mg/kg every 8 weeks. Although comparative data are lacking, limited data in patients who initially responded to 5 mg/kg but who lost response indicate that some patients may regain response with dose escalation. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment. 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.

Ulcerative colitis: 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data suggest that the clinical response is usually achieved within 14 weeks of treatment, i.e. three doses. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period. The safety and efficacy of re-administration, other than every 8 weeks, has not been established.

Ankylosing spondylitis: 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks. If a patient does not respond by 6 weeks (i.e. after 2 doses), no additional treatment with infliximab should be given.

Psoriatic arthritis: 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Psoriasis: 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. If a patient shows no response after 14 weeks (i.e. after 4 doses), no additional treatment with infliximab should be given.

Re-administration across indications: In case maintenance therapy is interrupted, and there is a need to restart treatment, use of a re-induction regimen is not recommended. In this situation, Remicade should be re-initiated as a single dose followed by the maintenance dose recommendations described above.

Elderly: Specific studies of Remicade in elderly patients have not been conducted. No major age-related differences in clearance or volume of distribution were observed in clinical studies. No dose adjustment is required.
Renal and/or hepatic impairment: Remicade has not been studied in these patient populations. No dose recommendations can be made.
Children:
Crohn's disease (6 to 17 years): 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data do not support further infliximab treatment in children and adolescents not responding within the first 10 weeks of treatment. Some patients may require a shorter dosing interval to maintain clinical benefit, while for others a longer dosing interval may be sufficient. Patients who have had their dose interval shortened to less than 8 weeks may be at greater risk for adverse reactions. Continued therapy with a shortened interval should be carefully considered in those patients who show no evidence of additional therapeutic benefit after a change in dosing interval. The safety and efficacy of Remicade have not been studied in children with Crohn's disease below the age of 6 years.
Ulcerative colitis (6 to 17 years): 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data do not support further infliximab treatment in paediatric patients not responding within the first 8 weeks of treatment. The safety and efficacy of Remicade have not been studied in children with ulcerative colitis below the age of 6 years.
Method of administration: Remicade should be administered intravenously over a 2 hour period. All patients administered Remicade 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 pre-treated 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. In carefully selected adult patients who have tolerated at least 3 initial 2-hour infusions of Remicade (induction phase) and are receiving maintenance therapy, consideration may be given to administering subsequent infusions over a period of not less than 1 hour. If an infusion reaction occurs in association with a shortened infusion, a slower infusion rate may be considered for future infusions if treatment is to be continued. Shortened infusions at doses > 6 mg/kg have not been studied.

CONTRAINDICATIONS: Hypersensitivity to the active substance, to other murine proteins, or to any of the excipients. Patients with tuberculosis or other severe infections such as sepsis, abscesses and opportunistic infections. Patients with moderate or severe heart failure (NYHA class III/IV).

SPECIAL WARNINGS & PRECAUTIONS:
Traceability: The tradename and the batch number of the administered product should be clearly recorded.
Infusion reactions and hypersensitivity: Infliximab has been associated with acute infusion-related reactions, including anaphylactic shock, and delayed hypersensitivity reactions. Acute infusion reactions including anaphylactic reactions may develop during (within seconds) or within a few hours following infusion. If acute infusion reactions occur, the infusion must be interrupted immediately. Emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway must be available. Patients may be pre-treated with e.g., an antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects.
Infections: Patients must be monitored closely for infections including tuberculosis before, during and after treatment with Remicade. Because the elimination of infliximab may take up to six months, monitoring should be continued throughout this period. Further treatment with Remicade must not be given if a patient develops a serious infection or sepsis. Patients taking TNF-blockers are more susceptible to serious infections. Tuberculosis, bacterial infections, including sepsis and

pneumonia, invasive fungal, viral, and other opportunistic infections have been observed in patients treated with infliximab.

Hepatitis B (HBV) reactivation: Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including infliximab, who are chronic carriers of this virus. Some cases have had fatal outcome. Patients should be tested for HBV infection before initiating treatment with Remicade. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Carriers of HBV who require treatment with Remicade should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, Remicade should be stopped and effective antiviral therapy with appropriate supportive treatment should be initiated.

Hepatobiliary events: Cases of jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed in the post-marketing experience of Remicade. Isolated cases of liver failure resulting in liver transplantation or death have occurred. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or ALT elevations ≥ 5 times the upper limit of normal develop(s), Remicade should be discontinued, and a thorough investigation of the abnormality should be undertaken.

Concurrent administration of TNF-alpha inhibitor and anakinra: Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNF_{α}-blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse reactions seen with combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNF_{α}-blocking agents. Therefore, the combination of Remicade and anakinra is not recommended.

Concurrent administration of TNF-alpha inhibitor and abatacept: In clinical studies concurrent administration of TNF-antagonists and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-antagonists alone, without increased clinical benefit. The combination of Remicade and abatacept is not recommended.

Concurrent administration with other biological therapeutics: There is insufficient information regarding the concomitant use of infliximab with other biological therapeutics used to treat the same conditions as infliximab. The concomitant use of infliximab with these biologics is not recommended because of the possibility of an increased risk of infection, and other potential pharmacological interactions.

Switching between biological DMARDS: Care should be taken and patients should continue to be monitored when switching from one biologic to another, since overlapping biological activity may further increase the risk for adverse reactions, including infection.

Vaccinations: It is recommended that patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating Remicade therapy. Patients on infliximab may receive concurrent vaccinations, except for live vaccines.

Live vaccines/therapeutic infectious agents: The concurrent administration of live vaccines with Remicade is not recommended.

Infant exposure *in utero*: In infants exposed *in utero* to infliximab, fatal outcome due to disseminated Bacillus Calmette-Guérin (BCG) infection has been reported following administration of BCG vaccine after birth. A twelve month waiting period following birth is recommended before the administration of live vaccines to infants exposed *in utero* to infliximab. If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant.

Infant exposure via breast milk: Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable.

Therapeutic infectious agents: Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with Remicade.
Autoimmune processes: The relative deficiency of TNF_{α} caused by anti-TNF therapy may result in the initiation of an autoimmune process. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Remicade and is positive for antibodies against double-stranded DNA, further treatment with Remicade must not be given.
Neurological events: Use of TNF-blocking agents, including infliximab, has been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of Remicade therapy. Discontinuation of Remicade should be considered if these disorders develop.
Malignancies and lymphoproliferative disorders: In the controlled portions of clinical studies of TNF-blocking agents, more cases of malignancies including lymphoma have been observed among patients receiving a TNF blocker compared with control patients. Caution should be exercised in considering treatment of patients with increased risk for malignancy due to heavy smoking. Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy. Caution should also be exercised in patients with psoriasis and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment. Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-blocking agents (initiation of therapy ≤ 18 years of age), including Remicade.
Heart failure: Remicade should be used with caution in patients with mild heart failure (NYHA class I/II). Patients should be closely monitored and Remicade must not be continued in patients who develop new or worsening symptoms of heart failure.
Haematologic reactions: There have been reports of pancytopenia, leucopenia, neutropenia, and thrombocytopenia in patients receiving TNF-blockers, including Remicade. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor). Discontinuation of Remicade therapy should be considered in patients with confirmed significant haematologic abnormalities.
Others: The long half-life of infliximab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on Remicade should be closely monitored for infectious and non-infectious complications, and appropriate actions should be taken. Failure to respond to treatment for Crohn's disease may indicate the presence of a fixed fibrotic stricture that may require surgical treatment. There is no evidence to suggest that infliximab worsens or causes fibrotic strictures.

SIDE EFFECTS:
Very common: viral infection (e.g. influenza, herpes virus infection), headache, upper respiratory tract infection, sinusitis, abdominal pain, nausea. **Common:** bacterial infections (e.g. sepsis, cellulitis, abscess), neutropenia, leucopenia, anaemia, lymphadenopathy, allergic respiratory symptom, depression, insomnia, vertigo, dizziness, hypoaesthesia, paraesthesia, conjunctivitis, tachycardia, palpitation, hypotension, hypertension, ecchymosis, hot flush, flushing, lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, epistaxis, gastrointestinal haemorrhage, diarrhoea, dyspepsia, gastroesophageal reflux, constipation, hepatic function abnormal, transaminases increased, new onset or worsening psoriasis including pustular psoriasis (primarily palm & soles), urticaria, rash, pruritus, hyperhidrosis, dry skin, fungal dermatitis, eczema, alopecia, arthralgia, myalgia, back pain, urinary tract infection, chest pain, fatigue, fever, injection site reaction, chills, oedema. **Uncommon:** tuberculosis, fungal infections (e.g. candidiasis, onychomycosis), thrombocytopenia, lymphopenia, lymphocytosis, anaphylactic reaction, lupus-like syndrome, serum sickness or serum sickness-like reaction, dyslipidaemia,

amnesia, agitation, confusion, somnolence, nervousness, seizure, neuropathy, keratitis, periorbital oedema, hordeolum, cardiac failure (new onset or worsening), arrhythmia, syncope, bradycardia, peripheral ischaemia, thrombophlebitis, haematoma, pulmonary oedema, bronchospasm, pleurisy, pleural effusion, intestinal perforation, intestinal stenosis, diverticulitis, pancreatitis, cheilitis, hepatitis, hepatocellular damage, cholecystitis, bullous eruption, seborrhoea, rosacea, skin papilloma, hyperkeratosis, abnormal skin pigmentation, pyelonephritis, vaginitis, impaired healing, autoantibody positive, weight increased. **Rare:** meningitis, 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, lymphoma, non-Hodgkin's lymphoma, Hodgkin's disease, leukaemia, melanoma, cervical cancer, agranulocytosis (including infants exposed *in utero* to infliximab), thrombotic thrombocytopenic purpura, pancytopenia, haemolytic anaemia, idiopathic thrombocytopenic purpura, anaphylactic shock, vasculitis, sarcoid-like reaction, apathy, transverse myelitis, central nervous system demyelinating disorders (multiple sclerosis-like disease and optic neuritis), peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy), endophthalmitis, cyanosis, pericardial effusion, circulatory failure, petechia, vasospasm, interstitial lung disease (including rapidly progressive disease, lung fibrosis and pneumonitis), autoimmune hepatitis, jaundice, toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, furunculosis, linear IgA bullous dermatosis (LABD), acute generalised exanthematous pustulosis (AGEP), lichenoid reactions, granulomatous lesion, complement factor abnormal. **Not known:** vaccine breakthrough infection (after *in utero* exposure to infliximab), hepatosplenic T-cell lymphoma (primarily in adolescents and young adult males with Crohn's disease or ulcerative colitis), Merkel cell carcinoma, Kaposi's sarcoma, cerebrovascular accidents in close temporal association with infusion, transient visual loss occurring during or within 2 hours of infusion, myocardial ischaemia/myocardial infarction, liver failure, worsening of symptoms of dermatomyositis, post-procedural complication (including infectious and non-infectious complications.
Refer to the SmPC for other side effects.

PREGNANCY: Women of childbearing potential should consider the use of adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last Remicade treatment.The available clinical experience is limited. Infliximab should only be used during pregnancy if clearly needed. Infliximab crosses the placenta and has been detected in the serum of infants up to 12 months following birth. After *in utero* exposure to infliximab, infants may be at increased risk of infection, including serious disseminated infection that can become fatal. Administration of live vaccines (e.g., BCG vaccine) to infants exposed to infliximab *in utero* is not recommended for 12 months after birth. If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant. Cases of agranulocytosis have also been reported.

LACTATION: Limited data from published literature indicate infliximab has been detected at low levels in human milk at concentrations up to 5% of the maternal serum level. Infliximab has also been detected in infant serum after exposure to infliximab via breast milk. While systemic exposure in a breastfed infant is expected to be low because infliximab is largely degraded in the gastrointestinal tract, the administration of live vaccines to a breastfed infant when the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable. Infliximab could be considered for use during breast-feeding.

FERTILITY: There are insufficient preclinical data to draw conclusions on the effects of infliximab on fertility and general reproductive function.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: Remicade may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of Remicade.

INTERACTIONS: No interaction studies have been performed. In rheumatoid arthritis, psoriatic arthritis and Crohn's disease patients, there are indications that concomitant use of methotrexate and other immunomodulators reduces the formation of antibodies against infliximab and increases the plasma concentrations of infliximab. However, the results are uncertain due to limitations in the methods used for serum analyses of infliximab and antibodies against infliximab. Corticosteroids do not appear to affect the pharmacokinetics of infliximab to a clinically relevant extent. The combination of Remicade with other biological therapeutics used to treat the same conditions as Remicade, including anakinra and abatacept, is not recommended. It is recommended that live vaccines not be given concurrently with Remicade. It is also recommended that live vaccines not be given to infants after *in utero* exposure to infliximab for 12 months following birth. If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant. Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable. It is recommended that therapeutic infectious agents not be given concurrently with Remicade.

LEGAL CLASSIFICATION: Prescription Only Medicine

MARKETING AUTHORISATION NUMBERS:
PLGB 00242/0746

MARKETING AUTHORISATION HOLDER: Janssen-Cilag Ltd 50-100 Holmers Farm Way High Wycombe Buckinghamshire HP12 4EG, UK

PACKS & PRICE: 1 vial of 100 mg: £419.62

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Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Janssen-Cilag Limited on 01494 567447 or at dsafety@its.jnj.com