

**5.04 TOFACITINIB,  
Tablet 5 mg,  
Oral liquid 1 mg per mL, 240 mL,  
Xeljanz<sup>®</sup>,  
Pfizer Australia Pty Ltd.**

**1 Purpose of submission**

1.1 The Category 2 submission requested a General Schedule, Authority Required (written) listing for tofacitinib (TOF) for the treatment of severe active juvenile idiopathic arthritis (JIA).

**Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)**

| Component      | Description  |
|----------------|--|
| Population     | Patients aged 2-17 years with active polyarticular course JIA in whom an adequate response has not been achieved with cDMARDs, alone or in combination with corticosteroids.   |
| Intervention   | Weight-based dosing regimen: <ul style="list-style-type: none"> <li>• 10 to &lt;20 kg: tofacitinib 3.2 mg twice daily (oral solution);</li> <li>• 20 to &lt;40 kg: tofacitinib 4 mg twice daily (oral solution);</li> <li>• ≥40 kg: tofacitinib 5 mg twice daily (oral solution or tablets)</li> </ul> |
| Comparator     | Adalimumab subcutaneously every 2 weeks (fortnightly) based on body weight: 10 to <30 kg: 20 mg; ≥30 kg: 40 mg.  |
| Outcomes       | Disease Flare,<br>PedACR30/50/70,<br>Safety  |
| Clinical claim | Tofacitinib is noninferior to adalimumab in terms of efficacy and safety.  |

Source: Table 1-1, p2 of the submission.

JIA=juvenile idiopathic arthritis; cDMARD=conventional disease modifying anti-rheumatic drugs; JIA=Juvenile Idiopathic Arthritis; PedACR=Paediatric American College of Rheumatology.

**2 Background**

**Registration status**

- 2.1 TOF oral liquid solution and oral tablets were registered in the Australian Register of Therapeutic Goods on 25 January 2023 for the JIA indication.
- 2.2 The TGA indication for JIA is ‘XELJANZ is indicated for the treatment of active polyarticular course juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis, extended oligoarthritis and systemic juvenile arthritis without systemic features for six months) and juvenile psoriatic arthritis in patients 2 years of age and older, who have responded inadequately to previous therapy with DMARDs.’
- 2.3 If listed, TOF would become the first Janus kinase (JAK) inhibitor and first oral treatment option available on the PBS for patients with severe active JIA. Current PBS-listed treatment options include three biological or targeted synthetic disease

modifying anti-rheumatic drugs (bDMARDs/tsDMARDs): etanercept (ETN), adalimumab (ADA) and tocilizumab (TOC). The sponsor requested listing of TOF on a cost-minimisation basis versus ADA.

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

### 3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

3.2 An abbreviated version of the requested restrictions for initial and continuing treatment is presented below.

| Name, restriction, manner of administration, form | Maximum quantity (packs)   | Maximum quantity (units) | No. of repeats | Dispensed price for Max. Qty | Proprietary name and manufacturer |
|---|--|--------------------------|----------------|------------------------------|-----------------------------------|
| TOFACITINIB                                       |  |                          |                |                              |                                   |
| <b>Initial 1, Initial 2 or Initial 3</b>          |  |                          |                |                              |                                   |
| 5mg tablet  | 1  | 56                       | 3              | \$1211.08 published          | Xeljanz®                          |
| 1mg/mL oral solution                              | 1  | 240 mL                   | 3              | \$■■■■ effective             | Pfizer Australia Pty Ltd          |
| <b>Continuing treatment</b>                       |  |                          |                |                              |                                   |
| 5mg tablet  | 1  | 56                       | 5              | \$1211.08 published          | Xeljanz®                          |
| 1mg/mL oral solution                              | 1  | 240 mL                   | 5              | \$■■■■ effective             | Pfizer Australia Pty Ltd          |
| <b>Category / Program:</b>                        | GENERAL – General Schedule (Code GE)   |                          |                |                              |                                   |
| <b>Prescriber type:</b>                           | <input checked="" type="checkbox"/> Medical Practitioners  |                          |                |                              |                                   |
| <b>Severity:</b>                                  | Severe   |                          |                |                              |                                   |
| <b>Condition:</b>                                 | Active Juvenile Idiopathic Arthritis   |                          |                |                              |                                   |
| <b>PBS Indication:</b>                            | Severe Active Juvenile Idiopathic Arthritis  |                          |                |                              |                                   |
| <b>Treatment phase:</b>                           | <b>Initial treatment 1 (new patient)</b>   |                          |                |                              |                                   |
| <b>Restriction:</b>                               | <input checked="" type="checkbox"/> Authority Required – In Writing  |                          |                |                              |                                   |
| <b>Treatment criteria:</b>                        | Must be treated by a rheumatologist OR undergoing treatment under the supervision of a paediatric rheumatology treatment centre.   |                          |                |                              |                                   |
| <b>Clinical criteria:</b>                         | Patient must have demonstrated severe intolerance of, or toxicity due to, methotrexate;<br>OR<br>Patient must have demonstrated failure to achieve an adequate response to 1 or more of the following treatment regimens: (i) oral or parenteral methotrexate at a dose of at least 20 mg per square metre weekly, alone or in combination with oral or intra-articular corticosteroids, for a minimum of 3 months; or (ii) oral methotrexate at a dose of at least 10 mg per square metre weekly together with at least 1 other disease modifying anti-rheumatic drug (DMARD), alone or in combination with corticosteroids, for a minimum of 3 months. |                          |                |                              |                                   |
| <b>Population criteria:</b>                       | Patient must be under 18 years of age.   |                          |                |                              |                                   |
| <b>Prescriber Instructions:</b>                   | The following criteria indicate failure to achieve an adequate response:<br>(a) an active joint count of at least 20 active (swollen and tender) joints;<br>OR<br>(b) at least 4 active joints from the following list:<br>(i) elbow, wrist, knee and/or ankle (assessed as swollen and tender);<br>and/or<br>(ii) shoulder, cervical spine and/or hip (assessed as pain in passive movement and restriction of passive movement, where pain and limitation of movement are due to active disease and not irreversible damage such as joint destruction or bony overgrowth).   |                          |                |                              |                                   |

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|---------------------------------|---|
|                                 | The joint count assessment must be performed preferably whilst still on DMARD treatment, but no longer than 4 weeks following cessation of the most recent prior treatment.<br><br>An assessment of a patient's response to an initial course of treatment must be conducted following a minimum of 12 weeks of therapy and no later than 4 weeks from the date of completion of the most recent course of treatment.   |
| <b>Treatment phase:</b>         | <b>Continuing treatment</b>   |
| <b>Restriction:</b>             | <input checked="" type="checkbox"/> Authority Required - In Writing   |
| <b>Treatment criteria:</b>      | Must be treated by a rheumatologist OR undergoing treatment under the supervision of a paediatric rheumatology treatment centre.  |
| <b>Clinical criteria:</b>       | Patient must have received this drug as their most recent course of PBS-subsidised biological medicine treatment for this condition,<br>AND<br>Patient must have demonstrated an adequate response to treatment with this drug,<br>AND<br>Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised under this restriction.   |
| <b>Prescriber Instructions:</b> | An adequate response to treatment is defined as:<br>(a) a reduction in the total active (swollen and tender) joint count by at least 50% from baseline, where baseline is at least 20 active joints;<br>OR<br>(b) a reduction in the number of the following active joints, from at least 4, by at least 50%:<br>(i) elbow, wrist, knee and/or ankle (assessed as swollen and tender); and/or<br>(ii) shoulder, cervical spine and/or hip (assessed as pain in passive movement and restriction of passive movement, where pain and limitation of movement are due to active disease and not irreversible damage such as joint destruction or bony overgrowth). |

Source: Tables 1-9 and 1-10, pp15-20 of the submission.

bDMARDs=biological disease modifying anti-rheumatic drugs.

3.3 For patients weighing  $\geq 40$  kg and able to swallow tablets, the requested quantity/repeats for the tablets permit 16 weeks of initial treatment and 24 weeks of continuing treatment. For other patients requiring the oral solution formulation (e.g.  $< 40$  kg or  $\geq 40$  kg and unable to swallow tablets), the requested quantity/repeats for the oral solution permit between 13.7 to 21.4 weeks of initial treatment and 20.6 to 32.1 weeks of continuing treatment depending on patient weight<sup>1</sup>. A dose reduction is required in patients with renal impairment (eGFR  $< 50$  mL/min) and moderate hepatic impairment, with half the total daily dose recommended.

3.4 The submission requested a General Schedule listing. In March 2019, the PBAC recommended TOC SC injection for severe active JIA with a General Schedule listing, but other treatments administered via SC injection (i.e. ADA and ETN) are still in Section 100, due to the PBS Reform arrangements. The PBS Reform arrangements allow public hospitals to prescribe and dispense PBS medicines from the General Schedule and Section 100 (Efficient Funding of Chemotherapy) to eligible patients, up to one month supply (this does not apply in non-PBS reform states i.e., NSW and ACT). The Pre-Sub-Committee Response (PSCR) stated that a General Schedule listing would

<sup>1</sup> Weight 10 to  $< 20$ kg: 21.4/32.1 weeks of initial/continuing treatment. Weight 20 to  $< 40$ kg: 17.1/25.7 weeks of initial/continuing treatment. Weight  $\geq 40$ kg: 13.7/20.6 weeks of initial/continuing treatment.

enable improved access in rural and remote locations. The ESC considered the most reasonable listing schedule for TOF appeared to be the General Schedule.

- 3.5 The variable weight-based dosing regimen leads to a wide variation in treatment durations with the oral solution by patient weight. The requested maximum number of repeats provides less than 16/24 weeks of initial/continuing treatment for patients  $\geq 40$  kg, and more than 16/24 weeks of initial/continuing treatment for patients  $< 40$  kg. Hence, it may be appropriate to include an administrative note stating the appropriate number of repeats for the oral liquid should be based on the weight-based table in the approved Product Information, for example:
- 10 to  $< 20$  kg (3.2 mg twice daily): 2/4 repeats for initial/continuing treatment would permit 16.1/26.8 weeks of initial/continuing treatment.
  - 20 to  $< 40$  kg (4 mg twice daily): 3/5 repeats for initial/continuing treatment would permit 17.1/25.7 weeks of initial/continuing treatment.
  - $\geq 40$  kg (5 mg twice daily): 4/6 repeats for initial/continuing treatment would permit 17.1/24 weeks of initial/continuing treatment.
- 3.6 The sponsor requested similar or equivalent restriction criteria for initial and continuing treatment with TOF as the bDMARDs/tsDMARDs currently listed for severe active JIA (e.g. ADA, ETN and TOC). The submission stated that a grandfathering clause will be needed to allow an estimated  $< 500$  patients from a planned patient familiarisation program to transition to PBS subsidised TOF under arrangements for continued therapy.
- 3.7 The requested restriction criteria were similar to current treatments. However, the clinical criteria for initial treatment is silent with respect to the maximum duration of treatment, but the balance of supply restriction states that treatment must provide no more than 16 weeks of initial treatment. The submission also included the population criterion 'Patient must be under 18 years of age.', for consistency these have been removed from the tofacitinib restriction (with the exception of initial 1).
- 3.8 The sponsor requested a Special Pricing Arrangement (SPA) to maintain the current published price of TOF 5 mg tablet in other indications (i.e. DPMQ = \$1211.08 for rheumatoid arthritis, psoriatic arthritis, ulcerative colitis) and an effective price based on a cost-minimisation approach to ADA (AEMP = \$, DMPQ = \$923.45). The sponsor also requested a flat pricing structure between the oral solution and tablet formulations. At the requested effective price, TOF oral solution is less costly than ADA for patients  $< 40$ kg but more costly for patients  $\geq 40$ kg. Across the population however (patients aged 2 to 17), the evaluation considered the average cost of treatment with TOF oral solution may be slightly higher than the average cost of treatment with ADA (see Economic analysis).
- 3.9 The sponsor also requested that the PBAC provide advice to the Minister, under Section 101(4AB) of the National Health Act 1953, that the TOF 1 mg per mL oral solution meets the criteria for an exempt item under Section 84AH, namely:

- It represents suitable therapy for patients with JIA.
- It is suitable for use by a particular subgroup of paediatric patients unable to swallow the solid dose formulation.
- No other form of TOF is suitable for this subgroup because other forms of TOF are solid dose formulations, and the oral solution is more suitable for paediatric patients because it allows accurate administration of the correct dose compared to the solid dose formulation.

If granted, this will exempt TOF from first new brand and price disclosure statutory price reductions. Exempt items, however, are not exempt from Anniversary Price reductions.

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

## 4 Population and disease

- 4.1 JIA is an umbrella term for a range of arthritic conditions beginning before 16 years of age, which persist for at least 6 weeks and have no other identifiable cause.<sup>2</sup> JIA is characterised by inflammation of the synovial membrane of an affected joint, causing pain, swelling, joint stiffness and limited movement. Potential complications of JIA may include skeletal abnormalities, foot problems, amyloidosis, osteoporosis and uveitis leading to cataract, glaucoma and blindness.
- 4.2 The International League of Associations for Rheumatology (ILAR) classifies JIA into seven subtypes: oligoarthritis; polyarthritis rheumatoid factor negative (RF-); polyarthritis rheumatoid factor positive (RF+); systemic JIA; enthesitis-related arthritis; psoriatic arthritis; undifferentiated. The submission stated that the main focus of the submission was patients with 'polyarticular course JIA' defined according to the ILAR as any subtype of JIA with 5 or more joints at 6 months or more after diagnosis. Based on this definition, the target population included patients with extended oligoarthritis, polyarthritis RF-, polyarthritis RF+ , and systemic JIA with active arthritis but without systemic symptoms.

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

## 5 Comparator

- 5.1 The submission nominated ADA as the main comparator, given it is the treatment most likely to be replaced in practice (current market share is approx. 60%).
- 5.2 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy,

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<sup>2</sup> Therapeutic Guidelines (eTG) March 2021 edition, Overview of juvenile idiopathic arthritis, accessed 29 November 2022.

the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect. The alternative therapies include ADA, ETN and TOC; the PBAC previously considered these to be of non-inferior comparative effectiveness and safety to one another (Clinical Claim section, TOC Public Summary Document, November 2013).

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician presented TOF as an alternative oral therapy for treatment of JIA. The clinician stated there is limited clinical experience using TOF for JIA however noted there are international guidelines which provides a framework in treating this population. The clinician stated the oral manner of administration for TOF will improve the experience of administration and compliance of patients with a needle phobia and other specific groups such as those with developmental delays and where support for parenteral therapy is limited, such as in regional and remote locations.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (11) and organisations (7) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with tofacitinib including major impacts of JIA on quality of life, noting reduction in pain and trauma associated with injectable treatments and the added benefits of having an oral therapy available for the paediatric population, TOF's effectiveness in JIA, and its manageable side effects. The PBAC specifically noted the number of comments from carers, family and organisations, including the Australian Rheumatology Association (ARA), Arthritis Australia, the National Paediatric Medicines Forum, Musculoskeletal Australia, Creaky Joints Australia, the Juvenile Arthritis Foundation Australia and Pain Australia concerning the amount of time off from school and work to manage the pain and trauma associated with JIA and the current injectable treatments available. The comments further noted the use of TOF orally was welcomed as it reduced stress and anxiety over administration of the alternative treatments in the needle form. The PBAC noted that this advice was supportive of the evidence provided in the submission.

### ***Clinical trials***

- 6.3 No head-to-head trials were available. The submission presented an indirect comparison between TOF and ADA using placebo as the common reference, based on

two randomised withdrawal trials: PROPEL and DE038. Details of the trials presented in the submission are provided in Table 2.

**Table 2: Trials and associated reports presented in the submission**

| Trial ID                | Protocol title/ Publication title   | Publication citation   |
|-------------------------|---|--|
| PROPEL<br>(NCT02592434) | Efficacy, Safety, and Tolerability of Tofacitinib for Treatment of Polyarticular Course Juvenile Idiopathic Arthritis (JIA) in Children and Adolescent Subjects.<br>Ruperto N et al. Tofacitinib in juvenile idiopathic arthritis: a double-blind, placebo-controlled, withdrawal phase 3 randomised trial. | Clinical Study Report, October 2019<br><br>The Lancet. 2021; 398(10315):1984-96. |
| DE038                   | Lovell DJ et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis.  | NEJM 2008; 359(8):810-820  |

Blue shading indicates data previously seen by the PBAC.

Source: Tables 2.3-2.4, pp27-28 of the submission.

6.4 The key features of the randomised trials are summarised in Table 3.

**Table 3: Key features of the included evidence**

| Trial (dates)                                | N   | Design/ duration   | Risk of bias      | Patient population   | Key outcomes   | Used |
|--|---|--|-------------------|--|--|------|
| <b>TOF v placebo</b>                         |   |  |                   |  |  |      |
| PROPEL<br>(June 2016 to May 2019)            | OL-LI: 225<br>(184 pcJIA)<br>DB: 173<br>(142 pcJIA) | MC, DB, PC; RWD,<br>18wk OL-LI & 26wk<br>DB phase, DB criteria:<br>PedACR30 in OL-LI | Low (DB<br>phase) | pcJIA, PsA or ERA; 2-<br>17 yrs; IR to i) MTX or<br>bDMARDs (pcJIA) or ii)<br>NSAIDs (PsA, ERA); | <u>Efficacy</u> <sup>^</sup> :<br>1°: Flare Wk18-44<br>2°: PedACR30/50/70<br>Wk44.         | ITC  |
| <b>ADA v placebo</b>                         |   |  |                   |  |  |      |
| DE038<br>(September 2002<br>to January 2005) | OL-LI: 171<br>DB: 133                               | MC, DB, PC, RWD,<br>16wk OL-LI & 32wk<br>DB phase, DB criteria:<br>PedACR30 in OL-LI | Low (DB<br>phase) | pcJIA; 4-17 yrs; IR to<br>NSAIDs or MTX  | <u>Efficacy</u> :<br>1°: Flare Wk16-48<br>(Non-MTX stratum)<br>2°: PedACR30/50/70<br>Wk48. | ITC  |

Blue shading indicates data previously seen by the PBAC.

Source: Table 2.5, p29 of the submission.

DB=double blind; MC=multi-centre; OL-LI=open label lead in; RWD=randomised withdrawal design; Ped=paediatric; ACR=American College of Rheumatology; pcJIA=polyarticular course juvenile idiopathic arthritis; MTX=methotrexate; IR=inadequate response; Wk=week; PsA=psoriatic arthritis; ERA=enthesitis-related arthritis; ITC=indirect treatment comparison; NSAIDs=non-steroidal anti-inflammatory drugs; bDMARDs=biological disease modifying anti-rheumatic drugs.

<sup>^</sup> Patients with PsA or ERA were excluded from the primary and key secondary efficacy outcomes but included in the exploratory efficacy

6.5 Both the PROPEL and DE038 trials were Phase 3 multi-centre randomised withdrawal trials, with an active open-label lead phase (18 weeks and 16 weeks, respectively) and a randomised placebo-controlled withdrawal phase (26 weeks and 32 weeks, respectively). Both trials enrolled patients with polyarticular course JIA and patients with an American College of Rheumatology paediatric 30 response (PedACR30) at the end of the open-label lead in were randomised 1:1 to either remain on active treatment or swap to placebo in the double-blind withdrawal phase.

6.6 The trial designs were similar, but there were also notable differences:

- The PROPEL trial comprised children of age 2 to <18 years, whereas DE038 comprised children of age 4 to <18 years.

- The PROPEL trial enrolled a small cohort of patients with juvenile psoriatic arthritis and juvenile enthesitis-related arthritis, who were excluded from the key efficacy analyses but were included in the safety analysis.
- The PROPEL trial enrolled patients with polyarticular course JIA who had an inadequate response to methotrexate or bDMARDs, whereas DE038 enrolled patients who had an inadequate response to NSAIDs or methotrexate (prior bDMARDs was an exclusion criteria). Consequently, the use of prior treatments (corticosteroids, methotrexate and prior bDMARDs) was much higher in PROPEL compared to DE038. The use of concomitant treatments (corticosteroids and methotrexate) was also potentially higher in PROPEL compared to DE038 based on available data.
- In the double-blind withdrawal phase, the PROPEL trial stratified patients by JIA subgroup and C-reactive protein level (normal, above normal), whereas DE038 stratified patients by concurrent methotrexate use.
- The open-label lead in phase was slightly longer in PROPEL (18 weeks) than DE038 (16 weeks), whereas the double-blind withdrawal phase was slightly longer in DE038 (32 weeks) compared to PROPEL (26 weeks).
- The discontinuation rules differed across the trials, given patients who experienced a disease flare had to discontinue treatment in PROPEL but could continue treatment in DE038. Consequently, discontinuation rates were much higher in PROPEL (29.2% for TOF; 52.9% for placebo) compared to DE038 (5.9% for ADA; 1.5% for placebo). Despite this difference, both trials classified patients who discontinued or experienced a flare as treatment non-responders (hence it was unlikely to affect the comparability of the key efficacy outcomes between the trials).
- The outcome definitions and six core response criteria/components used to determine disease flare and treatment response differed slightly. For example, PROPEL used reduced joint counts whereas DE038 trial used standard joint counts to determine number of affected joints, PROPEL used erythrocyte sedimentation rate whereas DE038 used C-reactive protein as the laboratory assessment of inflammation.

### ***Comparative effectiveness***

- 6.7 The clinically relevant outcome for JIA is the American College of Rheumatology 30% paediatric response criteria (PedACR30), defined as a  $\geq 30\%$  improvement from baseline in at least 3 of 6 response criteria without a  $\geq 30\%$  worsening in more than one of the remaining response criteria (p4, TOC, Public Summary Document, November 2013).
- 6.8 The submission also nominated 'disease flare' as a clinically relevant outcome in the randomised withdrawal trials, defined as a  $\geq 30\%$  worsening in at least 3 of 6 response

criteria without a  $\geq 30\%$  improvement in more than one of the remaining response criteria. In the context of the randomised withdrawal trials, the 'disease flare' outcome in the withdrawal phase essentially measures the relapse rate of PedACR30 responders (given enrolment in the withdrawal phase was conditional on PedACR30 response in the lead in phase).

6.9 The submission presented a series of indirect treatment comparisons using the Bucher method, comparing TOF and ADA (via a placebo common reference) for several clinical outcomes measured at the end of the withdrawal phase (disease flare, PedACR30, PedACR50, and PedACR70). The submission acknowledged several differences across the trials that would potentially violate the key transitivity assumption of the indirect treatment comparison, including differences in prior and concomitant treatment. The submission presented the following empirical strategy to provide the PBAC with more confidence in the indirect comparisons:

- To control for differences in prior methotrexate, the submission conducted the indirect comparisons for patients in PROPEL (polyarticular course JIA ITT population) versus DE038 (methotrexate stratum). Approximately 90% of patients enrolled in PROPEL had used prior methotrexate compared to all patients in the methotrexate stratum of DE038.
- To control for differences in prior bDMARDs, the submission compared PROPEL (polyarticular course JIA bDMARD naïve post hoc subgroup) versus DE038 (methotrexate stratum). All patients enrolled in DE038 were bDMARD naïve given it was an exclusion criterion.
- To control for differences in the use of concomitant methotrexate, the submission compared PROPEL (polyarticular course JIA methotrexate on study day 1 post hoc subgroup) versus DE038 (methotrexate stratum). The majority (approx. 75%) of patients enrolled in PROPEL were using concomitant methotrexate on day 1 of the study, but it was unknown whether these patients continued taking methotrexate throughout the trial.

6.10

6.11 Table 4 presents the key outcomes reported in PROPEL and DE038 (by the various subgroups and stratum) and results of the indirect treatment comparisons.

Table 4: Trial results and indirect treatment comparisons for key clinical outcomes, TOF vs ADA

|   | Trial ID, population           | Drug n/N (%) | Control n/N (%) | OR (95%CI)               | RR (95%CI)              | RD (95%CI)                 |
|---|--------------------------------|--------------|-----------------|--------------------------|-------------------------|----------------------------|
| <b>OUTCOME: Flare in DB phase</b>         |                                |              |                 |                          |                         |                            |
| TOF v PBO<br>Wk44   Wk18 <sup>^</sup>     | PROPEL, ITT                    | 21/72 (29.2) | 37/70 (52.9)    | <b>0.37 (0.18,0.73)</b>  | <b>0.55 (0.36,0.84)</b> | <b>-0.24 (-0.39,-0.08)</b> |
|   | PROPEL, MTX-d1                 | 15/52 (28.9) | 26/54 (48.2)    | <b>0.44 (0.20,0.97)</b>  | 0.60 (0.36,1.00)        | <b>-0.19 (-0.37,-0.01)</b> |
|   | PROPEL, bDMARDn                | 15/49 (30.6) | 23/50 (46.0)    | 0.52 (0.23,1.18)         | 0.67 (0.40,1.12)        | -0.15 (-0.34,0.04)         |
| ADA v PBO<br>Wk48   Wk16 <sup>^</sup>     | DE038, ITT                     | 27/68 (39.7) | 44/65 (67.7)    | 0.31 (0.15,0.64)         | <b>0.59 (0.42,0.82)</b> | <b>-0.28 (-0.44,-0.12)</b> |
|   | DE038, MTXs                    | 14/38 (36.8) | 24/37 (64.9)    | 0.32 (0.12,0.81)         | <b>0.57 (0.35,0.92)</b> | <b>-0.28 (-0.50,-0.06)</b> |
|   | DE038, non-MTXs                | 13/30 (43.3) | 20/28 (71.4)    | 0.31 (0.10,0.91)         | <b>0.61 (0.38,0.97)</b> | <b>-0.28 (-0.52,-0.04)</b> |
| <b>OUTCOME: PedACR30, end of DB phase</b> |                                |              |                 |                          |                         |                            |
| TOF v PBO<br>Wk44   Wk18 <sup>^</sup>     | PROPEL, ITT                    | 51/72 (70.8) | 33/70 (47.1)    | <b>2.72 (1.36,5.44)</b>  | <b>1.50 (1.13,2.01)</b> | <b>0.24 (0.08,0.39)</b>    |
|   | PROPEL, MTX-d1                 | 37/52 (71.2) | 28/54 (51.9)    | <b>2.29 (1.03,5.11)</b>  | <b>1.37 (1.01,1.87)</b> | <b>0.19 (0.01,0.37)</b>    |
|   | PROPEL, bDMARDn                | 34/49 (69.4) | 27/50 (54.0)    | <b>1.93 (0.85,4.40)</b>  | <b>1.28 (0.94,1.76)</b> | <b>0.15 (-0.04,0.34)</b>   |
| ADA v PBO<br>Wk48   Wk16 <sup>^</sup>     | DE038, ITT                     | 41/68 (60.3) | 23/65 (35.4)    | <b>2.77 (1.37,5.60)</b>  | <b>1.70 (1.16,2.49)</b> | <b>0.25 (0.08,0.41)</b>    |
|   | DE038, MTXs                    | 24/38 (63.2) | 14/37 (37.8)    | <b>2.82 (1.10,7.18)</b>  | <b>1.67 (1.03,2.70)</b> | <b>0.25 (0.03,0.47)</b>    |
|   | DE038, non-MTXs                | 17/30 (56.7) | 9/28 (32.1)     | 2.76 (0.94,8.07)         | 1.76 (0.95,3.29)        | 0.25 (-0.00,0.49)          |
| <b>OUTCOME: PedACR50, end of DB phase</b> |                                |              |                 |                          |                         |                            |
| TOF v PBO<br>Wk44   Wk18 <sup>^</sup>     | PROPEL, ITT                    | 48/72 (66.7) | 33/70 (47.1)    | <b>2.24 (1.14,4.42)</b>  | <b>1.41 (1.05,1.90)</b> | <b>0.20 (0.04,0.36)</b>    |
|   | PROPEL, MTX-d1                 | 34/52 (65.4) | 28/54 (51.9)    | 1.75 (0.80,3.83)         | 1.26 (0.91,1.74)        | 0.14 (-0.05,0.32)          |
|   | PROPEL, bDMARDn                | 31/49 (63.3) | 27/50 (54.0)    | 1.47 (0.66,3.28)         | 1.17 (0.84,1.63)        | 0.09 (-0.10,0.29)          |
| ADA v PBO<br>Wk48   Wk16 <sup>^</sup>     | DE038, ITT                     | 40/68 (58.8) | 23/65 (35.4)    | <b>2.61 (1.29,5.26)</b>  | <b>1.66 (1.13,2.44)</b> | <b>0.23 (0.07,0.40)</b>    |
|   | DE038, MTXs                    | 24/38 (63.2) | 14/37 (37.8)    | <b>2.82 (1.10,7.18)</b>  | <b>1.67 (1.03,2.70)</b> | <b>0.25 (0.03,0.47)</b>    |
|   | DE038, non-MTXs                | 16/30 (53.3) | 9/28 (32.1)     | 2.41 (0.83,7.03)         | 1.66 (0.88,3.13)        | 0.21 (-0.04,0.46)          |
| <b>OUTCOME: PedACR70, end of DB phase</b> |                                |              |                 |                          |                         |                            |
| TOF v PBO<br>Wk44   Wk18 <sup>^</sup>     | PROPEL, ITT                    | 39/72 (54.2) | 26/70 (37.1)    | <b>2.00 (1.02,3.91)</b>  | <b>1.46 (1.01,2.11)</b> | <b>0.17 (0.01,0.33)</b>    |
|   | PROPEL, MTX-d1                 | 28/52 (53.9) | 22/54 (40.7)    | 1.70 (0.79,3.66)         | 1.32 (0.88,1.99)        | 0.13 (-0.06,0.32)          |
|   | PROPEL, bDMARDn                | 28/49 (57.1) | 21/50 (42.0)    | 1.84 (0.83,4.09)         | 1.36 (0.91,2.04)        | 0.15 (-0.04,0.35)          |
| ADA v PBO<br>Wk48   Wk16 <sup>^</sup>     | DE038, ITT                     | 38/68 (55.9) | 18/65 (27.7)    | <b>3.31 (1.60,6.82)</b>  | <b>2.02 (1.29,3.15)</b> | <b>0.28 (0.12,0.44)</b>    |
|   | DE038, MTXs                    | 24/38 (63.2) | 10/37 (27.0)    | <b>4.63 (1.74,12.34)</b> | <b>2.34 (1.31,4.18)</b> | <b>0.36 (0.15,0.57)</b>    |
|   | DE038, non-MTXs                | 14/30 (46.7) | 8/28 (28.6)     | 2.19 (0.74,6.50)         | 1.63 (0.81,3.29)        | 0.18 (-0.06,0.43)          |
| <b>ITC: Flare</b>                         |                                |              |                 |                          |                         |                            |
|   | TOF (ITT) v ADA (MTXs)         |              |                 | 1.16 (0.35,3.78)         | 0.96 (0.51,1.83)        | 0.04 (-0.23,0.31)          |
|   | MTX: TOF (MTX-d1) v ADA (MTXs) |              |                 | 1.38 (0.40,4.75)         | 1.05 (0.52,2.13)        | 0.09 (-0.19,0.37)          |
|   | TOF (bDMARDn) v ADA (MTXs)     |              |                 | 1.63 (0.46,5.71)         | 1.18 (0.58,2.38)        | 0.13 (-0.16,0.42)          |
| <b>ITC: PedACR30</b>                      |                                |              |                 |                          |                         |                            |
|   | TOF (ITT) v ADA (MTXs)         |              |                 | 0.96 (0.30,3.10)         | 0.90 (0.51,1.57)        | -0.01 (-0.28,0.26)         |
|   | MTX: TOF (MTX-d1) v ADA (MTXs) |              |                 | 0.81 (0.24,2.79)         | 0.82 (0.46,1.45)        | -0.06 (-0.34,0.22)         |
|   | TOF (bDMARDn) v ADA (MTXs)     |              |                 | 0.68 (0.20,2.38)         | 0.77 (0.43,1.36)        | -0.10 (-0.39,0.19)         |
| <b>ITC: PedACR50</b>                      |                                |              |                 |                          |                         |                            |
|   | TOF (ITT) v ADA (MTXs)         |              |                 | 0.79 (0.25,2.53)         | 0.84 (0.48,1.49)        | -0.05 (-0.32,0.22)         |
|   | MTX: TOF (MTX-d1) v ADA (MTXs) |              |                 | 0.62 (0.18,2.11)         | 0.75 (0.42,1.35)        | -0.11 (-0.40,0.18)         |
|   | TOF (bDMARDn) v ADA (MTXs)     |              |                 | 0.52 (0.15,1.79)         | 0.70 (0.39,1.26)        | -0.16 (-0.45,0.13)         |
| <b>ITC: PedACR70</b>                      |                                |              |                 |                          |                         |                            |
|   | TOF (ITT) v ADA (MTXs)         |              |                 | 0.43 (0.13,1.42)         | 0.62 (0.31,1.24)        | -0.19 (-0.45,0.07)         |
|   | MTX: TOF (MTX-d1) v ADA (MTXs) |              |                 | 0.37 (0.11,1.27)         | 0.56 (0.28,1.15)        | -0.23 (-0.51,0.05)         |
|   | TOF (bDMARDn) v ADA (MTXs)     |              |                 | 0.40 (0.11,1.41)         | 0.58 (0.29,1.18)        | -0.21 (-0.50,0.08)         |

Blue shading indicates data previously seen by the PBAC. Errors identified during the evaluation corrected in the above table.

Source: Tables 2.26 to 2.29 and 2.32 to 2.39, pp71-77 of the submission.

PedACR=Paediatric American College of Rheumatology; ITT=intention to treat; TOF=tofacitinib; ADA=adalimumab; PBO=placebo; MTX=methotrexate; OR=odds ratio; RR=relative risk; RD=risk difference; CI=confidence interval; ITC=indirect treatment comparison; Wk=week; bDMARD=biologic disease modifying anti-rheumatic drug; DB=double blind; bDMARDn = bDMARD naive.

<sup>^</sup> PedACR30 response at Week 16 or 18

- 6.12 The trial results demonstrated that, in patients with PedACR30 response at Week 16-18 following initial active treatment, TOF and ADA were more effective than placebo at maintaining PedACR30 response and avoiding disease flare at Week 44-48. The results also demonstrated that patients who remained on active treatment at Week 16-18 were more likely to achieve PedACR50 and PedACR70 response at Week 44-48 compared to those who switched to placebo. The results of the indirect treatment comparisons found no statistically significant differences between TOF and ADA in terms of PedACR30 response or any of the other outcomes. The decision to exclude patients enrolled in the non-methotrexate stratum of DE038 from the indirect treatment comparison had little impact on the results given the point estimates of the treatment effects in DE038 were generally similar for patients with or without concomitant methotrexate.
- 6.13 The submission acknowledged that the point estimates from the indirect treatment comparisons numerically favoured ADA over TOF, but subsequently concluded that the evidence showed that TOF 'was at least as effective' as ADA. As the submission did not nominate a non-inferiority margin, the evaluation considered the submission's claim that TOF was at least as effective as ADA (i.e. at least non-inferior) was poorly justified. The placebo response rates also differed considerably across the trials despite the submission's attempt to compare similar populations / subgroups. This suggested that there may be other important differences across the trials, which may violate the transitivity assumption. In such cases, a relative measure (e.g. relative risk or odds ratio) may be preferred over an absolute measure (e.g. RD) given an imbalance in prognostic factors would not bias the indirect estimate if there is a constant relative treatment effect across trials.
- 6.14 Despite these concerns, the PBAC had previously accepted non-inferiority between existing treatments for severe active JIA based on similar indirect evidence. For example, the PBAC accepted that TOC was non-inferior to both ADA based on an indirect relative risk for PedACR30 of 0.80 (95%CI: 0.51, 1.26), and non-inferior to ETN based on an indirect relative risk for PedACR30 of 0.59 (95%CI: 0.32, 1.09) (Results of Trials and Clinical Claim, TOC, Public Summary Document, November 2013). The estimated lower bounds of the 95%CIs in those past decisions (i.e. 0.51 and 0.32) are similar to or below the corresponding estimates in the current submission between TOF and ADA (i.e. 0.43 to 0.51). In addition, the PBAC accepted non-inferiority despite noting differences between the trial populations and considerable variation in placebo response rates (Results of Trials, TOC, Public Summary Document, November 2013).
- 6.15 The submission also conducted supplementary indirect treatment comparisons between TOF and the other PBS-listed treatments (ETN and TOC) based on data from two additional trials, Lovell et al 2000 (ETN vs placebo) and CHERISH (TOC vs placebo). The PBAC had previously considered evidence from both trials (Lovell et al 2000 and CHERISH), and the submission concluded that TOF was also non-inferior to ETN and TOC given the lack of a statistically significant differences between treatments.

## Comparative harms

6.16 Table 5 presents a summary of adverse events reported in PROPEL by trial phase. The most commonly reported adverse reactions in the open-label lead in phase included infections (upper respiratory tract infection, nasopharyngitis, influenza), gastrointestinal disorders (nausea, vomiting, diarrhoea, abdominal pain) and headache. During the double-blind withdrawal phase, the incidence of infections remained elevated for patients who continued in the TOF arm whereas gastrointestinal disorders and headache were comparatively lower. The safety outcomes reported in PROPEL were consistent with the known safety profile of TOF in adult populations.

**Table 5: Summary of key adverse events in the trials**

|                                   | Open-label lead in phase | Double-blind withdrawal phase |            |
|-----------------------------------|--------------------------|-------------------------------|------------|
|                                   | TOF (N=225)              | TOF (N=88)                    | PBO (N=85) |
| Any AE, by patient                | 153 (68.0)               | 68 (77.3)                     | 63 (74.1)  |
| Serious AE, by patient (%)        | 7 (3.1)                  | 1 (1.1)                       | 2 (2.4)    |
| Severe AE, by patients (%)        | 5 (2.2)                  | 0                             | 3 (3.5)    |
| AE leading to disc. (%)           | 26 (11.6)                | 16 (18.2)                     | 29 (34.1)  |
| Deaths (%)                        | 0                        | 0                             | 0          |
| <b>Common TEAEs</b>               |                          |                               |            |
| Upper respiratory tract infection | 24 (10.7)                | 13 (14.8)                     | 9 (10.6)   |
| Nasopharyngitis                   | 10 (4.4)                 | 7 (8.0)                       | 3 (3.5)    |
| Influenza                         | 8 (3.6)                  | 3 (3.4)                       | 2 (2.4)    |
| Nausea                            | 13 (5.8)                 | NR                            | NR         |
| Vomiting                          | 13 (5.8)                 | 0                             | 4 (4.7)    |
| Abdominal pain                    | 8 (3.6)                  | 0                             | 3 (3.5)    |
| Diarrhoea                         | 6 (2.7)                  | 1 (1.1)                       | 2 (2.4)    |
| Pyrexia                           | 11 (4.9)                 | 4 (4.5)                       | 1 (1.2)    |
| Headache                          | 16 (7.1)                 | 2 (2.3)                       | 6 (7.1)    |

Source: Tables 2.21, pp59-60 of the submission; PROPEL CSR

TOF=tofacitinib; PBO=placebo; AE=adverse event; TEAE=treatment emergent adverse event.

6.17 Any meaningful comparison between TOF and ADA for safety outcomes is problematic because there was limited published safety data from DE038, and both trials reported safety outcomes differently. For example, the PROPEL trial reported the number of patients with an event whereas DE038 reported the number of events and rate of events per patient-year of treatment. Despite this, the submission conducted an indirect treatment comparison between TOF and ADA using the Bucher method for some safety outcomes. Based on this analysis, the submission concluded there was no statistically significant difference between TOF and ADA in terms of serious adverse events or risk of infection.

6.18 The indirect treatment comparison of safety outcomes presented in the submission was uninformative. The numbers of adverse events in DE038 were unverified and the analysis does not control for differences in treatment exposures across the trials. As discussed above, the double-blind withdrawal phase was six weeks longer in DE038 compared to PROPEL and the discontinuation rules differed when patients experienced a disease flare, which would likely impact on the incidence of adverse events. To provide the PBAC with a more meaningful comparison of TOF and ADA for

safety outcomes, safety data from PROPEL were compared to information provided in the March 2010 PBAC submission for ADA. Overall, the evaluation considered the general safety profile of TOF appeared comparable to ADA, albeit without the injection site reactions (not applicable for a tablet).

- 6.19 The submission noted that a number of pharmacovigilance studies are either ongoing or planned to better understand the risks associated with TOF, including several planned studies in children. Results from a recent long-term extension study of TOF (Study A3921133) in patients  $\geq 50$  years with moderate-severe rheumatoid arthritis found that TOF was associated with increased frequency of MACE, malignancy, mortality and thromboembolism compared to those patients prescribed TNF-alpha inhibitor. The submission argued that it was not appropriate to extrapolate the findings of the study to children with JIA, given the study included a CV risk-enriched population, malignancy is rare in children and the nature of rheumatoid arthritis is different to JIA. The submission noted that the incidence rates for MACE and malignancy were similar between TOF and TNF-alpha inhibitors for patients  $< 65$  years who had never smoked. The TGA Delegate's Overview (p27) noted that there are some unresolved concerns with the potential for serious adverse events associated with long-term use of TOF, which may result in further TGA action.

### **Benefits/harms**

- 6.20 A benefits and harms table is not presented as the submission made a claim of non-inferiority. Based on the clinical evidence presented in the submission, there were no expected clinically meaningful differences between TOF and ADA in terms of efficacy or safety. Differences in safety profiles are likely due to the different mechanism of action and route of administration, but overall rates of serious adverse events appear comparable. For example, although the rate of injection site reactions is relatively low with ADA ( $< 5\%$ ), TOF is not associated with injection site reactions as it is an orally administered treatment.

### **Clinical claim**

- 6.21 The submission described TOF as non-inferior to ADA in terms of effectiveness and safety. The clinical evidence presented in the submission adequately supported this claim; however, the long-term risks associated with the use of TOF in children is unknown (including impacts on growth and development). The ESC considered the claim of non-inferior comparative effectiveness and safety to ADA was adequately supported.
- 6.22 The PBAC considered that the claim of non-inferior comparative effectiveness and safety was reasonable.

## Economic analysis

6.23 The submission presented a cost minimisation approach between TOF and ADA, based on the published AEMP for ADA. The proposed equi-effective doses were based on the recommended doses:

- TOF (10 kg to <20 kg: 3.2 mg; 20 kg to <40 kg: 4 mg; ≥40 kg: 5 mg) twice daily
- ADA (15 kg to <30 kg: 20 mg; ≥30 kg: 40 mg) SC every two weeks.

The recommended doses in the product information (PI) documents differ slightly to those used in the PROPEL and DE038 trials. For TOF, the recommended dose in the draft PI consists of a simplified dosing regimen with fewer weight-based categories. For ADA, the recommended dose in the PI is based on the weight-based dosing regimen used in the open-label extension of DE038 rather than the body-surface area dose used in the lead-in and withdrawal phases. The therapeutic relativity sheets, however, include both ADA dosing regimens based on weight (as above) and body surface area (24 mg per m<sup>2</sup> SC every two weeks).

6.24 The cost-minimisation approach calculated the total drug costs over a two-year period with TOF 5 mg tablets (i.e. assuming all patients ≥40 kg) compared to ADA 20 mg or 40 mg SC injection, assuming no administration costs. The submission noted the flat pricing structure for ADA 20 mg and ADA 40 mg and requested a flat pricing structure between TOF 5 mg tablet and TOF 1 mg per mL oral solution, on the basis that the average cost of the oral solution was ‘essentially equal’.

**Table 6: Results of the cost-minimisation approach**

| Component                 | TOF  |                   | ADA<br>(20mg or 40mg)                    |
|---------------------------|--|-------------------|--|
|                           | 1mg/mL oral solution   | 5mg tablet        |  |
| AEMP / pack               | \$█  | \$█               | \$█                                      |
| Dose                      | 10 <20 kg: 3.2 mg BD;<br>20 <40 kg: 4 mg BD;<br>≥40 kg: 5 mg BD.   | ≥40 kg: 5 mg BD.  | <30 kg: 20 mg Q2W;<br>≥30 kg: 40 mg Q2W. |
| Quantity / pack           | 240 mg (240 mL) solution   | 56 x 5 mg tablets | 2 x 20 mg or 40 mg injections            |
| Scripts / 2 years         | Assumed average: 26<br>• 10 <20 kg: 19.5 <sup>a</sup><br>• 20 <40 kg: 24.4 <sup>a</sup><br>• ≥40 kg: 30.4 <sup>a</sup>       | 26                | 26                                       |
| Total cost / 2 years (\$) | Assumed average: \$21,282.04<br>• 10 <20 kg: \$█ <sup>a</sup><br>• 20 <40 kg: \$█ <sup>a</sup><br>• ≥40 kg: \$█ <sup>a</sup> | \$█               | \$█                                      |

Source: Tables 3.4 to 3.5, p92 of the submission.

TOF=tofacitinib; ADA=adalimumab; AEMP=Australian ex-manufacturer price.

<sup>a</sup> estimates assume 52.18 weeks (or 365.25 days) per year rather than 52 assumed for the main analysis

6.25 As each script of the oral solution provides for between 24 days and 37.5 days depending on the dose (i.e. weight), the treatment cost over two years using the oral solution increases from approx. \$█ for patients 10 to <20 kg to approx. \$█ for patients ≥40 kg. Whether the cost of treatment with TOF using the oral solution would be ‘effectively equal’ to the nominated comparator (i.e. approx. \$█) depends on the

proportional use of each dose with the oral solution. Based on the weight distribution of patients enrolled in PROPEL, the average cost of treatment using the oral solution may be slightly higher than the nominated comparator at the requested AEMP (approx. \$█). The submission, however, implied that patients weighing ≥40kg would switch to the tablet formulation in which case the average cost of the oral solution would be less than ADA. The PSCR stated the submission did not assume 100% of patients ≥40 kg would swap to the 5 mg tablet and provided various alternative assumptions and provided an analysis indicating that >60% of those patients would have to remain on the oral solution before the cost was greater than the 5 mg tablet. The PSCR also stated key opinion leaders estimated 10-25% of patients ≥40 kg would remain on the solution.

- 6.26 Alternatively, the evaluation considered it may be appropriate to price the oral solution on a cost per mg basis to the tablet, to ensure that the cost of treatment with the oral solution does not exceed the cost of treatment with the tablet.
- 6.27 The ESC considered the proposed pricing approach in the submission for the oral liquid was likely to be reasonable and considered there was a low risk the extent of use of the oral liquid in the ≥40kg population would lead to it being more costly than TOF tablets.

### ***Drug cost/patient/year***

- 6.28 Based on the proposed effective price (DPMQ= \$█), the annual drug cost of TOF 5 mg tablets is \$█ and the annual drug cost of TOF 1 mg per mL oral solution is \$█ to \$█ depending on weight.

### ***Estimated PBS usage & financial implications***

- 6.29 This submission was not considered by DUSC.
- 6.30 The submission estimated the financial implications of the proposed listing using a market share approach, assuming that TOF will substitute for current bDMARDs/tsDMARDs listed on the PBS for JIA (ADA, ETN and TOC). In addition, the submission assumed above-trend market growth given TOF would be the first oral treatment for patients and separately costed the treatment of <500 grandfather patients expected to enrol in a Patient Familiarisation Program. Table 7 outlining the key inputs relied on in the financial estimates.

Table 7: Key inputs for financial estimates

| Data   | Value  | Source   | Comment   |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
|--|--|--|---|-----------------|----------|----------------|----------------|----------------|----------------|-----|----------------|----------------|----------------|----------|----------------|----------------|----------------|-----|----------------|----------------|----------------|-----|----------------|----------------|----------------|-----------------|----------------|----------------|-----------------|---|---|--|---|
| <b>Eligible population</b>   |  |  |   |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| bDMARD/<br>tsDMARD<br>scripts, Year 0  | Ref (2021): 7005<br>- ADA 40mg: 3812<br>- ADA 20mg: 255<br>- ETN 50mg: 1158<br>- ETN 25mg: 976<br>- TOC IV 80mg: 166<br>- TOC IV 200mg: 125<br>- TOC IV 400mg: 172<br>- TOC SC 162mg[a]: 124<br>- TOC SC 162mg[b]: 217   | Script numbers sourced from Medicare Australia statistics; to simplify the model, the submission pooled item numbers with the same DPMQs, similar strength and similar treatment phase. Item numbers for TOC 162 mg [a] capture scripts for initial & continuing treatment, whereas TOC 162mg [b] capture scripts for continuing treatment only. | Reasonable. The submission attempted to standardise script numbers through script equivalence to TOF in a later step (see below). |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| bDMARD/<br>tsDMARD<br>scripts, market<br>growth by<br>drug without<br>TOF %  | <table border="1"> <thead> <tr> <th></th> <th>ADA</th> <th>ETN</th> <th>TOC</th> </tr> </thead> <tbody> <tr> <td>Yr1</td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> </tr> <tr> <td>Yr2</td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> </tr> <tr> <td>Yr3</td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> </tr> <tr> <td>Yr4</td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> </tr> <tr> <td>Yr5</td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> </tr> <tr> <td>Yr6</td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> </tr> </tbody> </table>                              |  | ADA   | ETN             | TOC      | Yr1            | █ <sup>1</sup> | █ <sup>1</sup> | █ <sup>1</sup> | Yr2 | █ <sup>1</sup> | █ <sup>1</sup> | █ <sup>1</sup> | Yr3      | █ <sup>1</sup> | █ <sup>1</sup> | █ <sup>1</sup> | Yr4 | █ <sup>1</sup> | █ <sup>1</sup> | █ <sup>1</sup> | Yr5 | █ <sup>1</sup> | █ <sup>1</sup> | █ <sup>1</sup> | Yr6             | █ <sup>1</sup> | █ <sup>1</sup> | █ <sup>1</sup>  | Script numbers sourced from Medicare Australia statistics. Linear extrapolation of scripts from 2018 to 2021, estimated separately for each bDMARD/tsDMARD. Growth rate in Yr1 refers to change from 2021 to 2023. Overall growth rate for the market is approximately █ <sup>1</sup> - █ <sup>1</sup> % per year.  | Assumed linear change of individual bDMARDs/tsDMARD implies a very large market share for ADA in Yr6 (█ <sup>1</sup> %), which may not be reasonable  |  |   |
|  | ADA  | ETN  | TOC   |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| Yr1  | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>  |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| Yr2  | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>  |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| Yr3  | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>  |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| Yr4  | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>  |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| Yr5  | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>  |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| Yr6  | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>  |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| TOF scripts,<br>market share<br>% (ignoring<br>addition<br>market<br>growth) | Yr1: █ <sup>1</sup><br>Yr2: █ <sup>1</sup><br>Yr3-6: █ <sup>1</sup> /year  | Assumption. The submission stated that it was reasonable to assume TOF would only replace a relatively small proportion of the market given there are already three alternative bDMARDs/tsDMARDs on the PBS.   | May be a potential underestimate given TOF would be the fourth treatment option for patients and first oral therapy.              |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| TOF<br>proportional<br>substitution<br>rates %                               | <table border="1"> <thead> <tr> <th></th> <th>ADA</th> <th>ETN</th> <th>TOC</th> </tr> </thead> <tbody> <tr> <td>Yr1</td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> </tr> <tr> <td>Yr2</td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> </tr> <tr> <td>Yr3</td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> </tr> <tr> <td>Yr4</td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> </tr> <tr> <td>Yr5</td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> </tr> <tr> <td>Yr6</td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> <td>█<sup>1</sup></td> </tr> </tbody> </table>                              |  | ADA   | ETN             | TOC      | Yr1            | █ <sup>1</sup> | █ <sup>1</sup> | █ <sup>1</sup> | Yr2 | █ <sup>1</sup> | █ <sup>1</sup> | █ <sup>1</sup> | Yr3      | █ <sup>1</sup> | █ <sup>1</sup> | █ <sup>1</sup> | Yr4 | █ <sup>1</sup> | █ <sup>1</sup> | █ <sup>1</sup> | Yr5 | █ <sup>1</sup> | █ <sup>1</sup> | █ <sup>1</sup> | Yr6             | █ <sup>1</sup> | █ <sup>1</sup> | █ <sup>1</sup>  | Assumption. The submission assumed a relative substitution rate of █ <sup>1</sup> % from ADA, █ <sup>1</sup> % from ETN and █ <sup>1</sup> % from TOC reflecting the approximate current market share of each bDMARD/tsDMARD. The estimated proportional substitution rates correspond to the projected script numbers of bDMARDs/tsDMARDs and the assumed market share of TOF. | The estimated proportional substitution rates do not account for differences in script relativities between TOF and the other bDMARDs/tsDMARDs, but this error was relatively minor given most script relativities are 1:1. |  |   |
|  | ADA  | ETN  | TOC   |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| Yr1  | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>  |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| Yr2  | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>  |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| Yr3  | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>  |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| Yr4  | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>  |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| Yr5  | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>  |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| Yr6  | █ <sup>1</sup>   | █ <sup>1</sup>   | █ <sup>1</sup>  |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| Script<br>relativities   | <table border="1"> <thead> <tr> <th></th> <th>TOF<br/>tablet</th> <th>TOF<br/>solution</th> </tr> </thead> <tbody> <tr> <td>ADA 40mg</td> <td>1:1<br/>(62.5%)</td> <td>1:1<br/>(37.5%)</td> </tr> <tr> <td>ADA 20mg</td> <td>-</td> <td>1:1</td> </tr> <tr> <td>ETN 50mg</td> <td>1:1</td> <td>-</td> </tr> <tr> <td>ETN 25mg</td> <td>-</td> <td>1:1</td> </tr> <tr> <td>TOC IV 80mg</td> <td>-</td> <td>1:1</td> </tr> <tr> <td>TOC IV 200mg</td> <td>-</td> <td>1:1</td> </tr> <tr> <td>TOC IV 400mg</td> <td>1:1</td> <td>-</td> </tr> <tr> <td>TOC SC 162mg[a]</td> <td>1:2<br/>(100%)</td> <td>1:3<br/>(100%)</td> </tr> <tr> <td>TOC SC 162mg[b]</td> <td>1:2<br/>(100%)</td> <td>1:3<br/>(100%)</td> </tr> </tbody> </table> |  | TOF<br>tablet   | TOF<br>solution | ADA 40mg | 1:1<br>(62.5%) | 1:1<br>(37.5%) | ADA 20mg       | -              | 1:1 | ETN 50mg       | 1:1            | -              | ETN 25mg | -              | 1:1            | TOC IV 80mg    | -   | 1:1            | TOC IV 200mg   | -              | 1:1 | TOC IV 400mg   | 1:1            | -              | TOC SC 162mg[a] | 1:2<br>(100%)  | 1:3<br>(100%)  | TOC SC 162mg[b] | 1:2<br>(100%)   | 1:3<br>(100%)   | Calculated based on recommended dosing regimens and duration of treatment provided by each script of treatment. The submission assumed:<br>- One script of TOF (tablets or oral solution) provided 28 days of treatment;<br>- Each script of TOC represented one patient.<br>- TOF tablets and oral solution would substitute for different formulations, depending on likely weight of patient.<br>To provide a breakdown for initial and continuing scripts, it was assumed that 62.5% of scripts are used for initiation treatment (with the exception of TOC | The estimated script relativities were poorly justified and several errors were identified. For example:<br>- The submission calculated script relativities assuming patients ≥40 kg would use TOF oral tablet and patients <40 kg ( ) would use TOF oral solution, but assumed TOF oral solution only provides 28 days of treatment for patients <40 kg (rather than ≥28 days in practice).<br>- Patients may need more than one script of TOC per IV administration depending on their weight, therefore the script relativity is likely 1:>1 |
|  | TOF<br>tablet  | TOF<br>solution  |   |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| ADA 40mg   | 1:1<br>(62.5%)   | 1:1<br>(37.5%)   |   |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| ADA 20mg   | -  | 1:1  |   |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| ETN 50mg   | 1:1  | -  |   |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| ETN 25mg   | -  | 1:1  |   |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| TOC IV 80mg  | -  | 1:1  |   |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| TOC IV 200mg   | -  | 1:1  |   |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| TOC IV 400mg   | 1:1  | -  |   |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| TOC SC 162mg[a]  | 1:2<br>(100%)  | 1:3<br>(100%)  |   |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |
| TOC SC 162mg[b]  | 1:2<br>(100%)  | 1:3<br>(100%)  |   |                 |          |                |                |                |                |     |                |                |                |          |                |                |                |     |                |                |                |     |                |                |                |                 |                |                |                 |   |   |  |   |

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| Data                              | Value  | Source  | Comment   |
|-----------------------------------|--|---|---|
|                                   |  | 162 mg[b], where 0% are initiation scripts).  | <ul style="list-style-type: none"> <li>- ETN 25 mg is dosed twice a week (rather than once a week), therefore the script relativity should be 1:2.</li> <li>- The submission double counted TOF scripts substituting for TOC 162 mg scripts.</li> <li>- The submission assumed TOF solution will substitute ADA 40 mg for initial treatment and TOF tablets will substitute ADA 40mg for continuing treatment.</li> </ul> |
| Grandfather patients              | Initial treatment (2 scripts)<br>- Yr1: [redacted] <sup>1</sup> patients<br>Continuing treatment (13.04 scripts/year for TOF tablet; 12 scripts/year for TOF solution)<br>- Yr1: [redacted] <sup>1</sup><br>- Yr2: [redacted] <sup>1</sup><br>- Yr3: [redacted] <sup>1</sup><br>- Yr4: [redacted] <sup>1</sup><br>- Yr5: [redacted] <sup>1</sup><br>- Yr6: [redacted] <sup>1</sup> | The submission stated the estimates include [redacted] <sup>1</sup> grandfather patients who may receive TOF in the sponsor's planned patient familiarisation scheme prior to PBS listing. The submission assumed 59.1% of patients would use TOF tablets and 40.9% TOF oral solution. To calculate the proportion continuing treatment, the submission assumed 83.3% of patients would meet the continuation criteria each year. | The submission may be double counting the [redacted] <sup>1</sup> grandfather patients in the analysis given the historical prescription data likely captured these patients and the submission accounted for additional market growth due to TOF separately (see below). The assumed scripts/year and continuation rate were unclear/unverified.   |
| Market growth due to TOF, scripts | Yr1: [redacted]% ([redacted] pts * 13 TOF scripts)<br>Yr2-6: [redacted]/year ([redacted] pts * 13 TOF scripts)   | The submission stated it was reasonable to assume some additional market growth given TOF would be the first oral therapy, but the number of currently untreated patients is likely small. The submission stated that the scripts and costs associated with additional patients were estimated separately in the excel spreadsheet due to 'issues with the template.'   | Potential underestimate as a much higher proportion of potentially eligible patients may currently go untreated due to needle aversion. The calculations also do not account for different script relativities, which assumes 1 bDMARD/tsDMARD script = 1 script of TOF.  |
| TOF DPMQ                          | 5mg tablet: \$ [redacted]<br>1mg/mL solution: \$ [redacted]  | Requested effective price   |   |
| bDMARD/tsDMARD DPMQs              | ADA 40mg: \$830.57<br>ADA 20mg: \$830.57<br>ETN 50mg: \$952.71<br>ETN 25mg: \$477.52<br>TOC IV 80mg: \$85.69<br>TOC IV 200mg: \$208.46<br>TOC IV 400mg: \$412.52<br>TOC SC 162mg: \$811.89   | Published DPMQ for corresponding item numbers (see above). The submission estimated a single weighted DPMQ for the S100 listing for ADA, ETN and TOC IV, assuming 70:30 split between public and private prices.  | Consistent with current published DPMQs. The submission stated that ADA, ETN and TOC are all F2 and do not have effective prices, but it was unknown whether there were indication specific prices.   |
| MBS costs                         | TOC IV (80mg, 200mg, 400mg): \$103.55 per script for administration  | MBS item number 14245   | Reasonable, though there may be more than one script per administration.  |

Source: pp97-113 of the submission.

ADA=adalimumab; ETN=etanercept; TOF=tofacitinib; TOC=tocilizumab; IV=intravenous; bDMARD= biological disease modifying anti-rheumatic drugs; tsDMARD= targeted synthetic disease modifying anti-rheumatic drugs.

The redacted values correspond to the following ranges:

<sup>1</sup> <500

6.31 Table 8 presents the estimated script numbers and costs to the PBS for the proposed listing of TOF for the severe active JIA.

**Table 8: Estimated use and financial implications**

|  | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|--|--------|--------|--------|--------|--------|--------|
| <b>Estimated bDMARD/ tsDMARD market without TOF</b>                                |        |        |        |        |        |        |
| <b>bDMARD scripts</b>  | 1      | 1      | 1      | 1      | 6      | 6      |
| <b>bDMARDs, net cost PBS/RPBS</b>  | 2      | 2      | 2      | 2      | 2      | 2      |
| <b>Estimated use and financial impact of TOF</b>                                   |        |        |        |        |        |        |
| <b>TOF scripts</b>   | 3      | 3      | 3      | 3      | 3      | 3      |
| TOF scripts, substitution of comparators   | 3      | 3      | 3      | 3      | 3      | 3      |
| TOF scripts, new patients – grandfather  | 4      | 4      | 4      | 4      | 4      | 4      |
| TOF scripts, new patients - market growth  | 4      | 4      | 4      | 4      | 4      | 4      |
| <b>TOF, net cost PBS/RPBS<sup>^</sup></b>  | 2      | 2      | 2      | 2      | 2      | 2      |
| <b>Estimated change in use and financial impact of comparators (ADA, ETN, TOC)</b> |        |        |        |        |        |        |
| <b>Comparator scripts (substituted)*</b>   | 4      | 4      | 4      | 4      | 4      | 4      |
| ADA (20mg / 40mg)  | 4      | 4      | 4      | 4      | 4      | 4      |
| ETN (25 mg / 50mg)   | 4      | 4      | 4      | 4      | 4      | 4      |
| TOC IV (80mg / 200mg / 400 mg)   | 4      | 4      | 4      | 4      | 4      | 4      |
| TOC SC   | 4      | 4      | 4      | 4      | 4      | 4      |
| <b>Comparators, net cost to PBS/RPBS</b>   | 5      | 5      | 5      | 5      | 5      | 5      |
| <b>Estimated financial implications for the PBS/RPBS and MBS</b>                   |        |        |        |        |        |        |
| Net change in administration of TOC IV   | 4      | 4      | 4      | 4      | 4      | 4      |
| <b>Net cost to MBS</b>   | 4      | 4      | 4      | 4      | 4      | 4      |
| <b>Net cost PBS/RPBS<sup>^</sup></b>   | 2      | 2      | 2      | 2      | 2      | 2      |

Some estimates corrected during the evaluation.

Source: pp97-113 of the submission.

ADA=adalimumab; ETN=etanercept; TOF=tofacitinib; TOC=tocilizumab; IV=intravenous; bDMARD= biological disease modifying anti-rheumatic drugs; tsDMARD= targeted synthetic disease modifying anti-rheumatic drugs;

<sup>^</sup> The estimates are in italics because the submission only estimated the total cost to the PBS/RPBS for TOF scripts due to market growth rather than the net cost to the PBS/RPBS (i.e. minus co-payment).

\* Reduction in bDMARD scripts corresponds to the TOF scripts that substitute for current bDMARDs, where differences in script numbers are due to difference script relativities assumed.

The redacted values correspond to the following ranges:

<sup>1</sup> 5,000 to < 10,000

<sup>2</sup> \$0 to <\$10 million

<sup>3</sup> 500 <5,000

<sup>4</sup> <500

<sup>5</sup> net cost saving

<sup>6</sup> 10,000 to < 20,000

6.32 The total cost to the PBS/RPBS of listing TOF was estimated to be \$0 to < \$10 million in Year 1, increasing to \$0 to < \$10 million in Year 6, and a total of \$0 to < \$10 million in the first 6 years of listing. A breakdown of the incremental cost was generated during the evaluation which illustrated that the estimated net cost to the PBS/RPBS was mostly driven by grandfather patients and substitution with existing bDMARDs/tsDMARDs rather than the assumed market growth (which only accounts for █% in Year 1 and █% in Year 6).

6.33 Overall, the evaluation considered the submission’s financial estimates model was unreliable given the historical prescription data would likely capture the < 500 grandfathered patients and a cost-minimisation to ADA (or the least costly alternative) means that substitution effects would be expected to have negligible financial impact.

Whether there would be an incremental cost to the PBS (the estimate in the submission corresponded to approx. 1% increase in the total market) depends on the extent of under treatment due to the lack of orally administered treatments. The literature suggests that a high proportion of children have a fear of needles that can result in avoidance of treatment in various settings other than JIA<sup>3</sup>. Hence, as the first oral treatment for a paediatric population, it may be reasonable to assume some market growth with TOF, but the magnitude of growth is uncertain. The PSCR stated historical prescription data did not capture all grandfathered patients as there a significant number of patients who are not being treated because of an aversion to needles.

### ***Quality Use of Medicines***

- 6.34 The submission stated that the sponsor was committed to carrying out risk minimisation strategies including maintaining and distributing TOF specific guides for prescribers and patients to educate clinicians and patients of the identified and potential risks of treatment. There are several planned and ongoing post-market surveillance studies, as detailed in the TGA risk management plan.

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

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<sup>3</sup> McLennon and Rogers. The fear of needles: a systematic review and meta-analysis. *Journal of Advanced Nursing*. 2019; 75:30-42.

## 7 PBAC Outcome

- 7.1 The PBAC recommended the General Schedule listing of tofacitinib (TOF) for the treatment of severe active juvenile idiopathic arthritis (JIA). The PBAC's recommendation was based on, among other matters, its assessment the cost-effectiveness of TOF would be acceptable if it were cost minimised to the least costly alternative therapy of adalimumab (ADA), etanercept (ETN) and tocilizumab (TOC).
- 7.2 The PBAC considered the equi-effective doses of TOF and the alternative therapies could be derived with reference to the therapeutic relativity sheets and relevant Product Information documents, noting the TOF equi-effective dose component was weight based and is as follows:
- 10 to <20 kg: TOF 3.2 mg twice daily (oral solution);
  - 20 to <40 kg: TOF 4 mg twice daily (oral solution); and
  - ≥40 kg: TOF 5 mg twice daily (oral solution or oral tablet).
- 7.3 The PBAC noted the comments from patient carers and organisations highlighted the impact of having to regularly perform injections on children to patients, families and caregivers and agreed there was a high need for a non-injectable alternative treatment for JIA in the paediatric population. The PBAC considered the availability of an oral therapy option may greatly reduce the stress and anxiety associated with JIA treatment for patients and families with an aversion to injections.
- 7.4 The PBAC considered it would be appropriate to align the listing of TOF with the other biologic or targeted synthetic disease modifying anti-rheumatic drugs (bDMARDs/tsDMARDs), with prescribing limited to medical practitioners, an initial treatment period of 16 weeks, followed by maintenance therapy with re-assessment at 24 week intervals. The PBAC noted it had recommended lowering the authority level for continuing therapy for TOC for JIA to a streamlined authority and considered it was appropriate for this changed to be flowed on to the listing of TOF (Review of PBS Authority Required (Written) listings – Tranche 6, March 2022 PBAC meeting). The PBAC advised the grandfather restriction should be removed from the listing after 12 months, in line with standard procedure. The PBAC noted flow-on changes to other JIA listings will be required to include tofacitinib in the list of eligible therapies.
- 7.5 The submission nominated ADA as the comparator. The PBAC considered this was reasonable however noted any of the currently PBS listed bDMARDs/tsDMARDs for JIA (including ETN and TOC) could be considered an alternative therapy to TOF for the treatment of JIA.
- 7.6 The submission described tofacitinib to be non-inferior in terms of comparative effectiveness and safety in JIA versus ADA. The PBAC noted no direct trials comparing TOF and ADA were available, and the submission relied on an indirect treatment comparison (ITC) with placebo as the common comparator to support the clinical claim.

- 7.7 The PBAC noted the results of the ITC versus ADA for the outcomes of disease flare, PedACR30, PedACR50 and PedACR70 found no statistically significant differences between the treatments. The Committee noted the results of the ITCs generally had wide 95% confidence intervals, however also noted this was not dissimilar to the comparison for TOC vs ETN or ADA ('Results of trials' section, tocilizumab Public Summary Document (PSD), November 2013 PBAC meeting). The PBAC also noted the submission presented additional subgroup analyses to account for different use of prior or concomitant therapies (methotrexate or other bDMARDs/tsDMARDs) which supported the clinical claim. Overall, the PBAC considered the claim of non-inferior comparative effectiveness was adequately supported.
- 7.8 With regards to safety, the PBAC considered the results of the PROPEL trial indicated the safety of TOF in JIA was comparable to its safety profile in adults and further considered that whilst there were limitations with the indirect comparison to ADA the available analyses supported a conclusion that TOF was likely to be of different (but not worse) safety to ADA, noting the differences in the safety profile of these agents.
- 7.9 The PBAC considered that a listing based on a cost minimisation approach, with costs over two years, consistent with the approach previously used for bDMARDs/tsDMARDs, was appropriate to determine the cost minimised price of TOF. The Committee noted the advice of the ESC and agreed the risk of substantial use of the oral liquid in the population weighing >40 kg was low and therefore considered it was reasonable for the oral liquid pack to be priced the same as the oral tablet pack. The PBAC considered the cost of TOF should be no greater than the alternative therapies.
- 7.10 The PBAC considered there was some uncertainty to the utilisation and financial estimates as TOF would be the first oral therapy in JIA, and as a paediatric condition, there was likely a cohort of patients who are untreated or undertreated with current injectable options, however also considered the size of this population as uncertain and difficult to estimate. The PBAC noted the submission had included an assumption TOF would grow the market and considered overall the estimates were likely to be reasonable.
- 7.11 The PBAC advised, under Section 101 (4AB) of the *National Health Act*, that the following circumstances exist in relation to the pharmaceutical item tofacitinib, oral liquid 1 mg per mL, 240 mL:
- i) The listed drug in the pharmaceutical item represents suitable therapy for a particular patient population (in this case, paediatric patients);
  - ii) The pharmaceutical item is suitable for use by a particular subgroup of that population because of either or both of the form and manner of administration of the drug in the item (in this case, as an oral liquid);
  - iii) No other pharmaceutical item that has the drug is suitable for use by that subgroup because of either or both of the form and manner of administration of

the drug in that other item (in this case, for paediatric patients weighing under 40 kg and/or cannot swallow tablets).

- 7.12 The PBAC recommended that the Early Supply Rule should not apply to the oral liquid but should apply to the oral tablets (similar to other TOF oral tablet listings).
- 7.13 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because tofacitinib is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over adalimumab or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 7.14 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## **8 Recommended listing**

- 8.1 Add new item for tofacitinib tablet and oral solution for JIA in line with the current JIA restrictions, and flow-on changes to other JIA listings to include tofacitinib in the list of eligible therapies. The restriction is to be finalised.

## **9 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.

## **10 Sponsor's Comment**

Xeljanz is the first oral therapy in JIA, a paediatric condition which has not had access to novel effective treatments for more than 9 years. Xeljanz addresses a high unmet need for children currently untreated or undertreated with current injectable options. Pfizer Australia welcomes the PBAC recommendation to list Xeljanz for the treatment of severe active juvenile idiopathic arthritis (JIA) and is working with the Department of Health to list Xeljanz on the PBS as early as possible.