



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Adalimumab

Proprietary Product Name: Humira

Sponsor: Abbott Australasia Pty Ltd (AbbVie Pty Ltd)

January 2014

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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of abbreviations

Abbreviation	Meaning
AE	Adverse event
ALS	Amyotrophic lateral sclerosis
ALT	Alanine transaminase
ANA	Anti-nuclear antibody
AP	Antero-posterior
AS	Ankylosing spondylitis
ASAS	Assessments in Spondyloarthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
AST	Aspartate transaminase
BASDAI	Bath Ankylosing Spondylitis disease activity index
BASFI	Bath Ankylosing Spondylitis functional index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BCG	Bacille Calmette-Guérin
BUN	Blood urea nitrogen
CD	Crohn's disease
CDC	Centers for Disease Control
CHF	Congestive heart failure
CNS	Central nervous system
CRP	C-reactive protein
CSR	Clinical study report
CTC	Common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTX-II	Type II collagen C-telopeptide
CVA	Cerebrovascular accident
CXR	Chest x-ray
DAE	Discontinuation due to adverse event

Abbreviation	Meaning
DB	Double-blind
DMARD	Disease-modifying anti-rheumatic drugs
ECG	Electrocardiogram
eow	Every other week
EQ-5D	European Quality of Life – 5 Dimensions questionnaire
F	Female
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAQ-S	Health Assessment Questionnaire modified for spondyloarthropathies
HCP	Health care provider
HCRU	Health care resource utilization
HLA-B27	Human leukocyte antigen-B27
hs-CRP	High sensitivity C-reactive protein
HSTCL	Hepatosplenic T-cell lymphoma
IBD	Inflammatory bowel disease
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IRB	Institutional review board
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
LOCF	Last observation carried forward
LFT	Liver function test
M	Male

Abbreviation	Meaning
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMP-3	Matrix metalloproteinase 3
MOS	Medical outcomes study
MRI	Magnetic resonance imaging
MTX	Methotrexate
NMSC	Non-melanoma skin cancer
nr-axSpA	Non-radiographic axial SpA
NRI	Non-responder imputation
NSAID	Nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OC	Observed case
OL	Open-label
PA	Posterior-anterior
PASS	Patient acceptable symptom state
PGA	Physician's Global Assessment of Disease Activity
PML	Progressive multifocal leukoencephalopathy
POR	Proof of receipt
PPD	Purified protein derivative
PPP	Per-protocol population
Ps	Psoriasis
PsA	Psoriatic arthritis
PT	Preferred term
PTGA	Patient's Global Assessment
PY	Patient-year
RBC	Red blood cell

Abbreviation	Meaning
RPLS	Reversible posterior leukoencephalopathy syndrome
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SF-36™V2	Short Form-36 Health Status Survey™ Version 2
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SJC	Swollen joint count
SOC	System organ class
SpA	Spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SSZ	Sulfasalazine
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TJC	Tender joint count
TNF	Tumor necrosis factor
UC	Ulcerative colitis
ULN	Upper limit of normal
US	United States
VAS	Visual analog scale
WBC	White blood cell
WPAI-SHP	Work Productivity and Activity Impairment – Specific Health Problem Questionnaire
VEGF _A	Vascular endothelial growth factor A

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of indications
<i>Decision:</i>	Withdrawn
<i>Date of decision:</i>	19 August 2013
<i>Active ingredient:</i>	Adalimumab
<i>Product name:</i>	Humira
<i>Sponsor's name and address:</i>	AbbVie Pty Ltd 32-34 Lord Street Botany NSW 2019
<i>Dose form:</i>	Solution for Injection
<i>Strengths:</i>	20 mg and 40 mg
<i>Container:</i>	Pre-filled syringe, vial and pen (latter two in 40 mg only).
<i>Approved therapeutic use:</i>	Not applicable
<i>Route of administration:</i>	Subcutaneously
<i>Dosage:</i>	Non-radiographic Axial Spondyloarthritis: 40 mg fortnightly
<i>ARTG number:</i>	Not applicable

Product background

Humira (adalimumab) is a Tumour necrosis factor (TNF)- α neutralising recombinant immunoglobulin (IgG₁) monoclonal antibody containing only human peptide sequences. It binds to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface receptors. Humira is produced by recombinant deoxyribonucleic acid (DNA) technology in a mammalian cell expression system.

This AusPAR describes the application by the sponsor to extend the indications for Humira (adalimumab) for:

Non-radiographic Axial Spondyloarthritis (axial spondyloarthritis without radiographic evidence of AS): Humira is indicated for reducing signs and symptoms in patients with non-radiographic axial spondyloarthritis.

Adalimumab has been previously considered by the TGA on numerous occasions, with the ankylosing spondylitis (AS) indication considered in June 2006.

The sponsor has explained the rationale for this indication as follows:

“Currently, there is an unmet medical need in patients with nr-axSpA who have disease features similar to patients with Ankylosing Spondylitis (AS), but who do not fulfil the modified New York criteria for AS by virtue of not having evidence of structural damage in the form of radiographic sacroiliitis. Not all patients with nr-

axSpA go on to develop radiographic sacroiliitis required to fulfil the modified New York criteria for a diagnosis of AS. While non-steroidal anti-inflammatory drugs (NSAIDs) are effective in treating the signs and symptoms of axial SpA in some patients, traditional anti-rheumatic therapies such as methotrexate and sulfasalazine are not effective for the axial component of spondyloarthritis and the use of systemic corticosteroids is not supported by evidence...The potential benefit of anti-TNF therapy in nr-axSpA has been acknowledged by the Assessments in Spondyloarthritis International Society (ASAS) working group that recently published their recommendations for the use of anti-TNF in axial SpA patients. This working group have proposed and validated new classification criteria for patients with axial SpA. Abbott has used this published ASAS criteria to classify nr-axSpA patients for the pivotal study."

Regulatory status

Adalimumab was first approved in Australia in 2003 for rheumatoid arthritis and is currently approved for use in a variety of conditions including psoriatic arthritis, ankylosing spondylitis, polyarticular juvenile idiopathic arthritis, psoriasis and Crohn's disease.¹

Adalimumab has been approved for a modified indication in the European Union (EU) under the Centralised Procedure (July 2012).

The submission is currently under evaluation in Canada, USA, Switzerland and New Zealand.

The data submitted to the TGA was the same as that submitted in the EU. The approved indication in the EU has also been combined with the AS indication under a new heading called Axial Spondyloarthritis as follows:

Axial spondyloarthritis

Ankylosing spondylitis(AS)

Humira is indicated for the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Axial spondyloarthritis without radiographic evidence of AS.

¹ Currently approved indications:

Rheumatoid Arthritis: Humira is indicated for reducing signs and symptoms, as well as inhibiting the progression of structural damage in adult patients with moderate to severely active rheumatoid arthritis. This includes the treatment of patients with recently diagnosed moderate to severely active disease who have not received methotrexate.

Humira can be used alone or in combination with methotrexate.

Psoriatic Arthritis: Humira is indicated for the treatment of signs and symptoms, as well as inhibiting the progression of structural damage, of moderate to severely active psoriatic arthritis in adult patients where response to previous DMARDs has been inadequate.

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

Crohn's Disease: Humira is indicated for the treatment of moderate to severe Crohn's disease in adults to reduce the signs and symptoms of the disease and to induce and maintain clinical remission in patients who have had an inadequate response to conventional therapies, or who have lost response to or are intolerant of infliximab.

Psoriasis: Humira is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Polyarticular Juvenile Idiopathic Arthritis: Humira in combination with methotrexate is indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients aged 4 years of age and older.

Humira can be given as monotherapy in case of intolerance or when continued treatment with methotrexate is inappropriate.

Humira is indicated for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and / or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The sponsor justified the development of adalimumab for the treatment of non-radiographic Axial Spondyloarthritis (nr-axSpA) with the following argument:

“Currently, there is an unmet medical need in patients with nr-axSpA who have disease features similar to patients with Ankylosing Spondylitis (AS), but who do not fulfil the modified New York criteria for AS by virtue of not having evidence of structural damage in the form of radiographic sacroiliitis.”

This patient group does not respond to traditional Disease-modifying anti-rheumatic drugs (DMARDs) such as Methotrexate (MTX) and sulfasalazine. Nonsteroidal anti-inflammatory drugs (NSAIDs) provide some symptom relief but some patients may not have sufficient response to this treatment. Whilst adalimumab and other anti-TNF therapies have been approved for the indication of Ankylosing spondylitis (AS), patients with nr-axSpA do not have access to (approved) treatments other than NSAIDs.

Contents of the clinical dossier

The submission contained the following clinical information:

- One efficacy/safety study: Study M10-791.
- Three files containing tabulations of pooled safety data

Paediatric data

The submission did not include paediatric data. There are no plans for a paediatric development program for non radiographic axial spondyloarthritis (nr-axSpA).

Good clinical practice

The studies presented in the present application were conducted in accordance with Good Clinical Practice.

Pharmacokinetics

There were no new pharmacokinetic data included in the dossier.

Pharmacodynamics

There were no new pharmacodynamic data included in the dossier.

Efficacy**Dosage selection for the pivotal studies**

The sponsor did not conduct dose finding studies for the present application. The dose selected for development appears to be based on the approved dose for the indication of AS.

Evaluator's conclusions on clinical efficacy for Non-Radiographic Axial SpA

Efficacy has been demonstrated for adalimumab in comparison with placebo for the indication of nr-axSpA over a 12 week period. The response rate was both clinically and statistically significant. The response was maintained in an open label follow-on study for up to 68 weeks. Response was greater in subjects with elevated C-reactive protein (CRP) at baseline and with shorter duration of symptoms. For those subjects with no concomitant Disease-modifying anti-rheumatic drugs (DMARDs) at baseline (monotherapy) there were five (26.3%) responders in the adalimumab group and none in the placebo.

The Assessments in Spondyloarthritis International Society (ASAS) worked on developing criteria for axial Spondyloarthritis (SpA) that include patients with and without definite radiographic sacroiliitis because "*radiographic changes may reflect the consequences of inflammation (structural damage) rather than inflammation itself, which may be readily detectable by magnetic resonance imaging (MRI), often years before the appearance of radiographic sacroiliitis*".² These criteria were developed using questionnaires, logistic regression, sensitivity and specificity analysis and were voted on by the members of the ASAS (Figure 1).

²Rudwaleit M. et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (Part II): validation and final selection. Ann Rheum Dis 2009;68:777-783.

Figure 1. ASAS classification criteria for Axial SpA (copied from Figure 2, Rudawaleit 2009a)

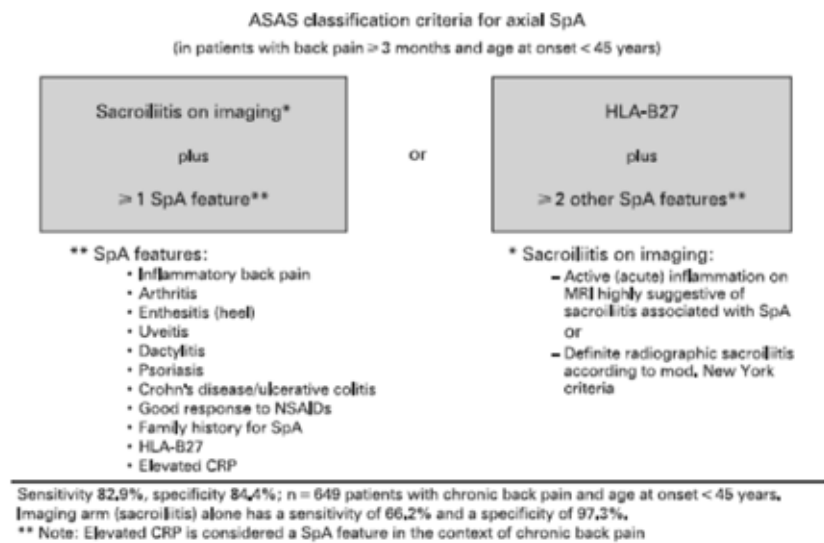


Figure 2 Final set of classification criteria for axial spondyloarthritis (SpA) selected by the Assessment of SpondyloArthritis international Society (ASAS). The criteria encompass both patients with and without definite radiographic sacroiliitis. According to the criteria, a patient with chronic back pain (≥ 3 months) and age at onset less than 45 years can be classified in the presence of sacroiliitis (either definite radiographic sacroiliitis or active inflammation of sacroiliac joints on magnetic resonance imaging (MRI), which is highly suggestive of sacroiliitis associated with SpA) plus at least one typical SpA feature, or in the presence of HLA-B27 plus at least two other SpA features. Sensitivity 82.9%, specificity 84.4%; n = 649 patients with chronic back pain and age at onset less than 45 years. The imaging arm (sacroiliitis) alone has a sensitivity of 66.2% and a specificity of 97.3%.
**Elevated C-reactive protein (CRP) is considered a SpA feature in the context of chronic back pain. NSAID, non-steroidal anti-inflammatory drug.

Radiographic axial SpA is currently an indication for adalimumab but non-radiographic axial SpA is currently not an indication. In order to demonstrate the efficacy and safety of adalimumab in non-radiographic axial SpA subjects with Ankylosing spondylitis (AS), Psoriatic arthritis (PsA) and rheumatoid arthritis (RA) (all current indications) needed to be excluded from the study population. The inclusion criteria and exclusion criteria satisfactorily define the study population (and this study population is the same as that intended for treatment).

The indication of nr-axSpA could be considered to be an extension of AS, which is currently an approved indication for adalimumab. This supports the dose regimen chosen for development for nr-axSpA.

The primary efficacy outcome measure was ASAS40³ response. This measure was a previously validated outcome measure and was developed independent of the development program. There were a large number of secondary outcome measures, all of which can be rationally applied to nr-axSpA. All of these outcome measures were supportive of efficacy compared with placebo over 12 weeks and maintenance of efficacy for up to 68 weeks.

The limitations of the efficacy data include:

- Few elderly subjects were included in Study M10-791 (only two subjects over the age of 65 years)
- There were no analyses to investigate drug-drug or drug-disease interactions; and drug dose, drug concentration, and relationship to response.
- Nr-axSpA is a chronic condition and there were no efficacy data extending beyond 68 weeks.

³ ASAS 40 is defined as at least a 40 percent improvement from baseline using the ASAS criteria.

Safety

Studies providing evaluable safety data

Study M10-791 provided evaluable safety data for this submission.

The sponsor provided some summary tables of safety data across all clinical trials of adalimumab. These tables relate to proposed changes in Product Information document for event rates for infection, malignancy and withdrawal due to adverse events (AEs). These rates have been adjusted to include data for the indication of nr-axSpA. The rates presented in the draft PI do correspond with those presented in the tabulations.

Pivotal studies that assessed safety as a primary outcome

There were no additional pivotal studies that assessed safety as a primary outcome.

Patient exposure

In Study M10-791, there were 190 subjects exposed to adalimumab, of whom 164 (86.3%) were exposed for ≥ 175 days, 147 (77.4%) were exposed for ≥ 343 days and 69 (36.3%) for ≥ 427 days. Total patient-years exposure was 193.3 years.

Postmarketing experience

No postmarketing data were included in the submission.

Evaluator's overall conclusions on clinical safety

Exposure to adalimumab for the indication of nr-axSpA is limited, with total exposure being 190 subjects of whom 147 were exposed for ≥ 343 days and total patient-years exposure was 193.3 years.

The rate of TEAEs during the 12 week double blind phase was similar to that for placebo. The rate of infections was similar to that for placebo. Injection site related AEs were more common with adalimumab than placebo: 8.4% subjects compared with 3.1% respectively. These injection site reactions were mild in nature. Allergic reactions were more common with adalimumab than placebo: nine (4.7%) subjects compared with one respectively. The rate of SAEs was similar for the two treatment groups. The rate of DAE was similar for the two treatment groups.

Overall, in those subjects exposed to adalimumab the profile of AEs was similar to that previously reported for adalimumab. There were three subjects with serious infectious AEs, one of which was Tuberculosis (TB). There were no reports of opportunistic infections (excluding TB), lymphomas, Non-melanoma skin cancer (NMSC), malignancies (excluding NMSC and lymphomas) or demyelinating disease.

There were two deaths during the study, neither of which appeared to be related to study treatment.

There were no new safety concerns apparent in the clinical data.

There were no indications of drug interactions, or of concomitant medication (including DMARDs) contributing to an increased risk of AEs.

The safety data is limited by the relatively small number of subjects exposed to adalimumab of the indication of nr-axSpA. However, the indication is similar to AS, and the patient group studied similar to others previously studied for other indications that adalimumab is already approved for. Hence, the adverse effects profile of adalimumab for the indication of nr-axSpA can be expected to be the same as that for the previously approved indications.

First round benefit-risk assessment

First round assessment of benefits

Efficacy has been demonstrated for adalimumab in comparison with placebo for the indication of nr-axSpA over a 12 week period. The response rate was both clinically and statistically significant. The response was maintained in an open label follow-on study for up to 68 weeks. Response was greater in subjects with elevated CRP at baseline and with shorter duration of symptoms. For those subjects with no concomitant DMARDs at baseline (monotherapy) there were five (26.3%) responders in the adalimumab group and none in the placebo.

The indication of nr-axSpA could be considered to be an extension of AS, which is currently an approved indication for adalimumab. This supports the dose regimen chosen for development for nr-axSpA.

The primary efficacy outcome measure was ASAS40 response. This measure was a previously validated outcome measure and was developed independent of the development program. There were a large number of secondary outcome measures, all of which can be rationally applied to nr-axSpA. All of these outcome measures were supportive of efficacy compared with placebo over 12 weeks, and maintenance of efficacy for up to 68 weeks.

The limitations of the efficacy data include:

- Few elderly subjects were included in Study M10-791 (only two subjects over the age of 65 years)
- There were no analyses to investigate drug-drug or drug-disease interactions; and drug dose, drug concentration and relationship to response.
- Nr-axSpA is a chronic condition and there were no efficacy data extending beyond 68 weeks.

First round assessment of risks

Exposure to adalimumab for the indication of nr-axSpA is limited, with total exposure being 190 subjects of whom 147 were exposed for ≥ 343 days and total patient-years exposure was 193.3 years.

The rate of treatment emergent AEs (TEAEs) during the 12 week double blind phase was similar to that for placebo. The rate of infections was similar to that for placebo. Injection site related AEs were more common with adalimumab than placebo: 8.4% subjects compared with 3.1% respectively. These injection site reactions were mild in nature. Allergic reactions were more common with adalimumab than placebo: nine (4.7%) subjects compared with one respectively. The rate of serious AEs (SAEs) was similar for the two treatment groups. The rate of Discontinuation due to adverse event (DAE) was similar for the two treatment groups.

Overall, in those subjects exposed to adalimumab the profile of AEs was similar to that previously reported for adalimumab. There were three subjects with serious infectious AEs, one of which was TB. There were no reports of opportunistic infections (excluding TB), lymphomas, NMSC, malignancies (excluding NMSC and lymphomas) or demyelinating disease.

There were two deaths during the study, neither of which appeared to be related to study treatment.

There were no new safety concerns apparent in the clinical data.

There were no indications of drug interactions or of concomitant medication (including DMARDs) contributing to an increased risk of AEs.

The safety data is limited by the relatively small number of subjects exposed to adalimumab of the indication of nr-axSpA. However, the indication is similar to AS and the patient group studied similar to others previously studied for other indications that adalimumab is already approved for. Hence, the adverse effects profile of adalimumab for the indication of nr-axSpA can be expected to be the same as that for the previously approved indications.

First round assessment of benefit-risk balance

The benefit-risk balance of adalimumab, given the proposed usage, was considered to be favourable.

First round recommendation regarding authorisation

The evaluator recommended that adalimumab should be approved for the additional indication of:

Non-Radiographic Axial Spondyloarthritis

Humira is indicated for reducing signs and symptoms in patients with non-radiographic axial spondyloarthritis

List of questions

The only questions raised by the evaluator concerned the draft Product Information document and discussion of these issues are beyond the scope of this AusPAR.

Second round evaluation of clinical data submitted in response to questions

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of adalimumab in the proposed usage were considered to be unchanged from those identified in the First Round Evaluation.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of adalimumab in the proposed usage were considered to be unchanged from those identified in the First Round Evaluation.

Second round assessment of benefit-risk balance

The benefit-risk balance of adalimumab, given the proposed usage, was considered to be favourable.

Second round recommendation regarding authorisation

The evaluator recommended that adalimumab should be approved for the additional indication of:

Non-Radiographic Axial Spondyloarthritis

Humira is indicated for reducing signs and symptoms in patients with non-radiographic axial spondyloarthritis

V. Pharmacovigilance findings**Risk management plan**

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown in Table 1.

Table 1. Summary of Ongoing Safety Concerns. Table continued across 3 pages.

Summary of ongoing safety concerns	
Important identified risks	<ul style="list-style-type: none"> · Serious infections including opportunistic infections, for example, invasive fungal infections, parasitic infections, legionellosis, and TB · Reactivation of hepatitis B · Pancreatitis · Lymphoma · Hepatosplenic T-cell Lymphoma · Leukemia · Non-melanoma Skin Cancer · Melanoma · Demyelinating disorders (including MS, GBS, and optic neuritis) · Immune reactions (including lupus-like reactions and allergic reactions) · Sarcoidosis · Congestive Heart Failure · Myocardial Infarction · Cerebrovascular Accident · Interstitial Lung Disease · Pulmonary embolism · Cutaneous vasculitis · SJS and erythema multiforme · Worsening and new onset of Ps · Haematologic disorders · Intestinal perforation

Summary of ongoing safety concerns	
	<ul style="list-style-type: none"> · Intestinal strictures in CD · Liver failure · Elevated ALT levels · Medication errors and maladministration
Important potential risks	<ul style="list-style-type: none"> · Other malignancies (except lymphoma, HSTCL, leukemia, NMSC and melanoma) · Vasculitis (non-cutaneous) · Progressive Multifocal Leukoencephalopathy · Reversible Posterior Leukoencephalopathy Syndrome · Amyotrophic Lateral Sclerosis · Colon cancer in UC patients · Infections in infants exposed to adalimumab <i>in utero</i> · Medication errors with paediatric vial · Off-label use
Important missing information	<ul style="list-style-type: none"> · Subjects with immune-compromised conditions (i.e., subjects with HIV, post-chemotherapy, organ transplant) · subjects with a history of clinically significant drug or alcohol abuse · Subjects with poorly controlled medical conditions such as uncontrolled diabetes or documented history of recurrent infections, unstable ischemic heart disease, CHF, recent cerebrovascular accidents · Subjects with history of listeriosis, history of histoplasmosis, active TB, persistent chronic or active infections requiring treatment with antibiotics, antivirals, or antifungals, history of viral hepatitis · Subjects with history of cancer, lymphoma, leukaemia, or lymphoproliferative disease; · subjects with history of neurologic symptoms suggestive of demyelinating disorders · Children < 18 years of age for PsA, AS, Ps, UC, SpA, HS, ERA, and uveitis indications · Children < 4 years of age for JIA and pedPs · Children < 6 years of age for pedCD and pedERA · Pregnant and lactating women · Subjects with renal or liver impairment · Patients taking concomitant biologic therapy · Long-term RA data beyond 5 years

Summary of ongoing safety concerns

- Long-term JIA data beyond 7.5 years
- Episodic treatment in JIA
- Long-term AS data beyond 5 years
- Short- and long-term SpA data
- Short- and long-term pedERA data
- Long-term PsA data beyond 3 years
- Long-term Ps data beyond 6 years
- Episodic treatment in Ps
- Short- and long-term HS data
- Long-term CD data beyond 5 years
- Episodic treatment in CD
- Long-term ped CD data beyond 2 years
- Long-term UC data
- Episodic treatment in UC;
- Short- and long-term uveitis data.

RA= Rheumatoid Arthritis; JIA= Polyarticular juvenile idiopathic arthritis PsA= Psoriatic arthritis; AS= Ankylosing spondylitis CD= Crohn's disease; Ps =Psoriasis; pedERA= Paediatric Enthesitis-related Arthritis; SpA= Spondyloarthritis; UC= Ulcerative Colitis

Evaluator comment

Notwithstanding the clinical and nonclinical evaluations, it was considered that the list of Ongoing Safety concerns was acceptable.

Pharmacovigilance plan

Routine pharmacovigilance was proposed by the sponsor for all Important identified and potential risks. Routine activities, as described by the sponsor include monitoring through long term clinical studies, registries and postmarketing surveillance activities.

There are multiple ongoing pharmacovigilance activities which apply to the other approved indications. For the purposes of this report the activities relating to the proposed application are described below.

- M10-791 is a 12 week randomised, double-blind, placebo controlled study to assess the efficacy and safety of adalimumab in subjects with axial spondyloarthritis followed by a 92 week⁴ open-label period. 192 subjects are enrolled and Australian patients are included. Interim data from this study (up to 68 weeks) was included as a pivotal study in this application.
- M10-883 is a 12 week randomised double-blind placebo controlled study to assess the efficacy and safety of adalimumab in the treatment of adult subjects with non-AS, non-PsA active peripheral spondyloarthritis. An open label period of this study will continue for 92 weeks.⁴ 73 subjects are enrolled and Australian patients are included. As these studies were ongoing at the time of this report, the protocols have not been evaluated in detail for the purposes of this evaluation. Nevertheless it was expected

⁴ Sponsor comment: "Since the publication of this RMP, the protocols for these studies have been amended to include a 144 week open-label extension."

that results of these studies will be communicated to the TGA via Periodic Safety Update Reports (PSURs) and updates to the RMP.

Risk minimisation activities

The sponsor stated that routine risk minimisation activities are not sufficient for the following safety concerns: serious infections, lymphoma, Hepatosplenic T-cell lymphoma (HSTCL), leukemia, NMSC, melanoma, demyelinating disorders, Congestive heart failure (CHF), medication errors and maladministration, other malignancies. For these safety concerns, an educational program was proposed as additional risk minimisation.

According to the RMP the program comprises the following elements:

- Patient Information Alert Card
- Humira safety monograph
- TB screening brochure
- TB screening checklist
- Publications on specific safety topics

In regard to routine risk minimisation the draft Product Information and Consumer Medicine Information were considered to be satisfactory.

The following table (Table 2) summarises the OPR's evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the second round OPR evaluation of the sponsor's responses.

Table 2. Reconciliation of issues outlined in the RMP report. Continued across 2 pages.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>1. Safety considerations may be raised by the clinical and non-clinical evaluators through the TGA's consolidated requests and/or the nonclinical and clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the Risk Management Plan and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.</p>	<p><i>The safety profile of adalimumab is well established and no safety issues requiring further consideration were raised in the TGA's consolidated request for information. AbbVie has not yet received a copy of the clinical evaluation report.</i></p>	<p>This was considered acceptable.</p>
<p>2. The sponsor should provide further detail of the education program for Australia including whether it is already in use, draft education materials and a distribution plan.</p>	<p><i>The sponsor has provided further detail and draft versions of the educational materials.</i></p>	<p>The current and planned activities as outlined in the sponsor's response were acceptable from a RMP standpoint. Such detail should be included in the Australian-specific Annex when it is next updated</p>

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
		and provided to the TGA.
<p>3. The RMP states that "affiliates are implementing country-specific evaluations". The sponsor should provide more detail on the Australian specific evaluation of the effectiveness of the education program.</p>	<p><i>Abbvie is currently developing an evaluation tool to assess the effectiveness of the Australian educational program. An online survey will be conducted by an independent third party vendor each year for 2 years after approval of new indications. Participants will be a representative cross section of potential Humira prescribers. Further evaluation will be conducted as appropriate and the educational program modified as necessary.</i></p>	<p>This approach was considered acceptable. Once developed, further detail of this assessment should be included in an updated to the risk minimisation section of the Australian-specific Annex and submitted to the TGA.</p>

It was considered that the sponsor's response to the TGA consolidated request for information adequately addressed all of the issues identified in the RMP evaluation report.

Outstanding issues

There were no outstanding issues in relation to the RMP for this submission.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

Implement RMP for Adalimumab (Edition 10.0, November 2011) with Australian Specific Annex (undated) and any future updates as a condition of registration.

PSUR

Note: In the EU, PSURs are required every 3 years for this product.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator has reviewed the submitted data, which included:

- 1 Phase III pivotal study (Study M10-791).
- 3 reports of analyses on infections/Infestations, non-infection and Humira SpA Label support.

The clinical evaluator recommended approval in the evaluation report for the indication as requested by the sponsor with no changes requested for the PI.

The benefits noted by the evaluator included:

- Clinically and statistically significant efficacy over a 12 week period compared to placebo.
- Maintenance of efficacy in an open label follow-up.
- Response was greater in those with elevated CRP at baseline and shorter duration of symptoms.
- Safety profile was consistent with previously reported studies and no new safety concerns.

The concerns or issues noted by the evaluator included:

- Few elderly subjects were included in the pivotal trial (only two over 65 years).
- No analyses of drug-drug or drug-disease interactions and relationship to response.
- No efficacy data beyond 68 weeks.
- Safety data is limited but the indication is similar to AS with a safety profile expected to be similar to other approved indications.

Pharmacology:

No clinical pharmacology studies were submitted.

Efficacy***Study M10-791***

This was a multicentre, multinational, randomised, double blind, placebo controlled, parallel group study of 40 mg adalimumab fortnightly compared with placebo, self administered subcutaneously for 12 weeks with an open label extension of 144 weeks (data to 68 weeks total has been provided) with 185 patients on 40 mg adalimumab (142 completed to week 68, 55% female, age 19-72 but only 2 subjects >65 years, mean 78kg). Patients were ≥ 18 years, had active axial spondyloarthritis not fulfilling the modified New York criteria for AS, an inadequate response to, intolerance to or a contraindication to NSAIDs, back pain of at least 3 months, MRI evidence of active inflammatory lesions of the sacroiliac joints or positive HLA-B27 plus some clinical criteria. Patients were excluded if they had AS, psoriasis or psoriatic arthritis, not on a stable DMARD or corticosteroid dose, unstable extra-articular manifestations or recent spinal surgery. Subjects could continue on their stable doses of DMARDs, prednisone, analgesics (except opioids but including tramadol) and/or NSAIDs. Treatment groups were similar at baseline including disease duration, axial SpA related conditions, prior and concomitant treatments (mean 2.9 years

of SpA diagnosis, mean 10 years of SpA symptoms, 48% active inflammatory lesions on MRI of the sacroiliac joint, 78% HLA-B27 positive, 97% inflammatory back pain, 39% elevated CRP, 35% prior DMARD use, 97% prior NSAID use) but there were slightly more patients who were HLA-B27 positive (82% versus 73%) and MRI of the sacroiliac joint positive (51% versus 46%) on adalimumab compared to placebo. 97% completed to Week 12 and 79% completed to Week 68 with the main reasons for discontinuations being adverse event, consent withdrawal and Other. Some 11% of subjects had protocol deviations. The study had 90% power to detect a difference in the primary endpoint.

The primary efficacy endpoint of ASAS40 response at Week 12 using the final analysis set (improvement of $\geq 40\%$ and absolute improvement of ≥ 20 units (scale 0-100) from baseline in ≥ 3 of 4 domains of patient global assessment (VAS score 0-100), total back pain (VAS score 0-100), function (BASFI score 0-100) and inflammation (average of two morning stiffness related BASDAI VAS scores) with no deterioration in the remaining domain) showed superiority of adalimumab compared to placebo of 36.3% versus 14.9%, $p < 0.001$ (ITT 34.7% versus 14.4%, $p < 0.001$). ASAS40 response appeared to be maintained to Week 24 (52%) and Week 68 (67%).

The subgroup analysis showed some patients had greater ASAS40 responses on adalimumab if they were males versus females (52% versus 21%), age < 40 years versus > 40 years (46% versus 21%), abnormal pooled CRP at baseline versus normal at baseline (55% versus 27%), HLA-B27 positive versus negative (40% versus 19%), concomitant DMARD use at baseline versus none (47% versus 34%), concomitant NSAID use at baseline versus none (39% versus 26%) and < 5 years symptom duration versus ≥ 5 years (49% versus 31%). A history of Inflammatory bowel disease (IBD) or uveitis at screening also had greater ASAS40 responses but the number of subjects was too low. Of these results, an abnormal baseline pooled CRP and < 5 years symptom duration were significant findings with age < 40 years of borderline significance.

The large number of secondary endpoints supported the efficacy of adalimumab compared with placebo at Week 12 and appeared to be maintained through to Week 68 (or Week 52 for some measures). These included ASAS20, ASAS5/6, Bath Ankylosing Spondylitis disease activity index (BASDAI 50), Short Form-36 Health Status Survey™ Version 2 (SF-36) physical component score and Health Assessment Questionnaire modified for spondyloarthropathies (HAQ) score modified for spondyloarthropathies. However there was no difference in biomarker measures of matrix metalloproteinase-3, type II collagen C-telopeptide or vascular endothelial growth factor A.

Safety

There were 190 patients exposed to adalimumab in the pivotal study of whom 147 were exposed for ≥ 343 days. Treatment emergent adverse events occurred in 58% on adalimumab versus 59% on placebo with the most common being nasopharyngitis (11.6% versus 3.1%) in the double blind period. Infections occurred in 29.5% of adalimumab subjects compared with 28.9% of placebo subjects (majority being upper respiratory tract infections) and mild injection site reactions occurred in 8.4% versus 3.1%. Nine subjects reported allergic reaction related TEAEs compared with one subject on placebo. Throughout the entire study, the TEAEs occurred in 79.5% of subjects on adalimumab with nasopharyngitis (17.9%) and spondylitis (10.5%) being the most common. There were three serious infections with one of them being tuberculosis. There were no reports of opportunistic infections (excluding TB), lymphomas, malignancies or demyelinating disease. Treatment related TEAEs occurred in 32.6% on adalimumab versus 21.6% on placebo during the double blind period increasing to 45.3% for the entire study with the most common being nasopharyngitis. There were two deaths (suicide and opioid toxicity). Serious adverse events occurred in 3.2% on adalimumab versus 1% on placebo which increased to 10% for the entire study with no clear pattern. Discontinuations occurred in

two adalimumab subjects versus one placebo subject, which increased to 6.3% of subjects for the entire study. Hepatic related events were similar at 4.2% on adalimumab versus 4.1% on placebo and 5.3% on adalimumab for the entire study. There were no significant changes in haematology, chemistry or vital signs.

Risk management plan

The Office of Product Review has accepted the Risk Management Plan (RMP) for Adalimumab (edition 10.0, November 2011) with Australian Specific Annex (undated) and recommended further changes to the Australian Specific Annex as outlined below from their report:

- Details of the education program for Australia
- Evaluation of the education program for Australia

The sponsor should address these matters in the Pre Advisory Committee on Prescription Medicines (ACPM) Response and follow up where appropriate with the TGA's Office of Product Review.

Risk-benefit analysis

Delegate considerations

Efficacy

Adalimumab has demonstrated superiority to placebo in one phase III trial in patients with axSpA over a 12 week period with efficacy appearing to be maintained up to 68 weeks in an open label follow up extension. The primary endpoint (ASAS 40) was a previously validated outcome measure which was developed independent of the development program. The primary endpoint was supported by a large number of secondary endpoints over 12 weeks and maintained for up to 68 weeks. The indication at present is broad and covers all age groups, all grades of disease severity (that is, mild, moderate and severe) and is currently not restricted to patients who have failed other treatments. The pivotal study required patients who were ≥ 18 years, must have had an inadequate response, intolerance or contraindication to NSAIDs, back pain of at least 3 months, MRI evidence of active inflammatory lesions of the sacroiliac joints or positive HLA-B27 plus some clinical criteria. In Europe, the indication has been restricted to adults with severe disease and diagnostic criteria of objective signs of inflammation by elevated CRP and/or MRI. The indication was also modified to be grouped with the AS indication under a new heading of Axial Spondyloarthritis. Usually diagnostic features are placed in the *Clinical Trials* section of the PI if the disease is well defined, however, ACPM's advice on this was requested by the Delegate. Subgroup analysis of the primary endpoint showed that patients with abnormal baseline pooled CRP and <5 years symptom duration had greater responses and these findings were significant for a treatment interaction.

Safety and RMP

Adalimumab has demonstrated an acceptable safety profile consistent with that seen for ankylosing spondylitis. The adverse effects profile is expected to be similar to other approved indications for adalimumab. The single pivotal study does however provide limited safety data but the sponsor is continuing this study for an additional 144 weeks of open label treatment and the submission of the final clinical study report will be made a condition of registration. There was a lack of patients over 65 years which the sponsor should address in the PI however the AS data are supportive. Treatment emergent adverse events, serious adverse events and discontinuations due to adverse events were similar to

placebo over the 12 week period with a similar rate of infections but mild injection site adverse events, allergic reactions and nasopharyngitis were more common with adalimumab. There were three serious infections including one case of tuberculosis. No new safety concerns appeared from the data and there were no reports of opportunistic infections (excluding TB), lymphomas, malignancies or demyelinating disease.

Data deficiencies

Only two elderly patients were included in the submission and the submitted data were only up to 68 weeks exposure.

Summary

Overall at present the submission appears approvable with demonstrated efficacy and an acceptable safety profile. The principal issue is the wording of the indication and whether it should be restricted.

ACPM's advice was requested on the following issues:

1. Is non-radiographic axial spondyloarthritis a disease with consistently defined and agreed diagnostic criteria that supports a new indication?
2. Should the indication be a subset of axial spondyloarthritis and combined with ankylosing spondylitis as in the EU?
3. Should the indication require inclusion of objective signs of inflammation and diagnostic criteria such as MRI and/or CRP or would this be more appropriate in the *Clinical Trials* section of the PI?
4. Should the indication be restricted to only severe forms of the disease, for use only in adults and for those who have had an inadequate response to or are intolerant of nonsteroidal anti-inflammatory drugs (that is, second line therapy)?

Delegate's questions for the sponsor

The sponsor was asked to address the following issues in the Pre-ACPM response:

1. Discuss the grades of disease severity for patients with nr-axSpA in the pivotal study, that is, mild, moderate and severe and provide an explanation as to why the indication in Europe was restricted to severe patients only.
2. Advise when the next update to the Australian Specific Annex to the RMP will be submitted to the TGA that addresses the matters raised by the RMP evaluator in the second round report.

Delegate's recommendation

The Delegate was inclined to approve this submission by Abbvie Pty Ltd to register Humira (adalimumab) for the new indication of treatment of non-radiographic axial spondyloarthritis based on the quality, safety and efficacy of the product being satisfactorily established for the indication below and for the reasons stated above in the Risk/Benefit Discussion:

Non-radiographic Axial Spondyloarthritis

Humira is indicated for reducing signs and symptoms in adult patients with active axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, who have had an inadequate response to, or are intolerant to, nonsteroidal anti-inflammatory drugs.

The indication should include adults and be amended as outlined above to those who have had an inadequate response to, or are intolerant to, nonsteroidal anti-inflammatory drugs as per the inclusion criteria of the study, however the wording may require amendments post ACPM.

Conditions of registration

The following are proposed as conditions of registration:

3. The implementation in Australia of the Risk Management Plan (RMP) for Adalimumab (edition 10.0, November 2011) with Australian Specific Annex (undated) and any subsequent revisions, as agreed with the TGA.
4. The following studies must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission:
 - a. Final study report for M10-791 including the 144 week open label extension.

Product Information and Consumer Medicine Information

The evaluator's recommendations for the PI and CMI should be implemented along with recommendations to the *Clinical Trials, Precautions* section and the *Indications*.

Consumer Medicine Information (CMI)

Please provide an updated CMI to incorporate the changes from this submission.

Response from sponsor

AbbVie Pty Ltd agreed with the Delegate's proposed actions as stated above.

The following extract summarises the sponsor's response to the questions raised in the Delegate's Overview.

1. The Delegate suggests the following changes to the PI

Indications:

- The indication should include adults and be amended as outlined below:

Non-radiographic Axial Spondyloarthritis

Humira is indicated for reducing signs and symptoms in adult patients with active axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, who have had an inadequate response to, or are intolerant to, nonsteroidal anti-inflammatory drugs.

Sponsor response:

AbbVie agreed to include the words "adults", "active", and "who have had an inadequate response to, or are intolerant to, nonsteroidal anti-inflammatory drugs" in the indication wordings.

2. Discuss the grades of disease severity for patients with nr-axSpa in the pivotal study, that is, mild, moderate and severe and why the indication in Europe was restricted to severe patients only.

Sponsor response:

Subjects in study M10-791 were required to have a Bath AS Disease Activity Index (BASDAI) ≥ 4 at both the Screening and Baseline visits which reflects moderate to severe disease activity.

The indication in Europe was limited to severe patients to align with the approved indication for ankylosing spondylitis.

3. Advise when the next update to the Australian Specific Annex to the RMP will be submitted to the TGA that addresses the matters raised by the RMP evaluator in the second round report.

Sponsor response:

The RMP has been updated and a copy was included with the sponsor's Pre-ACPM submission.

4. Is non-radiographic axial spondyloarthritis a disease with consistently defined and agreed diagnostic criteria that supports a new indication?

Sponsor response:

The sponsor believes that non-radiographic axial spondyloarthritis is a disease with consistently defined and agreed diagnostic criteria that supports a new indication.

Background to axial spondyloarthritis

Spondyloarthritis (SpA) is a group of diseases that share common clinical, radiographic, and genetic features.⁵ Included in this group are ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis, enteropathic or inflammatory bowel disease (IBD)-related arthritis, and undifferentiated SpA.⁵ Among these inflammatory diseases, there is an overlap of signs and symptoms. When evaluating patients for a diagnosis of SpA, a useful distinction that rheumatologists usually make is to first determine if patients have either predominantly axial or predominantly peripheral manifestations; the main reason being that the treatment should be directed to the most important manifestation.

Axial SpA (axSpA) is a chronic inflammatory disease that primarily affects the axial skeleton (the sacroiliac [SI] joints and spine). Patients diagnosed with axSpA can be distinguished from those who may have non-inflammatory causes of back pain based on a combination of any of the following signs and symptoms: the characteristics of the back pain (that is, worsening with rest and improvement with exercise suggest inflammatory back pain); accompanying peripheral (that is, enthesitis, arthritis, dactylitis) and extra-articular manifestations (that is, uveitis, IBD, psoriasis); the presence of the genetic marker human leukocyte antigen (HLA)-B27; the presence of signs of inflammation in the lab (that is, C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]); imaging evidence of inflammation on MRI of the SI joints, or structural damage on the radiographs of the SI joints.⁶

Historically, patients with axSpA were only identified when there was evidence of structural damage of the SI joints on the radiographs (radiographic sacroiliitis, as determined by the modified New York [mNY] criteria)⁷ and such patients were diagnosed as having AS. Advances in the knowledge of axSpA has led to the understanding that some patients who have the clinical manifestations typical of this disease may not have evidence of radiographic sacroiliitis at presentation and such patients are now diagnosed as having non-radiographic axSpA (nr-axSpA).⁸ Therefore, both AS and nr-axSpA represent the spectrum of axSpA, with the presence or absence of radiographic sacroiliitis as the only differentiating clinical feature.

Using radiographs to make a diagnosis of axial SpA presents several challenges. Radiographs detect sacroiliitis in the form of structural damage but not inflammation,

⁵Khan MA. Update on spondyloarthropathies. *Ann Intern Med* 2002;136:896-907.

⁶Rudwaleit M, van der Heijde D, Landewe R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777-83.

⁷van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361-8.

⁸Sieper J, van der Heijde D. Review: Nonradiographic axial spondyloarthritis: new definition of an old disease? *Arthritis Rheum* 2013;65:543-51.

thereby causing a delay in diagnosis for patients with axSpA without radiographic sacroiliitis (nr-axSpA).⁹

There is also variability in how radiographs are interpreted for the presence of radiographic sacroiliitis.¹⁰ With the advent of magnetic resonance imaging (MRI) it is now possible to visualise acute inflammatory lesions that can be highly suggestive of axial SpA in addition to structural changes.¹¹ The ability to detect acute inflammation in the axial skeleton by MRI is one way to facilitate a diagnosis of axial SpA, especially in patients with nr-axSpA, whose radiographs are negative or inconclusive for sacroiliitis.

Rationale for the development of the ASAS criteria

There is, on average, a delay of 5-10 years from the onset of symptoms to the diagnosis of AS using the mNY criteria.^{7, 12, 13}

It is well established that the development of radiographic sacroiliitis on plain radiographs reflecting structural damage in the SI joints (erosions, sclerosis, ankylosis, joint space changes) can take years to develop despite the presence of inflammation in the SI joints,⁵ thereby constituting a major contributor to the delay in diagnosis of AS. Moreover, not all nr-axSpA patients will go on to develop structural damage visible on radiographs and would therefore not progress to AS, though they have a similar burden of disease. A further contributory factor to the late diagnosis of this inflammatory spinal disease is the observation that axSpA accounts for only around 5% of patients with chronic back pain, resulting in a low level of disease awareness among back pain patients and referring health care providers.¹⁴

The Assessment of Spondyloarthritis international Society (ASAS) (an international group of experts in SpA from 37 member countries) has developed and validated classification criteria for patients with axSpA.^{6, 11} These criteria were developed to include patients with or without radiographic sacroiliitis by including both plain radiographs and MRI as imaging modalities.^{6, 11} These criteria identify both AS and nr-axSpA patients and therefore enable the conduct of clinical trials for the treatment of the broad axSpA population; including patients with nr-axSpA.^{6, 8, 11}

Prior to the ASAS criteria, the Amor and The European Spondyloarthropathy Study Group (ESSG) criteria were used to define the entire group of patients with peripheral and axial manifestations, regardless of the presence or absence of radiographic sacroiliitis.^{8, 11} However, these criteria do not distinguish patients based on predominant spinal inflammation. Furthermore, the Amor and ESSG criteria do not include information on MRI.^{8, 11}

Development and validation of the ASAS criteria

In order to provide an internationally accepted classification standard for research studies in patients with axSpA (AS and nr-axSpA), ASAS identified the need to establish new classification criteria. To start this process, candidate criteria for classification were developed in 2004, based mainly on clinical understanding of typical features seen in

⁹ Rudwaleit M, Khan MA, Sieper J. The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria? *Arthritis Rheum* 2005;52:1000-8.

¹⁰ Rudwaleit M, Haibel H, Baraliakos X, et al. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. *Arthritis Rheum* 2009;60:717-27.

¹¹ Rudwaleit M, Landewe R, van der Heijde D, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis* 2009;68:770-6.

¹² Feldtkeller E, Bruckel J, Khan MA. Scientific contributions of ankylosing spondylitis patient advocacy groups. *Curr Opin Rheumatol* 2000;12:239-47.

¹³ Feldtkeller E, Khan MA, van der Heijde D, et al. Age at disease onset and diagnosis delay in HLA-B27 negative versus positive patients with ankylosing spondylitis. *Rheumatol Int* 2003;23:61-6.

¹⁴ Underwood MR, Dawes P. Inflammatory back pain in primary care. *Br J Rheumatol* 1995;34:1074-7.

patients that are suspected to have SpA.⁷ This included the evaluation of ‘paper patients’ where clinical information from real patients (with and without axSpA) was provided on paper to ASAS rheumatologists, who are experts in the field of axSpA.¹¹ The focus of these candidate criteria was on patients with chronic back pain with age at onset <45 years^{6,11} because by the age of 45, approximately 95% of axSpA patients are symptomatic.¹³

As the next step, the candidate criteria were tested (validated) in a prospective study conducted between 2006 and 2008 across 25 centers with an ASAS rheumatologist in 16 countries. 6 Patients included in this validation study had undiagnosed chronic back pain and age of onset <45 years.⁶

ASAS centers included patients presenting at the outpatient clinic consecutively.⁶ In these patients (n=649), the diagnosis (of either “axSpA” or “no SpA”) made by the rheumatologists according to his/her expert opinion was used as the gold standard for the validation of these criteria.⁶

For the refinement of the candidate criteria, the ASAS data set was divided into two sets, which allowed the candidate criteria to be refined in the first data set and thereafter validated in the second data set.⁶ The results were presented to ASAS members in 2008 and the final set of candidate criteria were voted on by this group.⁶

The finalised ASAS criteria for axSpA are intended to be applied to patients with chronic back pain for ≥3 months with age of onset <45 years.⁶ There is an ‘imaging arm’ requiring the presence of sacroiliitis (on radiographs or MRI) in the context of at least one clinical feature, and a ‘clinical arm’ requiring the presence of HLA-B27 plus at least two other SpA features.⁶

The ASAS criteria were found to have a better sensitivity (82.9%) and specificity (84.4%) in the validation study compared with the Amor (69.4% and 78.4%, respectively) and ESSG (70.7% and 63.5%, respectively) criteria.^{6, 8} Following their development, the ASAS classification criteria for axSpA have been evaluated in a number of cohort studies with generally similar or better figures for sensitivity and specificity.^{15, 16}

The ASAS criteria for axSpA are intended for use primarily as classification criteria for axSpA for clinical trials and other research studies.^{6,8} In this respect, the ASAS classification criteria provide rheumatologists with a framework for evaluating the numerous features of axSpA when considering the diagnosis of this disease in a given patient. In daily practice, rheumatologists make the diagnosis of axSpA based on the ‘pattern recognition’ of typical clinical features⁶ which are assessed by detailed history, physical examination and targeted investigations including imaging.

Although the ASAS criteria reflect many important aspects and features of the disease, which are also used for making the diagnosis, they are not meant to be used as diagnostic criteria.⁸

Characteristics of axSpA patients and burden of disease

Population studies from a range of countries report prevalence estimates for AS between 0.1% to 1.4%¹⁷ and for SpA of around 0.3% to 1.9%.¹⁷

Recent data from the US (NHANES 2009- 2010¹⁸) report prevalence figures of 0.9% using the Amor criteria and 1.4% using EESG, which are similar to RA estimates of 0.5% to 1.0%

¹⁵ Moltó A, Paternotte S, Comet D, et al. Performances of the ASAS axial spondyloarthritis criteria for diagnostic and classification purposes in patients visiting a rheumatologist because of chronic back pain: The DECLIC study. *Arthritis Care Res (Hoboken)* 2013.

¹⁶ van den Berg R, de Hooze M, van Gaalen F, et al. Percentage of patients with spondyloarthritis in patients referred because of chronic back pain and performance of classification criteria: experience from the Spondyloarthritis Caught Early (SPACE) cohort. *Rheumatology (Oxford)* 2013.

¹⁷ Rudwaleit M, Sieper J. Referral strategies for early diagnosis of axial spondyloarthritis. *Nat Rev Rheumatol* 2012;8:262-8.

and it has been identified that approximately 70- 80% of all SpA patients have axial involvement.^{19, 20, 21}

The proportion of nr-axSpA patients among all axSpA patients ranges between 40% and 60% according to several national and international referral programs, and depends on the duration of back pain.^{17, 22}

Over time some patients will progress from nr-axSpA to AS. The rate of progression from nr-axSpA to AS (the development of definite radiographic sacroiliitis) is approximately 10% after 2 years and up to 60% after 10 years across studies.⁸ Given this, it is clear that not all axSpA patients will develop definite radiographic sacroiliitis.

Duration of back pain is one of the predictors for the development of AS in patients with nraxSpA; however other factors can act as predictors for progression in axSpA. Elevated CRP over time is a significant predictor for the development of radiographic sacroiliitis, as it is estimated that 25% of patients with nr-axSpA and elevated CRP levels will develop evidence of sacroiliitis on radiographs within 2 years.⁸ In addition, a study from Leeds, UK found that extended inflammation on MRI (sacroiliitis) predicted the development of radiographic sacroiliitis 8 years later.²³

Data from registries and randomized controlled studies indicate that patients with axSpA are often in their 30s or 40s^{10,24,25} and suffer from substantial axial pain, fatigue, morning stiffness and functional impairment.^{10, 17, 25, 26,27} The impact of these manifestations is assessed by the Bath Ankylosing Spondylitis Disease Activity Index and Functional Index (BASDAI and BASFI), visual analogue scale measurements of total pain/back pain, and global assessments of disease activity (patient and physician).²⁸

Stiffness, pain, and fatigue have been found to adversely influence quality of life and physical functioning among patients with axSpA.^{29,30} Furthermore, in these patients, increased disease activity, functional disability and fatigue severity have been found to be

¹⁸ NHANES= National Health and Nutrition Examination Survey

¹⁹ Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum* 2008;58:15-25.

²⁰ Myasoedova E, Davis JM, 3rd, Crowson CS, et al. Epidemiology of rheumatoid arthritis: rheumatoid arthritis and mortality. *Curr Rheumatol Rep* 2010;12:379-85.

²¹ Reveille JD, Witter JP, Weisman MH. Prevalence of axial spondylarthritis in the United States: estimates from a cross-sectional survey. *Arthritis Care Res (Hoboken)* 2012;64:905-10.

²² Poddubnyy D, Brandt H, Vahldiek J, et al. The frequency of non-radiographic axial spondyloarthritis in relation to symptom duration in patients referred because of chronic back pain: results from the Berlin early spondyloarthritis clinic. *Ann Rheum Dis* 2012;71:1998-2001.

²³ Bennett AN, McGonagle D, O'Connor P, et al. Severity of baseline magnetic resonance imaging-evident sacroiliitis and HLA-B27 status in early inflammatory back pain predict radiographically evident ankylosing spondylitis at eight years. *Arthritis Rheum* 2008;58:3413-8.

²⁴ Kiltz U, Baraliakos X, Karakostas P, et al. Do patients with non-radiographic axial spondylarthritis differ from patients with ankylosing spondylitis? *Arthritis Care Res (Hoboken)* 2012;64:1415-22.

²⁵ Haibel H, Rudwaleit M, Listing J, et al. Efficacy of adalimumab in the treatment of axial spondylarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial followed by an open-label extension up to week fifty-two. *Arthritis Rheum* 2008;58:1981-91.

²⁶ Sieper J, van der Heijde D, Dougados M, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis* 2013;72:815-22.

²⁷ Landewé R, Rudwaleit M, van der Heijde D, et al. Effect of Certolizumab Pegol on Signs And Symptoms of Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis: 24 Week Results of a Double-Blind Randomized Placebo-Controlled Phase 3 Axial Spondyloarthritis Study. *Arthritis Rheum*. 2012;64:S336.

²⁸ Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009;68 Suppl 2:ii1-44.

²⁹ Boonen A, van der Linden SM. The burden of ankylosing spondylitis. *J Rheumatol Suppl* 2006;78:4-11.

³⁰ Ward MM. Health-related quality of life in ankylosing spondylitis: a survey of 175 patients. *Arthritis Care Res* 1999;12:247-55.

associated with poorer mental health status.³¹ Poor health-related quality of life may be evidenced by decreased physical function and impaired work outcomes in these relatively young patients. There is evidence that the disease incurs a substantial economic impact on society or patients, with costs driven mainly by the loss of capacity to work.^{32,33, 34, 35,36 37, 38, 39}

Axial SpA has a deleterious effect on patients regardless of the presence (AS) or absence (nraxSpA) of evidence of sacroiliitis on radiographs.²⁴

Several studies have identified that the burden of subjective symptoms (for example, pain, perceived disease activity, fatigue) is comparable in nr-axSpA and AS patients^{10,24, 40,41} although spinal mobility and functional status (BASFI) are usually somewhat worse in AS than in nraxSpA due to the presence of structural damage in the former patient group.^{10,41,42}

Appropriateness of the ASAS criteria for classifying a patient group with limited treatment options in Australia

Application of the ASAS criteria in recent clinical trials has not only provided further validation for the concept of axSpA but has also demonstrated that patients from across the broad axSpA population, not just those with radiographic evidence of sacroiliitis, can derive benefit from proactive treatment of the signs and symptoms of active inflammatory disease.^{25, 26, 27} Axial SpA patients have been recognised for a long time in clinical practice (although by different nomenclature) and so the ASAS criteria are not defining or describing a new group of SpA patients, but are instead improving the classification of these patients.⁸

³¹ Da Costa D, Dritsa M, Ring A, et al. Mental health status and leisure-time physical activity contribute to fatigue intensity in patients with spondylarthropathy. *Arthritis Rheum* 2004;51:1004-8.

³² Boonen A, van der Heijde D, Landewe R, et al. Work status and productivity costs due to ankylosing spondylitis: comparison of three European countries. *Ann Rheum Dis* 2002;61:429- 37.

³³ Boonen A, van der Heijde D, Landewe R, et al. Direct costs of ankylosing spondylitis and its determinants: an analysis among three European countries. *Ann Rheum Dis* 2003;62:732-40.

³⁴ Kobelt G, Andlin-Sobocki P, Brophy S, et al. The burden of ankylosing spondylitis and the cost-effectiveness of treatment with infliximab (Remicade). *Rheumatology (Oxford)* 2004;43:1158-66.

³⁵ Kobelt G, Andlin-Sobocki P, Maksymowych WP. The cost-effectiveness of infliximab (Remicade) in the treatment of ankylosing spondylitis in Canada. *J Rheumatol* 2006;33:732-40.

³⁶ Ward MM. Functional disability predicts total costs in patients with ankylosing spondylitis. *Arthritis Rheum* 2002;46:223-31.

³⁷ van der Heijde D, Braun J, Rudwaleit M, et al. Improvements in work and household productivity after 24 weeks of certolizumab pegol in treatment of axial spondyloarthritis patients, including patients with ankylosing spondylitis: results of RAPID-axSpA study. Abstract #OP0107. *Ann Rheum Dis* 2012; 72 (suppl 3): 87

³⁸ van der Heijde D, Purcaru O, Kavanaugh A. High economic burden of axial spondyloarthritis related to paid work and household productivity at baseline in the RAPID-AxSpA study: Differences and similarities between ankylosing spondylitis and non-radiographic axial spondyloarthritis. Abstract #FRI0439. *Ann Rheum Dis* 2012;72 (suppl 3):87.

³⁹ Maksymowych WP, Mease PJ, Rao S, et al. Effect of adalimumab on function, health-related quality of life, work productivity, and daily activities in patients with non-radiographic axial spondyloarthritis. [abstract]. *Arthritis Rheum* 2011;63 Suppl 10:1312.

⁴⁰ Kiltz U, Baraliakos X, Karakostas P, et al. The degree of spinal inflammation is similar in patients with axial spondyloarthritis who report high or low levels of disease activity: a cohort study. *Ann Rheum Dis* 2012;71:1207-11.

⁴¹ Sieper J, Kivitz A, van Tubergen A, et al. Rapid improvements in patient-reported outcomes with certolizumab pegol in patients with axial spondyloarthritis, including ankylosing spondylitis: 24-week results of RAPID-axSpA study. *THU0360 Ann Rheum Dis* 2013;72:287.

⁴² Machado P, Landewé R, Braun J, et al. A stratified model for health outcomes in ankylosing spondylitis. *Ann Rheum Dis* 2011;70:1758-64.

Within Australia, nonsteroidal anti-inflammatory drugs (NSAIDs) and physical therapy are the initial treatments of choice in this setting⁴³, however, for those patients with nr-axSpA who are intolerant of or not adequately controlled by NSAIDs or in whom NSAIDs are contraindicated, limited treatment options exist. This highlights a need for clinical trials that could provide new therapies to improve patient health given that nr-axSpA patients exhibit comparable levels of disease activity and burden to those with AS. Recognition of active axSpA (AS and nr-axSpA) as an indication, regardless of evidence of sacroiliitis on radiographs, could therefore enable the application of appropriate and effective treatment strategies to better address patient needs.

Regardless of whether early and effective therapy affects disease progression or structural damage, appropriate treatment enables patients to have a better quality of life with less pain and less consequences of back pain such as reduced work productivity.^{17, 26, 27, 39, 44}

5. Should the indication be a subset of axial spondyloarthritis and combined with ankylosing spondylitis as in the EU?

Sponsor response:

As noted above, both ankylosing spondylitis and non-radiographic axial spondyloarthritis represent the spectrum of axial spondyloarthritis, with the presence or absence of radiographic sacroiliitis as the only differentiating clinical feature. Therefore, the sponsor considers that is appropriate for the proposed indication to be a subset of axial spondyloarthritis and combined with ankylosing spondylitis as in the EU.

Advisory committee considerations

The sponsor's application was not considered by the Advisory Committee on Prescription Medicines.

Outcome

Following discussion with the sponsor regarding concerns over the validity of the data and the need for re-analysis, the sponsor withdrew their submission on 19 August 2013, before a decision had been made by the TGA.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

⁴³van der Heijde D, Sieper J, Maksymowych WP, et al. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. *Ann Rheum Dis* 2011;70:905-8.

⁴⁴ van der Heijde D, Braun J, Rudwaleit M, et al. Increased Participation in Daily Activities After 24 Weeks of Certolizumab Pegol Treatment of Axial Spondyloarthritis Patients, Including Patients with Ankylosing Spondylitis: Results of a Phase 3 Double-Blind Randomized Placebo- Controlled Study. *Arthritis Rh*

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