fistula count relative to Baseline). Reduction in HS-related skin pain was assessed using a Numeric Rating Scale in patients who entered the study with an initial baseline score of 3 or greater on a 11 point scale.

At Week 12, a significantly higher proportion of patients treated with Humira versus placebo achieved HiSCR. At Week 12, a significantly higher proportion of patients in Study HS-II experienced a clinically relevant decrease in HS-related skin pain (see Table 12). Patients treated with Humira had significantly reduced risk of disease flare during the initial 12 weeks of treatment.

Table 12: Efficacy Results at 12 Weeks, HS Studies I and II

	HS Study I		HS Study II	
	Placebo	**Humira 40 mg Weekly**	**Placebo**	**Humira 40 mg Weekly**
Hidradenitis Suppurativa Clinical Response (HiSCR)[a]	N = 154 40 (26.0%)	N = 153 64 (41.8%) *	N=163 45 (27.6%)	N=163 96 (58.9%) ***
≥30% Reduction in Skin Pain[b]	N = 109 27 (24.8%)	N = 122 34 (27.9%)	N=111 23 (20.7%)	N=105 48 (45.7%) ***

* $P < 0.05$, *** $P < 0.001$, Humira versus placebo

[a] Among all randomised patients.

[b] Among patients with baseline HS-related skin pain assessment ≥ 3, based on Numeric Rating Scale 0 – 10; 0 = no skin pain, 10 = skin pain as bad as you can imagine.

Treatment with Humira 40 mg every week significantly reduced the risk of worsening of abscesses and draining fistulas. Approximately twice the proportion of patients in the placebo group in the first 12 weeks of Studies HS-I and HS-II, compared with those in the Humira group experienced worsening of abscesses (23.0% vs 11.4%, respectively) and draining fistulas (30.0% vs 13.9%, respectively).

Greater improvements at Week 12 from baseline compared to placebo were demonstrated in skin-specific health-related quality of life, as measured by the Dermatology Life Quality Index (DLQI; Studies HS-I and HS-II), patient global satisfaction with medication treatment as measured by the Treatment Satisfaction Questionnaire - medication (TSQM; Studies HS-I and HS-II), and physical health as measured by the physical component summary score of the SF-36 (Study HS-I).

In patients with at least a partial response to Humira 40 mg weekly at Week 12, the HiSCR rate at Week 36 was higher in patients who continued weekly Humira than in patients in whom dosing frequency was reduced to every other week, or in whom treatment was withdrawn (see Table 13).

Table 13: Proportion of Patients[a] Achieving HiSCR[b] at Weeks 24 and 36 After Treatment Reassignment from Weekly Humira at Week 12

	Placebo (treatment withdrawal) N = 73	Humira 40 mg every other week N = 70	Humira 40 mg weekly N = 70
Week 24	24 (32.9%)	36 (51.4%)	40 (57.1%)
Week 36	22 (30.1%)	28 (40.0%)	39 (55.7%)

[a] Patients with at least a partial response to Humira 40 mg weekly after 12 weeks of treatment.

[b] Patients meeting protocol-specified criteria for loss of response or no improvement were required to discontinue from the studies and were counted as nonresponders.

Among patients who were at least partial responders at Week 12, and who received continuous weekly Humira therapy, the HiSCR rate at Week 48 was 68.3% and at Week 96 was 65.1%. Longer term treatment with Humira 40 mg weekly for 96 weeks identified no new safety findings.

Among patients whose Humira treatment was withdrawn at Week 12 in Studies HS-I and HS-II, the HiSCR rate 12 weeks after re-introduction of Humira 40 mg weekly returned to levels similar to that observed before withdrawal (56.0 %).

Crohn's disease

The safety and efficacy of Humira were assessed in over 1500 patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 450) in randomised, double-blind, placebo-controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted and 80% of patients continued to receive at least one of these medications.

Induction of clinical remission (defined as CDAI < 150) was evaluated in two studies, CD Study I (CLASSIC I) and CD Study II (GAIN). In CD Study I, 299 TNF-antagonist naive patients were randomised to one of four treatment groups; placebo at Weeks 0 and 2, 160 mg Humira at Week 0 and 80 mg at Week 2, 80 mg at Week 0 and 40 mg at Week 2, and 40 mg at Week 0 and 20 mg at Week 2. In CD Study II, 325 patients who had lost response or were intolerant to infliximab were randomised to receive either 160 mg Humira at Week 0 and 80 mg at Week 2 or placebo at Weeks 0 and 2. The primary non-responders were excluded from the studies and therefore these patients were not further evaluated.

Maintenance of clinical remission was evaluated in CD study III (CHARM). In CD Study III, 854 patients received open-label 80 mg at Week 0 and 40 mg at Week 2. At Week 4 patients were randomised to 40 mg every other week, 40 mg every week, or placebo with a total study duration of 56 weeks. Patients in clinical response (decrease in CDAI ≥ 70) at Week 4 were stratified and analysed separately from those not in clinical response at Week 4. Corticosteroid taper was permitted after Week 8.

CD study I and CD study II induction of remission and response rates are presented in Table 14.

Table 14
Induction of Clinical Remission and Response
(Percent of Patients)

	CD Study I: Infliximab Naive Patients			CD Study II: Infliximab Experienced Patients	
	Placebo N=74	Humira 80/40 mg N = 75	Humira 160/80 mg N=76	Placebo N=166	Humira 160/80 mg N=159
Week 4					
Clinical remission	12%	24%	36%*	7%	21%*
Clinical response (CR-100)	24%	37%	49%**	25%	38%**

All p-values are pairwise comparisons of proportions for Humira *versus* placebo
* $p < 0.001$
** $p < 0.01$

Similar remission rates were observed for the 160/80 mg and 80/40 mg induction regimens by Week 8 and adverse events were more frequently noted in the 160/80 mg group.

In CD Study III, at Week 4, 58% (499/854) of patients were in clinical response and were assessed in the primary analysis. Of those in clinical response at Week 4, 48% had been previously exposed to other TNF-antagonists. Maintenance of remission and response rates are presented in Table 15. Clinical remission results remained relatively constant irrespective of previous TNF-antagonist exposure.

Disease-related hospitalisations and surgeries were statistically significantly reduced with adalimumab compared with placebo at Week 56.

Table 15
Maintenance of Clinical Remission and Response
(Percent of Patients)

	Placebo	40 mg Humira every other week	40 mg Humira every week
Week 26	**N=170**	**N=172**	**N=157**
Clinical remission	17%	40%*	47%*
Clinical response (CR-100)	27%	52%*	52%*
Patients in steroid-free remission for >=90 days[a]	3% (2/66)	19% (11/58)**	15% (11/74)**
Week 56	**N=170**	**N=172**	**N=157**
Clinical remission	12%	36%*	41%*
Clinical response (CR-100)	17%	41%*	48%*
Patients in steroid-free remission for > = 90 days[a]	5% (3/66)	29% (17/58)*	20% (15/74)**

* $p < 0.001$ for Humira *versus* placebo pairwise comparisons of proportions
** $p < 0.02$ for Humira *versus* placebo pairwise comparisons of proportions
[a] Of those receiving corticosteroids at baseline

Among patients who were not in response at Week 4, 43% of Humira maintenance patients responded by Week 12 compared to 30% of placebo maintenance patients. These results suggest that some patients who have not responded by Week 4 benefit from continued maintenance therapy through Week 12. Therapy continued beyond 12 weeks did not result in significantly more responses (see section 4.2).

117/276 patients from CD study I and 272/777 patients from CD studies II and III were followed through at least 3 years of open-label adalimumab therapy. 88 and 189 patients, respectively, continued to be in clinical remission. Clinical response (CR-100) was maintained in 102 and 233 patients, respectively.

Quality of life

In CD Study I and CD Study II, statistically significant improvement in the disease-specific inflammatory bowel disease questionnaire (IBDQ) total score was achieved at Week 4 in patients randomised to Humira 80/40 mg and 160/80 mg compared to placebo and was seen at Weeks 26 and 56 in CD Study III as well among the adalimumab treatment groups compared to the placebo group.

Ulcerative colitis

The safety and efficacy of multiple doses of Humira were assessed in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 with endoscopy subscore of 2 to 3) in randomised, double-blind, placebo-controlled studies.

In study UC-I, 390 TNF-antagonist naïve patients were randomised to receive either placebo at Weeks 0 and 2, 160 mg Humira at Week 0 followed by 80 mg at Week 2, or 80 mg Humira at Week 0 followed by 40 mg at Week 2. After Week 2, patients in both adalimumab arms received 40 mg eow. Clinical remission (defined as Mayo score ≤ 2 with no subscore > 1) was assessed at Week 8.

In study UC-II, 248 patients received 160 mg of Humira at Week 0, 80 mg at Week 2 and 40 mg eow thereafter, and 246 patients received placebo. Clinical results were assessed for induction of remission at Week 8 and for maintenance of remission at Week 52.

Patients induced with 160/80 mg Humira achieved clinical remission versus placebo at Week 8 in statistically significantly greater percentages in study UC-I (18% vs. 9% respectively, p=0.031) and study UC-II (17% vs. 9% respectively, p=0.019). In study UC-II, among those treated with Humira who were in remission at Week 8, 21/41 (51%) were in remission at Week 52.

Results from the overall UC-II study population are shown in Table 16.

Table 16
Response, Remission and Mucosal Healing in Study UC-II
(Percent of Patients)

	Placebo	**Humira 40 mg eow**
Week 52	**N=246**	**N=248**
Clinical Response	18%	30%*
Clinical Remission	9%	17%*
Mucosal Healing	15%	25%*
Steroid-free remission for ≥ 90 days [a]	6% (N=140)	13% * (N=150)

Week 8 and 52

Sustained Response	12%	24%**
Sustained Remission	4%	8%*
Sustained Mucosal Healing	11%	19%*

Clinical remission is Mayo score ≤ 2 with no subscore > 1;
Clinical response is decrease from baseline in Mayo score ≥ 3 points and $\geq 30\%$ plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1;
*$p < 0.05$ for Humira *vs.* placebo pairwise comparison of proportions
**$p < 0.001$ for Humira *vs.* placebo pairwise comparison of proportions
[a] Of those receiving corticosteroids at baseline

Of those patients who had a response at Week 8, 47% were in response, 29% were in remission, 41% had mucosal healing, and 20% were in steroid-free remission for ≥ 90 days at Week 52.

Approximately 40% of patients in study UC-II had failed prior anti-TNF treatment with infliximab. The efficacy of adalimumab in those patients was reduced compared to that in anti-TNF naïve patients. Among patients who had failed prior anti-TNF treatment, Week 52 remission was achieved by 3% on placebo and 10% on adalimumab.

Patients from studies UC-I and UC-II had the option to roll over into an open-label long-term extension study (UC III). Following 3 years of adalimumab therapy, 75% (301/402) continued to be in clinical remission per partial Mayo score.

Hospitalisation rates

During 52 weeks of studies UC-I and UC-II, lower rates of all-cause hospitalisations and UC-related hospitalisations were observed for the adalimumab-treated arm compared to the placebo arm. The number of all cause hospitalisations in the adalimumab treatment group was 0.18 per patient year *vs.* 0.26 per patient year in the placebo group and the corresponding figures for UC-related hospitalisations were 0.12 per patient year *vs.* 0.22 per patient year.

Quality of life

In study UC-II, treatment with adalimumab resulted in improvements in the Inflammatory Bowel Disease Questionnaire (IBDQ) score.

Uveitis

The safety and efficacy of Humira were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis, excluding patients with isolated anterior uveitis, in two randomised, double-masked, placebo-controlled studies (UV I and II). Patients received placebo or Humira at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. Concomitant stable doses of one non-biologic immunosuppressant were permitted.

Study UV I evaluated 217 patients with active uveitis despite treatment with corticosteroids (oral prednisone at a dose of 10 to 60 mg/day). All patients received a 2-week standardised dose of prednisone 60 mg/day at study entry followed by a mandatory taper schedule, with complete corticosteroid discontinuation by Week 15.

Study UV II evaluated 226 patients with inactive uveitis requiring chronic corticosteroid treatment (oral prednisone 10 to 35 mg/day) at baseline to control their disease. Patients subsequently underwent a mandatory taper schedule, with complete corticosteroid discontinuation by Week 19.

The primary efficacy endpoint in both studies was ´time to treatment failure´. Treatment failure was defined by a multi-component outcome based on inflammatory chorioretinal and/or inflammatory retinal vascular lesions, anterior chamber (AC) cell grade, vitreous haze (VH) grade and best corrected visual acuity (BCVA).

Patients who completed Studies UV I and UV II were eligible to enroll in an uncontrolled long-term extension study with an originally planned duration of 78 weeks. Patients were allowed to continue on study medication beyond Week 78 until they had access to Humira.

Clinical Response

Results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with Humira versus patients receiving placebo (See Table 17). Both studies demonstrated an early and sustained effect of Humira on the treatment failure rate versus placebo (see Figure 1).

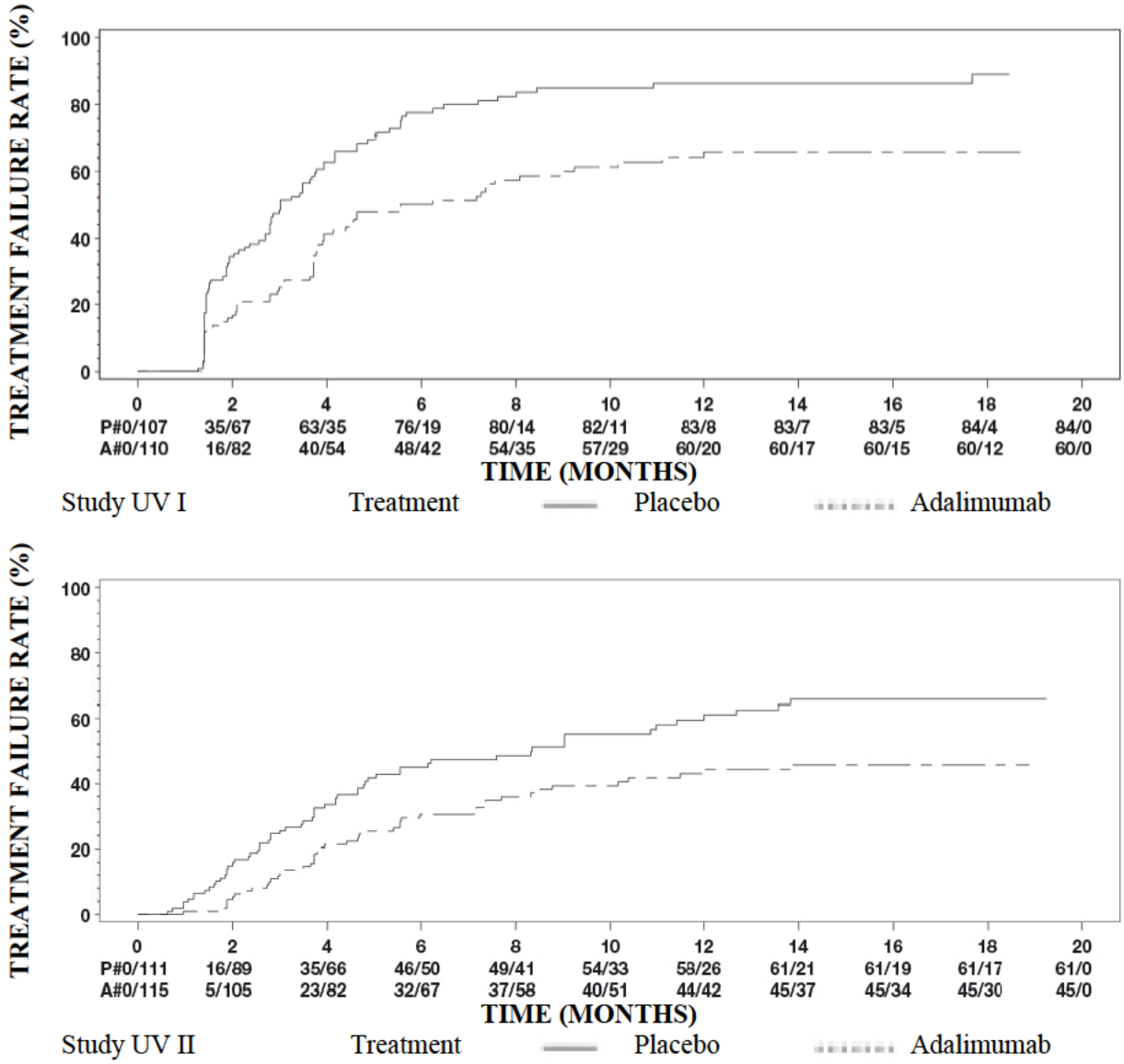
Table 17
Time to Treatment Failure in Studies UV I and UV II

Analysis Treatment	N	Failure N (%)	Median Time to Failure (months)	HR[a]	CI 95% for HR[a]	*P* Value[b]
Time to Treatment Failure At or After Week 6 in Study UV I						
Primary analysis (ITT)						
Placebo	107	84 (78.5)	3.0	--	--	--
Adalimumab	110	60 (54.5)	5.6	0.50	0.36, 0.70	< 0.001
Time to Treatment Failure At or After Week 2 in Study UV II						
Primary analysis (ITT)						
Placebo	111	61 (55.0)	8.3	--	--	--
Adalimumab	115	45 (39.1)	NE[c]	0.57	0.39, 0.84	0.004

Note: Treatment failure at or after Week 6 (Study UV I), or at or after Week 2 (Study UV II), was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

[a] HR of adalimumab vs placebo from proportional hazards regression with treatment as factor.
[b] 2-sided *P* value from log rank test.
[c] NE = not estimable. Fewer than half of at-risk subjects had an event.

Figure 1: Kaplan-Meier Curves Summarizing Time to Treatment Failure on or after Week 6 (Study UV I) or Week 2 (Study UV II)



Note: P# = Placebo (Number of Events/Number at Risk); A# = HUMIRA (Number of Events/Number at Risk).

In Study UV I statistically significant differences in favour of adalimumab versus placebo were observed for each component of treatment failure. In Study UV II, statistically significant differences were observed for visual acuity only, but the other components were numerically in favour of adalimumab.

Of the 424 subjects included in the uncontrolled long-term extension of Studies UV I and UV II, 60 subjects were regarded ineligible (e.g. due to deviations or due to complications secondary to diabetic retinopathy, due to cataract surgery or vitrectomy) and were excluded from the primary analysis of efficacy. Of the 364 remaining patients, 269 evaluable patients (74%) reached 78 weeks of open-label adalimumab treatment. Based on the observed data approach, 216 (80.3%) were in quiescence (no active inflammatory lesions, AC cell grade ≤ 0.5+, VH grade ≤ 0.5+) with a concomitant steroid dose ≤ 7.5 mg per day, and 178 (66.2%) were in steroid-free quiescence. BCVA was either improved or maintained (< 5 letters deterioration) in 88.6% of the eyes at week 78. Data beyond Week 78 were generally consistent

with these results but the number of enrolled subjects declined after this time. Overall, among the patients who discontinued the study, 18% discontinued due to adverse events, and 8% due to insufficient response to adalimumab treatment.

Quality of Life

Patient reported outcomes regarding vision-related functioning were measured in both clinical studies, using the NEI VFQ-25. Humira was numerically favoured for the majority of subscores with statistically significant mean differences for general vision, ocular pain, near vision, mental health, and total score in Study UV I, and for general vision and mental health in Study UV II. Vision related effects were not numerically in favour of Humira for colour vision in Study UVI and for colour vision, peripheral vision and near vision in Study UV II.

Immunogenicity

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

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. In the pivotal trials, anti-adalimumab antibodies were identified in 5.5% (58/1053) of patients treated with adalimumab, compared to 0.5% (2/370) on placebo. In patients not given concomitant methotrexate, the incidence was 12.4%, compared to 0.6% when adalimumab was used as add-on to methotrexate.

In patients with Crohn's disease, anti-adalimumab antibodies were identified in 7/269 subjects (2.6%) and in 19/487 subjects (3.9%) with ulcerative colitis.

In adult patients with psoriasis, anti-adalimumab antibodies were identified in 77/920 subjects (8.4%) treated with adalimumab monotherapy.

In adult plaque psoriasis patients on long term adalimumab monotherapy who participated in a withdrawal and retreatment study, the rate of antibodies to adalimumab after retreatment (11 of 482 subjects, 2.3%) was similar to the rate observed prior to withdrawal (11 of 590 subjects, 1.9%).

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

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

In patients with moderately to severely active paediatric ulcerative colitis, the rate of anti-adalimumab antibody development in patients receiving adalimumab was 3%.

Because immunogenicity analyses are product-specific, comparison of antibody rates with those from other products is not appropriate.

Paediatric population

Adolescent hidradenitis suppurativa

There are no clinical trials with Humira in adolescent patients with HS. Efficacy of adalimumab for the treatment of adolescent patients with HS is predicted based on the demonstrated efficacy and exposure-response relationship in adult HS patients and the likelihood that the disease course, pathophysiology, and drug effects are substantially similar to that of adults at the same exposure levels. Safety of the recommended adalimumab dose in the adolescent HS population is based on cross-indication safety profile of adalimumab in both adults and paediatric patients at similar or more frequent doses (see section 5.2).

Paediatric Crohn's disease

Humira was assessed in a multicentre, randomised, double-blind clinical trial designed to evaluate the efficacy and safety of induction and maintenance treatment with doses dependent on body weight (< 40 kg or ≥ 40 kg) in 192 paediatric subjects between the ages of 6 and 17 (inclusive) years, with moderate to severe Crohn´s disease (CD) defined as Paediatric Crohn's Disease Activity Index (PCDAI) score > 30. Subjects had to have failed conventional therapy (including a corticosteroid and/or an immunomodulator) for CD. Subjects may also have previously lost response or been intolerant to infliximab.

All subjects received open-label induction therapy at a dose based on their Baseline body weight: 160 mg at Week 0 and 80 mg at Week 2 for subjects ≥ 40 kg, and 80 mg and 40 mg, respectively, for subjects < 40 kg.

At Week 4, subjects were randomised 1:1 based on their body weight at the time to either the Low Dose or Standard Dose maintenance regimens as shown in Table 18.

Table 18
Maintenance regimen

Patient Weight	Low dose	Standard dose
< 40 kg	10 mg eow	20 mg eow
≥ 40 kg	20 mg eow	40 mg eow

Efficacy results

The primary endpoint of the study was clinical remission at Week 26, defined as PCDAI score ≤ 10.

Clinical remission and clinical response (defined as reduction in PCDAI score of at least 15 points from Baseline) rates are presented in Table 19. Rates of discontinuation of corticosteroids or immunomodulators are presented in Table 20.

Table 19
Paediatric CD Study
PCDAI Clinical Remission and Response

	Standard Dose 40/20 mg eow N = 93	Low Dose 20/10 mg eow N = 95	P value*
Week 26			
Clinical remission	38.7%	28.4%	0.075
Clinical response	59.1%	48.4%	0.073
Week 52			
Clinical remission	33.3%	23.2%	0.100
Clinical response	41.9%	28.4%	0.038

* p value for Standard Dose *versus* Low Dose comparison.

Table 20
Paediatric CD Study
Discontinuation of Corticosteroids or Immunomodulators and Fistula Remission

	Standard Dose 40/20 mg eow	Low Dose 20/10 mg eow	P value[1]
Discontinued corticosteroids	**N= 33**	**N=38**	
Week 26	84.8%	65.8%	0.066
Week 52	69.7%	60.5%	0.420
Discontinuation of Immunomodulators[2]	**N=60**	**N=57**	
Week 52	30.0%	29.8%	0.983
Fistula remission[3]	**N=15**	**N=21**	
Week 26	46.7%	38.1%	0.608
Week 52	40.0%	23.8%	0.303

[1] p value for Standard Dose *versus* Low Dose comparison.
[2] Immunosuppressant therapy could only be discontinued at or after Week 26 at the investigator's discretion if the subject met the clinical response criterion
[3] defined as a closure of all fistulas that were draining at Baseline for at least 2 consecutive post-Baseline visits

Statistically significant increases (improvement) from Baseline to Week 26 and 52 in Body Mass Index and height velocity were observed for both treatment groups.

Statistically and clinically significant improvements from Baseline were also observed in both treatment groups for quality of life parameters (including IMPACT III).

One hundred patients (n=100) from the Paediatric CD Study continued in an open-label long-term extension study. After 5 years of adalimumab therapy, 74.0% (37/50) of the 50 patients remaining in the study continued to be in clinical remission, and 92.0% (46/50) of patients continued to be in clinical response per PCDAI.

Paediatric ulcerative colitis

The safety and efficacy of Humira was assessed in a multicenter, randomized, double-blind, trial in 93 paediatric patients from 5 to 17 years of age with moderate to severe ulcerative colitis (Mayo score 6 to 12 with endoscopy subscore of 2 to 3 points, confirmed by centrally read endoscopy) who had an inadequate response or intolerance to conventional therapy. Approximately 16% of patients in the study had failed prior anti-TNF treatment. Patients who received corticosteroids at enrollment were allowed to taper their corticosteroid therapy after Week 4.

In the induction period of the study, 77 patients were randomized 3:2 to receive double-blind treatment with Humira at an induction dose 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; 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. Both groups received 0.6 mg/kg (maximum of 40 mg) at Week 4 and Week 6. Following an amendment to the study design, the remaining 16 patients who enrolled in the induction period received open-label treatment with Humira at the induction dose 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.

At Week 8, 62 patients who demonstrated clinical response per Partial Mayo Score (PMS; defined as a decrease in PMS ≥ 2 points and ≥ 30% from Baseline) were randomized equally to receive double-blind maintenance treatment with Humira at a dose of 0.6 mg/kg (maximum of 40 mg) every week (ew), or a maintenance dose of 0.6 mg/kg (maximum of 40 mg) every other week (eow). Prior to an amendment to the study design, 12 additional patients who demonstrated clinical response per PMS were randomized to receive placebo but were not included in the confirmatory analysis of efficacy.

Disease flare was defined as an increase in PMS of at least 3 points (for patients with PMS of 0 to 2 at Week 8), at least 2 points (for patients with PMS of 3 to 4 at Week 8), or at least 1 point (for patients with PMS of 5 to 6 at Week 8).

Patients who met criteria for disease flare at or after Week 12 were randomized to receive a re-induction dose of 2.4 mg/kg (maximum of 160 mg) or a dose of 0.6 mg/kg (maximum of 40 mg) and continued to receive their respective maintenance dose regimen afterwards.

Efficacy Results

The co-primary endpoints of the study were clinical remission per PMS (defined as PMS ≤ 2 and no individual subscore > 1) at Week 8, and clinical remission per FMS (Full Mayo Score) (defined as a Mayo Score ≤ 2 and no individual subscore > 1) at Week 52 in patients who achieved clinical response per PMS at Week 8.

Clinical remission rates per PMS at Week 8 for patients in each of the Humira double-blind induction groups are presented in Table 21.

Table 21: Clinical Remission per PMS at 8 Weeks

	Humira[a] Maximum of 160 mg at Week 0 / Placebo at Week 1 N=30	**Humira[b, c] Maximum of 160 mg at Week 0 and Week 1** N=47
Clinical remission	13/30 (43.3%)	28/47 (59.6%)

[a] Humira 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
[b] Humira 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
[c] Not including open-label Induction dose of Humira 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
Note 1: Both induction groups received 0.6 mg/kg (maximum of 40 mg) at Week 4 and Week 6
Note 2: Patients with missing values at Week 8 were considered as not having met the endpoint

At Week 52, clinical remission per FMS in Week 8 responders, clinical response per FMS (defined as a decrease in Mayo Score ≥ 3 points and ≥ 30% from Baseline) in Week 8 responders, mucosal healing (defined as Mayo endoscopy subscore ≤ 1) in Week 8 responders, clinical remission per FMS in Week 8 remitters, and the proportion of subjects in corticosteroid-free remission per FMS in Week 8 responders were assessed in patients who received Humira at the double-blind maximum 40 mg eow (0.6 mg/kg) and maximum 40 mg ew (0.6 mg/kg) maintenance doses (Table 22).

Table 22: Efficacy Results at 52 Weeks

	Humira[a] Maximum of 40 mg eow N=31	**Humira[b] Maximum of 40 mg ew** N=31
Clinical remission in Week 8 PMS responders	9/31 (29.0%)	14/31 (45.2%)
Clinical response in Week 8 PMS responders	19/31 (61.3%)	21/31 (67.7%)
Mucosal healing in Week 8 PMS responders	12/31 (38.7%)	16/31 (51.6%)
Clinical remission in Week 8 PMS remitters	9/21 (42.9%)	10/22 (45.5%)
Corticosteroid-free remission in Week 8 PMS responders[c]	4/13 (30.8%)	5/16 (31.3%)

[a] Humira 0.6 mg/kg (maximum of 40 mg) every other week
[b] Humira 0.6 mg/kg (maximum of 40 mg) every week
[c] In patients receiving concomitant corticosteroids at baseline
Note: Patients with missing values at Week 52 or who were randomized to receive re-induction or maintenance treatment were considered non-responders for Week 52 endpoints

Additional exploratory efficacy endpoints included clinical response per the Paediatric Ulcerative Colitis Activity Index (PUCAI) (defined as a decrease in PUCAI ≥ 20 points from Baseline) and clinical remission per PUCAI (defined as PUCAI < 10) at Week 8 and Week 52 (Table 23).

Table 23: Exploratory Endpoints Results per PUCAI

	Week 8	
	Humira[a] Maximum of 160 mg at Week 0 / Placebo at Week 1 N=30	**Humira[b,c] Maximum of 160 mg at Week 0 and Week 1** N=47
Clinical remission per PUCAI	10/30 (33.3%)	22/47 (46.8%)
Clinical response per PUCAI	15/30 (50.0%)	32/47 (68.1%)
	Week 52	
	Humira[d] Maximum of 40 mg eow N=31	**Humira[e] Maximum of 40 mg ew** N=31
Clinical remission per PUCAI in Week 8 PMS responders	14/31 (45.2%)	18/31 (58.1%)
Clinical response per PUCAI in Week 8 PMS responders	18/31 (58.1%)	16/31 (51.6%)

[a] Humira 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
[b] Humira 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
[c] Not including open-label Induction dose of Humira 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
[d] Humira 0.6 mg/kg (maximum of 40 mg) every other week
[e] Humira 0.6 mg/kg (maximum of 40 mg) every week
Note 1: Both induction groups received 0.6 mg/kg (maximum of 40 mg) at Week 4 and Week 6
Note 2: Patients with missing values at Week 8 were considered as not having met the endpoints
Note 3: Patients with missing values at Week 52 or who were randomized to receive re-induction or maintenance treatment were considered non-responders for Week 52 endpoints

Of the Humira-treated patients who received re-induction treatment during the maintenance period, 2/6 (33%) achieved clinical response per FMS at Week 52.

Quality of life

Clinically meaningful improvements from Baseline were observed in IMPACT III and the caregiver Work Productivity and Activity Impairment (WPAI) scores for the groups treated with Humira.

Clinically meaningful increases (improvement) from Baseline in height velocity were observed for the groups treated with adalimumab, and clinically meaningful increases (improvement) from Baseline in Body Mass Index were observed for subjects on the high maintenance dose of maximum 40 mg (0.6 mg/kg) ew.

Paediatric Uveitis

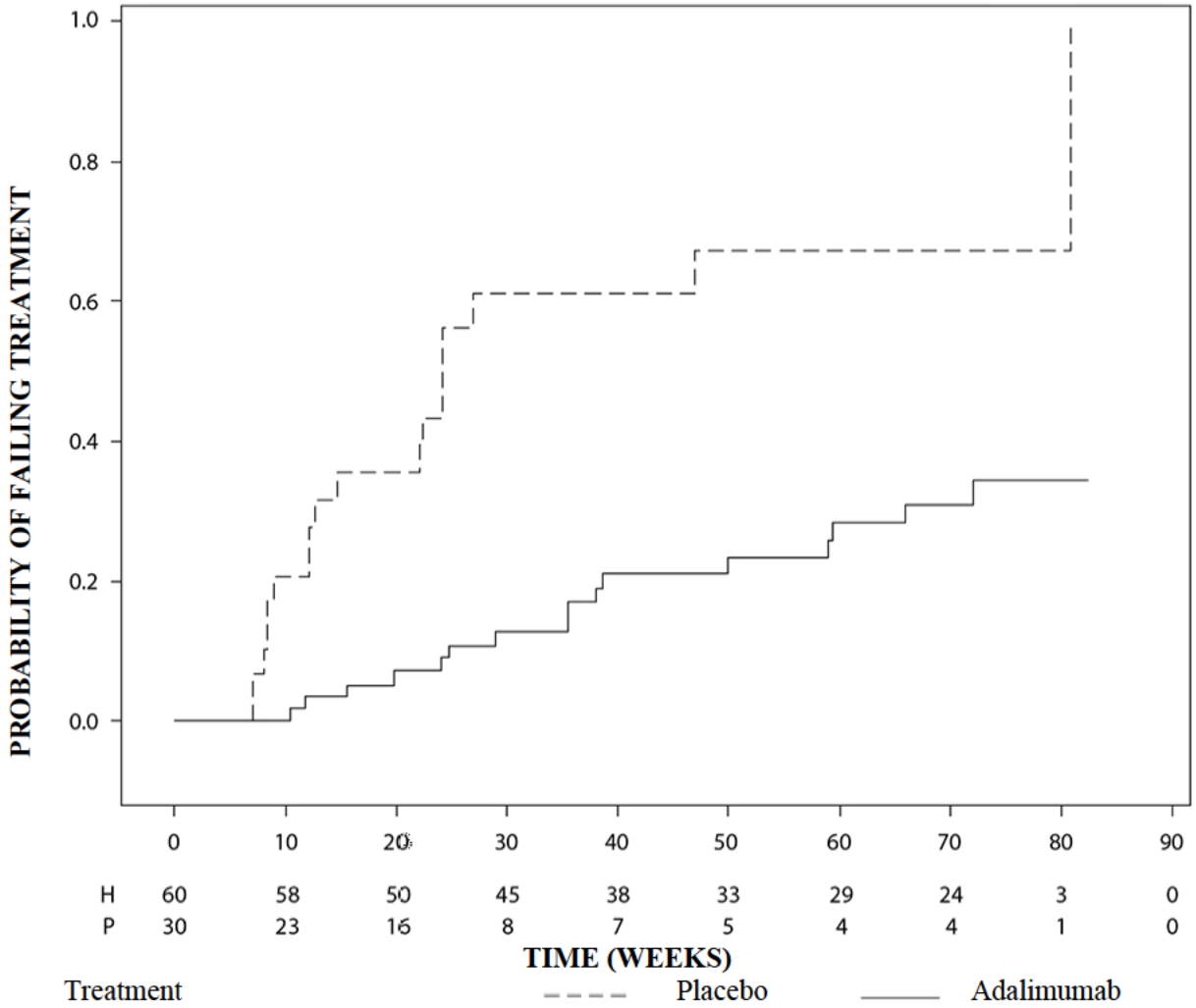
The safety and efficacy of Humira was assessed in a randomized, double-masked, controlled study of 90 paediatric patients from 2 to < 18 years of age with active JIA-associated noninfectious anterior uveitis who were refractory to at least 12 weeks of methotrexate treatment. Patients received either placebo or 20 mg adalimumab (if < 30 kg) or 40 mg adalimumab (if ≥ 30 kg) every other week in combination with their baseline dose of methotrexate.

The primary endpoint was 'time to treatment failure'. The criteria determining treatment failure were worsening or sustained non-improvement in ocular inflammation, partial improvement with development of sustained ocular co-morbidities or worsening of ocular co-morbidities, non-permitted use of concomitant medications, and suspension of treatment for an extended period of time.

Clinical Response

Adalimumab significantly delayed the time to treatment failure, as compared to placebo (See Figure 2, $P < 0.0001$ from log rank test).The median time to treatment failure was 24.1 weeks for subjects treated with placebo, whereas the median time to treatment failure was not estimable for subjects treated with adalimumab because less than one-half of these subjects experienced treatment failure. Adalimumab significantly decreased the risk of treatment failure by 75% relative to placebo, as shown by the hazard ratio (HR = 0.25 [95% CI: 0.12, 0.49]).

Figure 2: Kaplan-Meier Curves Summarizing Time to Treatment Failure in the Paediatric Uveitis Study



Note: P = Placebo (Number at Risk); H = HUMIRA (Number at Risk).

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5.2 Pharmacokinetic properties

Absorption and distribution

After subcutaneous administration of a single 40 mg dose, absorption and distribution of adalimumab was slow, with peak serum concentrations being reached about 5 days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%. After single intravenous doses ranging from 0.25 to 10 mg/kg, concentrations were dose proportional. After doses of 0.5 mg/kg (~40 mg), clearances ranged from 11 to 15 ml/hour, the distribution volume (V_{ss}) ranged from 5 to 6 litres and the mean terminal phase half-life was approximately two weeks. Adalimumab concentrations in the synovial fluid from several rheumatoid arthritis patients ranged from 31-96% of those in serum.

Following subcutaneous administration of 40 mg of adalimumab every other week in adult rheumatoid arthritis (RA) patients the mean steady-state trough concentrations were approximately 5 μg/ml (without concomitant methotrexate) and 8 to 9 μg/ml (with concomitant methotrexate), respectively. The serum adalimumab trough levels at steady-state increased roughly proportionally with dose following 20, 40 and 80 mg subcutaneous dosing every other week and every week.

In adult patients with psoriasis, the mean steady-state trough concentration was 5 μg/ml during adalimumab 40 mg every other week monotherapy treatment.

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

Adalimumab exposure in adolescent HS patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paediatric psoriasis, juvenile idiopathic arthritis, paediatric Crohn's disease, and enthesitis-related arthritis). The recommended adolescent HS dosing schedule is 40 mg every other week. Since exposure to adalimumab can be affected by body size, adolescents with higher body weight and inadequate response may benefit from receiving the recommended adult dose of 40 mg every week.

In patients with Crohn's disease, the loading dose of 80 mg Humira on Week 0 followed by 40 mg Humira on Week 2 achieves serum adalimumab trough concentrations of approximately 5.5 μg/ml during the induction period. A loading dose of 160 mg Humira on Week 0 followed by 80 mg Humira on Week 2 achieves serum adalimumab trough concentrations of approximately 12 μg/ml during the induction period. Mean steady-state trough levels of approximately 7 μg/ml were observed in Crohn's disease patients who received a maintenance dose of 40 mg Humira every other week.

In paediatric patients with moderate to severe CD, 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 randomised 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 randomised therapy, the mean (±SD) adalimumab trough concentrations at Week 52 were 9.5 ± 5.6 μg/ml for the Standard Dose group and 3.5 ± 2.2 μg/ml for the Low Dose group. The mean trough concentrations were maintained in 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).

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

Following the subcutaneous administration of body weight-based dosing of 0.6 mg/kg (maximum of 40 mg) every other week to paediatric 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.

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

Adalimumab exposure in paediatric uveitis patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paediatric psoriasis, juvenile idiopathic arthritis, paediatric Crohn's disease, and enthesitis-related arthritis). No clinical exposure data are available on the use of a loading dose in children < 6 years. The predicted exposures indicate that in the absence of methotrexate, a loading dose may lead to an initial increase in systemic exposure.

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, patients with adolescent HS, and paediatric patients ≥ 40 kg with CD and UC).

Exposure-response relationship in paediatric population

On the basis of clinical trial data in patients with JIA (pJIA and ERA), an exposure-response relationship was established between plasma concentrations and PedACR 50 response. The apparent adalimumab plasma concentration that produces half the maximum probability of PedACR 50 response (EC50) was 3 µg/ml (95% CI: 1-6 µg/ml).

Exposure-response relationships between adalimumab concentration and efficacy in paediatric patients with severe chronic plaque psoriasis were established for PASI 75 and PGA clear or minimal, respectively. PASI 75 and PGA clear or minimal increased with increasing adalimumab concentrations, both with a similar apparent EC50 of approximately 4.5 µg/ml (95% CI 0.4-47.6 and 1.9-10.5, respectively).

Elimination

Population pharmacokinetic analyses with data from over 1,300 RA patients revealed a trend toward higher apparent clearance of adalimumab with increasing body weight. After adjustment for weight differences, gender and age appeared to have a minimal effect on adalimumab clearance. The serum levels of free adalimumab (not bound to anti-adalimumab antibodies, AAA) were observed to be lower in patients with measurable AAA.

Hepatic or renal impairment

Humira has not been studied in patients with hepatic or renal impairment.

5.3 Preclinical safety data

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

An embryo-foetal developmental toxicity/perinatal developmental study has been performed in cynomolgus monkeys at 0, 30 and 100 mg/kg (9-17 monkeys/group) and has revealed no evidence of harm to the foetuses due to adalimumab. Neither carcinogenicity studies, nor a standard assessment of fertility and postnatal toxicity, were performed with adalimumab due to the lack of appropriate models for an antibody with limited cross-reactivity to rodent TNF and to the development of neutralising antibodies in rodents.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Polysorbate 80
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the pre-filled syringe or pre-filled pen in its outer carton in order to protect from light.

A single Humira pre-filled syringe or pre-filled pen may be stored at temperatures up to a maximum of 25°C for a period of up to 14 days. The syringe or pen must be protected from light, and discarded if not used within the 14-day period.

6.5 Nature and contents of container

Humira 80 mg solution for injection in pre-filled syringe
Humira 80 mg solution for injection in single-use pre-filled syringe (type I glass) with a plunger stopper (bromobutyl rubber) and a needle with a needle shield (thermoplastic elastomer).

Packs of:
- 1 pre-filled syringe (0.8 ml sterile solution) with 1 alcohol pad in a blister.

Humira 80 mg solution for injection in pre-filled syringe with automatic needle guard
Humira 80 mg solution for injection in single-use pre-filled syringe with automatic needle guard. The syringe is made from type I glass with a plunger stopper (bromobutyl rubber) and a needle with a needle

shield (thermoplastic elastomer).

Packs of:

- 1 pre-filled syringe with automatic needle guard (0.8 ml sterile solution) with 1 alcohol pad in a blister.

Humira 80 mg solution for injection in pre-filled pen
Humira 80 mg solution for injection in single-use pre-filled pen for patient use containing a pre-filled syringe. The syringe inside the pen is made from type 1 glass with a plunger stopper (bromobutyl rubber) and a needle with a needle shield (thermoplastic elastomer).

Packs of:

- 1 pre-filled pen (0.8 ml sterile solution), with 2 alcohol pads in a blister.
- 3 pre-filled pens (0.8 ml sterile solution), with 4 alcohol pads in a blister.

Not all presentations or pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen
Germany

8. MARKETING AUTHORISATION NUMBERS

Humira 80 mg solution for injection in pre-filled syringe
EU/1/03/256/020

Humira 80 mg solution for injection in pre-filled syringe with automatic needle guard
EU/1/03/256/026

Humira 80 mg solution for injection in pre-filled pen
EU/1/03/256/021
EU/1/03/256/027

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 September 2003
Date of latest renewal: 08 September 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

B. PACKAGE LEAFLET

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Package leaflet: Information for the patient

Humira 40 mg solution for injection in pre-filled syringe
adalimumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a **Patient Reminder Card**, which contains important safety information that you need to be aware of before you begin using Humira and during treatment with Humira. Keep this **Patient Reminder Card** with you.
- If you have any questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet
1. What Humira is and what it is used for
2. What you need to know before you use Humira
3. How to use Humira
4. Possible side effects
5 How to store Humira
6. Contents of the pack and other information
7. Injecting Humira

1. What Humira is and what it is used for

Humira contains the active substance adalimumab.

Humira is used to treat
- Rheumatoid arthritis
- Polyarticular juvenile idiopathic arthritis
- Enthesitis-related arthritis
- Ankylosing spondylitis
- Axial spondyloarthritis without radiographic evidence of ankylosing spondylitis
- Psoriatic arthritis
- Plaque psoriasis
- Hidradenitis suppurativa
- Crohn's disease
- Ulcerative colitis
- Non-infectious uveitis

The active ingredient in Humira, adalimumab, is a human monoclonal antibody. Monoclonal antibodies are proteins that attach to a specific target.

The target of adalimumab is a protein called tumour necrosis factor (TNFα), which is involved in the immune (defence) system and is present at increased levels in the inflammatory diseases listed above. By attaching to TNFα, Humira decreases the process of inflammation in these diseases.

Rheumatoid arthritis

Rheumatoid arthritis is an inflammatory disease of the joints.

Humira is used to treat moderate to severe rheumatoid arthritis in adults. You may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira.

Humira can also be used to treat severe, active and progressive rheumatoid arthritis without previous methotrexate treatment.

Humira can slow down the damage to the joints caused by the inflammatory disease and can help them move more freely.

Your doctor will decide if Humira should be used with methotrexate or alone.

Polyarticular juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis is an inflammatory disease of the joints.

Humira is used to treat polyarticular juvenile idiopathic arthritis in patients from 2 years of age. You may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira.

Your doctor will decide if Humira should be used with methotrexate or alone.

Enthesitis-related arthritis

Enthesitis-related arthritis is an inflammatory disease of the joints and the places where tendons join the bone.

Humira is used to treat enthesitis-related arthritis in patients from 6 years of age. You may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira.

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis are inflammatory diseases of the spine.

Humira is used to treat severe ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis in adults. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Psoriatic arthritis

Psoriatic arthritis is an inflammatory disease of the joints that is usually associated with psoriasis.

Humira is used to treat psoriatic arthritis in adults. Humira can slow down the damage to the joints caused by the disease and can help them move more freely. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

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Plaque psoriasis

Plaque psoriasis is a skin condition that causes red, flaky, crusty patches of skin covered with silvery scales. Plaque psoriasis can also affect the nails, causing them to crumble, become thickened and lift away from the nail bed which can be painful.

Humira is used to treat
- moderate to severe chronic plaque psoriasis in adults and
- severe chronic plaque psoriasis in children and adolescents aged 4 to 17 years for whom topical therapy and phototherapies have either not worked very well or are not suitable.

Hidradenitis suppurativa

Hidradenitis suppurativa (sometimes called acne inversa) is a chronic and often painful inflammatory skin disease. Symptoms may include tender nodules (lumps) and abscesses (boils) that may leak pus. It most commonly affects specific areas of the skin, such as under the breasts, the armpits, inner thighs, groin and buttocks. Scarring may also occur in affected areas.

Humira is used to treat
- moderate to severe hidradenitis suppurativa in adults and
- moderate to severe hidradenitis suppurativa in adolescents aged 12 to 17 years.

Humira can reduce the number of nodules and abscesses caused by the disease and the pain that is often associated with the disease. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Crohn's disease

Crohn's disease is an inflammatory disease of the digestive tract.

Humira is used to treat
- moderate to severe Crohn's disease in adults and
- moderate to severe Crohn's disease in children and adolescents aged 6 to 17 years

You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Ulcerative colitis

Ulcerative colitis is an inflammatory disease of the large intestine.

Humira is used to treat
- moderate to severe ulcerative colitis in adults and
- moderate to severe ulcerative colitis in children and adolescents aged 6 to 17 years.

You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Non-infectious uveitis

Non-infectious uveitis is an inflammatory disease affecting certain parts of the eye.

Humira is used to treat

- adults with non-infectious uveitis with inflammation affecting the back of the eye
- children with chronic non-infectious uveitis from 2 years of age with inflammation affecting the front of the eye

This inflammation may lead to a decrease of vision and/or the presence of floaters in the eye (black dots or wispy lines that move across the field of vision). Humira works by reducing this inflammation.

You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

2. What you need to know before you use Humira

Do not use Humira:

- If you are allergic to adalimumab or any of the other ingredients of this medicine (listed in section 6).
- If you have active tuberculosis or other severe infections (see "Warnings and precautions"). It is important that you tell your doctor if you have symptoms of infections, for example, fever, wounds, feeling tired, dental problems.
- If you have moderate or severe heart failure. It is important to tell your doctor if you have had or have a serious heart condition (see "Warnings and precautions").

Warnings and precautions

Talk to your doctor or pharmacist before using Humira.

Allergic reactions

- If you get allergic reactions with symptoms such as chest tightness, wheezing, dizziness, swelling or rash do not inject more Humira and contact your doctor immediately since, in rare cases, these reactions can be life threatening.

Infections

- If you have an infection, including long-term infection or an infection in one part of the body (for example, leg ulcer) consult your doctor before starting Humira. If you are unsure, contact your doctor.
- You might get infections more easily while you are receiving Humira treatment. This risk may increase if you have problems with your lungs. These infections may be serious and include:
  - tuberculosis
  - infections caused by viruses, fungi, parasites or bacteria
  - severe infection in the blood (sepsis)

  In rare cases, these infections can be life-threatening. It is important to tell your doctor if you get symptoms such as fever, wounds, feeling tired or dental problems. Your doctor may tell you to stop using Humira for some time.

- Tell your doctor if you live or travel in regions where fungal infections (for example, histoplasmosis, coccidioidomycosis or blastomycosis) are very common.

- Tell your doctor if you have had infections which keep coming back or other conditions that increase the risk of infections.

- If you are over 65 years you may be more likely to get infections while taking Humira. You and your doctor should pay special attention to signs of infection while you are being treated with Humira. It is important to tell your doctor if you get symptoms of infections, such as fever, wounds, feeling tired or dental problems.

Tuberculosis

- It is very important that you tell your doctor if you have ever had tuberculosis, or if you have been in close contact with someone who has had tuberculosis. If you have active tuberculosis, do not use Humira.

    - As cases of tuberculosis have been reported in patients treated with Humira, your doctor will check you for signs and symptoms of tuberculosis before starting Humira. This will include a thorough medical evaluation including your medical history and appropriate screening tests (for example, chest X-ray and a tuberculin test). The conduct and results of these tests should be recorded on your **Patient Reminder Card**.
    - Tuberculosis can develop during therapy even if you have received treatment for the prevention of tuberculosis.
    - If symptoms of tuberculosis (for example, cough that does not go away, weight loss, lack of energy, mild fever), or any other infection appear during or after therapy tell your doctor immediately.

Hepatitis B

- Tell your doctor if you are a carrier of the hepatitis B virus (HBV), if you have active HBV or if you think you might be at risk of getting HBV.
    - Your doctor should test you for HBV. In people who carry HBV, Humira can cause the virus to become active again.
    - In some rare cases, especially if you are taking other medicines that suppress the immune system, reactivation of HBV can be life-threatening.

Surgery or dental procedure

- If you are about to have surgery or dental procedures, please inform your doctor that you are taking Humira. Your doctor may recommend temporary discontinuation of Humira.

Demyelinating disease

- If you have or develop a demyelinating disease (a disease that affects the insulating layer around the nerves, such as multiple sclerosis), your doctor will decide if you should receive or continue to receive Humira. Tell your doctor immediately if you experience symptoms like changes in your vision, weakness in your arms or legs or numbness or tingling in any part of your body.

Vaccinations

- Certain vaccines may cause infections and should not be given while receiving Humira.

- Check with your doctor before you receive any vaccines.
- It is recommended that children, if possible, be given all the scheduled vaccinations for their age before they start treatment with Humira.
- If you received Humira while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately five months after the last Humira dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy so they can decide when your baby should receive any vaccine.

Heart failure

- If you have mild heart failure and are being treated with Humira, your heart failure status must be closely monitored by your doctor. It is important to tell your doctor if you have had or have a serious heart condition. If you develop new or worsening symptoms of heart failure (e.g. shortness of breath, or swelling of your feet), you must contact your doctor immediately. Your doctor will decide if you should receive Humira.

Fever, bruising, bleeding or looking pale

- In some patients the body may fail to produce enough of the blood cells that fight off infections or help you to stop bleeding. Your doctor may decide to stop treatment. If you develop a fever that does not go away, develop light bruises or bleed very easily or look very pale, call your doctor right away.

Cancer

- There have been very rare cases of certain kinds of cancer in children and adult patients taking Humira or other TNF blockers.
    - People with more serious rheumatoid arthritis that have had the disease for a long time may have a higher than average risk of getting lymphoma (a cancer that affects the lymph system) and leukaemia (a cancer that affects the blood and bone marrow).
    - If you take Humira the risk of getting lymphoma, leukaemia, or other cancers may increase. On rare occasions, an uncommon and severe type of lymphoma, has been seen in patients taking Humira. Some of those patients were also treated with azathioprine or 6-mercaptopurine.
    - Tell your doctor if you are taking azathioprine or 6-mercaptopurine with Humira.
    - Cases of non-melanoma skin cancer have been observed in patients taking Humira.
    - If new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.

- There have been cases of cancers, other than lymphoma in patients with a specific type of lung disease called Chronic Obstructive Pulmonary Disease (COPD) treated with another TNF blocker. If you have COPD, or are a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for you.

Autoimmune disease

- On rare occasions, treatment with Humira could result in lupus-like syndrome. Contact your doctor if symptoms such as persistent unexplained rash, fever, joint pain or tiredness occur.

Children and adolescents

- Vaccinations: if possible, children should be up to date with all vaccinations before using Humira.

Other medicines and Humira

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

You should not take Humira with medicines containing the following active substances due to increased risk of serious infection:
- anakinra
- abatacept.

Humira can be taken together with:
- methotrexate
- certain disease-modifying anti-rheumatic agents (for example, sulfasalazine, hydroxychloroquine, leflunomide and injectable gold preparations)
- steroids or pain medications including non-steroidal anti-inflammatory drugs (NSAIDs).

If you have questions, please ask your doctor.

Pregnancy and breast-feeding

- You should consider the use of adequate contraception to prevent pregnancy and continue its use for at least 5 months after the last Humira treatment.
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice about taking this medicine.
- Humira should only be used during a pregnancy if needed.
- According to a pregnancy study, there was no higher risk of birth defects when the mother had received Humira during pregnancy compared with mothers with the same disease who did not receive Humira.
- Humira can be used during breast-feeding.
- If you receive Humira during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy before the baby receives any vaccine. For more information on vaccines see the "Warnings and precautions" section.

Driving and using machines

Humira may have a small effect on your ability to drive, cycle or use machines. Room spinning sensation and vision disturbances may occur after taking Humira.

3. How to use Humira

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended doses for Humira in each of the approved uses are shown in the following table. Your doctor may prescribe another strength of Humira if you need a different dose.

Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or axial spondyloarthritis without radiographic evidence of ankylosing spondylitis		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	40 mg every other week	In rheumatoid arthritis, methotrexate is continued while using Humira. If your doctor decides that methotrexate is inappropriate, Humira can be given alone. If you have rheumatoid arthritis and you do not receive methotrexate with your Humira therapy, your doctor may decide to give Humira 40 mg every week or 80 mg every other week.

Polyarticular juvenile idiopathic arthritis		
Age or body weight	**How much and how often to take?**	**Notes**
Children, adolescents and adults from 2 years of age weighing 30 kg or more	40 mg every other week	Not applicable
Children and adolescents from 2 years of age weighing 10 kg to less than 30 kg	20 mg every other week	Not applicable

Enthesitis-related arthritis		
Age or body weight	**How much and how often to take?**	**Notes**
Children, adolescents and adults from 6 years of age weighing 30 kg or more	40 mg every other week	Not applicable
Children and adolescents from 6 years of age weighing 15 kg to less than 30 kg	20 mg every other week	Not applicable

Plaque psoriasis		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 80 mg (two 40 mg injections in one day), followed by 40 mg every other week starting one week after the first dose.	If you have an inadequate response, your doctor may increase the dosage to 40 mg every week or 80 mg every other week.
Children and adolescents from 4 to 17 years of age weighing 30 kg or more	First dose of 40 mg, followed by 40 mg one week later.	Not applicable

	Thereafter, the usual dose is 40 mg every other week.	
Children and adolescents from 4 to 17 years of age weighing 15 kg to less than 30 kg	First dose of 20 mg, followed by 20 mg one week later. Thereafter, the usual dose is 20 mg every other week.	Not applicable

Hidradenitis suppurativa		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by an 80 mg dose (two 40 mg injections in one day) two weeks later. After two further weeks, continue with a dose of 40 mg every week or 80 mg every other week, as prescribed by your doctor.	It is recommended that you use an antiseptic wash daily on the affected areas.
Adolescents from 12 to 17 years of age weighing 30 kg or more	First dose of 80 mg (two 40 mg injections in one day), followed by 40 mg every other week starting one week later.	If you have an inadequate response to Humira 40 mg every other week, your doctor may increase the dosage to 40 mg every week or 80 mg every other week. It is recommended that you use an antiseptic wash daily on the affected areas.

Crohn's disease		
Age or body weight	**How much and how often to take?**	**Notes**
Children, adolescents and adults from 6 years of age weighing 40 kg or more	First dose of 80 mg (two 40 mg injections in one day), followed by 40 mg two weeks later. If a faster response is required, the doctor may prescribe a first dose of 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg (two 40 mg injections in one day) two weeks later. Thereafter, the usual dose is 40 mg every other week.	Your doctor may increase the dosage to 40 mg every week or 80 mg every other week.

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Children and adolescents from 6 to 17 years of age weighing less than 40 kg	First dose of 40 mg, followed by 20 mg two weeks later. If a faster response is required, the doctor may prescribe a first dose of 80 mg (two 40 mg injections in one day), followed by 40 mg two weeks later. Thereafter, the usual dose is 20 mg every other week.	Your doctor may increase the dose frequency to 20 mg every week.

Ulcerative colitis		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg (two 40 mg injections in one day) two weeks later. Thereafter, the usual dose is 40 mg every other week.	Your doctor may increase the dosage to 40 mg every week or 80 mg every other week.
Children and adolescents from 6 years of age weighing less than 40 kg	First dose of 80 mg (two 40 mg injections in one day), followed by 40 mg (one 40 mg injection) two weeks later. Thereafter, the usual dose is 40 mg every other week.	You should continue taking Humira at your usual dose, even after turning 18 years of age.
Children and adolescents from 6 years of age weighing 40 kg or more	First dose of 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg (two 40 mg injections in one day) two weeks later. Thereafter, the usual dose is 80 mg every other week.	You should continue taking Humira at your usual dose, even after turning 18 years of age.

Non-infectious uveitis		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 80 mg (two 40 mg injections in one day), followed by 40 mg every other week starting one week after the first dose.	Corticosteroids or other medicines that influence the immune system may be continued while using Humira. Humira can also be given alone.
Children and adolescents from 2 years of age weighing less than 30 kg	20 mg every other week	Your doctor may prescribe an initial dose of 40 mg to be administered one week prior to the start of the usual dose of 20 mg every other week. Humira is recommended for use in combination with methotrexate.
Children and adolescents from 2 years of age weighing at least 30 kg	40 mg every other week	Your doctor may prescribe an initial dose of 80 mg to be administered one week prior to the start of the usual dose of 40 mg every other week. Humira is recommended for use in combination with methotrexate.

Method and route of administration

Humira is administered by injection under the skin (by subcutaneous injection).

Detailed instructions on how to inject Humira are provided in section 7 'Injecting Humira'.

If you use more Humira than you should

If you accidentally inject Humira more frequently than told to by your doctor or pharmacist, call your doctor or pharmacist and tell them that you have taken more. Always take the outer carton of the medicine with you, even if it is empty.

If you forget to use Humira

If you forget to give yourself an injection, you should inject the next dose of Humira as soon as you remember. Then take your next dose as you would have on your originally scheduled day, had you not forgotten a dose.

If you stop using Humira

The decision to stop using Humira should be discussed with your doctor. Your symptoms may return if you stop using Humira.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However, some may be serious and require treatment. Side effects may occur at least up to 4 months after the last Humira injection.

Tell your doctor immediately if you notice any of the following

- severe rash, hives or other signs of allergic reaction
- swollen face, hands, feet
- trouble breathing, swallowing
- shortness of breath with physical activity or upon lying down or swelling of the feet

Tell your doctor as soon as possible if you notice any of the following

- signs of infection such as fever, feeling sick, wounds, dental problems, burning on urination
- feeling weak or tired
- coughing
- tingling
- numbness
- double vision
- arm or leg weakness
- a bump or open sore that doesn't heal
- signs and symptoms suggestive of blood disorders such as persistent fever, bruising, bleeding, paleness

The symptoms described above can be signs of the below listed side effects, which have been observed with Humira.

Very common (may affect more than 1 in 10 people)

- injection site reactions (including pain, swelling, redness or itching)
- respiratory tract infections (including cold, runny nose, sinus infection, pneumonia)
- headache
- abdominal pain
- nausea and vomiting
- rash
- musculoskeletal pain

Common (may affect up to 1 in 10 people)

- serious infections (including blood poisoning and influenza)
- intestinal infections (including gastroenteritis)
- skin infections (including cellulitis and shingles)
- ear infections
- oral infections (including tooth infections and cold sores)
- reproductive tract infections
- urinary tract infection
- fungal infections
- joint infections
- benign tumours

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- skin cancer
- allergic reactions (including seasonal allergy)
- dehydration
- mood swings (including depression)
- anxiety
- difficulty sleeping
- sensation disorders such as tingling, prickling or numbness
- migraine
- nerve root compression (including low back pain and leg pain)
- vision disturbances
- eye inflammation
- inflammation of the eye lid and eye swelling
- vertigo (feeling of dizziness or spinning)
- sensation of heart beating rapidly
- high blood pressure
- flushing
- haematoma (collection of blood outside of blood vessels)
- cough
- asthma
- shortness of breath
- gastrointestinal bleeding
- dyspepsia (indigestion, bloating, heart burn)
- acid reflux disease
- sicca syndrome (including dry eyes and dry mouth)
- itching
- itchy rash
- bruising
- inflammation of the skin (such as eczema)
- breaking of finger nails and toe nails
- increased sweating
- hair loss
- new onset or worsening of psoriasis
- muscle spasms
- blood in urine
- kidney problems
- chest pain
- oedema (swelling)
- fever
- reduction in blood platelets which increases risk of bleeding or bruising
- impaired healing

Uncommon (may affect up to 1 in 100 people)

- opportunistic infections (which include tuberculosis and other infections that occur when resistance to disease is lowered)
- neurological infections (including viral meningitis)
- eye infections
- bacterial infections
- diverticulitis (inflammation and infection of the large intestine)
- cancer

- cancer that affects the lymph system
- melanoma
- immune disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis)
- vasculitis (inflammation of blood vessels)
- tremor (shaking)
- neuropathy (disorder of the nerves)
- stroke
- hearing loss, buzzing
- sensation of heart beating irregularly such as skipped beats
- heart problems that can cause shortness of breath or ankle swelling
- heart attack
- a sac in the wall of a major artery, inflammation and clot of a vein, blockage of a blood vessel
- lung diseases causing shortness of breath (including inflammation)
- pulmonary embolism (blockage in an artery of the lung)
- pleural effusion (abnormal collection of fluid in the pleural space)
- inflammation of the pancreas which causes severe pain in the abdomen and back
- difficulty in swallowing
- facial oedema (swelling of the face)
- gallbladder inflammation, gallbladder stones
- fatty liver
- night sweats
- scar
- abnormal muscle breakdown
- systemic lupus erythematosus (including inflammation of skin, heart, lung, joints and other organ systems)
- sleep interruptions
- impotence
- inflammations

Rare (may affect up to 1 in 1,000 people)

- leukaemia (cancer affecting the blood and bone marrow)
- severe allergic reaction with shock
- multiple sclerosis
- nerve disorders (such as eye nerve inflammation and Guillain-Barré syndrome that may cause muscle weakness, abnormal sensations, tingling in the arms and upper body)
- heart stops pumping
- pulmonary fibrosis (scarring of the lung)
- intestinal perforation (hole in the intestine)
- hepatitis
- reactivation of hepatitis B
- autoimmune hepatitis (inflammation of the liver caused by the body's own immune system)
- cutaneous vasculitis (inflammation of blood vessels in the skin)
- Stevens-Johnson syndrome (early symptoms include malaise, fever, headache and rash)
- facial oedema (swelling of the face) associated with allergic reactions
- erythema multiforme (inflammatory skin rash)
- lupus-like syndrome
- angioedema (localized swelling of the skin)
- lichenoid skin reaction (itchy reddish-purple skin rash)

Not known (frequency cannot be estimated from the available data)

- hepatosplenic T-cell lymphoma (a rare blood cancer that is often fatal)
- Merkel cell carcinoma (a type of skin cancer)
- Kaposi's sarcoma, a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appears as purple lesions on the skin
- liver failure
- worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)
- weight gain (for most patients, the weight gain was small)

Some side effects observed with Humira may not have symptoms and may only be discovered through blood tests. These include:

Very common (may affect more than 1 in 10 people)

- low blood measurements for white blood cells
- low blood measurements for red blood cells
- increased lipids in the blood
- elevated liver enzymes

Common (may affect up to 1 in 10 people)

- high blood measurements for white blood cells
- low blood measurements for platelets
- increased uric acid in the blood
- abnormal blood measurements for sodium
- low blood measurements for calcium
- low blood measurements for phosphate
- high blood sugar
- high blood measurements for lactate dehydrogenase
- autoantibodies present in the blood
- low blood potassium

Uncommon (may affect up to 1 in 100 people)

- elevated bilirubin measurement (liver blood test)

Rare (may affect up to 1 in 1,000 people)

- low blood measurements for white blood cells, red blood cells and platelet count

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Humira

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the label/blister/carton after EXP.

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

Alternative Storage:

When needed (for example when you are travelling), a single Humira pre-filled syringe may be stored at room temperature (up to 25°C) for a maximum period of 14 days – be sure to protect it from light. Once removed from the refrigerator for room temperature storage, the syringe **must be used within 14 days or discarded**, even if it is returned to the refrigerator.

You should record the date when the syringe is first removed from refrigerator and the date after which it should be discarded.

Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Humira contains

The active substance is adalimumab.
The other ingredients are mannitol, polysorbate 80 and water for injections.

What the Humira pre-filled syringe looks like and contents of the pack

Humira 40 mg solution for injection in pre-filled syringe is supplied as a sterile solution of 40 mg adalimumab dissolved in 0.4 ml solution.

The Humira pre-filled syringe is a glass syringe containing a solution of adalimumab. Each pack contains 1, 2, 4 or 6 pre-filled syringes for patient use with 1, 2, 4 or 6 alcohol pads, respectively.

Not all pack sizes may be marketed.

Humira may be available as a vial, a pre-filled syringe and/or a pre-filled pen.

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Manufacturer

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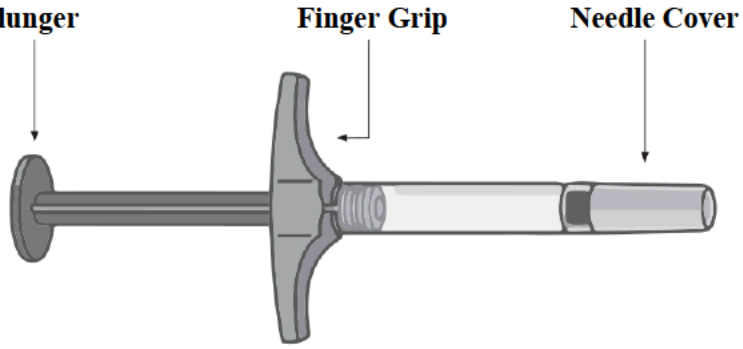
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.

7. Injecting Humira

- The following instructions explain how to give yourself a subcutaneous injection of Humira using the pre-filled syringe. First read all the instructions carefully and then follow them step by step.
- You will be instructed by your doctor, nurse or pharmacist on the technique of self-injection.
- Do not attempt to self-inject until you are sure that you understand how to prepare and give the injection.
- After proper training, the injection can be given by yourself or given by another person, for example, a family member or friend.
- Only use each pre-filled syringe for one injection.

Humira Pre-filled Syringe



Do not use the pre-filled syringe and call your doctor or pharmacist if the

- liquid is cloudy, discoloured, or has flakes or particles in it
- expiry (EXP) date has passed
- liquid has been frozen or left in direct sunlight
- pre-filled syringe has been dropped or crushed

Do not remove the needle cover until just before injection. Keep Humira out of the sight and reach of children.

STEP 1

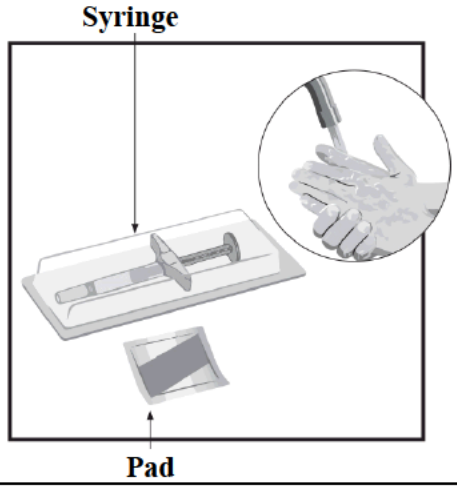
Take Humira out of the refrigerator.

Leave Humira at room temperature for **15 to 30 minutes** before injecting.

- **Do not** remove the needle cover while allowing Humira to reach room temperature
- **Do not** warm Humira in any other way. For example, **do not** warm it in a microwave or in hot water

STEP 2

Check the expiry (EXP) date. **Do not** use the pre-filled syringe if expiry (EXP) date has passed.



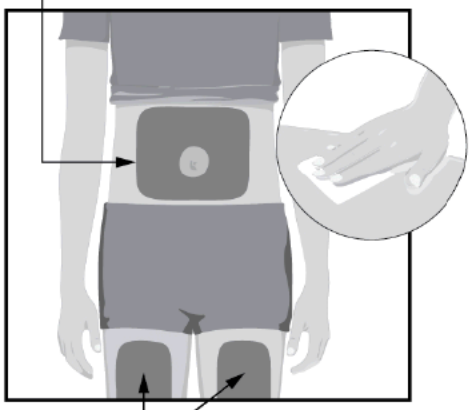
Place the following on a clean, flat surface

- 1 single-use pre-filled syringe and
- 1 alcohol pad

Wash and dry your hands.

STEP 3

Injectable Areas



Injectable Areas

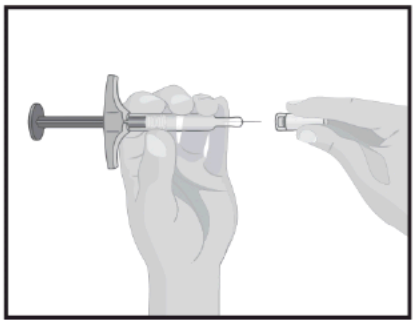
Choose an injection site:

- On the front of your thighs or
- Your belly (abdomen) at least 5 cm from your belly button (navel)
- At least 3 cm from your last injection site

Wipe the injection site in a circular motion with the alcohol pad.

- **Do not** inject through clothes
- **Do not** inject into skin that is sore, bruised, red, hard, scarred, has stretch marks, or areas with psoriasis plaques

STEP 4



Hold the pre-filled syringe in one hand.

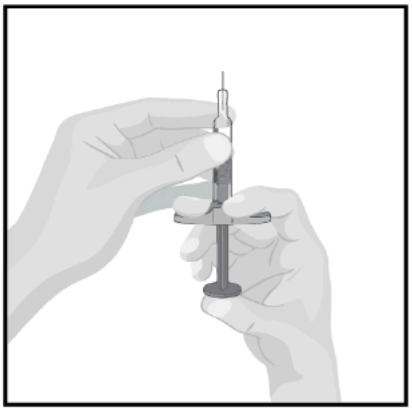
Check the liquid in the pre-filled syringe.

- Make sure the liquid is clear and colourless
- **Do not** use the pre-filled syringe if the liquid is cloudy or has particles
- **Do not** use the pre-filled syringe if it has been dropped or crushed

Gently pull the needle cover straight off with the other hand. Throw the needle cover away. Do not recap.

- **Do not** touch the needle with your fingers or let the needle touch anything

STEP 5



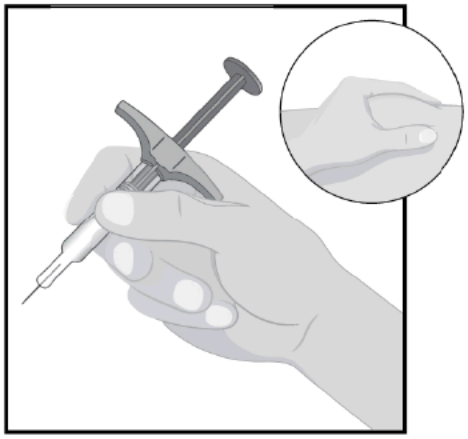
Hold the pre-filled syringe with the needle facing up.

- Hold the pre-filled syringe at eye level with one hand so you can see the air in the pre-filled syringe

Slowly push the plunger in to push the air out through the needle.

- It is normal to see a drop of liquid at the end of the needle

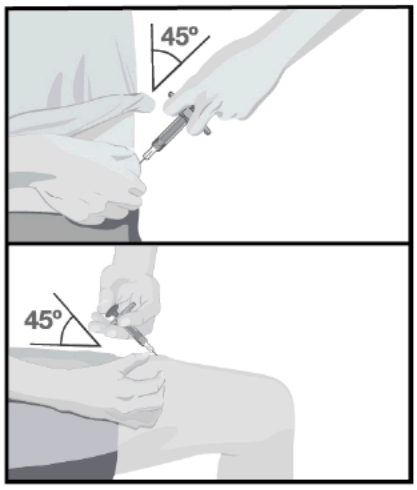
STEP 6



Hold the body of the pre-filled syringe in one hand between the thumb and index fingers, like you would a pencil.

Squeeze the skin at your injection site with your other hand to make a raised area and hold it firmly.

STEP 7

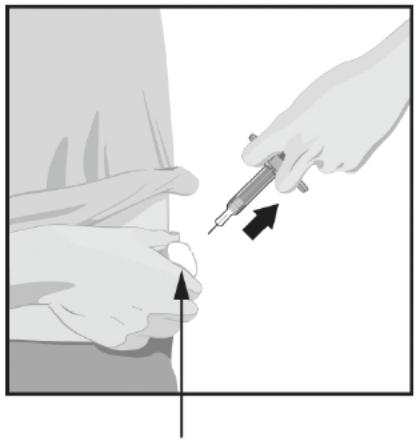


Insert the needle all the way into the skin at about a 45-degree angle with one quick, short motion.

- After the needle is in, let go of the skin you are holding

Slowly push the plunger all the way in until all of the liquid is injected and the pre-filled syringe is empty.

STEP 8



Cotton Ball

When the injection is completed, slowly pull the needle out of the skin while keeping the pre-filled syringe at the same angle.

After completing the injection, place a cotton ball or gauze pad on the skin over the injection site.

- **Do not** rub
- Slight bleeding at the injection site is normal

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STEP 9

Throw away the used pre-filled syringe in a special disposal container as instructed by your doctor, nurse or pharmacist. **Never** recap a needle.

- **Do not** recycle or throw the pre-filled syringe in the household waste
- **Always** keep the pre-filled syringe and the special disposal container out of the sight and reach of children

The needle cover, alcohol pad, cotton ball or gauze pad, blister and packaging may be put in your household waste.

Package leaflet: Information for the patient

Humira 40 mg solution for injection in pre-filled pen
adalimumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will also give you a **Patient Reminder Card**, which contains important safety information that you need to be aware of before you begin using Humira and during treatment with Humira. Keep this **Patient Reminder Card** with you.
- If you have any questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet
1. What Humira is and what it is used for
2. What you need to know before you use Humira
3. How to use Humira
4. Possible side effects
5 How to store Humira
6. Contents of the pack and other information
7. Injecting Humira

1. What Humira is and what it is used for

Humira contains the active substance adalimumab.

Humira is used to treat
- Rheumatoid arthritis
- Polyarticular juvenile idiopathic arthritis
- Enthesitis-related arthritis
- Ankylosing spondylitis
- Axial spondyloarthritis without radiographic evidence of ankylosing spondylitis
- Psoriatic arthritis
- Plaque psoriasis
- Hidradenitis suppurativa
- Crohn's disease
- Ulcerative colitis
- Non-infectious uveitis

The active ingredient in Humira, adalimumab, is a human monoclonal antibody. Monoclonal antibodies are proteins that attach to a specific target.

The target of adalimumab is a protein called tumour necrosis factor (TNFα), which is involved in the immune (defence) system and is present at increased levels in the inflammatory diseases listed above. By attaching to TNFα, Humira decreases the process of inflammation in these diseases.

Rheumatoid arthritis

Rheumatoid arthritis is an inflammatory disease of the joints.

Humira is used to treat moderate to severe rheumatoid arthritis in adults. You may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira.

Humira can also be used to treat severe, active and progressive rheumatoid arthritis without previous methotrexate treatment.

Humira can slow down the damage to the joints caused by the inflammatory disease and can help them move more freely.

Your doctor will decide if Humira should be used with methotrexate or alone.

Polyarticular juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis is an inflammatory disease of the joints.

Humira is used to treat polyarticular juvenile idiopathic arthritis in patients from 2 years of age. You may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira.

Your doctor will decide if Humira should be used with methotrexate or alone.

Enthesitis-related arthritis

Enthesitis-related arthritis is an inflammatory disease of the joints and the places where tendons join the bone.

Humira is used to treat enthesitis-related arthritis in patients from 6 years of age. You may first be given other disease-modifying medicines, such as methotrexate. If you do not respond well enough to these medicines, you will be given Humira.

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis are inflammatory diseases of the spine.

Humira is used to treat severe ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis in adults. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Psoriatic arthritis

Psoriatic arthritis is an inflammatory disease of the joints that is usually associated with psoriasis.

Humira is used to treat psoriatic arthritis in adults. Humira can slow down the damage to the joints caused by the disease and can help them move more freely. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Plaque psoriasis

Plaque psoriasis is a skin condition that causes red, flaky, crusty patches of skin covered with silvery scales. Plaque psoriasis can also affect the nails, causing them to crumble, become thickened and lift away from the nail bed which can be painful.

Humira is used to treat
- moderate to severe chronic plaque psoriasis in adults and
- severe chronic plaque psoriasis in children and adolescents aged 4 to 17 years for whom topical therapy and phototherapies have either not worked very well or are not suitable.

Hidradenitis suppurativa

Hidradenitis suppurativa (sometimes called acne inversa) is a chronic and often painful inflammatory skin disease. Symptoms may include tender nodules (lumps) and abscesses (boils) that may leak pus. It most commonly affects specific areas of the skin, such as under the breasts, the armpits, inner thighs, groin and buttocks. Scarring may also occur in affected areas.

Humira is used to treat
- moderate to severe hidradenitis suppurativa in adults and
- moderate to severe hidradenitis suppurativa in adolescents aged 12 to 17 years.

Humira can reduce the number of nodules and abscesses caused by the disease and the pain that is often associated with the disease. You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Crohn's disease

Crohn's disease is an inflammatory disease of the digestive tract.

Humira is used to treat
- moderate to severe Crohn's disease in adults and
- moderate to severe Crohn's disease in children and adolescents aged 6 to 17 years

You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Ulcerative colitis

Ulcerative colitis is an inflammatory disease of the large intestine.

Humira is used to treat
- moderate to severe ulcerative colitis in adults and
- moderate to severe ulcerative colitis in children and adolescents aged 6 to 17 years.

You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

Non-infectious uveitis

Non-infectious uveitis is an inflammatory disease affecting certain parts of the eye.

Humira is used to treat

- adults with non-infectious uveitis with inflammation affecting the back of the eye
- children with chronic non-infectious uveitis from 2 years of age with inflammation affecting the front of the eye

This inflammation may lead to a decrease of vision and/or the presence of floaters in the eye (black dots or wispy lines that move across the field of vision). Humira works by reducing this inflammation.

You may first be given other medicines. If you do not respond well enough to these medicines, you will be given Humira.

2. What you need to know before you use Humira

Do not use Humira:

- If you are allergic to adalimumab or any of the other ingredients of this medicine (listed in section 6).
- If you have active tuberculosis or other severe infections (see "Warnings and precautions"). It is important that you tell your doctor if you have symptoms of infections, for example, fever, wounds, feeling tired, dental problems.
- If you have moderate or severe heart failure. It is important to tell your doctor if you have had or have a serious heart condition (see "Warnings and precautions").

Warnings and precautions

Talk to your doctor or pharmacist before using Humira.

Allergic reactions

- If you get allergic reactions with symptoms such as chest tightness, wheezing, dizziness, swelling or rash do not inject more Humira and contact your doctor immediately since, in rare cases, these reactions can be life threatening.

Infections

- If you have an infection, including long-term infection or an infection in one part of the body (for example, leg ulcer) consult your doctor before starting Humira. If you are unsure, contact your doctor.
- You might get infections more easily while you are receiving Humira treatment. This risk may increase if you have problems with your lungs. These infections may be serious and include:
  - tuberculosis
  - infections caused by viruses, fungi, parasites or bacteria
  - severe infection in the blood (sepsis)

  In rare cases, these infections can be life-threatening. It is important to tell your doctor if you get symptoms such as fever, wounds, feeling tired or dental problems. Your doctor may tell you to stop using Humira for some time.

- Tell your doctor if you live or travel in regions where fungal infections (for example, histoplasmosis, coccidioidomycosis or blastomycosis) are very common.

- Tell your doctor if you have had infections which keep coming back or other conditions that increase the risk of infections.

- If you are over 65 years you may be more likely to get infections while taking Humira. You and your doctor should pay special attention to signs of infection while you are being treated with Humira. It is important to tell your doctor if you get symptoms of infections, such as fever, wounds, feeling tired or dental problems.

Tuberculosis

- It is very important that you tell your doctor if you have ever had tuberculosis, or if you have been in close contact with someone who has had tuberculosis. If you have active tuberculosis, do not use Humira.

    - As cases of tuberculosis have been reported in patients treated with Humira, your doctor will check you for signs and symptoms of tuberculosis before starting Humira. This will include a thorough medical evaluation including your medical history and appropriate screening tests (for example, chest X-ray and a tuberculin test). The conduct and results of these tests should be recorded on your **Patient Reminder Card**.
    - Tuberculosis can develop during therapy even if you have received treatment for the prevention of tuberculosis.
    - If symptoms of tuberculosis (for example, cough that does not go away, weight loss, lack of energy, mild fever), or any other infection appear during or after therapy tell your doctor immediately.

Hepatitis B

- Tell your doctor if you are a carrier of the hepatitis B virus (HBV), if you have active HBV or if you think you might be at risk of getting HBV.
    - Your doctor should test you for HBV. In people who carry HBV, Humira can cause the virus to become active again.
    - In some rare cases, especially if you are taking other medicines that suppress the immune system, reactivation of HBV can be life-threatening.

Surgery or dental procedure

- If you are about to have surgery or dental procedures, please inform your doctor that you are taking Humira. Your doctor may recommend temporary discontinuation of Humira.

Demyelinating disease

- If you have or develop a demyelinating disease (a disease that affects the insulating layer around the nerves, such as multiple sclerosis), your doctor will decide if you should receive or continue to receive Humira. Tell your doctor immediately if you experience symptoms like changes in your vision, weakness in your arms or legs or numbness or tingling in any part of your body.

Vaccinations

- Certain vaccines may cause infections and should not be given while receiving Humira.

- Check with your doctor before you receive any vaccines.
- It is recommended that children, if possible, be given all the scheduled vaccinations for their age before they start treatment with Humira.
- If you received Humira while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately five months after the last Humira dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy so they can decide when your baby should receive any vaccine.

Heart failure

- If you have mild heart failure and are being treated with Humira, your heart failure status must be closely monitored by your doctor. It is important to tell your doctor if you have had or have a serious heart condition. If you develop new or worsening symptoms of heart failure (e.g. shortness of breath, or swelling of your feet), you must contact your doctor immediately. Your doctor will decide if you should receive Humira.

Fever, bruising, bleeding or looking pale

- In some patients the body may fail to produce enough of the blood cells that fight off infections or help you to stop bleeding. Your doctor may decide to stop treatment. If you develop a fever that does not go away, develop light bruises or bleed very easily or look very pale, call your doctor right away.

Cancer

- There have been very rare cases of certain kinds of cancer in children and adult patients taking Humira or other TNF blockers.
  - People with more serious rheumatoid arthritis that have had the disease for a long time may have a higher than average risk of getting lymphoma (a cancer that affects the lymph system) and leukaemia (a cancer that affects the blood and bone marrow).
  - If you take Humira the risk of getting lymphoma, leukaemia, or other cancers may increase. On rare occasions, an uncommon and severe type of lymphoma, has been seen in patients taking Humira. Some of those patients were also treated with azathioprine or 6-mercaptopurine.
  - Tell your doctor if you are taking azathioprine or 6-mercaptopurine with Humira.
  - Cases of non-melanoma skin cancer have been observed in patients taking Humira.
  - If new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.
- There have been cases of cancers, other than lymphoma in patients with a specific type of lung disease called Chronic Obstructive Pulmonary Disease (COPD) treated with another TNF blocker. If you have COPD, or are a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for you.

Autoimmune disease

- On rare occasions, treatment with Humira could result in lupus-like syndrome. Contact your doctor if symptoms such as persistent unexplained rash, fever, joint pain or tiredness occur.

Children and adolescents

- Vaccinations: if possible, children should be up to date with all vaccinations before using Humira.

Other medicines and Humira

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

You should not take Humira with medicines containing the following active substances due to increased risk of serious infection:
- anakinra
- abatacept.

Humira can be taken together with:
- methotrexate
- certain disease-modifying anti-rheumatic agents (for example, sulfasalazine, hydroxychloroquine, leflunomide and injectable gold preparations)
- steroids or pain medications including non-steroidal anti-inflammatory drugs (NSAIDs).

If you have questions, please ask your doctor.

Pregnancy and breast-feeding

- You should consider the use of adequate contraception to prevent pregnancy and continue its use for at least 5 months after the last Humira treatment.
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice about taking this medicine.
- Humira should only be used during a pregnancy if needed.
- According to a pregnancy study, there was no higher risk of birth defects when the mother had received Humira during pregnancy compared with mothers with the same disease who did not receive Humira.
- Humira can be used during breast-feeding.
- If you receive Humira during your pregnancy, your baby may have a higher risk for getting an infection.
- It is important that you tell your baby's doctors and other health care professionals about your Humira use during your pregnancy before the baby receives any vaccine. For more information on vaccines see the "Warnings and precautions" section.

Driving and using machines

Humira may have a small effect on your ability to drive, cycle or use machines. Room spinning sensation and vision disturbances may occur after taking Humira.

3. How to use Humira

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended doses for Humira in each of the approved uses are shown in the following table.
Your doctor may prescribe another strength of Humira if you need a different dose.

Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or axial spondyloarthritis without radiographic evidence of ankylosing spondylitis		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	40 mg every other week	In rheumatoid arthritis, methotrexate is continued while using Humira. If your doctor decides that methotrexate is inappropriate, Humira can be given alone. If you have rheumatoid arthritis and you do not receive methotrexate with your Humira therapy, your doctor may decide to give Humira 40 mg every week or 80 mg every other week.

Polyarticular juvenile idiopathic arthritis		
Age or body weight	**How much and how often to take?**	**Notes**
Children, adolescents and adults from 2 years of age weighing 30 kg or more	40 mg every other week	Not applicable
Children and adolescents from 2 years of age weighing 10 kg to less than 30 kg	20 mg every other week	Not applicable

Enthesitis-related arthritis		
Age or body weight	**How much and how often to take?**	**Notes**
Children, adolescents and adults from 6 years of age weighing 30 kg or more	40 mg every other week	Not applicable
Children and adolescents from 6 years of age weighing 15 kg to less than 30 kg	20 mg every other week	Not applicable

Plaque psoriasis		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 80 mg (two 40 mg injections in one day), followed by 40 mg every other week starting one week after the first dose.	If you have an inadequate response, your doctor may increase the dosage to 40 mg every week or 80 mg every other week.
Children and adolescents from 4 to 17 years of age weighing 30 kg or more	First dose of 40 mg, followed by 40 mg one week later.	Not applicable

	Thereafter, the usual dose is 40 mg every other week.	
Children and adolescents from 4 to 17 years of age weighing 15 kg to less than 30 kg	First dose of 20 mg, followed by 20 mg one week later. Thereafter, the usual dose is 20 mg every other week.	Not applicable

Hidradenitis suppurativa		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by an 80 mg dose (two 40 mg injections in one day) two weeks later. After two further weeks, continue with a dose of 40 mg every week or 80 mg every other week, as prescribed by your doctor.	It is recommended that you use an antiseptic wash daily on the affected areas.
Adolescents from 12 to 17 years of age weighing 30 kg or more	First dose of 80 mg (two 40 mg injections in one day), followed by 40 mg every other week starting one week later.	If you have an inadequate response to Humira 40 mg every other week, your doctor may increase the dosage to 40 mg every week or 80 mg every other week. It is recommended that you use an antiseptic wash daily on the affected areas.

Crohn's disease		
Age or body weight	**How much and how often to take?**	**Notes**
Children, adolescents and adults from 6 years of age weighing 40 kg or more	First dose of 80 mg (two 40 mg injections in one day), followed by 40 mg two weeks later. If a faster response is required, the doctor may prescribe a first dose of 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg (two 40 mg injections in one day) two weeks later. Thereafter, the usual dose is 40 mg every other week.	Your doctor may increase the dosage to 40 mg every week or 80 mg every other week.

Children and adolescents from 6 to 17 years of age weighing less than 40 kg	First dose of 40 mg, followed by 20 mg two weeks later. If a faster response is required, the doctor may prescribe a first dose of 80 mg (two 40 mg injections in one day), followed by 40 mg two weeks later. Thereafter, the usual dose is 20 mg every other week.	Your doctor may increase the dose frequency to 20 mg every week.

Ulcerative colitis		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg (two 40 mg injections in one day) two weeks later. Thereafter, the usual dose is 40 mg every other week.	Your doctor may increase the dosage to 40 mg every week or 80 mg every other week.
Children and adolescents from 6 years of age weighing less than 40 kg	First dose of 80 mg (two 40 mg injections in one day), followed by 40 mg (one 40 mg injection) two weeks later. Thereafter, the usual dose is 40 mg every other week.	You should continue taking Humira at your usual dose, even after turning 18 years of age.
Children and adolescents from 6 years of age weighing 40 kg or more	First dose of 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg (two 40 mg injections in one day) two weeks later. Thereafter, the usual dose is 80 mg every other week.	You should continue taking Humira at your usual dose, even after turning 18 years of age.

Non-infectious uveitis		
Age or body weight	**How much and how often to take?**	**Notes**
Adults	First dose of 80 mg (two 40 mg injections in one day), followed by 40 mg every other week starting one week after the first dose.	Corticosteroids or other medicines that influence the immune system may be continued while using Humira. Humira can also be given alone.
Children and adolescents from 2 years of age weighing less than 30 kg	20 mg every other week	Your doctor may prescribe an initial dose of 40 mg to be administered one week prior to the start of the usual dose of 20 mg every other week. Humira is recommended for use in combination with methotrexate.
Children and adolescents from 2 years of age weighing at least 30 kg	40 mg every other week	Your doctor may prescribe an initial dose of 80 mg to be administered one week prior to the start of the usual dose of 40 mg every other week. Humira is recommended for use in combination with methotrexate.

Method and route of administration

Humira is administered by injection under the skin (by subcutaneous injection).

Detailed instructions on how to inject Humira are provided in section 7 'Injecting Humira'.

If you use more Humira than you should

If you accidentally inject Humira more frequently than told to by your doctor or pharmacist, call your doctor or pharmacist and tell them that you have taken more. Always take the outer carton of the medicine with you, even if it is empty.

If you forget to use Humira

If you forget to give yourself an injection, you should inject the next dose of Humira as soon as you remember. Then take your next dose as you would have on your originally scheduled day, had you not forgotten a dose.

If you stop using Humira

The decision to stop using Humira should be discussed with your doctor. Your symptoms may return if you stop using Humira.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

This Information is Confidential

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However, some may be serious and require treatment. Side effects may occur at least up to 4 months after the last Humira injection.

Tell your doctor immediately if you notice any of the following

- severe rash, hives or other signs of allergic reaction
- swollen face, hands, feet
- trouble breathing, swallowing
- shortness of breath with physical activity or upon lying down or swelling of the feet

Tell your doctor as soon as possible if you notice any of the following

- signs of infection such as fever, feeling sick, wounds, dental problems, burning on urination
- feeling weak or tired
- coughing
- tingling
- numbness
- double vision
- arm or leg weakness
- a bump or open sore that doesn't heal
- signs and symptoms suggestive of blood disorders such as persistent fever, bruising, bleeding, paleness

The symptoms described above can be signs of the below listed side effects, which have been observed with Humira.

Very common (may affect more than 1 in 10 people)

- injection site reactions (including pain, swelling, redness or itching)
- respiratory tract infections (including cold, runny nose, sinus infection, pneumonia)
- headache
- abdominal pain
- nausea and vomiting
- rash
- musculoskeletal pain

Common (may affect up to 1 in 10 people)

- serious infections (including blood poisoning and influenza)
- intestinal infections (including gastroenteritis)
- skin infections (including cellulitis and shingles)
- ear infections
- oral infections (including tooth infections and cold sores)
- reproductive tract infections
- urinary tract infection
- fungal infections
- joint infections
- benign tumours

- skin cancer
- allergic reactions (including seasonal allergy)
- dehydration
- mood swings (including depression)
- anxiety
- difficulty sleeping
- sensation disorders such as tingling, prickling or numbness
- migraine
- nerve root compression (including low back pain and leg pain)
- vision disturbances
- eye inflammation
- inflammation of the eye lid and eye swelling
- vertigo (feeling of dizziness or spinning)
- sensation of heart beating rapidly
- high blood pressure
- flushing
- haematoma (collection of blood outside of blood vessels)
- cough
- asthma
- shortness of breath
- gastrointestinal bleeding
- dyspepsia (indigestion, bloating, heart burn)
- acid reflux disease
- sicca syndrome (including dry eyes and dry mouth)
- itching
- itchy rash
- bruising
- inflammation of the skin (such as eczema)
- breaking of finger nails and toe nails
- increased sweating
- hair loss
- new onset or worsening of psoriasis
- muscle spasms
- blood in urine
- kidney problems
- chest pain
- oedema (swelling)
- fever
- reduction in blood platelets which increases risk of bleeding or bruising
- impaired healing

Uncommon (may affect up to 1 in 100 people)

- opportunistic infections (which include tuberculosis and other infections that occur when resistance to disease is lowered)
- neurological infections (including viral meningitis)
- eye infections
- bacterial infections
- diverticulitis (inflammation and infection of the large intestine)
- cancer

- cancer that affects the lymph system
- melanoma
- immune disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis)
- vasculitis (inflammation of blood vessels)
- tremor (shaking)
- neuropathy (disorder of the nerves)
- stroke
- hearing loss, buzzing
- sensation of heart beating irregularly such as skipped beats
- heart problems that can cause shortness of breath or ankle swelling
- heart attack
- a sac in the wall of a major artery, inflammation and clot of a vein, blockage of a blood vessel
- lung diseases causing shortness of breath (including inflammation)
- pulmonary embolism (blockage in an artery of the lung)
- pleural effusion (abnormal collection of fluid in the pleural space)
- inflammation of the pancreas which causes severe pain in the abdomen and back
- difficulty in swallowing
- facial oedema (swelling of the face)
- gallbladder inflammation, gallbladder stones
- fatty liver
- night sweats
- scar
- abnormal muscle breakdown
- systemic lupus erythematosus (including inflammation of skin, heart, lung, joints and other organ systems)
- sleep interruptions
- impotence
- inflammations

Rare (may affect up to 1 in 1,000 people)

- leukaemia (cancer affecting the blood and bone marrow)
- severe allergic reaction with shock
- multiple sclerosis
- nerve disorders (such as eye nerve inflammation and Guillain-Barré syndrome that may cause muscle weakness, abnormal sensations, tingling in the arms and upper body)
- heart stops pumping
- pulmonary fibrosis (scarring of the lung)
- intestinal perforation (hole in the intestine)
- hepatitis
- reactivation of hepatitis B
- autoimmune hepatitis (inflammation of the liver caused by the body's own immune system)
- cutaneous vasculitis (inflammation of blood vessels in the skin)
- Stevens-Johnson syndrome (early symptoms include malaise, fever, headache and rash)
- facial oedema (swelling of the face) associated with allergic reactions
- erythema multiforme (inflammatory skin rash)
- lupus-like syndrome
- angioedema (localized swelling of the skin)
- lichenoid skin reaction (itchy reddish-purple skin rash)

Not known (frequency cannot be estimated from the available data)

- hepatosplenic T-cell lymphoma (a rare blood cancer that is often fatal)
- Merkel cell carcinoma (a type of skin cancer)
- Kaposi's sarcoma, a rare cancer related to infection with human herpes virus 8. Kaposi's sarcoma most commonly appears as purple lesions on the skin
- liver failure
- worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)
- weight gain (for most patients, the weight gain was small)

Some side effects observed with Humira may not have symptoms and may only be discovered through blood tests. These include:

Very common (may affect more than 1 in 10 people)

- low blood measurements for white blood cells
- low blood measurements for red blood cells
- increased lipids in the blood
- elevated liver enzymes

Common (may affect up to 1 in 10 people)

- high blood measurements for white blood cells
- low blood measurements for platelets
- increased uric acid in the blood
- abnormal blood measurements for sodium
- low blood measurements for calcium
- low blood measurements for phosphate
- high blood sugar
- high blood measurements for lactate dehydrogenase
- autoantibodies present in the blood
- low blood potassium

Uncommon (may affect up to 1 in 100 people)

- elevated bilirubin measurement (liver blood test)

Rare (may affect up to 1 in 1,000 people)

- low blood measurements for white blood cells, red blood cells and platelet count

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Humira

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the label/blister/carton after EXP.

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

Alternative Storage:

When needed (for example, when you are travelling), a single Humira pre-filled pen may be stored at room temperature (up to 25°C) for a maximum period of 14 days – be sure to protect it from light. Once removed from the refrigerator for room temperature storage, the pen **must be used within 14 days or discarded**, even if it is returned to the refrigerator.

You should record the date when the pen is first removed from refrigerator and the date after which it should be discarded.

Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Humira contains

The active substance is adalimumab.
The other ingredients are mannitol, polysorbate 80 and water for injections.

What the Humira pre-filled pen looks like and contents of the pack

Humira 40 mg solution for injection in pre-filled pen is supplied as a sterile solution of 40 mg adalimumab dissolved in 0.4 ml solution.

The Humira pre-filled pen is a single-use grey and plum-coloured pen which contains a glass syringe with Humira. There are two caps – one is grey and labelled '1' and the other is plum and labelled '2'. There is a window on each side of the pen through which you can see the Humira solution inside the syringe.

The Humira pre-filled pen is available in packs containing 1, 2, 4 and 6 pre-filled pens. The 1 pre-filled pen pack comes with 2 alcohol pads (1 spare). For the 2, 4 and 6 pre-filled pen packs, each pre-filled pen comes with 1 alcohol pad.

Not all pack sizes may be marketed.

Humira may be available as a vial, a pre-filled syringe and/or a pre-filled pen.

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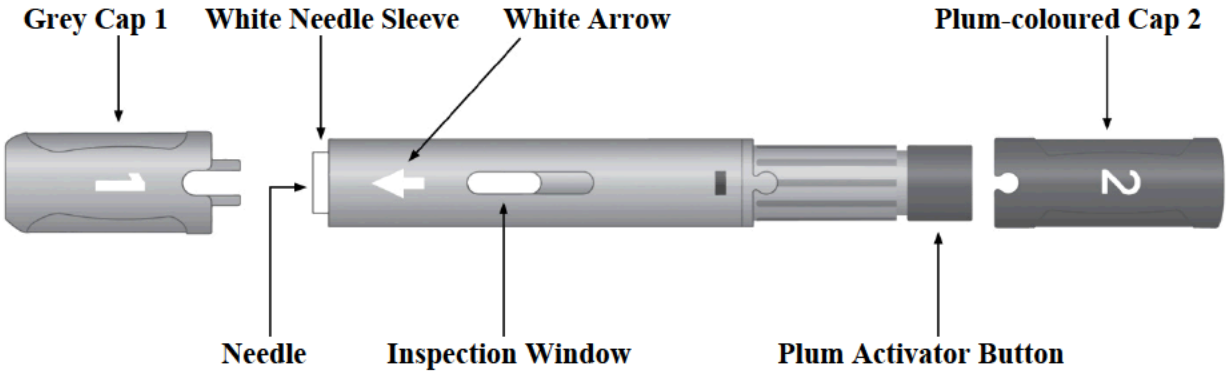
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

To listen to or request a copy of this leaflet in <Braille>, <large print> or <audio>, please contact the local representative of the Marketing Authorisation Holder.

7. Injecting Humira

- The following instructions explain how to give yourself a subcutaneous injection of Humira using the pre-filled pen. First read all the instructions carefully and then follow them step by step.
- You will be instructed by your doctor, nurse or pharmacist on the technique of self-injection.
- Do not attempt to self-inject until you are sure that you understand how to prepare and give the injection.
- After proper training, the injection can be given by yourself or given by another person, for example, a family member or friend.
- Only use each pre-filled pen for one injection.

Humira Pre-filled Pen



Do not use the pre-filled pen and call your doctor or pharmacist if the

- liquid is cloudy, discoloured, or has flakes or particles in it
- expiry (EXP) date has passed
- liquid has been frozen or left in direct sunlight
- pre-filled pen has been dropped or crushed

Do not remove the caps until just before injection. Keep Humira out of the sight and reach of children.