PRODUCT INFORMATION

NAME OF THE MEDICINE
AMGEVITA® 40 mg/0.4 ml solution for injection in pre-filled autoinjector.

Non-proprietary Name
Adalimumab 100 mg/ml

DESCRIPTION

AMGEVITA® (adalimumab) is a biosimilar medicine to the reference product HUMIRA® (adalimumab). The comparability of AMGEVITA with HUMIRA® has been demonstrated with regard to physicochemical characteristics and efficacy and safety outcomes (see **CLINICAL PHARMACOLOGY, CLINICAL TRIALS and ADVERSE EFFECTS**). The evidence for comparability supports the use of AMGEVITA for the listed indications.

AMGEVITA (adalimumab) is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. AMGEVITA was created using phage display technology resulting in fully human heavy and light chain variable regions, which confer specificity to human tumor necrosis factor (TNF), and human IgG1 heavy chain and kappa light chain sequences. AMGEVITA binds with high affinity and specificity to soluble tumor necrosis factor (TNF-alpha) but not lymphotoxin (TNF-beta). Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons.

AMGEVITA is supplied as a sterile, preservative-free solution of adalimumab for subcutaneous administration. The solution of AMGEVITA is clear and colourless to slightly yellow solution.

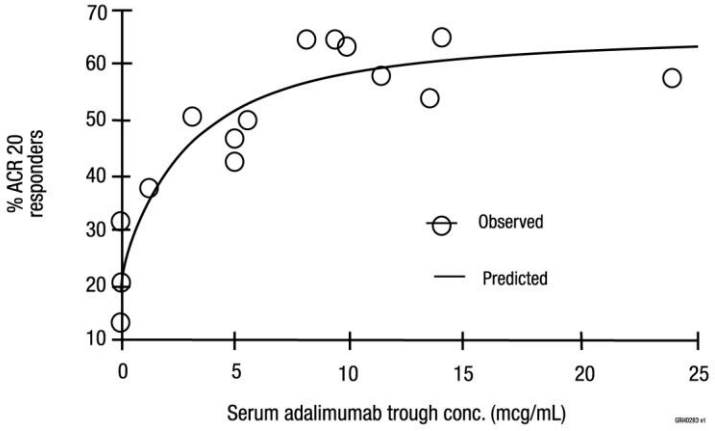
CLINICAL PHARMACOLOGY

General
Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of rheumatoid arthritis, including juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis patients and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis (Ps) plaques. In plaque psoriasis, treatment with adalimumab may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which adalimumab exerts its clinical effects is unknown.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of 1-2 × 10^{-10}M).

Pharmacodynamics
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 as well as a significant reduction in the expression of the TNF and inflammatory markers such as human leucocyte antigen (HLA-DR) and myeloperoxidase (MPO) in the colon of patients with Crohn's disease. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after adalimumab administration. Patients with RA, PsA and AS often experience mild to moderate anemia and decreased lymphocyte counts, as well as elevated neutrophil and platelet counts. Patients treated with adalimumab usually experienced improvement in these hematological signs of chronic inflammation.

The serum adalimumab concentration-efficacy relationship as measured by the American College of Rheumatology response criteria (ACR 20) appears to follow the Hill E_{max} equation as shown below:



EC_{50} estimates ranging from 0.8 to 1.4 mcg/ml were obtained through pharmacokinetic/pharmacodynamic modeling of swollen joint count, tender joint count and ACR 20 response from patients participating in Phase II and III trials.
Pharmacokinetics

Absorption
Following a single 40 mg subcutaneous (SC) administration of adalimumab to 59 healthy adult subjects, absorption and distribution of adalimumab was 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 were determined in several studies with intravenous doses ranging from 0.25 to 10 mg/kg. The distribution volume (V_{ss}) ranged from 4.7 to 6.0 L, 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 mcg/ml (without concomitant methotrexate (MTX)) and 8 to 9 mcg/ml (with concomitant MTX), 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 psoriasis, the mean steady-state trough concentration was 5 mcg/ml during adalimumab 40 mg eow without concomitant methotrexate 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 mcg/ml at Week 2 and Week 4. The mean steady-state trough concentration at Week 12 through Week 36 were approximately 8 to 10 mcg/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, result in mean steady-state concentrations of approximately 8 to 10 mcg/ml.

Population pharmacokinetic and pharmacokinetic/pharmacodynamic modelling and simulation predicted comparable adalimumab exposure and efficacy in patients treated with 80 mg every other week when compared with 40 mg every week (including adult patients with RA, HS, UC, CD or Ps, adolescent patients with HS, and pediatric patients ≥ 40 kg with CD).

Population pharmacokinetic analyses with data from over 1200 patients revealed that co-administration of MTX had an intrinsic effect on adalimumab apparent clearance (CL/F) (see **DRUG INTERACTIONS**). As expected, there was a trend towards higher apparent clearance of adalimumab with increasing body weight and in the presence of anti-adalimumab antibodies.

Other more minor factors were also identified; higher apparent clearance was predicted in patients receiving doses lower than the recommended dose, and in patients with high rheumatoid factor or CRP concentrations. These factors are not likely to be clinically important.

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 levels of approximately 12 mcg/ml at Week 2 and Week 4. Mean steady-state trough levels of approximately 7 mcg/ml were observed at Week 24 and Week 56 in Crohn's disease patients after receiving a maintenance dose of 40 mg adalimumab every other week.

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 mcg/ml during the induction period. Mean steady-state trough levels of approximately 8 mcg/ml were observed in ulcerative colitis patients who received a maintenance dose of 40 mg adalimumab every other week.

Special Populations
Pharmacokinetics in special populations were investigated using population pharmacokinetic analyses.

Geriatrics
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.

Pediatrics
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) who were 4 to 17 years, the mean trough steady-state (values measured from Week 20 to 48) serum adalimumab concentration was 5.6 ± 5.6 µg/ml (102% CV) for adalimumab without concomitant methotrexate and 10.9 ± 5.2 µg/ml (47.7% CV) with concomitant methotrexate. The mean steady-state trough serum adalimumab concentrations for patients weighing < 30 kg receiving 20 mg adalimumab subcutaneously every other week without concomitant methotrexate or with concomitant methotrexate were 6.8 µg/ml and 10.9 µg/ml, respectively. The mean steady-state trough serum adalimumab concentrations for patients weighing ≥ 30 kg receiving 40 mg adalimumab subcutaneously every other week without concomitant methotrexate or with concomitant methotrexate were 6.6 µg/ml and 8.1 µg/ml, respectively. In patients with polyarticular juvenile idiopathic arthritis (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.

Following the administration of 24 mg/m^2 (up to a maximum of 40 mg) subcutaneously every other week to patients with enthesitis-related arthritis, the mean trough steady-state (values measured at Week 24) serum adalimumab concentrations were 8.8 ± 6.6 µg/ml for adalimumab without concomitant methotrexate and 11.8 ± 4.3 µg/ml with concomitant methotrexate.

In pediatric 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, patients were randomized 1:1 to either the Standard Dose (40/20 mg 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 patients ≥ 40 kg (160/80 mg) and 10.6 ± 6.1 µg/ml for patients < 40 kg (80/40 mg).

For patients who stayed on their randomized 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 patients who continued to receive adalimumab treatment eow for 52 weeks. For patients who 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).

Adalimumab exposure in adolescent hidradenitis suppurativa (HS) patients was predicted using population pharmacokinetic modeling and simulation based on cross-indication pharmacokinetics in other pediatric patients (pediatric psoriasis, juvenile idiopathic arthritis, pediatric Crohn's disease, and enthesitis-related arthritis). The recommended adolescent HS dosing schedule of 40 mg every other week is predicted to provide serum adalimumab exposure similar to that observed in adult HS patients receiving the recommended adult dose of 40 mg every week.

Following the subcutaneous administration of body weight-based dosing of 0.6 mg/kg (maximum of 40 mg) every other week to pediatric patients with ulcerative colitis, the mean trough steady-state serum adalimumab concentration was 5.01 ± 3.28 µg/ml at Week 52. For patients who received 0.6 mg/kg (maximum of 40 mg) every week, the mean (±SD) trough steady-state serum adalimumab concentration was 15.7 ± 5.60 µg/ml at Week 52.

Gender
No gender-related pharmacokinetic differences were observed after correction for a patient's body weight.

Race
No differences in immunoglobulin clearance would be expected among races. From limited data in non-Caucasians, no important kinetic differences were observed for adalimumab.

Hepatic and Renal Insufficiency
No pharmacokinetic data are available in patients with hepatic or renal impairment.

Disease States
Healthy volunteers and patients with RA displayed similar adalimumab pharmacokinetics.

Comparability of AMGEVITA with HUMIRA®
AMGEVITA is pharmacokinetically similar to HUMIRA®.
Pharmacokinetic similarity was demonstrated between AMGEVITA and HUMIRA® following administration of a single 40 mg dose subcutaneously in 203 healthy adult subjects. Pharmacokinetic parameters such as maximum serum concentrations and area under the serum concentration time curves were compared. According to the bioequivalence testing, the 90% confidence intervals of the geometric mean test-to-reference ratios for these parameters fell within the protocol-specified criteria of 0.8 to 1.25 and concluded pharmacokinetic similarity between AMGEVITA and HUMIRA®.

PRE-CLINICAL SAFETY DATA

Preclinical data reveal no special hazard for humans based on studies of single dose toxicity, repeated dose toxicity, and genotoxicity.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Long-term animal studies of adalimumab have not been conducted to evaluate the carcinogenic potential or its effect on fertility.

No clastogenic or mutagenic effects of adalimumab were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.

CLINICAL TRIALS

COMPARABILITY OF AMGEVITA WITH HUMIRA®

CLINICAL TRIAL FOR RHEUMATOID ARTHRITIS (Study 20120262)
The efficacy and safety of AMGEVITA compared with HUMIRA® were assessed in a randomised active-control, double-blind study in patients ≥ 18 years of age with moderate to severe active rheumatoid arthritis with inadequate response to methotrexate. The patients had either rheumatoid factor or anti-cyclic citrullinated peptide positivity. The study evaluated 526 patients on stable doses of Methotrexate. Patients were randomised to receive 40 mg of AMGEVITA or HUMIRA® subcutaneously every other week for up to 22 weeks.

The percent of AMGEVITA-treated subjects achieving ACR 20 at week 24 in the RA Study is shown in **Table 1**. At week 24, 74.6% (194/260) subjects in the AMGEVITA group and 72.4% (189/261) subjects in the HUMIRA® group met the ACR 20 response criteria. The risk ratio (RR) of ACR 20 for AMGEVITA versus HUMIRA® was 1.039 with the 2-sided 90% confidence interval (CI) of (0.954, 1.133).

Table 1. Clinical Responses in RA Study similarity of AMGEVITA vs HUMIRA®

	AMGEVITA (24 weeks)	**HUMIRA® (24 weeks)**
ACR 20	74.6%	72.4%

The RR of ACR 20 primary endpoint was within the pre-specified margin and showed clinical equivalence between AMGEVITA and HUMIRA®.

The results of the components of the ACR response criteria for RA ABP-Study 1 are shown in **Table 2**. ACR response rates and improvement in all components of ACR response showed an absence of clinically meaningful differences between the two groups at week 24.

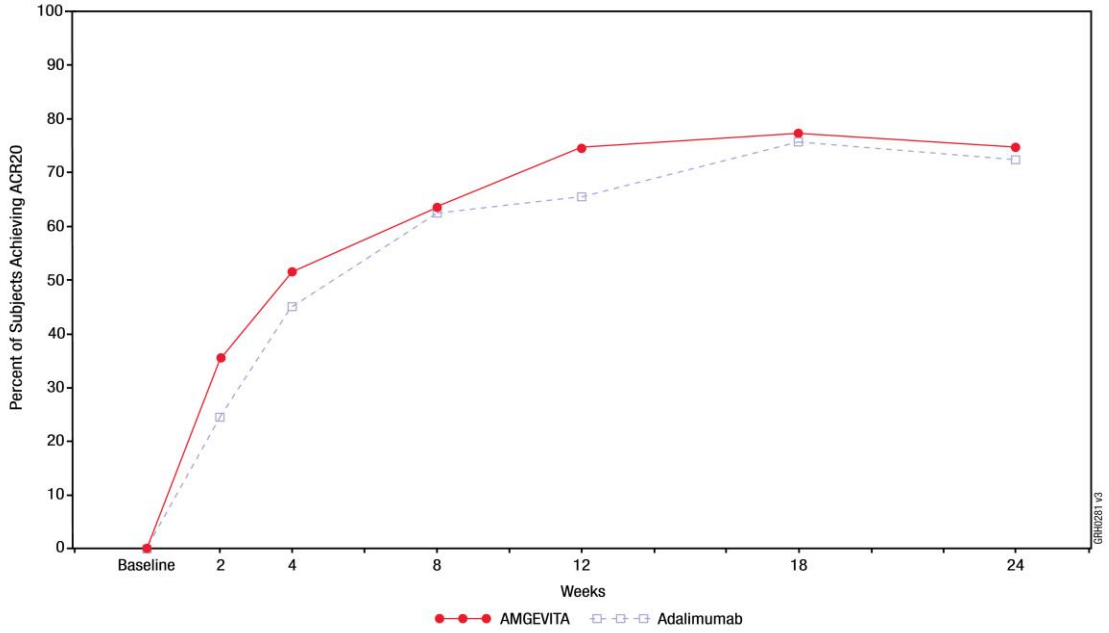
Table 2. Components of ACR Response

Parameter (median)	AMGEVITA[a] N = 264		HUMIRA®[a] N = 262	
	Baseline	**Week 24**	**Baseline**	**Week 24**
Number of tender joints (0-68)	21.0	4.0	20.5	4.0
Number of swollen joints (0-66)	12.0	2.0	12.0	2.0
Physician global assessment[b]	7.0	2.0	7.0	2.0
Patient global assessment[b]	7.0	3.0	7.0	3.0
Pain[c]	60.0	19.0	65.0	21.0
Disability index (HAQ)[d]	1.5	1.0	1.5	0.9
CRP (mg/L)	6.1	3.0	7.6	3.0

[a] 40 mg administered every other week
[b] Visual analogue scale; 0 = best, 10 = worst
[c] Pain scale; 0 = no pain; 100 = severe pain
[d] Disability Index of the Health Assessment Questionnaire; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity

The time course of ACR20 response is shown in **Figure 1**.

Figure 1. RA Study With AMGEVITA and HUMIRA® ACR 20 Responses Over 24 Weeks



CLINICAL TRIAL FOR PSORIASIS (Study 20120263)
The efficacy and safety of AMGEVITA were assessed in a randomised active-control, double-blind study in 350 patients ≥ 18 years of age with moderate to severe plaque psoriasis (Ps) who were candidates for systemic therapy or phototherapy. Patients had stable moderate to severe plaque Ps for at least 6 months, a body surface area (BSA) ≥ 10%, and Psoriasis Area and Severity Index (PASI) ≥ 12 at study entry. The patients received AMGEVITA or HUMIRA® at an initial loading dose of 80 mg administered SC on week 1/day1, followed by 40 mg SC given every other week starting one week after the loading dose. The PASI percent improvement from baseline was measured and compared with adalimumab (see **Table 3**) and it was within the pre-specified equivalence margin to demonstrate clinical equivalence between AMGEVITA and HUMIRA®.

Table 3. Efficacy Results at Week 16 in Ps Study AMGEVITA vs HUMIRA®

	AMGEVITA n = 175	HUMIRA® n = 175
PASI % Improvement from baseline	80.91	83.06

SD[a]	24.237	25.195

SD[a] = Standard deviation

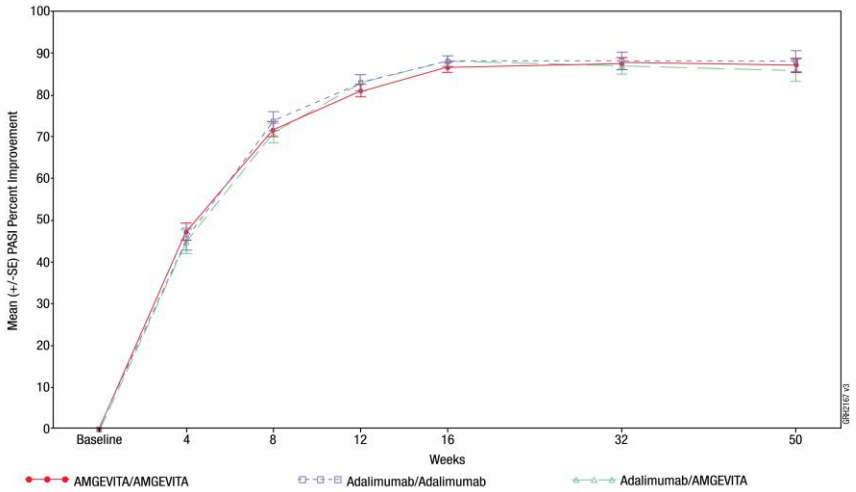
The primary endpoint was PASI percent improvement from baseline to week 16. At week 16, the PASI percent improvement from baseline was 80.9 in the AMGEVITA group and 83.1 in the HUMIRA® group. The least-squares (LS) mean difference of PASI percent improvement from baseline to week 16 between AMGEVITA and HUMIRA® was -2.18 with the 2-sided 95% CI of (-7.39, 3.02). The 95% CI was within the predefined equivalence margin, thus demonstrating clinical equivalence of AMGEVITA and HUMIRA®.

The Ps study was also designed to evaluate clinically meaningful differences in safety and immunogenicity in subjects who underwent a single transition from HUMIRA® to AMGEVITA at week 16 and to provide a descriptive comparison with patients who continued on HUMIRA®. The 350 subjects in the Ps study were initially randomised (1:1) to Treatment Group A (AMGEVITA) or Treatment Group B (HUMIRA®). At week 16, subjects with a PASI 50 response (50% or better improvement) continued on study for up to 52 weeks. Subjects who continued treatment beyond week 16 were re-randomised in a blinded fashion such that all subjects initially randomised to Treatment Group A (AMGEVITA) continued treatment with AMGEVITA (AMGEVITA/AMGEVITA) and subjects initially randomised to Treatment Group B (HUMIRA®) were re-randomised (1:1) to either continue treatment with HUMIRA®, Treatment Group B1 (HUMIRA®/HUMIRA®) or were transitioned to AMGEVITA, Treatment Group B2 (HUMIRA®/AMGEVITA). Subjects continued with their assigned treatment until week 48, when the last dose of assigned investigational product was administered and week 52 was the end of study.

The overall safety profile of the subjects who transitioned from HUMIRA® to AMGEVITA was similar to the subjects who remained on HUMIRA® throughout the study.

The mean PASI percent improvement from baseline over the duration of the study is shown in **Figure 2**.

Figure 2. Mean PASI Percent Improvement From Baseline Over the Duration of Ps Study



CLINICAL STUDY ON NAIL PSORIASIS

Psoriasis Study IV compared the efficacy and safety of adalimumab versus placebo in 217 adult patients with moderate to severe nail psoriasis. Patients received an initial dose of 80 mg HUMIRA® followed by 40 mg every other week (starting one week after the initial dose) or placebo for 26 weeks followed by open label HUMIRA® treatment for an additional 26 weeks. Nail psoriasis was assessed using the Modified Nail Psoriasis Severity Index (mNAPSI) and the Physician's Global Assessment of Fingernail Psoriasis (PGA-F). A statistically significantly higher proportion of patients randomized to HUMIRA® achieved at least a 75% improvement in mNAPSI (mNAPSI 75) at Week 26, as compared with patients randomized to placebo (see **Table 4**). The percent improvement in NAPSI was statistically significantly greater in HUMIRA® patients compared with placebo at Week 16 (44.2% vs 7.8%) and at Week 26 (56.2% vs 11.5%).

A statistically significant higher proportion of patients in the HUMIRA® group achieved a PGA-F of "clear" or "minimal" with at least a 2-grade improvement from Baseline at Week 26 compared with placebo. In this study, HUMIRA® demonstrated a treatment benefit in nail psoriasis patients with different extents of skin involvement (BSA≥10% and BSA<10% and ≥5%) and a statistically significant improvement in scalp psoriasis compared with placebo.

Table 4. Efficacy Results at 26 Weeks

Endpoint	**Placebo N = 108**	**HUMIRA® 40 mg eow N = 109**
≥ mNAPSI 75 (%)	3.4	46.6[a]
PGA-F clear/minimal and ≥ 2-grade improvement (%)	6.9	48.9[a]
Percent Change in Total Fingernail NAPSI (%)	-11.5	-56.2[a]
mNAPSI = 0 (%)	0	6.6[b]
Change in Nail Pain Numeric Rating Scale	-1.1	-3.7[a]
Change in Nail Psoriasis Physical Functioning Severity score	-0.8	-3.7[a]

Endpoint	Placebo N = 108	HUMIRA® 40 mg eow N = 109
B-SNIPI 50 Scalp (%)	N = 12 0.4	N = 18 58.3[b]

[a] p<0.001, HUMIRA® vs. placebo
[b] p<0.05, HUMIRA® vs. placebo

B-SNIPI 50: At least a 50% reduction in scalp component of Brigham Scalp Nail Inverse Palmo-Plantar Psoriasis index (B-SNIPI) among subjects with Baseline scalp score of 6 or greater

Of those who continued to receive adalimumab treatment until Week 52, 65.0% achieved mNAPSI 75 response and 61.3% achieved PGA-F response.

Adalimumab-treated patients showed statistically significant improvements at Week 26 from baseline compared with placebo in the DLQI (Dermatology Life Quality Index). The mean decrease (improvement) from baseline at Week 26 was 8.0 in the HUMIRA® group (N = 94) and 1.9 in the placebo group (N = 93).

IMMUNOGENICITY OF ADALIMUMAB

Patients in rheumatoid arthritis studies I, II, and III were tested at multiple time points for anti-adalimumab antibodies during the 6 to 12 month period. Approximately 5.5% (58 of 1,062) of adult rheumatoid arthritis patients receiving adalimumab developed low-titre antibodies to adalimumab at least once during treatment, which were neutralising *in vitro*. Patients treated with concomitant MTX had a lower rate of antibody development than patients on adalimumab monotherapy (1% versus 12%). No apparent correlation of antibody development to adverse events was observed. With monotherapy, patients receiving fortnightly dosing may develop antibodies more frequently than those receiving weekly dosing. In patients receiving the recommended dosage of 40 mg fortnightly as monotherapy, the ACR 20 response was lower among antibody-positive patients than among antibody-negative patients. The long-term immunogenicity of adalimumab is unknown.

In pJIA Study I a greater percentage of patients developed antibodies to adalimumab compared to adult rheumatoid arthritis patients. Antibody formation was lower when adalimumab was given together with methotrexate in comparison with use as monotherapy. There was no apparent correlation between the presence of antibodies and adverse events. Anti-adalimumab antibodies were identified in 15.8% (27/171) of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 25.6% (22/86), compared to 5.9% (5/85) when adalimumab was used as add-on to methotrexate.

In pJIA Study II anti-adalimumab antibodies were identified in 7% (1/15) of patients, and the one patient was receiving concomitant methotrexate.

In patients with enthesitis-related arthritis, anti-adalimumab antibodies were identified in 11% (5/46) of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 14% (3/22), compared to 8% (2/24) when adalimumab was used as add-on to methotrexate.

In paediatric patients with moderately to severely active Crohn's disease, the rate of antibody development in patients receiving adalimumab was 3.3%.

In patients with ankylosing spondylitis, the rate of development of anti-adalimumab antibodies in adalimumab-treated patients was comparable to patients with rheumatoid arthritis. In patients with psoriatic arthritis, the rate of antibody development in patients receiving adalimumab monotherapy was comparable to patients with rheumatoid arthritis; however, in patients receiving concomitant methotrexate the rate was 7% compared to 1% in rheumatoid arthritis. The immunogenicity rate was 8% for psoriasis patients who were treated with adalimumab monotherapy.
In patients with Crohn's disease, anti-adalimumab antibodies were identified in 2.6% (7/269) of patients treated with adalimumab.

In patients with ulcerative colitis, anti-adalimumab antibodies were identified in 3.9% (19/487) of patients treated with adalimumab. However, due to the limitation of the assay conditions, antibodies to adalimumab could be detected only when serum adalimumab levels were < 2 micrograms/ml. Among the patients whose serum adalimumab levels were < 2 micrograms/ml (approximately 25% of total patients studied), the immunogenicity rate was 20.7%.

In plaque psoriasis patients on long-term adalimumab without concomitant methotrexate who participated in a withdrawal and retreatment study, the rate of anti-adalimumab antibodies after retreatment was similar to the rate observed prior to withdrawal.
In patients with paediatric psoriasis, anti-adalimumab antibodies were identified in 13% (5/38) of subjects treated with 0.8 mg/kg adalimumab monotherapy. 37 of the 38 subjects completed the initial double-blind period (16 weeks) of Study M04-717, and one subject entered the long-term follow up period after Week 4.

In patients with moderate to severe hidradenitis suppurativa, anti-adalimumab antibodies were identified in 10/99 subjects (10.1%) treated with adalimumab.

In patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab.

The data reflect the percentage of patients whose test results were considered positive for antibodies to adalimumab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. For these reasons, comparison of the incidence of antibodies to adalimumab with the incidence of antibodies to other products may be misleading.

IMMUNOGENICITY of AMGEVITA

Differences in assay methodology for measuring immunogenicity prevents direct comparison of immunogenicity rates between AMGEVITA and HUMIRA® or other biologics in different studies. In the RA and Ps studies, binding ADA activity was determined using a bridging immunoassay and the neutralising ADA activity was determined using a TNFα-ligand binding based bioassay.

Immunogenicity in the RA study
Patients were tested at multiple time points for antibodies to AMGEVITA and HUMIRA® during the 26-week study period. The incidence of developing binding antibodies was 38.3% (101/264) in the AMGEVITA group and 38.2% (100/262) in the HUMIRA® group; the incidence of developing neutralising antibodies was 9.1% (24/264) in the AMGEVITA group and 11.1% (29/262) in the HUMIRA® group. The immunogenicity profile of AMGEVITA was similar to HUMIRA®.

Immunogenicity in the Ps study
Patients in the Ps study were tested at multiple time points for antibodies to HUMIRA® and AMGEVITA during the 52-week study period. The incidence of developing binding antibodies through the duration of the study was 68.4% (104/152) in the AMGEVITA/AMGEVITA group, 74.7% (59/79) in the HUMIRA®/HUMIRA® group, and 72.7% (56/77) in the HUMIRA®/AMGEVITA group; the incidence of developing neutralising antibodies was 13.8% (21/152) in the AMGEVITA/AMGEVITA group, 20.3% (16/79) in the HUMIRA®/HUMIRA® group, and 24.7% (19/77) in the HUMIRA®/AMGEVITA group. The HUMIRA®/AMGEVITA group reflects data for subjects exposed to both HUMIRA® and AMGEVITA before and after the transition. The safety and immunogenicity profiles of patients who transitioned from HUMIRA® to AMGEVITA were comparable to those who continued on HUMIRA® until the end of the study (week 52).

INDICATIONS

Rheumatoid Arthritis
AMGEVITA is indicated for reducing signs and symptoms, including major clinical response and clinical remission, inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active rheumatoid arthritis.
AMGEVITA can be used alone or in combination with methotrexate or other disease modifying anti-rheumatic drugs (DMARDs).

Psoriatic Arthritis
AMGEVITA is indicated for reducing the signs and symptoms of active arthritis in patients with psoriatic arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.

AMGEVITA can be used alone or in combination with disease modifying anti-rheumatic drugs.

Axial Spondyloarthritis

Ankylosing Spondylitis
AMGEVITA is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Non-radiographic Axial spondyloarthritis (Axial Spondyloarthritis without radiographic evidence of AS)
AMGEVITA is indicated for reducing signs and symptoms in patients with active non-radiographic axial spondyloarthritis (nr-axSpA) but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

Plaque Psoriasis
AMGEVITA is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy and when other systemic therapies are medically less appropriate.

Crohn's Disease
AMGEVITA is indicated for the treatment of moderately to severely active Crohn's disease in adults patients who have inadequate response to conventional therapy. AMGEVITA is also indicated for treatment in adult patients with moderately to severely active Crohn's Disease who 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 with an inadequate response to conventional systemic HS therapy.

Uveitis
AMGEVITA is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

Paediatrics

Juvenile idiopathic arthritis

Polyarticular Juvenile Idiopathic Arthritis
AMGEVITA in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients aged above 2 years old who had an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs). AMGEVITA can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Enthesitis-Related Arthritis
AMGEVITA is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy.

Pediatric Crohn's Disease
AMGEVITA is indicated for the treatment of moderately to severely active Crohn's disease in pediatric patients (6 to 17 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and/or an immunomodulator, or who are intolerant to or have contraindication for such therapies.

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 paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

Adolescent hidradenitis suppurativa

AMGEVITA is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adolescents from 12 years of age with an inadequate response to conventional systemic hidradenitis suppurativa (HS) therapy.

Pediatric Ulcerative Colitis
AMGEVITA is indicated for treatment of moderately to severely active ulcerative colitis in patients aged 6 years and above 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.

DOSAGE AND ADMINISTRATION

Rheumatoid Arthritis, Psoriatic Arthritis and Axial Spondyloarthritis (Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis)

The recommended dose of AMGEVITA for adult patients with rheumatoid arthritis, psoriatic arthritis, or axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis) is 40 mg administered every other week as a single dose via subcutaneous injection. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, analgesics or other DMARDs may be continued during treatment with AMGEVITA.

In rheumatoid arthritis, some patients not taking concomitant MTX may derive additional benefit from increasing the dosage of AMGEVITA to 40 mg every week or 80 mg every other week (optional).

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.

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

Beyond 16 weeks, patients with inadequate response to AMGEVITA 40 mg every other week may benefit from an increase in dosage to 40 mg every week or 80 mg every other week. The benefits and risks of continued 40 mg weekly or 80 mg every other week therapy should be carefully reconsidered in a patient with an inadequate response after the increase in dosage. If adequate response is achieved with 40 mg every week or 80 mg every other week, the dosage may subsequently be reduced to 40 mg every other week.

Crohn's Disease
The recommended AMGEVITA induction dose regimen for adult patients with severe Crohn's Disease is 80 mg at week 0 followed by 40 mg at week 2. In case there is a need for a more rapid response to therapy, the regimen 160 mg at week 0 (dose can be administered as 160 mg in one day or as 80 mg per day for two consecutive days), 80 mg at week 2, can be used with the awareness that the risk for adverse events is higher during induction.

After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Alternatively, if a patient has stopped AMGEVITA and signs and symptoms of disease recur, AMGEVITA may be re-administered. There is little experience from re-administration after more than 8 weeks since the previous dose.

Some patients who experience decrease in their response may benefit from an increase in dosage to 40 mg AMGEVITA every week or 80 mg every other 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 160 mg in one day or as 80 mg 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 dosage to 40 mg AMGEVITA every week or 80 mg every other week.

Available data suggest that clinical response is usually achieved within 2-8 weeks of treatment. Adalimumab should only be continued in patients who have responded during the first 8 weeks of therapy.

Hidradenitis Suppurativa
The recommended AMGEVITA dose regimen for adult patients with hidradenitis suppurativa (HS) is 160 mg initially at Day 1 (given as 160 mg in one day or as 80 mg per day for two consecutive days), followed by 80 mg two weeks later at Day 15. Two weeks later (Day 29) continue with a dose of 40 mg every week or 80 mg every other 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, prescriber should consider to discontinue the treatment.

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. There is limited experience in the initiation of treatment with AMGEVITA alone. Treatment with AMGEVITA can be initiated in combination with corticosteroids and/or with other non-biologic immunomodulatory agents. Concomitant corticosteroids may be tapered in accordance with clinical practice starting two weeks after initiating treatment with AMGEVITA.

Paediatrics

Juvenile idiopathic arthritis

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 5**). AMGEVITA is administered every other week via subcutaneous injection.

Table 5. AMGEVITA Dose for Patients with Polyarticular Juvenile Idiopathic Arthritis

Patient Weight	Dosing Regimen
10 kg to < 30 kg	20 mg every other week
≥ 30 kg	40 mg every other week

AMGEVITA has not been studied in patients with polyarticular JIA less than 2 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.

There is no relevant use of AMGEVITA in children aged less than 2 years in this indication. AMGEVITA may be available in other strengths and/or presentations depending on the individual treatment needs.

Enthesitis-Related Arthritis
The recommended dose of AMGEVITA for patients from 6 years of age with enthesitis-related arthritis is based on body weight (**Table 6**). AMGEVITA is administered every other week via subcutaneous injection.

AMGEVITA may be available in different strengths and/or presentations.

Table 6. AMGEVITA Dose for Patients with Enthesitis-Related Arthritis

Patient Weight	Dosing Regimen
15 kg to < 30 kg	20 mg every other week
≥ 30 kg	40 mg every other week

AMGEVITA has not been studied in patients with enthesitis-related arthritis aged less than 6 years.

Pediatric 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 (**Table 7**). AMGEVITA is administered via subcutaneous injection. AMGEVITA may be available in different strengths and/or presentations.

Table 7. AMGEVITA Dose for Paediatric Patients with Crohn's disease

Patient Weight	Induction Dose	Maintenance Dose Starting at Week 4
< 40 kg	• 40 mg at Week 0 and • 20 mg at Week 2 In case there is a need for a more rapid response to therapy with the awareness that the risk for adverse events may be higher with use of the higher induction dose, the following dose may be used: • 80 mg at week 0 and 40 mg at week 2	20 mg every other week
≥ 40 kg	• 80 mg at week 0 and 40 mg at week 2 In case there is a need for a more rapid response to therapy with the awareness that the risk for adverse events may be higher with use of the higher induction dose, the following dose may be used: • 160 mg at week 0 (dose can be administered as 160 mg in one day or as 80 mg per day for two consecutive days) and 80 mg at week 2.	40 mg every other week

Patients who experience insufficient response may benefit from an increase in dosage:

- < 40 kg: 20 mg every week
- ≥ 40 kg: 40 mg every week or 80 mg every other week

Continued therapy should be carefully considered in a subject not responding by week 12. There is no relevant use of AMGEVITA in children aged less than 6 years for this indication.

AMGEVITA may be available in other strengths and/or presentations depending on the individual treatment needs.

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 8**). AMGEVITA is administered via subcutaneous injection. AMGEVITA may be available in different strengths and/or presentations.

Table 8. AMGEVITA Dose for Paediatric Patients with Plaque Psoriasis

Patient Weight	Dosing Regimen
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.
The safety of AMGEVITA in paediatric patients with plaque psoriasis has been assessed for a mean of 13 months.
There is no relevant use of AMGEVITA in children aged less than 4 years in this indication.

Paediatric Uveitis

The recommended dose of AMGEVITA for paediatric patients 2 years of age and older with chronic non-infectious uveitis is based on body weight (**Table 9**). AMGEVITA is administered via subcutaneous injection. AMGEVITA may be available in other strengths and/or presentations.

In paediatric uveitis, there is no experience in the treatment with AMGEVITA without concomitant treatment with methotrexate.

Table 9. AMGEVITA Dose for Paediatric Patients with Uveitis

Patient Weight	Dosing Regimen
< 30 kg	20 mg every other week in combination with methotrexate
≥ 30 kg	40 mg every other week in combination with methotrexate

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. No clinical data are available on the use of a AMGEVITA loading dose in children < 6 years of age (see **Pharmacokinetic properties** section).
There is no relevant use of AMGEVITA in children aged less than 2 years in this indication.

It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis.

Adolescent hidradenitis suppurativa (from 12 years of age, weighing at least 30 kg)
There are no clinical trials with AMGEVITA in adolescent patients with hidradenitis suppurativa (HS). The posology of AMGEVITA in these patients has been determined from pharmacokinetic modeling and simulation.

The recommended AMGEVITA dose in adolescent patients from 12 years of age weighing at least 30 kg with hidradenitis suppurativa is 80 mg at Week 0 followed by 40 mg every other week starting at Week 1 via subcutaneous injection.

AMGEVITA may be available in different strengths and/or presentations.

In adolescent patients with inadequate response to AMGEVITA 40 mg every other week, an increase in dosage to 40 mg every week or 80 mg every other week may be considered.

Antibiotics may be continued during treatment with AMGEVITA if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with AMGEVITA.

Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period.

Should treatment be interrupted, AMGEVITA may be re-introduced as appropriate.

The benefit and risk of continued long-term treatment should be periodically evaluated.

There is no relevant use of AMGEVITA in children aged less than 12 years in this indication.

Pediatric Ulcerative Colitis
The recommended dose of AMGEVITA for patients from 6 to 17 years of age with ulcerative colitis is based on body weight (**Table 10**). AMGEVITA is administered via subcutaneous injection. AMGEVITA may be available in different strengths and/or presentations.

Table 10. AMGEVITA Dose for Pediatric Ulcerative Colitis

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

* Pediatric patients who turn 18 years of age while on AMGEVITA should continue their prescribed maintenance dose.

Continued therapy beyond 8 weeks should be carefully considered in patients not showing signs of response within this time period.

There is no relevant use of AMGEVITA in children aged less than 6 years in this indication.

AMGEVITA may be available in different strengths and/or presentations depending on the individual treatment needs.

Preparation of AMGEVITA

AMGEVITA is intended for use under the guidance and supervision of a physician. Patients may self-inject AMGEVITA if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in injection technique. Sites for self-injection include 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 discoloration prior to administration, whenever solution and container permit.

AMGEVITA should not be mixed in the same syringe or vial with any other medicine. Any unused product or waste material should be disposed of in accordance with local requirements.

Paediatric Use
AMGEVITA has not been studied in children less than 2 years of age.

The safety and efficacy of AMGEVITA in paediatric patients for indications other than juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis), paediatric Crohn's disease, paediatric plaque psoriasis, paediatric uveitis, adolescent hidradenitis suppurativa and pediatric ulcerative colitis have not been established.

Geriatric Use
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. No overall differences in effectiveness were observed between these subjects and younger subjects. No dose

adjustment is needed for this population.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

In order to improve traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infections
Serious infections, due to bacterial, mycobacterial, invasive fungal (disseminated or extrapulmonary histoplasmosis, aspergillosis, coccidioidomycosis) viral, parasitic or other opportunistic infections have been reported in patients receiving TNF-blocking agents. Sepsis, rare cases of tuberculosis, candidiasis, listeriosis, Legionellosis and pneumocystis have also been reported with the use of TNF-antagonists, including adalimumab. Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicemia. Hospitalization 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 them to infections.

Treatment with AMGEVITA should not be initiated in patients with active infections including chronic or localized infections until infections are controlled. In patients who have been exposed to tuberculosis, and patients who have traveled in areas of high risk of tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, the risk and benefits of treatment with AMGEVITA should be considered prior to initiating therapy (see **Other Opportunistic Infections**).

As with other TNF-antagonists, 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 infections are controlled.
Physicians should exercise caution when considering the use of AMGEVITA in patients with a history of recurring infection or with underlying conditions, which may predispose patients to infections.

Tuberculosis
Tuberculosis including reactivation and new onset of tuberculosis, has been reported in patients receiving adalimumab. Reports included cases of pulmonary and extrapulmonary (i.e. disseminated).

Before initiation of therapy with AMGEVITA, all patients should be evaluated for both active and 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 tuberculosis infections should be initiated prior to therapy with AMGEVITA. When tuberculin skin testing is performed for latent tuberculosis 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 tuberculosis should be considered especially in patients who have immigrated from or traveled to countries with a high prevalence of tuberculosis or who had close contact with a person with active tuberculosis.
If active tuberculosis 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 in patients with several or significant risk factors for tuberculosis despite a negative test for tuberculosis and in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. The decision to initiate anti-tuberculosis therapy in these patients should only be made after taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy. If necessary, consultation should occur with a physician with expertise in the treatment of tuberculosis.

Anti-tuberculosis treatment of patients with latent tuberculosis infection reduces the risk of reactivation in patients receiving treatment with AMGEVITA. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with AMGEVITA. Also, active tuberculosis has developed in patients receiving AMGEVITA whose screening for latent tuberculosis infection was negative, and some patients who have been successfully treated for active tuberculosis have redeveloped active tuberculosis while being treated with TNF-blocking agents.

Patients receiving AMGEVITA should be monitored for signs and symptoms of active tuberculosis, particularly because tests for latent tuberculosis 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.

Patients should be instructed to seek medical advice if signs/symptoms suggestive of a tuberculosis infection (e.g. persistent cough, wasting/weight loss, low grade fever) occur during or after therapy with AMGEVITA.
[+]as permitted by local regulations.

Other Opportunistic Infections
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, dyspnea, and/or pulmonary infiltrates, or other serious systemic 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 the 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 TNF-blockers has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF-blocker therapy. Prescribers should exercise caution in prescribing TNF-blockers 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 or 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 treatment should be initiated.

Neurologic Events
TNF-antagonists, including adalimumab, have 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, and optic neuritis, and peripheral demyelinating disease, including Guillain 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 central demyelinating disorders.

Malignancies
In the controlled portions of clinical trials of TNF-antagonist, 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 conclusions. Furthermore, there is an increased background lymphoma risk in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates the risk estimation. During the long-term open label trials with adalimumab, the overall rate of malignancies was similar to what would be expected for an age, gender and race matched general population. With the current knowledge, a possible risk for the development of lymphomas, or other malignancies in patients treated with a TNF-antagonist cannot be excluded.

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 postmarketing reports.

Very rare postmarketing 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-mercaptopurine use for inflammatory bowel disease. The potential risk with the combination of azathioprine or 6-mercaptopurine and AMGEVITA should be carefully considered. The causal association of HSTCL with adalimumab is not clear.

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

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.

Cases of acute and chronic leukemia have been reported in association with postmarketing 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 leukemia, even in the absence of TNF-blocking therapy.

With current data 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.

Allergic
Serious allergic reactions associated with adalimumab were rare 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.

Hematologic Events
Rare reports of pancytopenia including aplastic anemia have been reported with TNF-blocking agents. Adverse events of the hematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been reported with adalimumab. The causal relationship of these reports to adalimumab remains unclear. 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 hematologic abnormalities.

Concurrent administration of biologic 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 adalimumab and anakinra is not recommended.

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

Immunosuppression
In a study of 64 patients with RA 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- and B-cells and NK-cells, monocyte/macrophages, and neutrophils.

Vaccinations
In a randomized, 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 pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating AMGEVITA therapy.

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

Administration of live vaccines to infants exposed to adalimumab *in utero* is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

Congestive Heart Failure
Adalimumab has not been formally studied in patients with congestive heart failure (CHF), however, in clinical studies with another TNF-antagonist, a higher rate of serious CHF-related adverse events including worsening CHF and new onset CHF have been reported. Cases of worsening CHF have also been reported in patients receiving adalimumab. Physicians should exercise caution when using AMGEVITA in patients who have heart failure and monitor them carefully.

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 (see **Adverse Effects, Autoantibodies**).

Geriatric Use
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 a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

DRUG INTERACTIONS

When adalimumab was administered to 21 RA patients on stable MTX therapy, there were no statistically significant changes in the serum MTX concentration profiles. In contrast, after single and multiple dosing, MTX reduced adalimumab apparent clearances by 29% and 44% respectively. The data do not suggest the need for dose adjustment of either adalimumab or MTX.

Interactions between adalimumab and drugs other than MTX have not been evaluated in formal pharmacokinetic studies. In clinical trials, no interactions have been observed when adalimumab was administered with commonly used DMARDs (sulfasalazine, hydrochloroquine, leflunomide and parenteral gold), glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs or analgesics.

Drug/Laboratory Test Interaction
There is no known interference between adalimumab and laboratory tests.

PREGNANCY AND LACTATION

Pregnancy
An embryo-fetal perinatal developmental toxicity study has been performed in cynomolgus monkeys at dosages up to 100 mg/kg (373 times human AUC when given 40 mg SC) and has revealed no evidence of harm to the fetuses due to adalimumab.

In a prospective cohort pregnancy exposure registry, 257 women with RA or CD treated with adalimumab at least during the first trimester and 120 women with RA or CD not treated with adalimumab were enrolled.

There were no significant differences in the overall rates for the primary endpoint of major birth defects (adjusted Odds Ratio 0.84, 95% Confidence Interval (CI) 0.34, 2.05) as well as the secondary endpoints which included minor birth defects, spontaneous abortion, preterm delivery, low birth weight, and serious or opportunistic infections. No stillbirths or malignancies were reported.

Although the registry has methodological limitations, including small sample size and non-randomized study design, the data show no increased risk of adverse pregnancy outcomes in women with RA or CD treated with adalimumab in comparison to women with RA or CD not treated with adalimumab. In addition, data from postmarketing surveillance does not establish the presence of a drug-associated risk.

Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection. Administration of live vaccines to infants exposed to adalimumab *in utero* is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

Labor and Delivery
There are no known effects of adalimumab on labor or delivery.

Nursing Mothers

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 ingested immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability, systemic effects of adalimumab in a breast fed infant are unlikely. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for adalimumab and any potential adverse effects on the breastfed child from adalimumab or from the underlying maternal condition.

ADVERSE EFFECTS

Rheumatoid Arthritis, Juvenile Idiopathic Arthritis (Polyarticular Juvenile Idiopathic Arthritis and Enthesitis-Related Arthritis), Psoriatic Arthritis, Axial Spondyloarthritis (Ankylosing Spondylitis, and Non-radiographic Axial Spondyloarthritis), Crohn's Disease, Ulcerative Colitis, Psoriasis, Hidradenitis Suppurativa and Uveitis clinical trials

Adalimumab was studied in 9506 patients in pivotal controlled and open label trials for up to 60 months or more. These trials included rheumatoid arthritis patients with short term and long-term disease, juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis) as well as psoriatic arthritis, axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis), Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa and uveitis patients.

The controlled pivotal studies involved 6089 patients receiving adalimumab and 3801 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.

Adverse events at least possibly causally-related to adalimumab, both clinical and laboratory, are displayed by system organ class and frequency (very common ≥1/10; common ≥1/100 to <1/10; uncommon ≥1/1000 to <1/100; rare ≥ 1/10,000 to <1/1000) in **Table 11** below. 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 **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS** and **ADVERSE EFFECTS**.

Table 11. Adverse Reactions in Clinical Studies

System Organ Class	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, necrotizing 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

System Organ Class	Frequency	Adverse Reaction
		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
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 neoplasms (including breast cancer, lung neoplasm and thyroid neoplasm), melanoma**
Blood and the lymphatic system disorders*	Very Common	leucopenia (including neutropenia and agranulocytosis), anemia
	Common	thrombocytopenia, leucocytosis
	Uncommon	idiopathic thrombocytopenic purpura
	Rare	pancytopenia
Immune system disorders*	Common	hypersensitivity, allergies (including seasonal allergy)
Metabolism and nutrition disorders	Very Common	lipids increased
	Common	hypokalemia, uric acid increased, blood sodium abnormal, hypocalcemia, hyperglycemia, hypophosphotemia, blood potassium increased, dehydration
Psychiatric disorders	Common	mood alterations (including depression), anxiety, insomnia
Nervous system disorders*	Very Common	headache
	Common	paraesthesias (including hypoasthesia) 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	arrhythmia, 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
	Uncommon	chronic obstructive pulmonary disease, interstitial lung disease, pneumonitis
Gastrointestinal disorders	Very Common	abdominal pain, nausea and vomiting
	Common	GI hemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome
	Uncommon	pancreatitis, dysphagia, face edema
Hepato-biliary disorders*	Very Common	liver enzymes elevated
	Uncommon	cholecystitis and cholelithiasis, bilirubin increased, hepatic steatosis

System Organ Class	Frequency	Adverse Reaction
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
Musculoskeletal and connective tissue disorders	Very Common	musculoskeletal pain
	Common	muscle spasms (including blood creatinine 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, edema
	Uncommon	inflammation
Investigations	Common	coagulation and bleeding disorders (including activated partial thromboplastin time prolonged), autoantibody tests positive (including double stranded DNA antibody), blood lactate dehydrogenase increased
	Not known	Weight increased[1)]
Injury, poisoning and procedural complications*	Common	impaired healing

* Further information found in CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and ADVERSE EFFECTS
** Includes open label extension studies

[1)] The mean weight change from baseline for adalimumab ranged from 0.3 kg to 1.0 kg across adult indications compared to (minus) -0.4 kg to 0.4 kg for placebo over a treatment period of 4-6 months. Weight increase of 5-6 kg has also been observed in long-term extension studies with mean exposures of approximately 1-2 years without control group, particularly in patients with Crohn's disease and Ulcerative colitis. The mechanism behind this effect is unclear but could be associated with the anti-inflammatory effect of adalimumab.

Hidradenitis Suppurativa
The safety profile for patients with hidradenitis suppurativa treated with adalimumab weekly was consistent with the known safety profile of adalimumab.

Uveitis
The safety profile for patients with non-infectious uveitis treated with adalimumab was consistent with the known safety profile of adalimumab.

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

Injection Site Reactions
In the pivotal controlled trials in adults and children, 12.9% of patients treated with adalimumab developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 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 pediatric studies with adalimumab, serious infections (including fatal infections, which occurred rarely) have been reported, which include reports of tuberculosis (including miliary and extrapulmonary locations) and invasive opportunistic infections (e.g. disseminated histoplasmosis, pneumocystis carinii pneumonia, aspergillosis and listeriosis).

Malignancies and Lymphoproliferative Disorders
No malignancies were observed in 249 pediatric patients with an exposure of 655.6 patient-years during adalimumab trials in patients with juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis).

In addition, no malignancies were observed in 192 pediatric patients with an exposure of 498.1 patient years during a adalimumab trial in pediatric patients with Crohn's disease.

No malignancies were observed in 93 pediatric patients with an exposure of 65.3 patient years during adalimumab trial in pediatric patients with ulcerative colitis.

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, axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis), 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 1000 patient-years among 5291 adalimumab-treated patients versus a rate of 6.3 (3.4, 11.8) per 1000 patient-years among 3444 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 1000 patient-years among adalimumab-treated patients and 3.2 (1.3, 7.6) per 1000 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 1000 patient-years among adalimumab-treated patients and 0.6 (0.1, 4.5) per 1000 patient-years among control patients.

The rate (95% confidence interval) of lymphomas was 0.7 (0.2, 2.7) per 1000 patient-years among adalimumab-treated patients and 0.6 (0.1, 4.5) per 1000 patient-years among control patients.

The observed rate of malignancies, other than lymphoma and non-melanoma skin cancers, is approximately 8.5 per 1000 patient years in the controlled portion of clinical trials and in ongoing and completed open label extension studies. The observed rate of non-melanoma skin cancers is approximately 9.6 per 1000 patient years, and the observed rate of lymphomas is approximately 1.3 per 1000 patient years. The median duration of these studies is approximately 3.3 years and included 6427 patients who were on adalimumab for at least 1 year or who developed a malignancy within a year of starting therapy, representing over 26439.6 patient years of therapy.

Autoantibodies
Patients had serum samples tested for autoantibodies at multiple time points in RA 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 titers reported positive titers at week 24.

Two patients out of 3989 treated with adalimumab in all RA, PsA and AS studies developed clinical signs suggestive of new onset lupus-like syndrome. The patients 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 diseases 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 immunosuppresants (e.g. MTX, corticosteroids). Some of these patients required hospitalization. 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 adalimumab 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 × 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 × 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 × ULN occurred in 1.5% of adalimumab-treated patients and 1.0% of control-treated patients. In controlled Phase 3 trials of adalimumab (initial dose of 80 mg then 40 mg every other week), in patients treated with plaque psoriasis with a control period duration ranging from 12 to 24 weeks. ALT elevations ≥ 3 × ULN occurred in 1.8% of adalimumab-treated patients and 1.8% 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 × ULN occurred in 0.3% of adalimumab-treated patients and 0.6% of control-treated patients.

In controlled Phase 3 trials of adalimumab (40 mg every other week), in patients with axial spondyloarthriris (ankylosing spondylitis and non-radiographic axial spondyloarthritis) with a control period of 12 to 24 weeks, ALT elevations ≥ 3 × 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 × 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 × 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 pediatric 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 × 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 PYs and 119.8 PYs in Humira-treated and control-treated patients, respectively, ALT elevations ≥3 × ULN occurred in 2.4% of Humira-treated patients and 2.4% of control-treated patients.

In the controlled Phase 3 trial of adalimumab in patients with pediatric ulcerative colitis (N = 93) which evaluated efficacy and safety of a maintenance dose of 0.6 mg/kg (maximum of 40 mg) every other week (N = 31) and a maintenance dose of 0.6 mg/kg (maximum of 40 mg) every week (N = 32), following body weight adjusted induction dosing of 2.4 mg/kg (maximum of 160 mg) at Week 0 and Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2 (N = 63), or an induction dose of 2.4 mg/kg (maximum of 160 mg) at Week 0, placebo at Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2 (N = 30), ALT elevations ≥ 3 × ULN occurred in 1.1% (1/93) of patients.

No ALT elevations ≥ 3 × ULN occurred in the Phase 3 trial of HUMIRA® 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 postmarketing 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-Mercaptopurine
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 Postmarketing 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 adalimumab exposure.

Table 12. Additional Adverse Reactions from Postmarketing Surveillance or Phase IV Clinical Trials

System Organ Class	Adverse Reaction
Infections and infestations	Diverticulitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	Hepatosplenic T-cell lymphoma, leukemia, Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin), Kaposi's sarcoma**
Immune system disorders*	Anaphylaxis, sarcoidosis
Nervous system disorders*	Demyelinating disorders (e.g. optic neuritis, Guillain-Barré syndrome), cerebrovascular accident
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism, pleural effusion, pulmonary fibrosis
Gastrointestinal disorders*	Intestinal perforation
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, lichenoid skin reactions**
Musculoskeletal and connective tissue disorders	Lupus-like syndrome
Cardiac disorders	Myocardial infarction
General disorders and administration site conditions	Pyrexia

* Further information is found elsewhere in CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and ADVERSE EFFECTS.
** occurring in patients receiving a TNF-antagonist including adalimumab

Comparability of AMGEVITA with HUMIRA®
Both the AMGEVITA Rheumatoid Arthritis (RA) and Psoriasis (Ps) Studies showed clinical equivalence between AMGEVITA and HUMIRA® (see **CLINICAL TRIALS**).

Table 13 and **Table 14** below show comparative data for adverse events between AMGEVITA and HUMIRA® from the RA and Ps studies, respectively.

The data in **Table 13** reflect exposure to AMGEVITA in 264 subjects and HUMIRA® in 262 subjects in the RA Study treated at the recommended dose and schedule for a median of 480 mg doses (see **CLINICAL TRIALS**). 52.3% of all subjects had at least 1 treatment-emergent adverse event during the study, and similar proportions were reported in each treatment group (50.0% in ABP 501 group and 54.6% in adalimumab group). The overall safety profile of AMGEVITA is similar to that of HUMIRA®.

Table 13. Adverse Events Reported by ≥ 2% of Patients Treated With AMGEVITA and HUMIRA® in RA Study

Adverse Events (Preferred Term)	AMGEVITA (n = 264)	HUMIRA® (n = 262)
Nasopharyngitis	6.4%	7.3%
Headache	4.5%	4.2%
Arthralgia	3.0%	3.4%
Cough	2.7%	3.1%
Upper respiratory tract infection	1.5%	3.8%
Hypertension	2.3%	1.9%
Bronchitis	2.3%	1.9%
Back pain	1.9%	2.3%
Alanine aminotransferase increased	2.7%	1.1%
Diarrhoea	2.3%	1.5%
Rheumatoid arthritis	1.5%	2.3%
Pharyngitis	0.8%	2.7%

The data in **Table 14** reflect exposure to AMGEVITA/AMGEVITA in 152 subjects, HUMIRA®/HUMIRA® in 79 subjects, and HUMIRA®/AMGEVITA in 77 subjects in the Ps study treated at the recommended dose and schedule for a median of 1040 mg doses (see **CLINICAL TRIALS)**. 82.1% of subjects, from baseline to end of study, had at least 1 treatment emergent adverse event and similar proportions were reported across treatment groups (86.2% of subjects in Treatment Group A (AMGEVITA/AMGEVITA), 78.5% of subjects in Treatment Group B1 (HUMIRA®/HUMIRA®), and 85.7% of subjects in Treatment Group B2 (HUMIRA®/AMGEVITA). The overall safety profiles of the AMGEVITA/AMGEVITA, HUMIRA®/HUMIRA® and HUMIRA®/AMGEVITA groups were similar.

Table 14. Adverse Events Reported by ≥ 2% of Patients Treated with AMGEVITA, Adalimumab or Adalimumab switched to AMGEVITA in Ps Study

Adverse Events (Preferred Term)	AMGEVITA/ AMGEVITA (n = 152)	HUMIRA®/HUMIRA® (n = 79)	HUMIRA®/ AMGEVITA[a] (n = 77)
Nasopharyngitis	27.0%	27.8%	32.5%
Headache	8.6%	17.7%	9.1%
Upper respiratory tract infection	11.8%	11.4%	10.4%
Arthralgia	5.9%	10.1%	6.5%
Psoriasis	7.2%	6.3%	5.2%
Diarrhea	3.3%	6.3%	13.0%
Back pain	6.6%	6.3%	2.6%
Oropharyngeal pain	2.6%	7.6%	3.9%
Pruritus	2.6%	2.5%	9.1%
Hypertension	5.3%	6.3%	0.0%
Rhinitis	2.6%	5.1%	3.9%
Toothache	3.3%	2.5%	5.2%

	AMGEVITA/ AMGEVITA (n = 152)	HUMIRA®/HUMIRA® (n = 79)	HUMIRA®/ AMGEVITA[a] (n = 77)
Gastroenteritis	3.9%	2.5%	2.6%
Psoriatic arthropathy	2.6%	0.0%	2.6%
Sinusitis	2.6%	3.8%	2.6%
Abdominal pain	1.3%	2.5%	3.9%
Cough	2.0%	2.5%	3.9%
Pain in extremity	2.6%	3.8%	1.3%
Nausea	2.0%	1.3%	3.9%
Conjunctivitis	0.7%	3.8%	2.6%
Bronchitis	0.7%	0.0%	5.2%
Gamma-glutamyltransferase increased	3.9%	1.3%	0.0%
Pharyngitis	2.6%	2.5%	1.3%
Injection site pain	0.0%	5.1%	2.6%
Tonsillitis	2.0%	2.5%	0.0%
Dyspnoea	1.3%	1.3%	2.6%
Contusion	0.7%	0.0%	6.5%
Dermatitis contact	3.9%	0.0%	0.0%
Influenza	1.3%	1.3%	3.9%
Alanine aminotransferase increased	3.3%	0.0%	1.3%
Myalgia	2.6%	2.5%	0.0%
Oral herpes	1.3%	1.3%	2.6%
Blood pressure increased	1.3%	3.8%	0.0%
Musculoskeletal pain	0.7%	1.3%	2.6%
Dental caries	2.0%	2.5%	0.0%
Gastroeosophageal reflux disease	0.7%	1.3%	3.9%
Injection site reaction	1.3%	1.3%	2.6%
Seasonal allergy	2.0%	0.0%	2.6%
Depression	1.3%	2.5%	0.0%
Muscle spasm	2.6%	0.0%	0.0%
Urinary tract infection	1.3%	0.0%	2.6%
Dyspepsia	0.7%	2.5%	1.3%
Ligament strain	1.3%	2.5%	0.0%
Skin papilloma	0.7%	1.3%	2.6%
Injection site swelling	0.0%	1.3%	2.6%
Migraine	0.0%	2.5%	1.3%
Pulpitis dental	0.7%	0.0%	2.6%
Excoriation	0.7%	0.0%	2.6%
Intertrigo	0.7%	0.0%	2.6%
Spinal pain	0.0%	1.3%	2.6%
Thermal burn	0.7%	0.0%	2.6%

	AMGEVITA/ AMGEVITA (n = 152)	HUMIRA®/HUMIRA® (n = 79)	HUMIRA®/ AMGEVITA[a] (n = 77)
Tinea pedis	0.7%	2.5%	0.0%
Decreased appetite	0.0%	0.0%	2.6%
Neutropenia	0.0%	0.0%	2.6%
Cystitis	0.0%	2.5%	0.0%
Diffuse alopecia	0.0%	0.0%	2.6%
Hypercholesterolaemia	0.0%	0.0%	2.6%
Rhinnorrhoea	0.0%	0.0%	2.6%
Urticaria	0.0%	0.0%	2.6%

[a] This group reflects data for subjects exposed to both HUMIRA® and AMGEVITA before and after the transition of HUMIRA® subjects to AMGEVITA

OVERDOSAGE

The maximum tolerated dose of adalimumab has not been established in humans. No dose-limiting toxicities have been observed during clinical trials with adalimumab. Multiple doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. 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.

LIST OF EXCIPIENTS

L-lactic acid
Sucrose
Polysorbate 80
Sodium hydroxide (for pH adjustment)
Water for injection

INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

STORAGE

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Keep AMGEVITA in the outer carton in order to protect from light.
The pre-filled syringe or pre-filled autoinjector may be stored at temperatures up to a maximum of 25°C for a period of up to 14 days. The pre-filled syringe or pre-filled autoinjector must be protected from light, and discarded if not used within the 14-day period.

HOW SUPPLIED

AMGEVITA 40 mg/0.4 ml solution for injection in pre-filled autoinjector
0.4 ml solution for injection in pre-filled autoinjector for patient use containing a pre-filled syringe (type I glass). The autoinjector is a single use, disposable, handheld, mechanical injection device.

Packs sizes of one, two, four and six pre-filled autoinjectors.
Not all pack sizes may be marketed.

Product Registration Holder

Amgen Biopharmaceuticals Malaysia Sdn Bhd
Common Ground, 1 Powerhouse,
Horizon Penthouse, No. 1,
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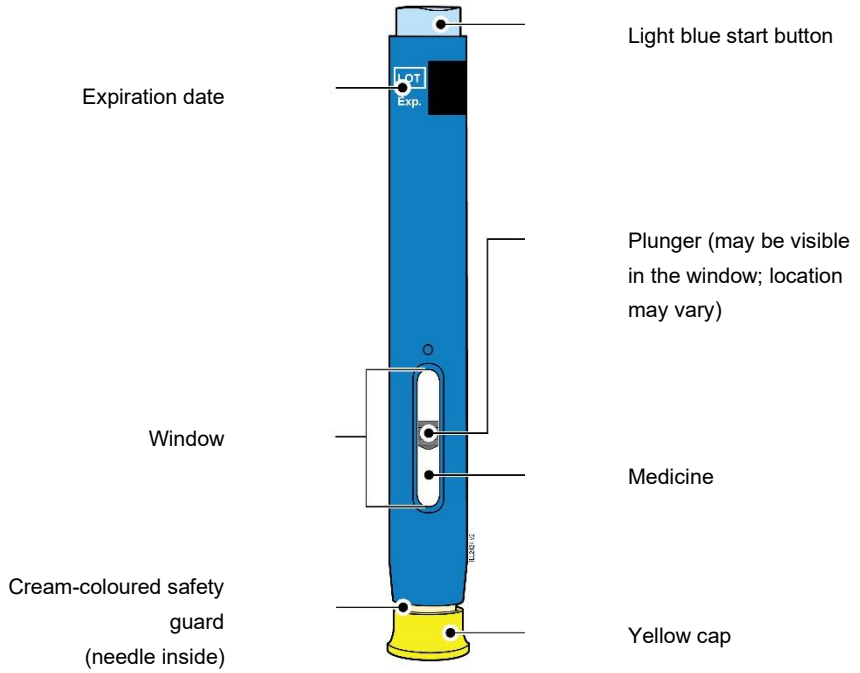
HUMIRA® is a registered trademark owned or licensed by AbbVie Biotechnology Ltd.

MYAMGHCFPI01

INSTRUCTIONS FOR USE 40 mg / 0.4 ml

Getting to know your SureClick pre-filled autoinjector



1	**Important information you need to know before injecting AMGEVITA**

Using your AMGEVITA SureClick pre-filled autoinjector:

- It is important that you do not try to give yourself the injection until you have fully read and understood these instructions for use and unless you have received training from your doctor or healthcare provider.
- **Do not** use the pre-filled autoinjector if the carton is damaged or seal is broken.
- **Do not** use the pre-filled autoinjector after the expiration date on the label.
- **Do not** shake the pre-filled autoinjector.
- **Do not** remove the yellow cap from the pre-filled autoinjector until you are ready to inject.
- **Do not** use the pre-filled autoinjector if it has been frozen.
- **Do not** use the pre-filled autoinjector if it has been dropped on a hard surface. Part of the pre-filled autoinjector may be broken even if you cannot see the break. Use a new pre-filled autoinjector and call your doctor or healthcare provider.

Important: Keep the pre-filled autoinjector and sharps disposal container out of the sight and reach of children.

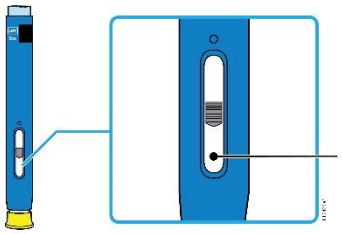
2	**Preparing to inject AMGEVITA**

2a	**Wait 30 minutes for the pre-filled autoinjector to reach room temperature.**

WAIT
30
minutes

- Remove the number of pre-filled autoinjectors you need for your injection and put any unused pre-filled autoinjectors back into the refrigerator.
- Let the pre-filled autoinjector warm up naturally.
- **Do not** heat with hot water, a microwave, or direct sunlight.
- **Do not** shake the pre-filled autoinjector at any time.
- **Do not** place pre-filled autoinjector back in refrigerator after it has reached room temperature
- Using the pre-filled autoinjector at room temperature allows for a more comfortable injection**.**

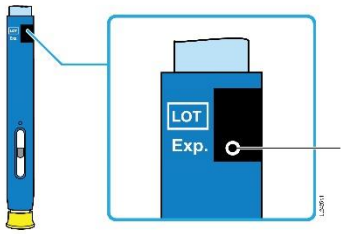
2b	**Inspect the medicine. It should be clear and colourless to slightly yellow.**



Medicine

- It is okay to see air bubbles.
- **Do not** use if the medicine is cloudy, discoloured or has flakes.

2c	**Check the expiration date (EXP.) and inspect the pre-filled autoinjector for damage.**



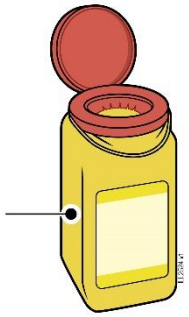
Expiry date

- **Do not** use if the expiration date has passed.
- **Do not** use the pre-filled autoinjector if:
  - The yellow cap is missing or loose.
  - It has cracks or broken parts.
  - It has been dropped on a hard surface.
- Make sure you have the right medicine and dose.

Important: If the medicine is cloudy, discoloured, or contains flakes, call your doctor or healthcare provider.

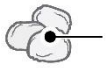
3	**Getting ready for your injection**
3a	**Gather and place items for your injection on a clean, well-lit surface.**

Sharps disposal container



Alcohol wipe

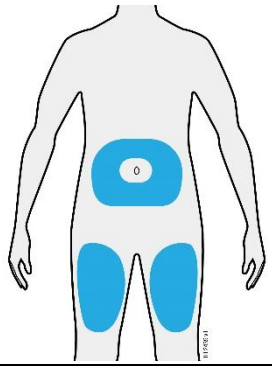
Plaster



Cotton ball or gauze pad

- AMGEVITA pre-filled autoinjector (room temperature)
- Sharps disposal container
- Alcohol wipe
- Plaster
- Cotton ball or gauze pad

3b	**Inject in one of these locations.**



- Inject in your thigh or belly (except 5 cm around your belly button).
- Choose a different site for each injection
- Wash your hands thoroughly with soap and water.
- Clean injection site with an alcohol wipe.
- Let your skin dry on its own.
- **Do not** touch this area again before injecting.

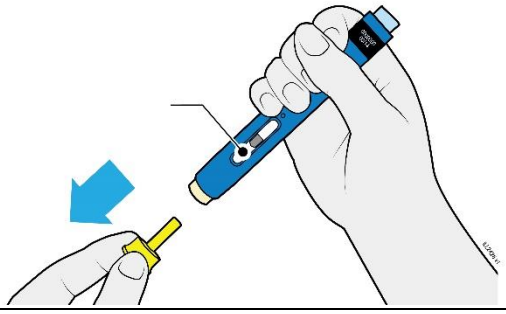
Important: Avoid areas with scars, stretch marks, or where skin is tender, bruised, red or hard.

4	**Injecting AMGEVITA**

Important: Only remove the yellow cap when you can inject right away (within 5 minutes) because the medicine can dry out.

4a	**Hold the pre-filled autoinjector so you can see the window. Pull the yellow cap straight off. You may need to pull hard.**

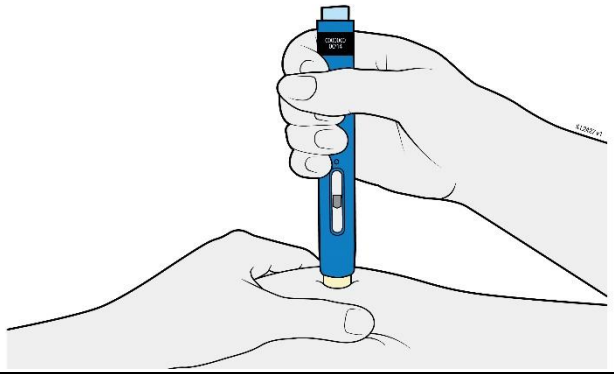
Window should be visible



- **Do not** twist, bend or wiggle the yellow cap to pull off.
- **Never** put the needle cap back on. It may damage the needle.
- **Do not** put your finger inside the cream-coloured safety guard.
- It is normal to see a drop of medicine at the end of the needle or cream-coloured safety guard.

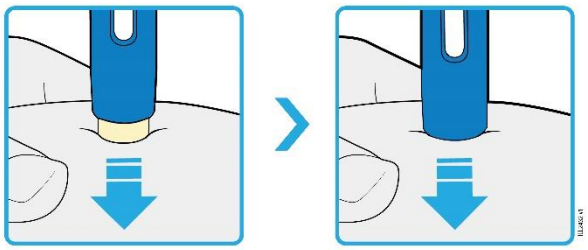
4b	**Pinch the skin to create a firm surface at the injection site. Place the cream-coloured safety guard straight against the skin.**

PINCH



- Keep the skin **pinched** until the injection is finished.
- Make sure you can see the window.
- Make sure the autoinjector is positioned straight on the injection site (at a 90 degree angle).

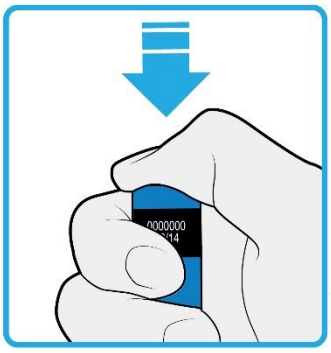
PUSH
and hold against skin



4c	**Firmly push down until the cream-coloured safety guard stops moving. Hold down; do not lift.**

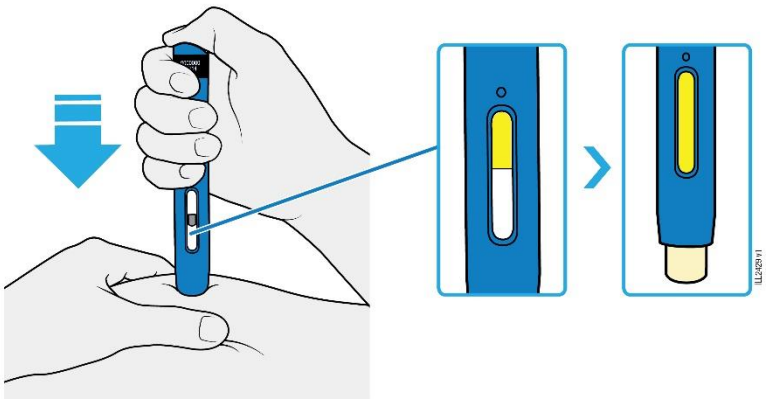
- The cream-coloured safety guard pushes in and unlocks the light blue start button

PRESS
light blue start button



4d	**Keep pushing down firmly and press the light blue start button to start the injection.**
•	You may hear or feel a click.
•	The window starts to turn yellow.
•	It is okay to let go of the light blue button.

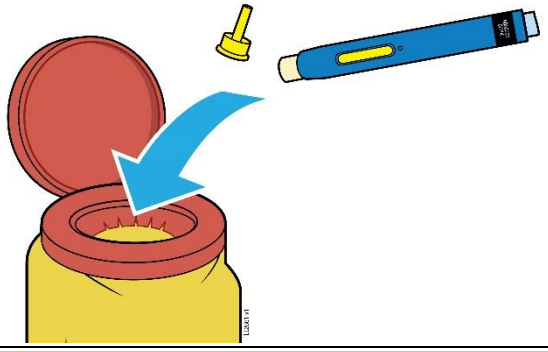
WATCH CONFIRM
window will turn fully yellow



4e	**Keep pushing down. When the window is fully yellow, the injection is complete**
•	The injection may take up to **10** seconds to complete.
•	You may hear or feel a click.
•	Lift the pre-filled autoinjector away from your skin.
•	The cream-coloured safety guard locks around the needle.

Important: If the window has not turned yellow, or it looks like the medicine is still coming out, you have not received a full dose. Call your doctor or healthcare provider immediately.

5	Disposing and finishing AMGEVITA



Important: Do not throw away the pre-filled autoinjector into your household trash.

5a	Place the used pre-filled autoinjector and yellow cap in the sharps container
•	**Do not** re-use the pre-filled autoinjector
•	**Do not** touch the cream-coloured safety guard
5b	**Check injection site.**
•	**Do not** rub the injection site.
•	If there is blood, press a cotton ball or gauze pad on your injection site. Apply a plaster if necessary.

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