6.01 ADALIMUMAB,
Injection 20 mg in 0.2 mL pre-filled syringe,
Injection 40 mg in 0.4 mL pre-filled syringe,
Injection 40 mg in 0.4 mL pre-filled pen,
Injection 80 mg in 0.8 mL pre-filled syringe,
Injection 80 mg in 0.8 mL pre-filled pen,
Humira®,
AbbVie Pty Ltd.

1. Purpose of submission
	1. The Category 2 submission requested a General Schedule Authority Required (STREAMLINED) listing for adalimumab (Humira®) for the treatment of immune-mediated inflammatory disease (IMID) in paediatric patients.
	2. The submission requested that adalimumab be PBS-listed as an indication-agnostic listing to allow patients with the greatest risk of permanent disability and/or psychological distress to receive treatment with adalimumab.
2. Background
	1. The submission claimed that children in Australia with IMIDs are currently disadvantaged in terms of access to treatment compared to other countries such as the United States, Canada, United Kingdom, Germany and New Zealand. The submission stated that extending the PBS listing of adalimumab to allow access by paediatric patients with IMIDs would align with treatment guidelines and international best practice.
	2. The submission claimed many of the current PBS restriction criteria for Humira for paediatric patients are clinically inappropriate, as they:
* have historically been based on the restriction criteria for adult disease and are not reflective of childhood disease presentations
* mandate prior failure or intolerance of conventional systemic therapy, even for patients with the most severe disease and those in need of immediate treatment to prevent irreversible outcomes
* do not allow for flexible doses.
	1. The submission stated that early, aggressive treatment of childhood IMIDs may alter the natural course of a child’s disease history. Benefits cited included:
* fewer disruptions in education, less impact on psychosocial development, and reduced need to make life decisions based on their medical condition.
* health economic benefits of improved access to treatment: fewer medical appointments, hospitalisations and surgeries; reduced permanent disability and the need for allied health services.
* greater contribution to the economy by parents (and eventually the children) through increased productivity, reduced absenteeism, increased employment and reduced reliance on social welfare.
	1. The submission cited the Inquiry into childhood rheumatic diseases: Interim report by the House of Representatives (HoR) Standing Committee on Health, Aged Care and Sport, and claimed the submission seeks to partly address Recommendation 14:

‘The Committee recommends the Australian Government’s Department of Health in partnership with the Pharmaceutical Benefits Advisory Committee, experts, patient groups and sponsoring companies conduct an urgent review into:

* + access to treatments for juvenile arthritis including access to drugs not currently available in Australia, and
	+ limitations on access to existing listed medications that prevent patients receiving the most effective medications.’
	1. The submission also stated that extending the PBS listing for adalimumab aligns with the Standing Committee on Health, Aged Care and Sport’s recommendation to repurpose older medicines in Australia, as it will provide paediatric populations with a high unmet need with a medicine that has already been approved in other jurisdictions, used for less common medical conditions, is already being used off-label, and is likely to be less commercially profitable.

Registration status

* 1. Humira is Therapeutic Goods Administration (TGA) registered for the following indications in children and adolescents:
	+ Juvenile idiopathic arthritis: polyarticular juvenile idiopathic arthritis in patients ≥ 2 years of age who have had inadequate response to ≥ 1 disease modifying anti-rheumatic drugs (DMARDs); enthesitis-related arthritis in children who have had an inadequate response to, or are intolerant to, conventional therapy
	+ Moderate to severe Crohn disease in children ≥ 6 years (and adults) in patients who have had an inadequate response to conventional therapies, or who have lost response to or are intolerant to infliximab
	+ Psoriasis: severe chronic plaque psoriasis in children ≥ 4 years and adolescents who have had an inadequate response to or are inappropriate candidates for topical therapy or phototherapy; moderate to severe chronic plaque psoriasis in adults who are candidates for systemic therapy or phototherapy
	+ Active moderate to severe hidradenitis suppurativa (HS) in adults and adolescents ≥ 12 years with an inadequate response to conventional systemic HS therapy.
	1. In addition, Humira is TGA registered for the following indications in adults:
	+ Moderate to severely active rheumatoid arthritis
	+ Psoriatic arthritis
	+ Ulcerative colitis
	+ Non-infectious intermediate, posterior and pan-uveitis.
	1. Humira is TGA-registered for active ankylosing spondylitis with no age specified.
	2. The Economics Sub Committee (ESC) noted that the requested listing will include paediatric indications that adalimumab is TGA-registered for and will also allow use in indications not currently TGA-registered.

Previous PBAC consideration

* 1. Humira was first listed on the PBS on 1 May 2004 for the treatment of severely active rheumatoid arthritis in adults, following a recommendation for listing by the PBAC at its December 2003 meeting.
	2. The PBAC first considered the listing of Humira for a paediatric indication at its March 2010 meeting. At this meeting, the PBAC recommended listing Humira (20 mg/0.4 mL and 40 mg/0.8 mL pre-filled syringe) for the treatment of severe active polyarticular course juvenile idiopathic arthritis (Section 12, adalimumab, Public Summary Document (PSD), March 2010 PBAC meeting).
	3. At its November 2014 meeting the PBAC recommended extending the listing of Humira (20 mg/0.4 mL and 40 mg/0.8 mL) to include listing for the treatment of severe refractory Crohn disease in paediatric patients aged 6-17 years (paragraph 7.1, adalimumab, PSD, November 2014 PBAC meeting).
	4. At its March 2016 meeting the PBAC recommended listing Humira (40 mg/0.8 mL) for the treatment of moderate to severe ulcerative colitis (paragraph 7.1, adalimumab, PSD, March 2016 PBAC meeting). The March 2016 submission agreed to broaden the restriction to include paediatric patients as well as adult patients as suggested by the PBAC at its July 2015 and November 2015 considerations. However, the submission maintained its proposed restriction limiting to adult patients was consistent with the TGA registered indication (Table 1, adalimumab, PSD, March 2016 PBAC meeting).
	5. At its December 2016 meeting, the PBAC recommended listing Humira (40 mg/0.8 mL) for the treatment of moderate-to-severe hidradenitis suppurativa (adalimumab, PSD, November 2016 PBAC meeting with December 2016 Addendum). The recommended listing had no restrictions on patient age.
	6. The sponsor made a resubmission to request a General Schedule Authority Required (Telephone/Online) listing for adalimumab for the treatment of patients with vision-threatening non-infectious uveitis, which was also considered by the PBAC at its March 2024 meeting. The submission noted there was partial overlap in patient populations between the two submissions.

Current PBS listings

* 1. Humira is currently PBS-listed for the following indications for paediatric patients:
* Severe active juvenile idiopathic arthritis (Population criteria: patient must be under 18 years of age): Humira 20 mg/0.2 mL, 40 mg/0.4 mL prefilled syringe; 40 mg/0.4 mL pre-filled pen (Authority Required (Telephone/Online) for initial/first continuing treatment; Authority Required (STREAMLINED) for continuing treatment).
* Severe Crohn disease (Population criteria: patient must be aged 6-17 years inclusive): Humira 20 mg/0.2 mL, 40 mg/0.4 mL, 80 mg/0.8 mL pre-filled syringe; 40 mg/0.4 mL, 80 mg/0.8 mL pre-filled pen (Authority Required (written)). The 80 mg/0.8 mL dose forms are not subsidised for continuing treatment.
* Moderate to severe ulcerative colitis (Population criteria: patient must be 6 years of age or older): Humira 20 mg/0.2 mL, 40 mg/0.4 mL, 80 mg/0.8 mL pre-filled syringe; 40 mg/0.4 mL, 80 mg/0.8 mL pre-filled pen (Authority Required (written)) for initial treatment, Authority Required (Telephone/Online) for continuing treatment where relevant (the 80 mg/0.8 mL dose forms are not subsidised for continuing treatment)).
	1. In addition, Humira is currently PBS-listed for the following conditions with no age criteria specified:
* Complex refractory Fistulising Crohn disease: Humira 40 mg/0.4 mL and 80 mg/0.8 mL pre-filled syringe and pre-filled pen (Authority Required (written)). The 80 mg/0.8 mL dose forms are not subsidised for continuing treatment.
* Hidradenitis suppurativa: Humira 80 mg/0.8 mL pre-filled syringe; 40 mg/0.4 mL, 80 mg/0.8 mL pre-filled pen (Authority Required (written) for initial treatment, Authority Required (Telephone/Online) for continuing treatment).

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

1. Requested listing
	1. Suggested additions proposed by the Secretariat are in italics and deletions are crossed out with strikethrough.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT****medicinal product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of****Rpts** | **Available brands** |
| ADALIMUMAB |
| adalimumab 20 mg/0.2 mL injection, 2 x 0.2 mL syringes | NEW | 1 | 2 | 5 | Humira |
| adalimumab 40 mg/0.4 mL injection, 2 x 0.4 mL syringes | NEW | 2 | 4 | 4 | Humira |
| adalimumab 40 mg/0.4 mL injection, 2 x 0.4 mL pen devices | NEW | 2 | 4 | 4 | Humira |
| adalimumab 80 mg/0.8 mL injection, 0.8 mL pen device | NEW | 3 | 3 | 0 | Humira |
| adalimumab 80 mg/0.8 mL injection, 0.8 mL syringe | NEW | 3 | 3 | 0 | Humira |
|  |
| **Restriction Summary [new] / Treatment of Concept: [new]**  |
| **Concept ID** (for internal Dept. use) | **Category / Program:** GENERAL – General Schedule (Code GE)  |
| **Prescriber type:** [x] Medical Practitioners  |
| **Restriction type:** [x] Authority Required (Streamlined) [new]  |
|  |  | ***Administrative Advice:*** *No increase in the maximum quantity or number of units may be authorised.* |
|  | ***Administrative Advice:*** *No increase in the maximum number of repeats may be authorised.* |
|  | **~~Episodicity:~~** ~~[blank]~~  |
| **Severity:** Disease severity considered sufficient to cause substantial detriment to patient's immediate or future health or quality of life |
| **Condition:** Immune-mediated inflammatory diseases |
|  | **Indication:** Immune-mediated inflammatory diseases |
|  | **Treatment Phase:** Initial treatment |
|  | **Clinical criteria:** |
|  | *Patient must have a c*~~C~~onfirmed diagnosis of an immune-mediated inflammatory disease which, in the opinion of the treating specialist, would derive clinical benefit from treatment with adalimumab; |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have, at the time of application, disease severity considered sufficient to cause substantial detriment to patient’s immediate or future health or quality of life, according to at least 2 measures of disease severity or quality of life impact (at least 1 must be an objective measure) appropriate to the patient’s condition and age; |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must not have experienced an inadequate response to this therapy; |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must not receive more than 16 weeks *of* treatment *with this biological medicine* under this restriction. |
|  | **Treatment criteria:** |
|  | Must be treated by a specialist paediatric clinician or specialist clinician with experience in treating the disease. |
|  | **Population criteria:** |
|  | Patient must be under 18 years of age. |
|  | **Prescribing Instructions:** The assessment of disease severity and quality of life impact must be documented in the patient’s medical records and must be no more than 4 weeks old at the time of the authority application. |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **MEDICINAL PRODUCT****medicinal product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of****Rpts** | **Available brands** |
| ADALIMUMAB |
| adalimumab 20 mg/0.2 mL injection, 2 x 0.2 mL syringes | NEW | 2 | 4 | 6 | Humira |
| adalimumab 40 mg/0.4 mL injection, 2 x 0.4 mL syringes | NEW | 2 | 4 | 6 | Humira |
| adalimumab 40 mg/0.4 mL injection, 2 x 0.4 mL pen devices | NEW | 2 | 4 | 6 | Humira |
| adalimumab 80 mg/0.8 mL injection, 0.8 mL pen device | NEW | 1 | 2 | 6 | Humira |
| adalimumab 80 mg/0.8 mL injection, 0.8 mL syringe | NEW | 1 | 2 | 6 | Humira |
|  |
| **Restriction Summary [new] / Treatment of Concept: [new]**  |
| **Concept ID** (for internal Dept. use) | **Category / Program:** GENERAL – General Schedule (Code GE)  |
| **Prescriber type:** [x] Medical Practitioners  |
| **Restriction type:** [x] Authority Required (Streamlined) [new]  |
|  |  | ***Administrative Advice:*** *No increase in the maximum quantity or number of units may be authorised.* |
|  | ***Administrative Advice:*** *No increase in the maximum number of repeats may be authorised.* |
|  | **~~Episodicity:~~** ~~[blank]~~  |
| **Severity:** Disease severity considered sufficient to cause substantial detriment to patient’s immediate or future health or quality of life |
| **Condition:** Immune-mediated inflammatory diseases |
|  | **Indication:** Immune-mediated inflammatory diseases |
|  | **Treatment Phase:** Continuing treatment |
|  | **Clinical criteria:** |
|  | *Patient must have a c*~~C~~onfirmed diagnosis of an immune-mediated inflammatory disease which, in the opinion of the treating specialist, would derive clinical benefit from treatment with adalimumab; |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have previously received PBS-subsidised treatment with this drug for this condition; |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have demonstrated an adequate clinical response to treatment according to the objective and/or subjective measures of disease recorded at baseline; |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must not receive more than 28 weeks *of* treatment *per continuing treatment course authorised* under this restriction. |
|  | **Treatment criteria:** |
|  | Must be treated by a specialist paediatric clinician or specialist clinician with experience in treating the disease. |
|  | **Population criteria:** |
|  | Patient must be under 18 years of age. |
|  | **Prescribing Instructions:** An adequate response to treatment is defined as:* A clinically meaningful improvement in the measures of disease severity and/or quality of life impact that were used to establish baseline severity

The assessment of adequate response to treatment must be documented in the patient’s medical records and must be no more than 4 weeks old at the time of the authority application. |
|  |
| **Restriction Summary [new] / Treatment of Concept: [new]**  |
| **Concept ID**(for internal Dept. use) | **Category / Program:** GENERAL – General Schedule (Code GE) |
| **Prescriber type:** [x] Medical Practitioners  |
| **Restriction type:** [x] Authority Required (STREAMLINED) [new]  |
|  | **Indication:** Immune-mediated inflammatory diseases |
|  | **Treatment Phase:** Continuing adult with paediatric history |
|  | **Clinical criteria:** |
|  | *Patient must have a c*onfirmed diagnosis of an immune-mediated inflammatory disease which, in the opinion of the treating specialist, would derive clinical benefit from treatment with adalimumab; |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have previously received PBS-subsidised treatment with this drug for this condition; |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have demonstrated an adequate clinical response to treatment according to the objective and/or subjective measures of disease recorded at baseline; |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must not receive more than 28 weeks *of* treatment under this restriction. |
|  | **Treatment criteria:** |
|  | Must be treated by a specialist paediatric clinician or specialist clinician with experience in treating the disease. |
|  | **Population criteria:** |
|  | Patient must be *at least* ~~over~~ 18 years of age. |
|  | **Prescribing Instructions:** An adequate response to treatment is defined as:* A clinically meaningful improvement in the measures of disease severity and/or quality of life impact that were used to establish baseline severity

The assessment of adequate response to treatment must be documented in the patient’s medical records and must be no more than 4 weeks old at the time of the authority application. |
|  |
| **Restriction Summary [new] / Treatment of Concept: [new]**  |
| **Concept ID**(for internal Dept. use) | **Category / Program:** GENERAL – General Schedule (Code GE) |
|  | **Prescriber type:** [x] Medical Practitioners  |
|  | **Restriction type:** [x] Authority Required (STREAMLINED) [new]  |
|  | **Indication:** Immune-mediated inflammatory diseases |
|  | **Treatment Phase:** Initial PBS-subsidised treatment in a patient who has previously received non-PBS subsidised therapy with this drug (grandfather) |
|  | **Clinical criteria:** |
|  | Patient must have ~~previously~~ received non-PBS subsidised treatment with this drug for ~~their~~ *this* condition prior to 1 [month and year]; |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have documented history of an immune-mediated inflammatory disease which, in the opinion of the treating specialist, would derive clinical benefit from treatment with adalimumab; |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must have had disease severity considered sufficient to cause substantial detriment to patient's immediate or future health or quality of life, according to at least 2 measures of disease severity or quality of life impact (at least 1 must be an objective measure) appropriate to the patient's condition and age; |
|  | ***AND*** |
|  | ***Clinical criteria:*** |
|  | *Patient must have demonstrated an adequate clinical response to treatment according to the objective and/or subjective measures of disease recorded at baseline;* |
|  | **AND** |
|  | **Clinical criteria:** |
|  | Patient must not receive more than 28 weeks *of* treatment *with this biological medicine* under this restriction. |
|  | **Treatment criteria:** |
|  | Must be treated by a specialist paediatric clinician or specialist clinician with experience in treating the disease. |
|  | **Population criteria:** |
|  | Patient must be under 18 years of age. |
|  | **Prescribing Instructions:** The baseline assessment of disease severity and quality of life impact must be documented in the patient’s medical records. |
|  | ***Prescribing Instructions:*** *An adequate response to treatment is defined as:** *A clinically meaningful improvement in the measures of disease severity and/or quality of life impact that were used to establish baseline severity*

*The assessment of adequate response to treatment must be documented in the patient’s medical records and must be no more than 4 weeks old at the time of the authority application.* |
|  | ***Administrative Advice:*** *Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.* |
|  | ***Administrative Advice:*** *This Grandfather restriction will cease to operate 12 months after the date specified in the clinical criteria.* |

* 1. The submission stated that it requested an indication-agnostic listing to allow children who have the greatest risk of permanent disability and/or psychological distress (in the opinion of the treating clinician) to receive immediate treatment with adalimumab. The submission requested the listings be Authority Required (STREAMLINED) to allow for immediate access for patients who should commence treatment without delay and to reduce administrative burden for prescribers.
	2. The current PBS listings for Humira for paediatric populations are Authority Required (written) or Authority Required (Telephone/Online) for initial and first continuing treatment. The Authority requirements for continuing treatment varies depending on the indication (see paragraphs 2.16-2.17).
	3. The submission noted the maximum quantity and number of repeats were calculated based on the highest approved dosing regimen for paediatric patients (patients with Crohn disease who are ≥ 40kg and require a dose of 80 mg adalimumab every 2 weeks). A similar approach was taken for the requested maximum quantity and number of repeats for patients accessing treatment through the proposed Continuing and Grandfather treatment phases. The maximum quantity requested for patients receiving treatment under the ‘Continuing adult with paediatric IMID history’ restriction was calculated based on adult dosing requirements.
	4. The requested maximum quantities and repeats differ from the maximum quantities and repeats for adalimumab that are currently PBS-listed for certain indications. In many instances the requested maximum quantities and repeats are higher than those currently PBS-listed.
	5. The Pre-Sub Committee Response (PSCR) stated the intent of the requested restriction was that patients who access and subsequently fail to respond to another PBS-subsidised biological treatment for an IMID would not be able to access treatment via this restriction. It stated the sponsor would be open to including a statement in the listing to clarify this and that patients who would qualify under existing listings for adalimumab should not access treatment through the requested listing.
	6. The PSCR noted the proposed clinical criteria in the requested listing was developed in conjunction with clinician working groups, who considered the criteria should be flexible to include both disease severity measures and patient-reported quality of life measures to provide an overall assessment of the patient’s disease severity. It considered that rather than specifying particular measures in the restriction criteria, the choice of measure should be left with the treating physician to reflect the variable presentations of IMIDs in children. The PSCR provided the following examples of scores and measures that may be used to assess severity of particular IMIDs:
* Rheumatology conditions: swollen and tender joint counts, overall Physician Global Assessment, Childhood Myositis Assessment Scale (CMAS)/Manual Muscle Testing and a subset of Eight Muscles (MMT8) (Juvenile Dermatomyositis), Patient/Parent Global Assessment of wellbeing.
* Gastroenterology conditions: Paediatric Crohn’s Disease Activity Index (PCDAI), Paediatric Ulcerative Colitis Activity Index (PUCAI), endoscopic scores, magnetic resonance enterography, intestinal ultrasound scores (including bowel wall thickness), faecal calprotectin.
* Dermatology conditions: Psoriasis Activity and Severity Index (PASI), Hidradenitis Suppurativa Clinical Response (HiSCR), Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN) (Steven Johnson Syndrome/Toxic Epidermal Necrolysis), Children’s Dermatology Life Quality Index (CDLQI).

The ESC noted the extensive consultation undertaken with various clinical groups in the preparation of this submission.

* 1. The PSCR acknowledged the requested maximum quantity and repeats differ from the maximum quantities and repeats for current PBS-listings for adalimumab. However, it argued that the requested 28 weeks maximum treatment duration better aligns with patients’ usual scheduling of appointments with their specialist (i.e. every 3 to 6 months).

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

1. Population and disease
	1. Adalimumab is a recombinant human immunoglobulin monoclonal antibody. Adalimumab binds to tumour necrosis factor (TNF) and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Elevated levels of TNF are found in the synovial fluid of rheumatoid arthritis, including juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis patients and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques, which contribute to the inflammatory response, the proliferation and decreased maturation of keratinocytes and to the associated vascular damages that are characteristic of the disease (Humira Product Information).
	2. The submission requested an indication-agnostic PBS-listing for the treatment of IMIDs in paediatric patients, to cover all possible IMIDs in which adalimumab is expected to be used.
	3. The submission proposed the population be limited to patients who, in the opinion of the treating clinician, may derive clinical benefit from treatment with adalimumab, and to patients whose disease severity is considered sufficient to cause substantial detriment to their immediate or future health or quality of life, according to at least one objective measure of disease severity appropriate for the patient's condition and age. The requested listing stated at least two measures of disease severity or quality of life impact must be used to assess impact on quality of life, of which at least one must be an objective measure.
	4. The following IMIDs which may be treated with adalimumab were noted in the submission:
* inflammatory arthritides,
* uveitis,
* inflammatory bowel diseases,
* psoriasis,
* rarer inflammatory diseases: sarcoidosis; chronic recurrent multifocal osteomyelitis; synovitis, acne, pustulosis, hyperostosis and osteitis syndrome; Behcet’s disease; juvenile dermatomyositis; chronic vasculitis; chronic erythema multiforme; pyoderma gangrenosum (PG); pyogenic arthritis, PG and acne (PAPA) and related neutrophilic dermatoses,
* acute, severe inflammatory conditions (short term use in the hospital setting): Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, Toxic Shock Syndrome and Kawasaki disease.
	1. The submission noted there are differences in treatment and outcomes in rural and regional Australia compared to metropolitan areas, and differences based on public versus private treatment and a patient’s socioeconomic status. There are also differences in medicines included in state and individual hospital formularies. The submission stated that including adalimumab on the PBS for paediatric indications could help to improve equitable access to effective treatment through removing geographic and facility-based barriers to treatment. It could also reduce pressure on hospitals and private clinics through reductions in in-patient care requirements, noting patients in remission will have reduced healthcare needs compared to those with active disease.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

1. Comparator
	1. The submission did not nominate a comparator.
	2. Any other medicine used for the management of IMIDs in paediatric patients could be considered comparators to adalimumab. These could include:
* For severe active juvenile idiopathic arthritis: etanercept, tocilizumab, tofacitinib, hydroxychloroquine, sulfasalazine.
* For moderate to severe ulcerative colitis and Crohn disease: infliximab, mesalazine, olsalazine, sulfasalazine.
* For complex refractory Fistulising Crohn disease: ustekinumab, infliximab.
* Psoriasis: acitretin, ustekinumab, etanercept.
* Azathioprine, mercaptopurine, methotrexate.
	1. The PSCR disagreed that any other PBS-listed conventional or biological DMARDs could be considered comparators to adalimumab for the proposed population and place in therapy. It argued that as the proposed restriction is indication-agnostic and intended for children with the greatest risk of permanent disability and/or psychological distress, there were too many complex and multifarious factors to allow for an appropriate comparator. The ESC considered that while this may be true for rare conditions, comparators are appropriate for the main indications of use.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

1. Consideration of the evidence

Sponsor hearing

* 1. The sponsor requested a hearing for this item. Clinicians commented on the effectiveness of adalimumab for paediatric IMIDs, including rarer conditions, and presented clinical case studies of children presenting with IMIDs who would benefit from treatment with adalimumab but who would not be eligible to received PBS subsided therapy through the current PBS listings for adalimumab. Clinicians commented that earlier treatment with a biological medication was associated with better patient outcomes, disease remission, and prevention of long term complications. Challenges with daily activities (e.g. physical, social and education development) and quality of life for both the child and family were noted by the clinicians, and that earlier access to adalimumab would benefit these patients and their families. Clinicians stated that the requested listing would support patients to have more timely access to adalimumab, treatment would generally be used for 2 years before trialling a withdrawal, and that patients would only continue treatment with adalimumab if a benefit was seen.

Consumer comments

* 1. The PBAC noted and welcomed the input from individuals (6), health care professionals (3) and organisations (4) via the Consumer Comments facility on the PBS website. The comments noted the effectiveness of adalimumab for paediatric IMIDs in improving disease symptoms and quality of life, and that it could be easily administered. Comments also stated the current PBS restrictions for this medication did not reflect current practice, and did not allow use in all paediatric patients who would benefit from treatment. One comment stated that for rarer conditions there is a lack of robust research, and treatment approaches are based on consensus opinion. Comments were supportive of the requested listing, stating that it would allow access to adalimumab earlier in the treatment course and lead to better patient outcomes.
	2. Comments stated the current PBS restrictions created delays in patients accessing adalimumab, which could worsen patient outcomes. This included the paperwork currently required to prescribe adalimumab through the PBS, which could delay treatment for patients.
	3. Comments noted the financial strain to the family due to managing paediatric IMIDs, costs associated with accessing adalimumab when not living close to a hospital pharmacy supplying the medication (e.g. freight costs) and challenges with courier services delivering the medication.
	4. Some comments noted adverse effects experienced with adalimumab, however others stated it had a good safety profile and has been used for many years.

Clinical place for the proposed therapy

* 1. The submission outlined the following patient populations who may access adalimumab through the proposed indication-agnostic PBS-listing and provided the below justifications for the requested listing. This list was informed by expert opinion from clinician working groups comprising paediatric rheumatologists, gastroenterologists and dermatologists, and through a literature review.
* Inflammatory arthritides: the submission stated current PBS listings for paediatric juvenile idiopathic arthritis excludes patients with isolated sacroiliac and/or spinal disease (even though it is listed for ankylosing spondylitis in adults) and patients who have <4 active joints involved who have high risk of erosive disease (due to involvement of the hip, wrist, ankle, jaw/temporomandibular joint).
* The Australian Paediatric Rheumatology Group and the Juvenile Arthritis Foundation stated in their submissions to the HoR Inquiry that specifying an arbitrary number of joints affected plus failure of methotrexate to access biologic treatment does not reflect the increased understanding of disease progression and potential benefits of early, aggressive treat-to-target approaches.
* The American College of Rheumatology (ACR) Guidelines and NHS Policy Statement recommend anti-TNF agents as first line treatment for patients where sacroiliitis or axial arthritis is present.[[1]](#footnote-1),[[2]](#footnote-2)
* The National Institute for Health and Care Excellence (NICE) recommendation for adalimumab (and etanercept) in juvenile idiopathic arthritis was inclusive of polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis and psoriatic juvenile idiopathic arthritis (with an acknowledgement that outcomes between populations was generalisable and based on clinical expert opinion).[[3]](#footnote-3)

The submission claimed the requested PBS listing for adalimumab would be aligned with international best practice for these indications.[[4]](#footnote-4)

* Uveitis: the submission stated that children with juvenile idiopathic arthritis-associated uveitis can currently only access adalimumab on the PBS if they meet the required number of swollen and tender joints. The submission claimed that uveitis is present in approximately 20% of patients with oligoarticular juvenile idiopathic arthritis and only 5% of patients with polyarticular juvenile idiopathic arthritis.[[5]](#footnote-5) The submission further claimed that in patients with oligoarticular juvenile idiopathic arthritis the uveitis can be more impactful in terms of disease severity compared to joint disease, and claimed that patients who would benefit the most from adalimumab cannot currently access it through the PBS.
* Clinical practice guidelines produced by the ACR, the Single Hub and Access point for Paediatric Rheumatology in Europe (SHARE) and the Childhood Arthritis and Rheumatology Research Alliance (CARRA) recommend adalimumab as the first line biologic treatment for the treatment of juvenile idiopathic arthritis-associated uveitis in certain situations.[[6]](#footnote-6),[[7]](#footnote-7),[[8]](#footnote-8) The ACR guidelines conditionally recommend starting methotrexate and a monoclonal antibody TNF inhibitor immediately for children and adolescents with juvenile idiopathic arthritis with severe active chronic anterior uveitis and sight threatening complications over methotrexate monotherapy.6 The CARRA guidelines state that patients who fail methotrexate should be considered for the TNF inhibitor consensus treatment plan (3 months of treatment is required before assessing methotrexate efficacy). If patients are not intolerant of methotrexate, a TNF inhibitor should be added to methotrexate (rather than replace). The TNF inhibitor consensus treatment plan can be considered for patients who are methotrexate-naïve with uncontrolled uveitis and severe disease, and methotrexate should be started simultaneously.7 Recommendations from the SHARE initiative state that TNF inhibitors (with adalimumab preferred) is recommended in patients with uveitis that is refractory or resistant to DMARD treatment (methotrexate).8This is consistent with the recommendation from The Australian and New Zealand Juvenile Idiopathic Arthritis-Uveitis Working Group, which recommend methotrexate as the first choice of conventional systemic immunosuppressive drug, and adalimumab as the first choice of biologic systemic immunosuppressive drug.[[9]](#footnote-9)
* The ACR guidelines recommend starting methotrexate and a monoclonal antibody TNFi immediately in children and adolescents with juvenile idiopathic arthritis with severe active chronic anterior uveitis and sight-threatening complications, over methotrexate monotherapy.
* The submission stated that patients with non-infectious uveitis of other aetiologies without joint involvement have limited options to access adalimumab, despite the potential risk of vision loss. The submission stated that the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) Paediatric, Glaucoma and Uveitis Special Interest Groups made a submission to the HoR Inquiry into Childhood Rheumatic Disease, with the suggestion that ‘adalimumab is PBS-listed for uveitis without joint involvement under the cotreatment of a paediatric rheumatologist.’
* Inflammatory bowel diseases: the submission claimed the inflammatory burden and disease severity in inflammatory bowel disease can be greater in paediatric patients compared to adults.
* The submission stated for patients with high risk Crohn disease, in particular high-risk patients with perianal, stricturing or penetrating disease, or with severe growth retardation, international guidelines recommend the use of anti-TNF biologic therapies as first-line therapy, as well as proactive therapeutic drug level monitoring and escalation of therapy where necessary to maintain trough levels within the therapeutic range.[[10]](#footnote-10),[[11]](#footnote-11)
* The submission stated that flexibility to optimise dosing in children with inflammatory bowel disease can have a steroid-sparing effect, potentially reducing steroid-related complications observed in children, and minimising side effects that can be of concern to patients (weight gain, insomnia, ‘moon face’).[[12]](#footnote-12),[[13]](#footnote-13) One of the references cited (Costello R et al) was a survey of adults, who rated weight gain as the most important adverse effect, followed by insomnia, ‘moon face’ and other adverse effects which were ranked at the same level of importance.
* Psoriasis: The submission stated that adalimumab is not currently PBS-listed for paediatric patients with chronic plaque psoriasis.
* Patients can access etanercept and ustekinumab if they meet the disease severity and prior failed therapy criteria aligned to the existing adult restriction criteria (lesions present ≥ 6 months; baseline psoriasis area and severity score (PASI) ≥ 15; failure of 2 out of 3 conventional therapies). The submission stated these criteria are clinically inappropriate for paediatric patients, as children often present with significant involvement in isolated body areas (facial, scalp, nail) which is visually confronting and functionally debilitating (hands and feet)[[14]](#footnote-14), but with insufficient body surface area involved to meet the PASI threshold. There can be practical challenges to using phototherapy in children, such as school absenteeism and fear of isolation in the phototherapy cabinet.
* The submission stated that delays in initiating an effective biologic treatment for chronic plaque psoriasis can lead to significant comorbidities and psychological impact, including a higher prevalence of obesity, diabetes mellitus, hypertension, juvenile arthritis, Crohn disease and psychiatric disorders.14,[[15]](#footnote-15)
* The submission stated that adalimumab could also be used for guttate psoriasis flares and acute pustular psoriasis flares that require hospitalisation and treatment with methotrexate (with adalimumab supporting earlier discharge and return to normal family function, and ongoing outpatient treatment and management).
* Rarer autoinflammatory diseases: The submission stated there are a number of less common IMIDs where adalimumab may be used in clinical practice in Australia (summarised in paragraph 4.4). The submission claimed making adalimumab accessible for these patients through the proposed indication-agnostic listing would help address inequities in access to effective treatments for these children.
* Acute, severe inflammatory conditions: The submission stated clinician working groups identified a number of conditions where adalimumab may be used in hospitalised patients, based either on evidence available in the literature or personal clinical experience (outlined in paragraph 4.4). It is anticipated by the experts that these conditions would require short-term use of adalimumab.

Clinical evidence

* 1. The submission presented a literature search which it stated focused on the evidence for adalimumab for the treatment of paediatric indications. The literature search found 17 randomised controlled trials (including phase 3 registrational studies) and 6 non-randomised interventional trials in open-label extension studies (Table 1).

**Table 1:** Trials presented in the submission

| Trial ID | Protocol title/ Publication title | Publication citation |
| --- | --- | --- |
| **Randomised controlled trials** |
| EudraCT 2007-003358-27 | Horneff G, Fitter S, et al. Double-blind, placebo-controlled randomized trial with adalimumab for treatment of juvenile onset ankylosing spondylitis (JoAS): significant short term improvement | Arthritis Res Ther. 2012; 14(5): R230 |
| NCT00409682IMAgINE-1 | Efficacy and Safety of Adalimumab in Pediatric Subjects With Moderate to Severe Crohn's Disease | 2011 |
| NCT00048542 | Study of Human Anti-TNF Monoclonal Antibody Adalimumab in Children With Polyarticular Juvenile Idiopathic Arthritis (JIA) | 2020  |
| NCT01166282 | A Study of the Efficacy and Safety of Adalimumab in Pediatric Subjects With Enthesitis Related Arthritis | 2016 |
| NCT01251614 | A Double Blind Study in Pediatric Subjects With Chronic Plaque Psoriasis, Studying Adalimumab vs. Methotrexate | 2013 |
| NCT01385826 | Effect of Adalimumab for the Treatment of Uveitis in Juvenile Idiopathic Arthritis (ADJUVITE) | 2015 |
| NCT02065557ENVISION-1 | Croft NM, Faubion Jr WA, et al. Efficacy and safety of adalimumab in paediatric patients with moderate-to-severe ulcerative colitis (ENVISION I): a randomised, controlled, phase 3 study | Lancet Gastroenterol Hepatol. 2021; 6(8):616-27. |
| NCT02256462 | Pediatric Crohn's Disease Adalimumab Level-based Optimization Treatment (PAILOT) Trial | 2018 |
| NCT02772965COMBINE | Low Dose Oral Methotrexate in Pediatric Crohn's Disease Patients Initiating Anti-Tumor Necrosis Factor (Anti-TNF) Therapy (COMBINE) | 2023 |
| NCT02840175 | Treatment Tapering in JIA With Inactive Disease (AJIBIOREM) | 2020 |
| NCT02852694 | Reduce Risk for Crohn's Disease Patients | 2022 |
| NCT03816397ADJUST | Acharya NR, Ebert CD, et al. Discontinuing adalimumab in patients with controlled juvenile idiopathic arthritis-associated uveitis (ADJUST-Adalimumab in Juvenile Idiopathic Arthritis-associated Uveitis Stopping Trial): study protocol for a randomised controlled trial | Trials. 2020; 21(1):887. |
| NCT03828019ADVISE | Adalimumab vs. Conventional Immunosuppression for Uveitis Trial (ADVISE) | In progress |
| NCT04646187 | De-escalation of Anti-TNF Therapy in Inflammatory Bowel Disease (FREE) | In progress |
| NCT05015335 | The Efficacy and Safety of Adalimumab in Non-infectious Anterior Pediatric Uveitis With Peripheral Vascular Leakage | 2021 |
|  | Polgreen LE, Kunin-Batson A, et al. Pilot study of the safety and effect of adalimumab on pain, physical function, and musculoskeletal disease in mucopolysaccharidosis types I and II | Mol Genet Metab Rep. 2017; 75-80. |
| SYCAMOREISRCTN10065623EudraCT 2010-021141-41 | A randomised controlled trial of the clinical effectiveness, safety and cost-effectiveness of adalimumab in combination with methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis (SYCAMORE Trial) | Trials. 2014; 15:14. |
| **Non-randomised interventional trials** |
| NCT00775437 | Active Juvenile Idiopathic Arthritis (JIA) Compassionate Use | 2013 |
| NCT00686374 | Efficacy and Long Term Safety of Adalimumab in Pediatric Subjects Who Have Demonstrated Clinical Response in M06-806 | 2017 |
| NCT02632175 | Long-term Safety and Efficacy Study of Adalimumab in Pediatric Subjects With Ulcerative Colitis | In progress |
| NCT04588818 | Adalimumab Plus Methotrexate for the Treatment of Pediatric Uveitis | 2023 |
| NCT05540743 | Biologic Therapy in Pediatric JIA Uveitis | In progress |
| NCT00690573 | Safety, Efficacy, and Pharmacokinetics of Adalimumab in Japanese Children With Juvenile Rheumatoid Arthritis | 2011 |

Source: Submission: A\_Summary Systematic Literature Review

* 1. The literature search found adalimumab had been studied for the treatment of:
* inflammatory arthritides in 173 paediatric patients
* inflammatory bowel disease in 457 patients
* non-infectious uveitis in 76 patients
* plaque psoriasis in 77 patients
* mucopolysaccharidosis types I and II in 1 patient.
	1. In addition, the literature search found 253 observational studies and 76 case series and reports reviewing efficacy outcomes, 105 observational studies looking at safety outcomes, and 72 reviews on both safety and efficacy. The submission stated the published observational evidence for the use of adalimumab included:
* 3,382 children with inflammatory arthritides (including polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, juvenile psoriatic arthritis, sacroiliitis, and axial spondyloarthritis)
* 5,438 children with inflammatory bowel disease (including very early onset inflammatory bowel disease, ulcerative colitis, Crohn disease and associated phenotypes)
* 1,311 children with uveitis of all aetiological origins
* 392 children with either plaque, pustular or rupioid psoriasis
* 93 patients with other rare auto-inflammatory diseases or acute inflammatory conditions.
	1. The submission further stated that the literature search also identified 92 observational studies with safety-related endpoints, encompassing 4,914 patients globally.
	2. The ESC noted the literature provided primarily focused on the safety of adalimumab rather than efficacy in particular conditions, and also included real world data. The pre-PBAC response disagreed with this, and claimed evidence provided investigated both efficacy and safety outcomes.
	3. The ESC noted the Juvenile Arthritis Foundation Australia’s IMPACT (Investigating the Mental, Physical, Social and Financials CosTs) study[[16]](#footnote-16) and its main findings, and the impacts of childhood rheumatic diseases on patients including therapy, costs and quality of life. The ESC noted that juvenile idiopathic arthritis led to a significant reduction in quality of life.

Comparative effectiveness

* 1. The submission did not provide any study results comparing the safety and efficacy of adalimumab to other treatments for the treatment of paediatric IMIDs. However, the submission did provide the following information regarding the use of adalimumab compared to other therapies for certain conditions:
* Inflammatory bowel diseases:
* azathioprine is generally an effective first-line immunosuppressive treatment for ulcerative colitis. However, this is not the same for conventional immunosuppressive treatments mandated in Crohn disease (especially in high-risk patients with perianal, stricturing or penetrating disease, or with severe growth retardation). International guidelines recommend the use of anti-TNF biologic therapies first-line in these high-risk patients.
* Flexibility to optimise dosing in children with inflammatory bowel disease can have a steroid-sparing effect, reducing the risk of adverse effects from corticosteroids such as weight gain, insomnia and ‘moon face’.
* Uveitis:
* The ACR guidelines recommend starting combination therapy with a monoclonal antibody TNFi in conjunction with methotrexate in children and adolescents with juvenile idiopathic arthritis with severe active chronic anterior uveitis and sight-threating complications, compared to methotrexate monotherapy.

Safety considerations

* 1. The Humira Product Information states: ‘The safety and efficacy of Humira has not been established in other forms of juvenile idiopathic arthritis (JIA) such as systemic JIA or oligoarticular JIA. The long term effects of Humira on the growth and development of children have not been studied. Treatment with Humira should only be initiated in patients with paediatric Crohn’s disease following diagnosis by a specialist gastroenterologist, where other diseases with potentially similar presentations (e.g., Inflammatory Bowel Disease (IBD) associated with chronic granulomatous disease) have been ruled out. Humira has not been studied in children with Crohn’s disease aged less than 6 years.’
	2. The submission cited a publication by Horneff et al, which was an analysis of safety events across 7 randomised and open-label trials of adalimumab and their open-label extensions (Horneff et al, 2018)[[17]](#footnote-17). There were 577 paediatric patients included in the analysis, representing 1,440.7 patient-years of adalimumab exposure across polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, chronic plaque psoriasis and Crohn disease:
* The most commonly reported adverse events (events/100 patient-years (PY)) were upper respiratory tract infections (24.3/100 PY), nasopharyngitis (17.3/100 PY), and headache (19.9/100 PY).
* Serious infections (4.0/100 PY) were the most frequent serious adverse events across indications; the most commonly reported was pneumonia (0.6/100 PY). Serious infection rates were 2.7, 0.8, and 6.6/100 PY in patients with juvenile idiopathic arthritis, psoriasis and Crohn disease, respectively.
* No events of malignancies were reported.
* One death (accidental fall) occurred in a patient with psoriasis.
	1. The submission provided the Update to the Periodic Safety Update Report for: Adalimumab (reporting interval of 1 January 2023 to 30 June 2023), which stated that there was no new efficacy or safety information received that had a significant impact on the benefit/risk evaluation of adalimumab.
	2. The report stated that there was one new safety signal identified during the interval, outlined in Table 2.

**Table 2: Safety signals (closed or ongoing) during the PSUR Update Reporting Interval 1 January 2023 through 30 June 2023**

|  |  |
| --- | --- |
| **Signal Term** | Neuropsychiatric disorders |
| **Date Detected** | 21 February 2023 |
| **Status (New, Ongoing or Closed)** | Closed |
| **Date Closed (for Closed Signals)** | 12 May 2023 |
| **Source of Signal** | FDA |
| **Reason for Evaluation and Summary of Key Data** | On 21 February 2023, AbbVie received a Request for Information from the FDA for a comprehensive analysis of specific neuropsychiatric adverse events coincident with adalimumab and a cumulative summary of drug utilization rates for adalimumab in the United States and worldwide |
| **Method of Signal Evaluation** | Case Series Analysisa |
| **Action(s) Taken or Planned** | Signal not confirmed. There is no evidence of a causal relationship between the neuropsychiatric medical concepts of suicide, depression, anxiety, delirium/disorientation or hallucinations/paranoia/acute psychosis/psychotic disorder/mania and adalimumab based on clinical trial data and postmarketing reports. No changes to the CCDS or Risk Management Plan are recommended at this time. The data reviewed in this report do not change the established benefit risk profile of adalimumab, which remains favorable |

Source: Attachment 4 ADA 30 June 2023 PSUR Update

AbbVie: AbbVie Inc.; CCDS: Company Core Data Sheet; FDA: Food and Drug Administration; PSUR: Periodic Safety Update Report

aCase Series Analysis: MAH standardized analysis includes review of cases from MAH postmarketing and clinical trial databases and literature

* 1. The report stated that there had been no actions taken for safety reasons during the interval covered by this update.
	2. A benefits and harms table is not presented as the submission did not make a clinical claim.
	3. The ESC noted that a broad listing for adalimumab with no restrictions on indications differs from the listings for similar medicines. It expressed concern about broadening the listing to include conditions in which efficacy has not been established, given the drug is not without risks (known adverse events and immunosuppressive effects), the extent of which are unclear in the paediatric setting. The ESC also noted that there were different levels of evidence for the use of adalimumab in children for different indications.

Clinical claim

* 1. The submission did not include a clinical claim.

Economic analysis

* 1. The submission did not provide an economic analysis.
	2. The PSCR stated ‘While the cost-effective price of adalimumab (Humira) has not been formally established in these patient groups, AbbVie refers to the NICE recommendation for adalimumab and etanercept in JIA,[[18]](#footnote-18) which was inclusive of polyarticular juvenile idiopathic arthritis (pJIA), enthesitis-related arthritis (ERA) and psoriatic JIA, where it was acknowledged that the outcomes between populations were overall generalisable and therefore likely to be equally cost-effective at a given price.’
	3. The ESC noted that as there was no economic analysis presented for any of the proposed indications there was no basis for assessing cost-effectiveness. No reference points of previous decisions were nominated. A parallel application for adalimumab for uveitis, which is a relative common feature of some of the indications in this submission, presented a cost-effectiveness analysis with a base incremental cost-effectiveness ratio (ICER) of $25,000 to < $35,000. That ICER was very sensitive to time horizon and assumed ocular benefits and a specific disease duration. When used in younger patients, adalimumab is likely to be used for a longer period compared to older patients, considering that treatment will be started earlier and in most situations adalimumab will be used to control (rather than cure) the condition.
	4. The submission requested the following dispensed price for maximum quantity (DPMQ) for the different strengths of Humira:

**Table 3: Requested DPMQ for Humira**

|  |  |  |  |
| --- | --- | --- | --- |
| **Listing** | **Maximum quantity (packs)** | **Maximum quantity (units)** | **Requested DPMQ** |
| **Initial treatment** |
| 80 mg in 0.8 mL pre-filled syringe80 mg in 0.8 mL pre-filled pen | 3 | 3 | $2,014.38 |
| 40 mg in 0.4 mL pre-filled syringe40 mg in 0.4 mL pre-filled pen | 2 | 4 | $1,345.59 |
| 20 mg in 0.2 mL pre-filled syringe | 1 | 2 | $706.70 |
| **Continuing treatment** |
| 80 mg in 0.8 mL pre-filled syringe80 mg in 0.8 mL pre-filled pen | 2 | 2 | $1,345.59 |
| 40 mg in 0.4 mL pre-filled syringe40 mg in 0.4 mL pre-filled pen | 2 | 4 | $1,345.59 |
| 20 mg in 0.2 mL pre-filled syringe | 2 | 4 | $1,345.59 |

Source: Attachment 2: ADA Paed IMIDs Proposed Restrictions

DPMQ: dispensed price for maximum quantity

* 1. All requested DPMQs are consistent with the current DPMQ for the General Schedule listings of Humira as of January 2024 for the respective strengths and quantities, with the exception of the requested DPMQ for the 20 mg in 0.2 mL pre-filled syringe. There is currently no PBS-listing for this strength with a maximum quantity of 4 units. The current DPMQ for Humira 20 mg in 0.2 mL pre-filled syringe for a maximum quantity of 2 units is $706.70.

Drug cost/patient/year

* 1. Table 4 outlines the maximum drug cost per patient per year based on the indication, assuming the highest recommended dose and induction treatment.

Table 4: **Maximum drug cost per patient per year based on indication**

| Indication | Maximum dose | Cost/patient/month | Cost/patient/year |
| --- | --- | --- | --- |
| Juvenile idiopathic arthritis | 40 mg every 2 weeks | $672.80 | $8,746.40 |
| Enthesitis-related arthritis | 40 mg every 2 weeks | $672.80 | $8,746.40 |
| Crohn disease | Induction: 160 mg (Day 0), 80 mg (Day 14)Maintenance: 80 mg every 2 weeks | Month 1: $2,014.38Month 2 onwards: $1,345.59 | $18,161.46 |
| Ulcerative colitis | Induction: 160 mg (Day 0), 80 mg (Day 14)Maintenance: 40 mg every 2 weeks | Month 1: $2,014.38Month 2 onwards: $672.80 | $10,087.98 |
| Psoriasis | Induction: 40 mg (Week 0), 40 mg (Week 1)Maintenance: 40 mg every 2 weeks (from week 3) | Month 1: $1,345.59Month 2 onwards: $672.80 | $9,419.19 |
| Hidradenitis suppurativa | Induction: 80 mgMaintenance: 80 mg every 2 weeks (from Week 1) | Month 1: $2,014.38Month 2 onwards: $1,345.59 | $18,161.46 |
| Uveitis | Induction: 80 mgMaintenance: 40 mg every 2 weeks (from Week 1) | Month 1: $1,345.59Month 2: $672.80 | $9,419.19 |

Source: Based on requested DPMQ in Attachment 2 of the submission

Estimated PBS usage & financial implications

* 1. This submission was not considered by DUSC.
	2. The PSCR provided estimates of expected use and financial implications for the first 6 years of listing (see Table 5). The PSCR stated that estimates are based on expert opinion and available evidence, and considered that estimates are likely to be over-estimated as they do not account for future price reductions.

Table : **Estimated use and financial implications**

|  | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
| --- | --- | --- | --- | --- | --- | --- |
| Estimated extent of use (all strengths) |
| Number of patients treated | 　|　1` | 　|　1 | 　|　2 | 　|　2 | 　|　2 | 　|　2 |
| Number of scripts dispenseda | 　|　2 | 　|　3 | 　|　3 | 　|　3 | 　|　3 | 　|　3 |
| Estimated financial implications of adalimumab (all strengths) |
| Cost to PBS/RPBS less copayments | 　|　4 | 　|　4 | 　|　4 | 　|　4 | 　|　4 | 　|　5 |

Source: Utilisation and cost workbook

a Assuming 12 scripts per year as estimated by the submission.

*The redacted values correspond to the following ranges:*

*1 < 500*

*2 500 to < 5,000*

*3 5,000 to < 10,000*

*4 $0 to < $10 million*

*5 $10 million to < $20 million*

* 1. The total cost to the PBS/RPBS of listing adalimumab for the requested restriction was estimated to be $10 million to < $20 million in Year 6, and a total of $50 million to < $60 million in the first 6 years of listing. The ESC considered this to be uncertain but plausible.
	2. The estimated financial implications do not account for any potential financial implications of other PBS-listed medicines if adalimumab replaces the use of other therapies.
	3. The PSCR stated the proposed population estimates include, but are not limited to, patients who have been diagnosed with an IMID for which adalimumab is currently PBS-listed but who do not meet the eligibility requirements of the existing restrictions. The estimates do not include patients with uveitis. The ESC considered this is likely to cover the majority of potentially eligible patients.
	4. The submission estimated a minor increase in uptake of adalimumab by the paediatric population relative to the whole population currently accessing treatment with adalimumab through the PBS. It estimated 500 to < 5,000 additional paediatric patients would access adalimumab through the requested listing (< 500 patients through the grandfather listing and < 500 new patients) (Table 6).

**Table 6: Estimated patient numbers based on state/territory and condition**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Tertiary Institution** | **State** | **Relative proportion** | **Dermatology** | **Gastro****IBD (CD & UC)** | **Rheumatology** | **Grandfather** |
| **PsO** | **Other** | **Inflammatory arthritides & uveitis** | **Other** |
| TCH Westmead | NSW | 1 | ||||1 | ||||1 | - | ||||1 | ||||1 |  |
| SCH Randwick | NSW | ||||1 | ||||1 | - | ||||1 | ||||1 |  |
| Monash Children’s Hospital | VIC | 0.8 | ||||1 | ||||1 | - | ||||1 | ||||1 |  |
| RCH Melbourne | VIC | ||||1 | ||||1 | - | ||||1 | ||||1 |  |
| Queensland Children’s Hospital | QLD | 0.7 | ||||1 | ||||1 | - | ||||1 | ||||1 |  |
| Women’s and Children’s Hospital Adelaide | SA | 0.2 | ||||1 | ||||1 | - | ||||1 | ||||1 |  |
| Perth Children’s Hospital | WA | 0.4 | ||||1 | ||||1 | - | ||||1 | ||||1 |  |
| n/a | TAS | 0.1 | ||||1 | ||||1 | - | ||||1 | ||||1 |  |
| n/a | NT | 0.03 | ||||1 | ||||1 | - | ||||1 | ||||1 |  |
| n/a | ACT | 0.1 | ||||1 | ||||1 | - | ||||1 | ||||1 |  |
| Sum total |  |  | **||||**1 | **||||**1 | **||||**1**a** | **||||**1 | **||||**1 | **||||**1**b** |
| Total |  |  |  |  |  |  |  | **||||**1**c** |

Source: Attachment 5 ADA Paed IMID patient estimates

ACT: Australian Capital Territory; CD: Crohn disease; Gastro: gastroenterology; IBD: inflammatory bowel disease; n/a: not applicable; NSW: New South Wales; NT: Northern Territory; PsO: psoriasis; QLD: Queensland; RCH: The Royal Children’s Hospital; SA: South Australia; SCH: Sydney Children’s Hospital; TAS: Tasmania; TCH: The Children’s Hospital; UC: ulcerative colitis; VIC: Victoria; WA: Western Australia

a For IBD patients, it is anticipated that the proposed restriction criteria will not expand the eligible population (aside from a small number of patients < 6 years old), rather will be used to treat high-risk patients earlier in their disease course, without the need to fail systemic immunosuppressants first. Therefore this estimate is based on approximately 10% of the existing utilisation in across both CD and UC, and will be essentially cost neutral as these patients will access treatment via the IMID restriction, rather than via the existing CD or UC restrictions.

b Expert opinion has indicated that their estimates are inclusive of existing compassionate supply patients therefore this has been factored into overall estimates.

c The submission provided a total of 307 patients. This has been updated to 309 to reflect the patient numbers provided for the different conditions. Excludes estimated number of patients in the grandfather category

*The redacted values correspond to the following ranges:*

*1<500*

* 1. The submission stated that as the assessment of treatment eligibility is individualised and based on clinician judgement, the estimated number of patients who would be treated under the proposed restrictions was informed by expert opinion based on their current patient population.The estimates are informed by expert clinical opinion and may not account for differences in individual prescribing practices. Furthermore, as the requested listing involves subjective assessment from individual prescribers. The number of patients accessing adalimumab through the requested listing could be higher than estimated.
	2. The PSCR argued that the estimated patient numbers provided the best approximation given the lack of Australian epidemiological and registry data for paediatric patients. It stated that clinicians working in both public and private practice, and in metropolitan and regional services, were asked to provide estimates of patient numbers. It stated that the number of paediatric specialists and paediatric hospitals in Australia is small and variability in evidence-based prescribing was minimal.
	3. It was considered that for the rarer auto-inflammatory diseases the number of patients is low and as such the potential utilisation may be slightly overestimated due to the numerical rounding of estimates for less‑populated states and territories.
	4. The submission stated that following the initial period of higher uptake driven by the prevalent patient population, the number of incident patients could be reasonably expected to decrease over subsequent years before stabilising.
	5. The estimated number of patients accessing Humira through the grandfather listing was based on the number of patients currently receiving compassionate access to Humira on a continuing basis across all indications. The submission stated they were not aware of any other programs supplying adalimumab to paediatric patients on compassionate access programs.
	6. The submission estimated the number of patients treated for rarer inflammatory diseases (outlined in paragraph 4.4) is low, with fewer than 5 patients across all conditions reviewed each year at the major children’s hospitals.
	7. The ESC noted there was a lack of information on potential impact on use of adalimumab if paediatric patients currently accessing other PBS-listed bDMARDs do not meet the response or other criteria for these listings, and subsequently access adalimumab through the requested listing. The PSCR stated it was not the intent of the requested listing to allow patients who access and subsequently fail to respond to another PBS-subsidised biological treatment for an IMID to then access adalimumab through the requested listing (see paragraph 3.5).
	8. The submission claimed that any budget impact would be minimal due to the small number of patients relative to the current reimbursed populations in both paediatric and adult patients. However, regardless of the relative cost, the financial impact of the proposed change needs to be considered. The submission further claimed any costs would be outweighed by the potential benefits of treating these patients and alleviating the burden of disease for these patients and their families. This has not been modelled through an economic evaluation.
	9. The ESC considered the utilisation and financial estimates presented in this submission were complex and uncertain. For conditions where there is already a listed indication, the numbers are likely to be reasonable estimates. However, the proposed listing allows substantial clinician discretion which makes estimates of uptake difficult to predict. For conditions outside of these listed indications, there is a high level of uncertainty due to a limited and uncertain evidence base. However, in a paediatric population, deviation from the financial and utilisation estimates is likely to be relatively small.
	10. The submission claimed that the Humira brand of adalimumab, at its current price, is more cost-effective than when it was first PBS-listed for patients with juvenile idiopathic arthritis, with a 48% reduction in the effective approved ex-manufacturer price (AEMP) due to statutory price reductions. The submission stated that the reduction in price is expected to continue due to price disclosure, thereby increasing the cost-effectiveness of increased access, and that with the lower price adalimumab is likely to be cost-effective in the requested expanded populations.
	11. The proposed listing may include a patient population with less severe disease, or who have received fewer prior treatments for their condition, compared to the current PBS-listed indications for adalimumab. While the likelihood of cost-effectiveness increases with decreasing prices, the cost-effective price of adalimumab has not been established in these patient groups.
	12. The PSCR argued that the requested listing would not include patients with less severe diseases, but would allow children with aggressive, severe disease to receive treatment with adalimumab earlier in their disease course to prevent disease progression and limit long term disability and psychological impact. It argued that this is a small, but critical, group of patients that paediatric specialists can identify through an overall assessment of their current disease course, biomarkers, pathophysiological features and through the individual prescriber’s experience and judgement. The PSCR stated that the majority of clinicians who would prescribe adalimumab under the requested restriction would be experienced in the management of paediatric IMIDs. It argued that it would be unlikely that prescribers would choose to use adalimumab in patients whose disease severity and/or impact on quality of life was not severe enough to warrant the benefit-risk profile of adalimumab, nor would they be likely to continue treatment if the patient was not receiving benefit.
	13. The PSCR stated that while the cost-effective price of adalimumab had not been formally established in these patient groups, it requested the PBAC consider the 48% reduction in AEMP for Humira and the further 18.25% price reduction occurring in April 2024. It reiterated its claim that at the reduced price Humira is a cost-effective treatment.

 *For more detail on PBAC’s view, see section 7 PBAC outcome.*

1. PBAC Outcome
	1. The PBAC deferred making a recommendation to list adalimumab (Humira) on the PBS as a General Schedule Authority Required (STREAMLINED) listing for the treatment of IMIDs in paediatric patients to allow further consultation with relevant clinical groups.
	2. The PBAC noted the recommendations from the Inquiry into childhood rheumatic diseases: Interim report and consumer comments supporting increased access to adalimumab through the PBS for paediatric conditions. The PBAC acknowledged the importance of access to adalimumab through the PBS for conditions in which there is evidence for its use.
	3. The PBAC noted that the submission covered situations where there was no PBS listing for a particular IMID, and situations where adalimumab was listed on the PBS for a condition, but the clinical criteria may not be suitable for paediatric presentations of the disease.
	4. The PBAC noted that IMID was not a condition on its own, and the requested listing encompassed some conditions where adalimumab was TGA registered and there was evidence available for the efficacy of adalimumab, and some rarer conditions for which adalimumab was not TGA-registered. The PBAC noted the submission did not provide any evidence for the use of adalimumab in these rarer non-registered conditions. The PBAC considered that for these rarer conditions use would most commonly occur in hospitals as inpatient use. The PBAC therefore advised that it would not be appropriate to list adalimumab for the proposed broad IMID indication. However, the PBAC advised that for those indications where there was evidence for the use of adalimumab in children, unnecessary barriers to accessing adalimumab on the PBS should be removed.
	5. The PBAC noted the following conditions were TGA-registered indications for adalimumab, and adalimumab was currently PBS-listed for these indications to allow use in children: hidradenitis suppurativa, psoriatic arthritis, plaque psoriasis, juvenile idiopathic arthritis, ulcerative colitis and Crohn disease. For some conditions there were also multiple alternatives available on the PBS. The PBAC recalled that at its March 2016 meeting it had recommended an age-agnostic listing for adalimumab for moderate to severe ulcerative colitis, where the sponsor had previously requested restricting the listing to adults only.
	6. The PBAC noted that a separate request to list adalimumab for the treatment of patients with vision-threatening non-infectious uveitis was being considered at the same PBAC meeting.
	7. The PBAC therefore considered ankylosing spondylitis should be its focus as the only condition for which there was sufficient evidence for using adalimumab where the PBAC had not made a recommendation to allow use in children.
	8. The PBAC acknowledged potential barriers with the current PBS listings of adalimumab for paediatric patients. For example, the clinical criteria specified in the current adult listing for ankylosing spondylitis were not appropriate requirements for children with this condition, and the maximum doses allowed in the listings for Crohn disease and ulcerative colitis may not reflect current clinical practice. As such, age-agnostic listings that do not consider the restriction criteria from a paediatric perspective are not sufficient.
	9. The PBAC was therefore of a mind to recommend changes to the current listings of adalimumab for ankylosing spondylitis, ulcerative colitis and Crohn disease to reflect available evidence and current clinical practice in paediatric patients. However, the PBAC required further clinical input before making such recommendations. The PBAC requested the Department engage with relevant clinical groups to review the current eligibility criteria for the PBS listings of adalimumab for ankylosing spondylitis, ulcerative colitis and Crohn disease, and revise these where necessary so that they reflect current evidence and clinical practice. The revised listings would be brought to the PBAC for further consideration.

**Outcome:**

Deferred

1. **Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

1. **Sponsor’s Comment**

Existing PBS listings for certain immune-mediated inflammatory diseases do not reflect paediatric disease presentations or current clinical practice. AbbVie is disappointed that the PBAC did not accept the request for a broad indication for IMIDs, however remains committed to continuing to work with all stakeholders to expedite removal of existing barriers to earlier, expanded access so that Australian children with certain IMIDs can realise better disease, quality of life, and life-course outcomes as soon as possible.

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