PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

Patients treated with **AMGEVITA®** are at increased risk for developing serious infections that may lead to hospitalisation or death (see section 4.8).

AMGEVITA® should be discontinued if a patient develops a serious infection or sepsis.

1. NAME OF MEDICINE

AMGEVITA® 20 mg solution for injection in pre-filled syringe.

AMGEVITA® 40 mg solution for injection in pre-filled syringe.

AMGEVITA® 40 mg solution for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AMGEVITA® 20 mg solution for injection in pre-filled syringe

Each single dose pre-filled syringe contains 20 mg of adalimumab in 0.4 ml (50 mg/ml) solution.

AMGEVITA® 40 mg solution for injection in pre-filled syringe

Each single dose pre-filled syringe contains 40 mg of adalimumab in 0.8 ml (50 mg/ml) solution.

AMGEVITA® 40 mg solution for injection in pre-filled pen

Each single dose pre-filled pen contains 40 mg of adalimumab in 0.8 ml (50 mg/ml) solution.

Adalimumab is a recombinant human monoclonal antibody produced in Chinese Hamster Ovary cells.

Contains sugar (sucrose).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

AMGEVITA® 20 mg solution for injection in pre-filled syringe

AMGEVITA® 40 mg solution for injection in pre-filled syringe

Solution for injection (injection).

AMGEVITA® 40 mg solution for injection in pre-filled pen (SureClick)

Solution for injection (injection).

Clear and colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults

Rheumatoid Arthritis (RA)

AMGEVITA® is indicated for the treatment of moderate to severe rheumatoid arthritis in adult patients, including recently diagnosed patients who have not been previously treated with methotrexate (MTX). AMGEVITA® has been shown to induce clinical remission, reduces the rate of progression of structural damage as measured by X-ray and improves physical function, when given in combination with methotrexate.

AMGEVITA® can be used in combination with methotrexate or given as monotherapy in the case of intolerance to methotrexate or when continued treatment with methotrexate is deemed inappropriate.

Psoriatic Arthritis (PsA)

AMGEVITA® is indicated for reducing signs and symptoms of psoriatic arthritis.

AMGEVITA® has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and improves physical function.

AMGEVITA® can be used alone or in combination with disease modifying anti-rheumatic medicines (DMARDs).

Psoriasis

AMGEVITA® is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or Phototherapy when other systemic therapies are medically less appropriate.

AMGEVITA® is indicated for moderate to severe nail psoriasis in adult patients who are candidates for systemic therapy

Axial Spondyloarthritis including Ankylosing Spondylitis (AS)

AMGEVITA® is indicated for the treatment of adults with severe axial spondyloarthritis, including ankylosing spondylitis, who have had an inadequate response to conventional therapy or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Ankylosing Spondylitis

AMGEVITA® is indicated for the treatment of adults with active Ankylosing spondylitis who have had an inadequate response to conventional therapy.

Chron’s Disease

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

AMGEVITA® is also indicated for reducing signs and symptoms and inducing clinical remission in these patients if they have lost response to or are intolerant to infliximab.

Ulcerative Colitis

AMGEVITA® 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/or 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Hidradenitis Suppurativa

AMGEVITA® is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients, including treatment of inflammatory lesions and prevention of worsening of abscesses and draining fistulas.

Uveitis

AMGEVITA® is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients.

Paediatrics

Polyarticular Juvenile Idiopathic Arthritis

AMGEVITA® is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients two years of age and older. AMGEVITA® can be used alone or in combination with methotrexate.

Paediatric Crohn's Disease

AMGEVITA® is indicated for reducing signs and symptoms and inducing and maintaining clinical

remission in paediatric patients, 6 years of age and older, with moderately to severely active Crohn's Disease who have had an inadequate response to conventional therapy.

Paediatric Plaque Psoriasis

AMGEVITA® is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapy.

Paediatric Uveitis

AMGEVITA® is indicated for the treatment of chronic non-infectious uveitis in paediatric patients 2 years of age and older

4.2 Posology and Method of Administration

AMGEVITA® treatment should be initiated and supervised by specialist medical practitioner experienced in the diagnosis and treatment of conditions for which AMGEVITA® is indicated. Patients treated with AMGEVITA® should be given the special alert card.

After proper training in injection technique, patients may self-inject with AMGEVITA® if their medical practitioner determines that it is appropriate and with medical follow-up as necessary.

During treatment with AMGEVITA®, other concomitant therapies (e.g., corticosteroids and/or immunomodulatory agents) should be optimised.

Posology:

Adults

Rheumatoid Arthritis

The recommended dose of AMGEVITA® for adult patients with rheumatoid arthritis is 40 mg administered every other week as a single dose via subcutaneous injection. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory medicines, analgesics or other DMARD's may be continued during treatment with AMGEVITA®.

Regarding combination with disease-modifying anti-rheumatic drugs other than methotrexate see section 4.4.

In monotherapy, some patients who experience decrease in their response may benefit from an increase in dose intensity to 40 mg of AMGEVITA® every week.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Psoriatic Arthritis

The recommended dose of AMGEVITA® for adult patients with psoriatic arthritis is 40 mg administered every other week as a single dose via subcutaneous injection.
Glucocorticoids, salicylates, nonsteroidal anti-inflammatory medicines, analgesics or disease modifying anti-rheumatic drugs can be continued during treatment with AMGEVITA®.

Axial Spondyloarthritis including Ankylosing Spondylitis

The recommended dose of AMGEVITA® for patients with Axial spondyloarthritis including ankylosing spondylitis is 40 mg administered every other week as a single dose via subcutaneous injection. Glucocorticoids, salicylates, nonsteroidal anti-inflammatory medicines, analgesics or disease modifying anti-rheumatic medicines can be continued during treatment with AMGEVITA®.

Crohn's Disease

The recommended AMGEVITA® dose regimen for adult patients with Crohn's disease is 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days), 80 mg at Week 2, followed two weeks later by a maintenance dose of 40 mg every other week via subcutaneous injection.
Aminosalicylates, corticosteroids, and/or immunomodulatory agents (e.g. 6-mercaptopurine and azathioprine) may be continued during treatment with AMGEVITA®.

Some patients may derive additional benefit from increasing the dosing frequency of AMGEVITA® to 40 mg every week.

Some patients who have not responded by week 4 may benefit from continued maintenance therapy through week 12. Continued therapy should be carefully reconsidered in a patient not responding within this time period. During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Ulcerative Colitis

The recommended AMGEVITA® induction dose regimen for adult patients with moderate to severe ulcerative colitis is 160 mg at Week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days) and 80 mg at Week 2. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Aminosalicylates, corticosteroids, and/or immunomodulatory agents (e.g., 6-mercaptopurine and azathioprine) may be continued during treatment with AMGEVITA®.

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Some patients who experience decrease in their response may benefit from an increase in dosing frequency to 40 mg AMGEVITA® every week.

Available data suggest that clinical response is usually achieved within 2-8 weeks of treatment.

AMGEVITA® should only be continued in patients who have responded during the first 8 weeks of therapy.

Plaque Psoriasis

The recommended dose of AMGEVITA® for adult patients is an initial dose of 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week starting one week after the initial dose.

Beyond 16 weeks, patients with inadequate response may benefit from an increase in dosing frequency to 40 mg every week. The benefits and risks of continued weekly

AMGEVITA® therapy should be carefully reconsidered in a patient with an inadequate response 24 weeks after the increase in dosing frequency.

Hidradenitis Suppurativa

The recommended AMGEVITA® dose regimen for adult patients with hidradenitis suppurativa (HS) is 160 mg initially at Day 1 (given as four 40 mg injections in one day or as two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later at Day 15 (given as two 40 mg injections in one day). Two weeks later (Day 29) continue with a dose of 40 mg every week. Antibiotics may be continued during treatment with AMGEVITA® if necessary.

Should treatment need to be interrupted, AMGEVITA® may be re-introduced. In patients without any benefit after 12 weeks of treatment, continued therapy should be reconsidered.

Uveitis

The recommended dose of AMGEVITA® for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose.

AMGEVITA® can be used alone or in combination with corticosteroids, which may be tapered in accordance with clinical practice, or other non-biologic immunomodulatory agents.

Paediatrics

Polyarticular Juvenile Idiopathic Arthritis

The recommended dose of AMGEVITA® for patients from 2 years of age with polyarticular juvenile idiopathic arthritis (JIA) is based on body weight (Table 1).

Methotrexate, glucocorticoids, NSAIDs and/or analgesics may be continued during treatment with AMGEVITA®. AMGEVITA® may be available in other strengths and/or presentations depending on the individual treatment needs.

Table 1:

Paediatric Patients (2 years of age and older)	**DOSE**

10 to < 30 kg	20 mg every other week
≥ 30 kg	40 mg every other week

Adalimumab has not been studied in patients with polyarticular juvenile idiopathic arthritis less than two years of age or in patients with a weight below 10 kg.

Available data suggest that clinical response is usually achieved within 12 weeks of treatment.

Continued therapy should be carefully reconsidered in a patient not responding within this time period.

Paediatric Crohn's Disease

The recommended dose of AMGEVITA® for patients from 6 to 17 years of age with Crohn's Disease is based on body weight. AMGEVITA® is administered via subcutaneous injection. Adalimumab may be available in other strengths and/or presentations depending on the individual treatment needs.

Table 2: AMGEVITA® Dose for Paediatric Patients with Chron's Disease.

Patient Weight	Induction Dose	Maintenance dose Starting at Week 4
< 40 kg	• 80 mg at Week 0 and • 40 mg at Week 2	20 mg every other week
≥ 40 kg	• 160 mg at Week 0 and • 80 mg at Week 2	40 mg every other week

Some patients may benefit from increasing the frequency to weekly if a disease flare or an inadequate response is experienced during maintenance dosing.

Adalimumab has not been studied in children with Crohn's Disease age less than 6 years.

Paediatric Plaque Psoriasis:

The recommended AMGEVITA® dose for patients from 4 to 17 years of age with plaque psoriasis is based on body weight (Table 3). AMGEVITA® is administered via subcutaneous injection.

Adalimumab may be available in other strengths and/or presentations.

Table 3:

Patients Weight	Dose
15 kg to< 30 kg	Initial dose of 20 mg, followed by 20 mg given every other week starting one week after the initial dose
≥ 30 kg	Initial dose of 40 mg, followed by 40 mg given every other week starting one week after the initial dose

Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this time period.

If retreatment with AMGEVITA® is indicated, the above guidance on dose and treatment duration should be followed.

There is no relevant use of adalimumab in children aged less than 4 years in this indication.

Paediatric Uveitis:

The recommended dose of AMGEVITA® for patients 2 years of age and older with chronic non-infectious uveitis is based on body weight as shown below (Table 4).

AMGEVITA® is administered via subcutaneous injection. Adalimumab may be available in other strengths and/or presentations.

AMGEVITA® may be used in combination with methotrexate or other non-biologic immunomodulatory agents based on clinical judgment

Table 4: AMGEVITA® dose by weight for patients with paediatric uveitis

Patients (2 years of age and older)	Dose
< 30 kg	20 mg every other week
≥ 30 kg	40 mg every other week

When AMGEVITA® is initiated a loading dose of 40 mg for patients < 30 kg or 80 mg for patients ≥ 30 kg may be administered one week prior to the start of maintenance therapy.

Adalimumab has not been studied in patients with chronic non-infections uveitis less than 2 years of age.

Method of Administration

AMGEVITA® is intended for use under the guidance and supervision of a medical practitioner.

Patients may self-inject AMGEVITA® if their medical practitioner determines that it is appropriate and with medical follow-up, as necessary, after proper training in injection technique. Sites for self-injection include the thigh or abdomen. Injection sites should be rotated. New injections should never be given into areas where the skin is tender, bruised, red or hard.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

AMGEVITA® should not be mixed in the same syringe with other medicine.

Any unused product or waste material should be disposed of in accordance with local requirements.

Full instructions for use are provided in the patient information leaflet.

Paediatric Use

Adalimumab has not been studied in children less than 2 years of age.

Use in Elderly

Of the total number of subjects in clinical studies with adalimumab, 9.4 % were 65 and over, while approximately 2.0 % were 75 and over. No overall differences in effectiveness were observed between these subjects and younger subjects.

No dose adjustment is needed for this population.

4.3 Contraindications

AMGEVITA® should not be administered to patients with known hypersensitivity to adalimumab or any of its excipients.

AMGEVITA® is contraindicated in:

- Moderate to severe cardiac failure (NHYA class III/IV).
- Active tuberculosis or other severe infections.
- Concomitant use with live vaccines

4.4 Special Warnings and Precautions for Use

Infections

Serious infections, including sepsis, due to bacterial, mycobacterial, invasive fungal (disseminated or extrapulmonary histoplasmosis, aspergillosis, coccidioidomycosis), viral, parasitic, or other opportunistic infections have been reported in patients using TNF-antagonists including adalimumab. Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicaemia. Hospitalisation or fatal outcomes associated with infections have been reported. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease could predispose the infections.

Treatment with AMGEVITA® should not be initiated in patients with active infections, including chronic or localised infections, until infections are controlled. In patients that have been exposed to Tuberculosis, and patients who have travelled in areas of high risk of tuberculosis or endemic mycosis, such as histoplasmosis, coccidioidomycosis, or blastomycosis, the risk and benefits of treatment with AMGEVITA® should be considered prior to initiating therapy.
Patients should be monitored closely for infections, including tuberculosis, before, during and after treatment with AMGEVITA®.

Patients who develop a new infection while undergoing treatment with AMGEVITA®, should be monitored closely and undergo a complete diagnostic evaluation.
Administration of AMGEVITA® should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled.

Medical practitioners should exercise caution when considering the use of AMGEVITA® in patients with a history of recurrent infection or with underlying conditions that may predispose patients to infections.

Tuberculosis (TB)

Tuberculosis, including reactivation and new onset of tuberculosis, has been reported in patients receiving adalimumab. Reports included cases of pulmonary and extra-pulmonary (i.e. disseminated) tuberculosis. Invasive fungal infections, and other opportunistic infections have been observed in patients receiving adalimumab. Some of these infections, including tuberculosis, have been fatal.

Before initiation of therapy with AMGEVITA®, all patients must be evaluated for both active or inactive ("latent") tuberculosis infection. This evaluation should include a detailed medical assessment of patient history of tuberculosis or possible previous exposure to people with active tuberculosis and previous and/or current immunosuppressive therapy.

Appropriate screening tests (e.g. chest X-ray and tuberculin skin test) should be performed in accordance with local recommendations.

Treatment of latent TB infection should be initiated prior to therapy with AMGEVITA®.

When tuberculin skin test is performed for latent TB infection, an induration size of 5 mm or greater, should be considered positive, even if vaccinated previously with Bacille Calmette-Guerin (BCG).

The possibility of undetected latent TB should be considered especially in patients who have immigrated from or travelled to countries with a high prevalence of TB or who had close contact with a person with active TB.

If active TB is diagnosed, AMGEVITA® therapy must not be initiated.

If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylactic treatment before the initiation of AMGEVITA®, and in accordance with local recommendations.

Use of anti-tuberculosis prophylactic treatment should also be considered before the initiation of AMGEVITA® in patients with several or significant risk factors for TB despite a negative test for TB and in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed.

The decision to initiated anti-TB therapy in these patients should only be made after taking into account both the risk for latent TB infection and the risks of anti-TB therapy. If necessary, consultation should be made with a physician with expertise in the treatment of TB.

Anti-TB treatment of patients with latent TB infection reduces the risk of reactivation in patients receiving treatment with AMGEVITA®. Despite prophylactic treatment for TB, cases of reactivated TB have occurred in patients treated with adalimumab.

Also, active TB has developed in patients receiving adalimumab whose screening for latent TB infection was negative, and some patients who have been successfully treated for active TB have redeveloped TB while being treated with TNF blocking agents.

Patients receiving AMGEVITA® should be monitored for signs and symptoms of active TB, particularly because tests for latent TB infection may be falsely negative. The risk of false negative tuberculin skin test results should be considered especially in patients who are severely ill or immunocompromised.

Prescribers are reminded of the risk of false-negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

As HIV positive patients have a high incidence of cutaneous anergy, which may result in false negative tuberculin tests, particular attention should be given to the diagnosis of latent TB infection in these patients. No data exists on the use of adalimumab in HIV positive patients. Therefore, the risks of serious infections must be carefully balanced with the benefits of AMGEVITA® treatment prior to the initiation of therapy in HIV positive patients.

Patients should be instructed to seek medical advice if signs/symptoms suggestive of a TB infection (e.g. persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with AMGEVITA®.

Extra care should be taken with HIV positive patients where clinical course of TB may be particularly aggressive.

<u>Other Opportunistic Infections</u>

Opportunistic infections, including invasive fungal infections, have been observed in patients receiving adalimumab. These infections are not consistently recognized in patients taking TNF-blockers and this has resulted in delays in appropriate treatment, sometimes resulting in fatal outcomes.

Patients taking TNF-blockers are more susceptible to serious fungal infections such as histoplasmosis, coccidioidomycosis, blastomycosis, aspergillosis, candidiasis, and other opportunistic infections. Those who develop fever, malaise, weight loss, sweats, cough, dyspnoea, and/or pulmonary infiltrates, or other serious systematic illness with or without concomitant shock should promptly seek medical attention for a diagnostic evaluation. For patients who reside or travel in regions where mycoses are endemic, invasive fungal infections should be suspected if they develop the signs and symptoms of possible systemic fungal infection. Patients are at risk of histoplasmosis and other invasive fungal infections and hence clinicians should consider empiric antifungal treatment until pathogen(s) are identified. 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. Patients who develop a severe fungal infection are also advised to stop the TNF-blocker until infections are controlled.

Hepatitis B Reactivation

Use of adalimumab 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 supress the immune system, which may also contribute to HBV reactivation.

Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating adalimumab therapy.

Prescribers should exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.

Adequate data are not available on the safety and efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. In

patients who develop HBV reactivation, AMGEVITA® should be stopped and effective anti-viral therapy with appropriate supportive therapy should be initiated.

Neurological Events

Adalimumab has been associated in rare cases with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis, optic neuritis, and peripheral demyelinating disease, including Guillian Barré syndrome. Prescribers should exercise caution in considering the use of AMGEVITA® in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of AMGEVITA® should be considered if any of these disorders develop. There is a known association between intermediate uveitis and central demyelinating disorders. Neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of AMGEVITA® therapy and regularly during treatment to assess for pre-existing or developing central demyelinating disorders.

Malignancies

In the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies including lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. The size of the control group and limited duration of the controlled portions of studies precludes the ability to draw firm conclusion.

Malignancies, some fatal, have been reported among children and adolescents who received treatment with TNF-blocking agents. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. The malignancies occurred after a median of 30 months of therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous post-marketing reports.

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving adalimumab. Thus, additional caution should be exercised in considering AMGEVITA® treatment of these patients.

Post-marketing reports of hepatosplenic T-cell lymphoma (HSTCL), a rare aggressive lymphoma that is often fatal, have been identified in patients treated with adalimumab. Most of the patients had prior infliximab therapy as well as concomitant azathioprine or 6-mecaptopurine use for inflammatory bowel disease.

All patients, and in particular patients with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of PUVA treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with AMGEVITA®.

Acute and chronic leukaemia have been reported in association with post-marketing TNF-blocker use in rheumatoid arthritis and other indications. Patients with rheumatoid arthritis may be at a higher risk (up to 2-fold) than the general population for the development of leukaemia, even in the absence of TNF-blocking therapy.

It is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations.

Allergy

Serious allergic reactions associated with adalimumab were reported during clinical trials.

Reports of serious allergic reactions, including anaphylaxis have been received following adalimumab administration. If an anaphylactic reaction or other serious allergic reaction occurs, administration of AMGEVITA® should be discontinued immediately and appropriate therapy initiated.

Haematologic Events

Rare reports of pancytopenia including aplastic anaemia have been reported with TNF-blocking

agents. Adverse events of the haematologic system, including medically significant cytopenia (e.g. thrombocytopaenia, leucopoenia) have been reported with adalimumab.

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) while on AMGEVITA®. Discontinuation of AMGEVITA® therapy should be considered in patients with confirmed significant haematologic abnormalities.

Concurrent Administration of Biologic Disease-Modifying Anti-Rheumatic Drugs (DMARDS) or TNF-Antagonists

Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF-antagonist, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNF-antagonists. Therefore, the combination of AMGEVITA® and anakinra is not recommended.

Concomitant administration of adalimumab with other DMARDS (e.g. anakinra and abatacept) or other TNF antagonists is not recommended based upon the increased risk for infections and other pharmacological interactions.

Immunosuppression

In a study of 64 patients with rheumatoid arthritis that were treated with adalimumab, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T-, B, - NK-cells, monocyte/macrophages, and neutrophils.

Vaccinations

In a randomised, double-blind, placebo- controlled study in 226 adult rheumatoid arthritis patients treated with adalimumab, antibody responses to concomitant pneumococcal and influenza vaccines were assessed. Protective antibody levels to the pneumococcal antigens were achieved by 86 % of patients in the adalimumab group compared to 82 % in the placebo group. A total of 37 % of adalimumab -treated subjects and 40 % of placebo-treated subjects achieved at least a 2-fold

increase in at least 3 out of 5 pneumococcal antigens. In the same study 98 % of patients in the adalimumab group and 95 % in the placebo group achieved protective antibody levels to the influenza antigens. A total of 52 % of adalimumab -treated subjects and 63 % of placebo-treated subjects achieved at least a 4-fold increase in at least 2 out of 3 influenza antigens.

It is recommended that paediatric patients, if possible, be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating AMGEVITA® therapy.

Patients on AMGEVITA® may receive concurrent vaccinations, except for live vaccines. No data is available on the secondary transmission of infection by live vaccines in patients receiving adalimumab.

In the event a woman becomes pregnant during AMGEVITA® therapy, administration of live vaccines to the infant is not recommended for 5 months following the mother's last AMGEVITA® injection during pregnancy.

Congestive Heart Failure

Cases of worsening congestive heart failure have been reported in patients receiving adalimumab. AMGEVITA® should be used with caution in patients with mild heart failure (NYHA class I/II). AMGEVITA® is contraindicated in moderate to severe heart failure (see section 4.3). Treatment with AMGEVITA® must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Autoimmune Processes

Treatment with adalimumab may result in the formation of autoimmune antibodies.
The impact of long-term treatment with adalimumab on the development of autoimmune diseases is unknown. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with AMGEVITA®, treatment should be discontinued.

Drug/Laboratory Test Interaction

There is no known interference between adalimumab and laboratory tests.

Elderly

The frequency of serious infection among adalimumab treated subjects over 65 years of age was higher than for those under 65 years of age. Of the total number of subjects in clinical studies of adalimumab, 9,4 % were 65 years and over, while approximately 2,0 % were 75 and over. Because there is higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

Immunogenicity for Adalimumab

Formation of anti-adalimumab antibodies is associated with increased clearance and reduced efficacy of adalimumab There is no apparent correlation between the presence of anti-adalimumab antibodies and adverse events.

Patients in RA Studies I, II and III were tested at multiple timepoints for antibodies to adalimumab during the 6-to-12-month period. In the pivotal trials, anti-adalimumab antibodies were identified in 58/1053 (5,5 %) patients treated with adalimumab, compared to 2/370 (0,5 %) on placebo. In patients not given concomitant methotrexate, the incidence was 12,4 %, compared to 0,6 % when adalimumab was used as add-on to methotrexate.

In patients with psoriatic arthritis, adalimumab antibodies were identified in 38/376 subjects (10 %) treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 13,5 % (24/178 subjects), compared to 7 % (14/198 subjects) when adalimumab was used as add-on to methotrexate.

In patients with ankylosing spondylitis antibodies were identified in 17/204 subjects (8,3 %) treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 16/185 (8,6 %), compared to 1/19 (5,3 %) when adalimumab was used as add-on to methotrexate.

In patients with Crohn's Disease, adalimumab antibodies were identified in 7/269 subjects (2,6 %) treated with adalimumab.

Because immunogenicity analyses are product-specific, comparison of antibody rates with those from other products is not appropriate. In patients with psoriasis, anti-adalimumab antibodies were identified in 77/920 subjects (8,4 %) treated with adalimumab monotherapy.

Immunogenicity Data for **AMGEVITA®**

If formation of anti-adalimumab binding antibodies with a clinically significant effect is suspected, contact Amgen to discuss antibody testing.:
Amgen South Africa (Pty) Ltd.
Email: safety-south-africa@amgen.com
Tel: +27 (0)11 100 5300

In Study 20120262, patients with moderate to severe rheumatoid arthritis, the incidence of antibodies to AMGEVITA® was found to be similar to adalimumab. The number of subjects that developed binding antibodies during the study was 101 (38.3 %) for those receiving AMGEVITA® versus 100 (38.2 %) for those receiving adalimumab. The number of subjects that developed neutralizing antibodies during the study was 24 (9.1 %) for those receiving AMGEVITA® and 29 (11.1 %) for those receiving adalimumab.

In Study 20120263, patients with plaque psoriasis, the incidence of antibodies to AMGEVITA® was found to be similar to adalimumab. Post-baseline (through week 16), 96 (55.2 %) subjects in the AMGEVITA® treatment group and 110 (63.6 %) subjects in the adalimumab treatment group tested positive for the development of binding antibodies. The number of subjects that tested positive for neutralizing antibodies during the study was 17 (9.8 %) for those receiving AMGEVITA® and 24 (13.9 %) for those receiving adalimumab. From baseline to the end of the study, among subjects who were re-randomized following a single switch, 104 (68.4 %) subjects in the AMGEVITA®/AMGEVITA® treatment group, 59 (74.7 %) subjects in the adalimumab/adalimumab treatment group, and 56

(72.7 %) subjects in the adalimumab/AMGEVITA® treatment group tested positive for the development of binding ADAs. 21 (13.8 %) subjects in the AMGEVITA®/ AMGEVITA® treatment group, 16 (20.3 %) subjects in the adalimumab/adalimumab treatment group, and 19 (24.7 %) subjects in the adalimumab/AMGEVITA® treatment group tested positive for the development of neutralizing antibodies.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the test method and may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to AMGEVITA® with the incidence of antibodies to other products may be misleading.

As with all therapeutic proteins, there is potential for immunogenicity. Differences in assay methodology for measuring immunogenicity prevent direct comparison of immunogenicity rates between AMGEVITA® and adalimumab or other biologics in different studies. In Study 20120262, binding anti-drug antibodies (ADA) activity was determined using an electrochemiluminescent bridging immunoassay and the neutralizing ADA activity was determined using a target binding bioassay. In Study 20120263, binding ADA activity was determined using an electrochemiluminescent bridging immunoassay and the neutralizing ADA activity was determined using a non-cell based bioassay.

4.5 Interaction with other Medicines and other forms of Interaction

Adalimumab has been studied in rheumatoid arthritis patients taking concomitant methotrexate. The data does not suggest the need for dose adjustment of either adalimumab or methotrexate. Interactions between adalimumab and other medicines other than methotrexate have not been evaluated in formal pharmacokinetic studies. In clinical trials, no interactions have been observed when adalimumab was administered with commonly used DMARD’s (sulfasalazine, hydroxychloroquine, leflunomide and parenteral gold), glucocorticoids, salicylates, nonsteroidal anti-

inflammatory medicines or analgesics. There is no experience with the efficacy and safety in patients previously treated with other TNF antagonists.

4.6 Fertility, Pregnancy and Lactation

Women of Childbearing Potential

Women of childbearing potential should consider the use of adequate contraception to prevent pregnancy and continue its use for at least five months after the last AMGEVITA® treatment.

Pregnancy

A large number (approximately 2 100) of prospectively collected pregnancies exposed to adalimumab resulting in live birth with known outcomes, including more than 1 500 exposed during the first trimester, does not indicate an increase in the rate of malformation in the newborn.

In a prospective cohort registry, 257 women with rheumatoid arthritis (RA) or Crohn's Disease (CD) treated with adalimumab at least during the first trimester and 120 women with RA or CD not treated with adalimumab were enrolled. The primary endpoint was the birth prevalence of major birth defects. The rate of pregnancies ending with at least one live born infant with a major birth defect was 6/69 (8,7 %) in the adalimumab-treated women with RA and 5/74 (6,8 %) in the untreated women with RA (unadjusted OR 1,31; 95 % CI 0,38 - 4,52) and 16/152 (10,5 %) in the adalimumab-treated women with CD and 3/32 (9,4 %) in the untreated women with CD (unadjusted OR 1,14; 95 % CI 0,31 – 4,16). The adjusted OR (accounting for baseline differences) was 1,10 (95 % CI 0,45 –2,73) with RA and CD combined. There were no distinct differences between adalimumab-treated and untreated women for the secondary endpoints spontaneous abortions, minor birth defects, preterm delivery, birth size and serious or opportunistic infections and no stillbirths or malignancies were reported. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomized design.

In a developmental toxicity study conducted in monkeys, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. Preclinical data on postnatal toxicity of adalimumab are not available.

Due to its inhibition of TNFα, adalimumab administered during pregnancy could affect normal immune responses in the newborn. AMGEVITA® should only be used during pregnancy if clearly needed.

AMGEVITA® may cross the placenta into the serum blood of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection. Administration of live vaccines (e.g., BCG vaccine) to infants exposed to AMGEVITA® in utero is not recommended for 5 months following the mother's last AMGEVITA® injection during pregnancy.

Labour and Deliver

There is no known effect of AMGEVITA® on labour or delivery.

Breastfeeding

Limited information from the published literature indicates that adalimumab is excreted in breast milk at very low concentrations with the presence of adalimumab in human milk at concentrations of 0,1 % to 1 % of the maternal serum level. Given orally, immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability. No effects on the breastfed newborns/infants are anticipated. Consequently, adalimumab can be used during breastfeeding.

Fertility

Preclinical data on fertility effects of adalimumab are not available.

4.7 Effects on ability to drive and use machines

Adalimumab may influence the ability to drive and use machines.

Vertigo and visual impairment may occur following administration of adalimumab (see section 4.8).

4.8 Undesirable Effects

Summary of Safety Profile

Adalimumab was studied in 9 506 patients in pivotal controlled and open label trials for up to 60 months. These trials included rheumatoid arthritis patients with short term and long term standing disease, juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis) as well as psoriatic arthritis, ankylosing spondylitis, axial spondyloarthritis including ankylosing spondylitis, Crohn's Disease, ulcerative colitis, psoriasis, hidradenitis suppurativa and uveitis patients. The controlled pivotal studies involve 6 089 patients receiving adalimumab and 3 801 patients receiving placebo or active comparator during the controlled period.

The proportion of patients who discontinued treatment due to adverse events during the double blind, controlled portion of pivotal studies was 5.9 % for patients taking adalimumab and 5.4 % for control treated patients.

Approximately 13 % of patients can be expected to experience injection site reactions, based on one of the most common adverse events with adalimumab in controlled clinical studies.

Tabulated List of Adverse Events

The following list of adverse reactions is based on experience from clinical trials and on post-marketing experience and are displayed by system organ class and frequency in table below: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The highest frequency seen among the various indications has been included. An asterisk (*) appears in the SOC column if further information is found elsewhere in sections 4.3, 4.4 and 4.8.

Table 5: Adverse reactions in clinical studies

MeDRA System Organ Class (SOC)	Frequency	Adverse Reaction
Infections and infestations	Very common	Respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral)
	Common	Systemic infections (including sepsis, candidiasis and influenza) Intestinal infections (including gastroenteritis viral) Skin and soft tissue infections (including paronychia, cellulitis, impetigo, necrotising fasciitis and herpes zoster) Ear infections Oral infections (including herpes simplex, oral herpes and tooth infections) Reproductive tract infections (including vulvovaginal mycotic infection) Urinary tract infections (including pyelonephritis) Fungal infections Joint infections
	Uncommon	Opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and *mycobacterium avium* complex infection) Neurological infections (including viral meningitis) Eye infections Bacterial infections

MeDRA System Organ Class (SOC)	Frequency	Adverse Reaction
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	Common	Benign neoplasm Skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma)
	Uncommon	Lymphoma** Solid organ neoplasm (including breast cancer, lung neoplasm and thyroid neoplasm) Melanoma**
Blood and the lymphatic system disorders*	Very common	Leukopenia (including neutropenia and agranulocytosis) Anaemia
	Common	Thrombocytopenia Leucocytosis
	Uncommon	Idiopathic thrombocytopenic purpura
	Rare	Pancytopenia
Immune system disorders*	Common	Hypersensitivity (including seasonal allergy)
Metabolism and nutrition disorders	Very common	Lipids increased
	Common	Hypokalaemia Uric acid increased Blood sodium abnormal Hypocalcaemia Hyperglycaemia Hypophosphatemia Dehydration
Psychiatric disorders	Common	Mood alterations (including depression) Anxiety Insomnia
Nervous system disorders	Very common	Headache

MeDRA System Organ Class (SOC)	Frequency	Adverse Reaction
	Common	Paraesthesias (including hypoesthesia) Migraine Nerve root compression
	Uncommon	Tremor Neuropathy
	Rare	Multiple sclerosis
Eye disorders	Common	Visual impairment Conjunctivitis Blepharitis Eye swelling
	Uncommon	Diplopia
Ear and labyrinth disorders	Common	Vertigo
	Uncommon	Deafness Tinnitus
Cardiac disorders*	Common	Tachycardia
	Uncommon	Dysrhythmia Congestive heart failure
	Rare	Cardiac arrest
Vascular disorders	Common	Hypertension Flushing Haematoma
	Uncommon	Vascular arterial occlusion Thrombophlebitis Aortic aneurysm
Respiratory, thoracic and mediastinal disorders*	Common	Cough Asthma Dyspnoea

MeDRA System Organ Class (SOC)	Frequency	Adverse Reaction
	Uncommon	Chronic obstructive pulmonary disease Interstitial lung disease Pneumonitis
Gastrointestinal disorders	Very common	Abdominal pain Nausea Vomiting
	Common	GI haemorrhage Dyspepsia Gastroesophageal reflux disease Sicca syndrome
	Uncommon	Pancreatitis, Dysphagia, Face oedema
Hepato-biliary disorders*	Very common	Liver enzymes elevated
	Uncommon	Cholecystitis and cholelithiasis Bilirubin increased Hepatic steatosis
Skin and subcutaneous tissue disorders	Very common	Rash (including exfoliative rash)
	Common	Pruritus Urticaria Bruising (including purpura) Dermatitis (including eczema) Onychoclasis Hyperhidrosis
	Uncommon	Night sweats Scar
	Very common	Musculoskeletal pain

MeDRA System Organ Class (SOC)	Frequency	Adverse Reaction
Musculoskeletal and connective tissue disorders	Common	Muscle spasms (including blood creatine phosphokinase increased)
	Uncommon	Rhabdomyolysis Systemic lupus erythematosus
Renal and urinary disorders	Common	Haematuria Renal impairment
	Uncommon	Nocturia
Reproductive system and breast disorders	Uncommon	Erectile dysfunction
General disorders and administration site conditions	Very common	Injection site reaction (including injection site erythema)
	Common	Chest pain Oedema
	Uncommon	Inflammation
Investigations	Common	Coagulation and bleeding disorders (including activated partial thromboplastin time prolonged) Autoantibody test positive (including double stranded DNA antibody) Blood lactate dehydrogenase increased
Injury, poisoning and procedural complications	Common	Impaired healing

* further information is found elsewhere in sections 4.3, 4.4 and 4.8

** including open-label extension studies

Paediatric Populations

In general, the adverse reactions in paediatric patients were similar in frequency and type to those seen in adult patients.

Description of selected adverse reactions

Injection site reaction

In the pivotal controlled trials in adults and children, 12.9 % of patients treated with adalimumab developed injection site reactions (erythematic and/or itching, haemorrhage, pain or swelling). compared with 7.2 % of patients receiving control treatment. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

Infections

In the pivotal controlled trials in adults and children, the rate of infection was 1.51 per patient year in the adalimumab treated patients and 1.46 per patient year in the control-treated patients. The incidence of serious infections was 0.04 per patient year in adalimumab -treated patients and 0.03 per patient year in control-treated patients.

The infections consisted primarily of nasopharyngitis, upper respiratory tract infections and sinusitis. Most patients continued on adalimumab after the infection resolved.

In the controlled and open label adult and paediatric studies with adalimumab, serious infections (including fatal infections, which occurred rarely) have been reported, which include reports of tuberculosis (including miliary and extrapulmonary locations) at an overall rate of approximately 0.026/1 000 patient years and invasive opportunistic infections (e.g. disseminated histoplasmosis, pneumocystis carinii pneumonia, aspergillosis and listeriosis) at an overall rate of approximately 0.0075/1 000 patient years.

Malignancies and Lymphoproliferative Disorders

During the controlled portions of pivotal adalimumab trials in adults at least 12 weeks in duration in patients with moderately to severely active rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, axial spondyloarthritis including ankylosing spondylitis, Crohn's Disease, ulcerative colitis, hidradenitis suppurativa, psoriasis and uveitis, malignancies, other than lymphoma and non-

melanoma skin cancer, were observed at a rate (95 % confidence interval) of 6.8 (4.4, 10.5) per 1 000 patient-years among 5 291 adalimumab treated patients versus a rate of 6.3 (3.4, 11.8) per 1 000 patient-years among 3 444 control patients (median duration of treatment was 4.0 months for adalimumab and 3.8 months for control-treated patients).

The rate (95 % confidence interval) of non-melanoma skin cancers was 8,8 (6.0, 13.0) per 1 000 patient years among adalimumab treated patients and 3.2 (1.3, 7.6)per 1 000 patient-years among control patients.

Of these skin cancers, squamous cell carcinomas occurred at rates (95 % confidence interval) of 2.7 (1.4, 5.4) per 1 000 patient years among adalimumab treated patients and 0.6 (0.1, 4.5) per 1 000 patient years among control patients.

The rate (95 % confidence interval) of lymphomas was 0.7 (0.2, 2.7) per 1 000 patient-years among adalimumab treated patients and 0.6 (0.1, 4.5) per 1 000 patient-years among control patients.

The observed rate of malignancies, other than lymphoma and non-melanoma skin cancers, is approximately 8.5 per 1 000 patient years in the controlled portion of clinical trials and in ongoing and completed open label extension studies. The observed rate of nonmelanoma skin cancers is approximately 9.6 per 1 000 patient years, and the observed rate of lymphomas is approximately 1.3 per 1 000 patient years. The median duration of these studies is approximately 3.3 years and included 6 427 patients who were on adalimumab for at least 1 year or who developed a malignancy within a year of starting therapy, representing over 26 439.6 patient years of therapy.

Autoantibodies

Patients had serum samples tested for autoantibodies at multiple time points in rheumatoid arthritis Studies I-V. In these adequate and well-controlled trials, 11.9 % of patients treated with adalimumab and 8.1 % of placebo and active control-treated patients that had negative baseline anti-nuclear antibody titres reported positive titres at week 24. Two patients out of 3 989 treated with adalimumab in all RA, PsA and AS studies developed clinical signs suggestive of new-onset lupus-like syndrome. The patient improved following discontinuation of therapy. No patients developed lupus nephritis or

central nervous system symptoms. The impact of long-term treatment with adalimumab on the development of autoimmune disease is unknown

Psoriasis: New Onset and Worsening

Cases of new onset psoriasis, including pustular psoriasis and palmoplantar psoriasis, and cases of worsening of pre-existing psoriasis have been reported with the use of TNF blockers, including adalimumab. Many of these patients were taking concomitant immunosuppressants (e.g. MTX, corticosteroids). Some of these patients required hospitalisation. Most patients had improvement of their psoriasis following discontinuation of their TNF blocker. Some patients have had recurrences of the psoriasis when they were re-challenged with a different TNF blocker.

Discontinuation of AMGEVITA® should be considered for severe cases and those that do not improve or that worsen despite topical treatments.

Liver Enzyme Elevations

In controlled Phase 3 trials of adalimumab (40 mg SC every other week), in patients with RA and PsA with a control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.7 % of adalimumab-treated patients and 1.6 % of control treated patients. Since many of the patients in these trials were also taking medications that cause liver enzyme elevations (e.g. NSAIDS, MTX), the relationship between adalimumab and the liver enzyme elevations is not clear.

In controlled Phase 3 trials of adalimumab (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week), in patients with Crohn's Disease with a control period duration ranging from 4 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 0.9 % of adalimumab -treated patients and 0,9 % of control-treated patients.

In controlled Phase 3 trials of adalimumab (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week), in patients with ulcerative colitis with a control period duration ranging from 1 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 1.5 % of adalimumab -treated patients and 1.0 % of control-treated patients.

In controlled trials of adalimumab (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in patients with hidradenitis suppurativa with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3 % of adalimumab-treated patients and 0.6 % of control-treated patients.

In controlled Phase 3 trials of adalimumab (initial dose of 80 mg then 40 mg every other week), in patients with plaque psoriasis with a control period duration ranging from 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 1.8 % of adalimumab-treated patients and 1.8 % of control-treated patients.

In controlled Phase 3 trials of adalimumab (40 mg every other week), in patients with ankylosing spondylitis and axial spondyloarthritis with a control period of 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 2.1 % of adalimumab-treated patients and 0.8 % of control-treated patients.

In controlled Phase 3 trials of adalimumab (40 mg every other week), in patients with ankylosing spondylitis and axial spondyloarthritis with a control period of 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 2,1 % of adalimumab-treated patients and 0,8 % of control-treated patients. In controlled Phase 3 trials of adalimumab in patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years and enthesitis-related arthritis who were 6 to 17 years, ALT elevations ≥ 3 x ULN occurred in 6.1 % of adalimumab-treated patients and 1.3 % of control-treated patients. Most ALT elevations occurred with concomitant methotrexate use. No ALT elevations ≥ 3 x ULN occurred in the Phase 3 trial of adalimumab in patients with polyarticular juvenile idiopathic arthritis who were 2 to < 4 years.

In the Phase 3 trial of adalimumab in patients with paediatric Crohn's Disease which evaluated efficacy and safety of two body weight adjusted maintenance dose regimens following body weight adjusted induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6 % (5/192) of patients, of whom 4 were receiving concomitant immunosuppressants at baseline.

In controlled trials of adalimumab (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in patients with uveitis with an exposure of 165.4 Person-Years (PYs) and

119.8 PYs in adalimumab-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4 % of adalimumab-treated patients and 2.4 % of control-treated patients.

No ALT elevations ≥ 3 x ULN occurred in the Phase 3 trial of adalimumab in paediatric patients with plaque psoriasis.

Across all indications in clinical trials patients with raised ALT were asymptomatic and, in most cases, elevations were transient and resolved on continued treatment. However, there have been very rare post-marketing reports of severe hepatic reactions including liver failure in patients receiving TNF blockers, including adalimumab. The causal relationship to adalimumab treatment remains unclear.

Concurrent treatment with azathioprine/6-marcaptopurine

In adult Crohn's Disease studies, higher incidences of malignant and serious infection related adverse events were seen with the combination of adalimumab and azathioprine/6 mercaptopurine compared with adalimumab alone.

Additional adverse reactions from post-marketing surveillance or Phase IV clinical trials

Adverse events have been reported during post-approval use of adalimumab. 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 exposure.(See Table 6 below).

Table 6: Additional adverse reactions from post-marketing surveillance or phase IV clinical trials	
MeDRA System Organ Class (SOC)	**Adverse reaction**
Immune system disorders*	Anaphylaxis Sarcoidosis
Hepatobiliary disorders*	Reactivation of Hepatitis B

	Liver failure Hepatitis
Skin and subcutaneous tissue disorders*	Cutaneous vasculitis Stevens Johnson Syndrome Angioedema New onset or worsening of psoriasis (including palmoplantar pustular psoriasis) Erythema multiforme Alopecia
Gastrointestinal disorders*	Intestinal perforation
Nervous system disorders*	Demyelinating disorders (e.g. optic neuritis, Guillain-Barre syndrome) Cerebrovascular accident
Musculoskeletal and connective tissue disorders	Lupus-like syndrome
Cardiac disorders	Myocardial infarction
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	Hepatosplenic T-cell lymphoma Leukaemia Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)
Infections and infestations	Diverticulitis
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism Pleural effusion Pulmonary fibrosis
General disorders and administration site conditions	Pyrexia
* Further information found elsewhere in sections 4.3, 4.4 and 4.8	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

Alternatively, suspected adverse events can be reported to:

Amgen South Africa (Pty) Ltd.

Tel: +27 (0)11 100 5300

Email: safety-south-africa@amgen.com

4.9 Overdose

The maximum tolerated dose of adalimumab has not been established in humans.

In overdose, side effects can be anticipated and/or be of increased severity.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacological classification: A 30.2 Antibodies.

Mechanism of Action

Adalimumab is a monoclonal antibody which binds specifically to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors.

The relationship between these pharmacodynamic activities and the mechanism(s) by which adalimumab exerts its clinical effects is unknown.

Pharmacodynamic Effects

After treatment with adalimumab, a rapid decrease in levels of acute phase reactants of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) and serum cytokines (IL-6) was observed compared to baseline in patients with RA.

A decrease in CRP levels was also observed in patients with JIA Crohn's Disease, ulcerative colitis and hidradenitis suppurativa. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodelling responsible for cartilage destruction were also decreased after adalimumab administration.

Patients with RA, PsA and AS often experience mild to moderate anaemia and decreased lymphocyte counts, as well as elevated neutrophil and platelet count.

Patients treated with adalimumab usually experienced improvement in these haematological signs of chronic inflammation.

5.2 Pharmacokinetic Properties

Absorption

Following a single 40 mg subcutaneous (SC) administration of adalimumab to 59 healthy adult subjects, absorption and distribution of adalimumab were slow, with mean peak serum concentration being reached about five days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64 %.

Distribution and elimination

The single dose pharmacokinetics of adalimumab was determined in several studies with intravenous doses ranging from 0.25 to 10 mg/kg. The distribution volume (Vss) ranged from 4.7 to 6.0, indicating that adalimumab distributes approximately equally between the vascular and extravascular fluids. Adalimumab is slowly eliminated, with clearances typically under 12 ml/h. The mean terminal phase half-life was approximately two weeks, ranging from 10 to 20 days across studies. The clearance and

half-life were relatively unchanged over the studied dose range, and the terminal half-life was similar after IV and SC administration.

Adalimumab concentrations in the synovial fluid from several RA patients ranged from 31 % to 96 % of those in serum.

Steady-state pharmacokinetics

Accumulation of adalimumab was predictable based on the half-life following SC administration of 40 mg of adalimumab every other week to patients with RA, with mean steady-state trough concentrations of approximately 5 µg/ml (without concomitant methotrexate) and 8 to 9 µg/ml (with concomitant methotrexate), respectively. The serum adalimumab trough levels at steady state increased approximately proportionally with dose following 20, 40 and 80 mg every other week and every week SC dosing. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time.

In patients with Crohn's Disease, the loading dose of 160 mg adalimumab on week 0 followed by 80 mg adalimumab on week 2 achieves mean serum adalimumab trough concentrations of approximately 12 µg/ml at week 2 and week 4. Mean steady-state trough levels of approximately 7 µg/ml were observed at week 24 and week 56 in Crohn's Disease patients who received a maintenance dose of 40 mg adalimumab every other week.

In patients with psoriasis, the mean steady-state trough concentration was 5 µg/ml during adalimumab 40 mg every other week monotherapy treatment. In patients with hidradenitis suppurativa, a dose of 160 mg adalimumab on Week 0 followed by 80 mg on Week 2 achieved serum adalimumab trough concentrations of approximately 7 to 8 µg/ml at Week 2 and Week 4. The mean steady-state trough concentration at Week 12 through Week 36 were approximately 8 to 10 µg/ml during adalimumab 40 mg every week treatment.

In patients with uveitis, a loading dose of 80 mg adalimumab on Week 0 followed by 40 mg adalimumab every other week starting at Week 1, resulted in mean steady- state concentrations of approximately 8 to 10 µg/ml.

Population pharmacokinetic analyses with data from over 1 200 patients revealed that co-administration of methotrexate had an intrinsic effect on adalimumab apparent clearance (CL/F). There was a trend towards higher apparent clearance of adalimumab with increasing bodyweight and in the presence of anti-adalimumab antibodies.

Other more minor factors identified were higher apparent clearance in patients receiving doses lower than the recommended dose, and in patients with high rheumatoid factor or CRP concentrations.

In patients with ulcerative colitis, a loading dose of 160 mg adalimumab on week 0 followed by 80 mg adalimumab on week 2 achieves serum adalimumab trough concentrations of approximately 12 µg/ml during the induction period. Mean steady- state trough levels of approximately 8 µg/ml were observed in ulcerative colitis patients who received a maintenance dose of 40 mg adalimumab every other week.

The pharmacokinetics of AMGEVITA® is similar to HUMIRA.

Special Populations

Pharmacokinetics in special populations were investigated using population pharmacokinetics analyses.

Elderly

Age appeared to have a minimal effect on adalimumab apparent clearance. From the population analyses, the mean weight-adjusted clearances in patients 40 to 65 years (n = 850) and 65 years (n = 287) were 0.33 and 0.30 ml/h/kg, respectively.

Hepatic and Renal Insufficiency

No pharmacokinetic data is available in patients with hepatic or renal impairment.

Disease States

Healthy volunteers and patients with rheumatoid arthritis displayed similar adalimumab pharmacokinetics.

Paediatric Population

Following the administration of 24 mg/m^2 (up to a maximum of 40 mg) subcutaneously every other week to patients with polyarticular juvenile idiopathic arthritis (JIA) the mean trough steady-state (values measured from Week 20 to 48) serum adalimumab concentration was 5.6 ± 5.6 µg/ml (102 % CV) adalimumab monotherapy and 10.9 ± 5.2 µg/ml (47 % CV) with concomitant methotrexate. The mean steady state trough serum adalimumab concentrations for subjects weighing < 30 kg receiving 20 mg adalimumab subcutaneously every other week as monotherapy or with concomitant methotrexate were 6.8 µg/ml and 10.9 µg/ml, respectively. The mean steady-state trough serum adalimumab concentrations for subjects weighing ≥ 30 kg receiving 40 mg adalimumab subcutaneously every other week as monotherapy or with concomitant methotrexate were 6.6 µg/ml and 8.1 µg/ml, respectively. In patients with polyarticular JIA who were 2 to < 4 years old or aged 4 and above weighing < 15 kg dosed with adalimumab 24 mg/m^2, the mean trough steady-state serum adalimumab concentrations was 6.0 ± 6.1 µg/ml (101 % CV) for adalimumab without concomitant methotrexate and 7.9 ± 5.6 µg/ml (71.2 % CV) with concomitant methotrexate.

In paediatric patients with moderately to severely active Crohn's Disease, the open- label adalimumab induction dose was 160/80 mg or 80/40 mg at Weeks 0 and 2, respectively, dependent on a body weight cut-off of 40 kg. At Week 4, subjects were randomized 1:1 to either the Standard Dose (40/20 mg every other week (eow)) or Low Dose (20/10 mg eow) maintenance treatment groups based on their body weight. The mean (±SD) serum adalimumab trough concentrations achieved at Week 4 were 15.7 ± 6.6 µg/ml for subjects ≥ 40 kg (160/80 mg) and 10.6 ± 6.1 µg/ml for subjects < 40 kg (80/40 mg).

For subjects who stayed on their randomised therapy, the mean (±SD) adalimumab trough concentrations at Week 52 were 9.5 ± 5.6 µg/ml for the Standard Dose group and 3.5 ± 2.2 µg/ml for the Low Dose group.

The mean trough concentrations were maintained in subjects who continued to receive adalimumab treatment eow for 52 weeks. For subjects whose dose escalated from eow to weekly regimen, the mean (±SD) serum concentrations of adalimumab at Week 52 were 15.3 ± 11.4 µg/ml (40/20 mg, weekly) and 6.7 ± 3.5 µg/ml (20/10 mg weekly).

Following the administration of 0.8 mg/kg (up to a maximum of 40 mg) subcutaneously every other week to paediatric patients with chronic plaque psoriasis, the mean ± SD steady-state adalimumab trough concentration was approximately 7.4 ± 5.8 µg/ml (79 % CV).

Medicine Interactions – Methotrexate

When adalimumab was administered to patients on stable methotrexate therapy, there were no statistically significant changes in the serum methotrexate concentration profiles. In contrast, after single and multiple dosing, methotrexate reduced adalimumab apparent clearances by 29 % and 44 % respectively (see section 4.5).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Glacial acetic acid

Sucrose

Polysorbate 80

Sodium hydroxide (for pH adjustment)

Water for injection

6.2 Incompatibilities*:*

Interactions between adalimumab and medicines other than methotrexate have not been evaluated in formal pharmacokinetic studies. In the absence of compatibility studies, this medicine must not be mixed with other medicines. This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life*:*

36 Months

6.4 Special Precautions for Storage

Store between 2 and 8 ºC (in a refrigerator) and store the syringe or pen in the outer carton.
Do not freeze.
Keep AMGEVITA® in the outer carton in order to protect from light.
Keep out of reach of children.
A single AMGEVITA® pre-filled syringe or pre-filled pen may be stored for 14 days at or below 25 °C. The pre-filled syringe or pre-filled pen must be protected from light, and any unused portion should be discarded if not used within the 14-day period.

6.5 Nature and contents of container

AMGEVITA® 20 mg solution for injection in single-use pre-filled syringe (type I glass) with a plunger stopper (grey bromobutyl rubber) steel and a needle with a needle shield (thermoplastic elastomer).

Pack size of one pre-filled syringe, placed in an outer carton.

AMGEVITA® 40 mg solution for injection in single-use pre-filled syringe (type I glass) with a plunger stopper (grey bromobutyl rubber) steel and a needle with a needle shield (thermoplastic elastomer).

Pack sizes of one and two pre-filled syringes, placed in an outer carton.

Not all pack sizes may be marketed.

AMGEVITA® 40 mg solution for injection in single-use pre-filled pen. The pre-filled pen is a single use, disposable, handheld, mechanical (spring-based) injection device which consists of a pre-filled syringe contained within two subassemblies:

- The front subassembly (blue) is designed to hold the pre-filled syringe with staked needle and non-rigid needle shield.
- The rear subassembly (blue) contains a plunger rod (blue) and spring that drives dose delivery.

Pack sizes of one and two pre-filled pens, placed in an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Detailed instructions for use are provided in the package leaflet.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Amgen South Africa (Pty) Ltd.

Building D, Ballyoaks Office Park,

35 Ballyclare Drive,

Bryanston Ext. 7, 2021,

South Africa

8. REGISTRATION NUMBER(S)

AMGEVITA® 20 mg: 51/30.1/0677

AMGEVITA® 40 mg PFP and PFS: 51/30.1/0678

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 February 2020

10 DATE OF REVISION OF THE TEXT

20 October 2022