6.15 TOFACITINIB
Tablet 5 mg, 10 mg,
Xeljanz®,
Pfizer Australia Pty Ltd.

1 Purpose of Application

1.1 The minor submission requested the PBAC review its advice that tofacitinib should be treated as interchangeable on an individual patient basis with other drugs, for moderate-to-severe ulcerative colitis (MSUC) and severe psoriatic arthritis (PsA), under section 101(3BA) of the *National Health Act 1953* ('the Act'). The submission also requested the PBAC review its interchangeability advice for other biologics listed on the PBS for severe active rheumatoid arthritis (RA) and severe chronic plaque psoriasis (CPP).

1.2 The submission also requested the PBAC consider providing further explanation in minutes and public summary documents on the rationale for interchangeability advice made during its consideration of applications.

2 Background

2.1 On 1 August 2007, section 84AG of the Act was introduced, which allows the Minister to determine therapeutic groups. The Explanatory Memorandum to the *National Health Amendment (Pharmaceutical Benefits Scheme) Bill 2007*[1] ('the 2007 Amendment') states that therapeutic groups are "groups of drugs which are interchangeable on an individual patient basis [and] are grouped together for pricing purposes – because the drugs provide the same health outcome, they are priced similarly".

2.2 Section 84AG (1A) of the Act requires the Minister to obtain the advice in writing of the PBAC in relation to the proposed determination. In making such a determination, the Minister may have regard to advice (if any) given by the PBAC to the effect that a drug or medicinal preparation should, or should not, be treated as interchangeable on an individual patient basis with another drug or medicinal preparation.

2.3 Under section 101(3BA) of the Act, if the PBAC makes a positive recommendation for a drug or medicinal preparation, it must specify whether the drug or medicinal preparation and another drug or medicinal preparation should be treated as interchangeable on an individual patient basis. It is a matter for the PBAC, taking into

[1] Explanatory memorandum, National Health Amendment (Pharmaceutical Benefits Scheme) Bill 2007, (Commonwealth of Australia)

account relevant considerations, to form an opinion concerning the drug and another drug, that does or does not support a specification under section 101(3BA).

3 Current situation

3.1 The submission requested the PBAC review its interchangeability advice for tofacitinib and other PBS listed drugs for MSUC, PsA, RA and CPP. The submission argued the current advice provided for these drugs is inconsistent with the interpretation of "interchangeable on an individual patient basis" in statements made by Department officials and a previous Chair of the PBAC to parliamentary enquiries in 2007 and 2010. Specifically, the submission claims that the PBAC's current advice regarding interchangeability is not appropriate due to the following factors:

- Tofacitinib does not belong to the same therapeutic class as the other drugs with which the PBAC has said it should be treated as interchangeable
- Tofacitinib has a different mechanism of action to other drugs with which the PBAC has said it has should be treated as interchangeable
- The PBAC has previously advised that some drugs with the same mechanism of action should not be treated as interchangeable with one another, which is inconsistent with the advice that they should now all be treated as interchangeable with tofacitinib
- For the MSUC and PsA indications, not all of the drugs the PBAC advised should be treated as interchangeable were considered to be of non-inferior safety and efficacy to each other.

Furthermore, the submission requested that Public Summary Documents include a detailed explanation of the basis for the determination of interchangeability.

3.2 The PBAC noted that a recommendation that two or more drugs should be treated as interchangeable does not mean that both drugs are appropriate in every circumstance for every patient – rather, that the outcomes are comparable at a whole-of-population level for these treatments. The selection of most appropriate treatment for a patient remains, first and foremost, a decision for the prescribing clinician.

3.3 Summaries of PBS-listed drugs for the treatment of RA, PsA, MSUC and CPP, and the current interchangeability advice for those drugs (as recorded in their respective Public Summary Documents[2]) are outlined below.

3.4 The PBAC noted correspondence received from AbbVie Pty Ltd which supported the submission's request that the PBAC consider providing further explanation in minutes and public summary documents on the rationale for interchangeability advice made during its consideration of applications.

[2] Public Summary Documents only available from the July 2005 PBAC meeting onwards. References to earlier meetings refer to the PBAC minutes. Public Summary Documents not available for all items considered at Special/Intra-cycle/Extraordinary meetings of the PBAC.

Ulcerative colitis

3.5 The following drugs are PBS-listed (or recommended and not currently listed) for the treatment of MSUC:

- Tumour necrosis factor-α (TNF-α) inhibitors: infliximab, adalimumab and golimumab
- α4β7 integrin inhibitors: vedolizumab
- Janus-kinase (JAK) inhibitors: tofacitinib (not currently listed)

3.6 The PBAC's current advice (tofacitinib, March 2019) is that adalimumab, golimumab, infliximab, tofacitinib and vedolizumab should be treated as interchangeable. As noted above, the submission suggests that this advice was inconsistent with earlier advice about interchangeability of some of those drugs.

3.7 In March 2016, the PBAC considered adalimumab to be inferior to infliximab for MSUC (Paragraph 7.1, adalimumab Public Summary Document, March 2016). The PBAC also considered golimumab was non-inferior in terms of efficacy and safety to vedolizumab and adalimumab in both induction and maintenance therapy; and inferior to infliximab for efficacy for induction, but non-inferior to infliximab for safety and for efficacy in maintenance therapy (Paragraph 7.3, golimumab Public Summary Document, November 2017). When it considered tofacitinib at its March 2019 meeting, the PBAC considered the evidence presented did not support a conclusion that it provided a significant improvement in efficacy or reduction in toxicity compared to any of the currently listed biologics for MSUC (Paragraph 7.5, tofacitinib Public Summary Document, March 2019).

Psoriatic arthritis

3.8 The following drugs and therapeutic classes are PBS-listed (or recommended and not listed) for the treatment of severe PsA:

- TNF-α inhibitors: infliximab, etanercept, adalimumab, golimumab and certolizumab pegol;
- Interleukin-12/23 (IL-12/IL-23) inhibitors: ustekinumab
- Interleukin-17 (IL-17) inhibitors: secukinumab, ixekizumab
- JAK inhibitors: tofacitinib

3.9 The PBAC's current advice for severe PsA (tofacitinib, November 2018) is that adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, secukinumab, tofacitinib and ustekinumab should be treated as interchangeable. As noted above, the submission suggests that this advice was inconsistent with earlier advice about interchangeability of some of those drugs.

3.10 In PsA, the PBAC considered ustekinumab was non-inferior to certolizumab pegol and inferior to adalimumab, and as such this placed both drugs in the south-west quadrant

of the cost-effectiveness plane compared to other bDMARDs for PsA (Paragraph 6.5, ustekinumab Public Summary Document, November 2015). The PBAC also considered secukinumab was of non-inferior comparative efficacy to certolizumab pegol and ustekinumab (Paragraph 7.5, secukinumab Public Summary Document, March 2016) and that ixekizumab was non-inferior in terms of comparative efficacy and safety versus the main comparator (secukinumab) and supplementary comparators adalimumab, certolizumab pegol and ustekinumab (Paragraph 7.3, ixekizumab Public Summary Document, July 2018). When it considered tofacitinib at its November 2018 meeting, the PBAC considered there was some uncertainty around the claim of non-inferior comparative effectiveness to adalimumab, and considered the results of indirect comparisons with certolizumab pegol and ustekinumab undertaken during the evaluation supported a conclusion of non-inferior effectiveness between tofacitinib and these therapies (Paragraphs 7.5 and 7.6, tofacitinib Public Summary Document, November 2018).

Rheumatoid arthritis

3.11 The following drugs and therapeutic classes are PBS-listed (or recommended and not listed) for the treatment of severe active RA:

- TNF-α inhibitors: infliximab, etanercept, adalimumab, golimumab and certolizumab pegol;
- Anti-CD28 antibodies: abatacept
- Interleukin-6 (IL-6) inhibitors: tocilizumab, sarilumab (not currently listed)
- Anti-CD20 antibodies: rituximab
- JAK inhibitors: tofacitinib, baricitinib

3.12 The PBAC's current advice for severe RA (sarilumab, November 2018) is that abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, sarilumab, tocilizumab and tofacitinib should be treated as interchangeable. As noted above, the submission suggests that this advice was inconsistent with earlier advice about interchangeability of some of those drugs.

Chronic plaque psoriasis

3.13 The following drugs and therapeutic classes are PBS- listed (or recommended and not listed) for the treatment of severe CPP:

- Anti CD-11 inhibitors: (efalizumab – delisted)
- TNF-α inhibitors: infliximab, etanercept, adalimumab, (certolizumab pegol)
- IL-12/IL-23 inhibitors: ustekinumab
- IL-17 inhibitors: secukinumab, ixekizumab
- IL-23 inhibitors: guselkumab, tildrakizumab, risankizumab

3.14 The PBAC's current advice for CPP (risankizumab, July 2019) is that risankizumab, adalimumab, etanercept, guselkumab, infliximab, secukinumab, tildrakizumab and ustekinumab should be treated as interchangeable. As noted above, the submission suggests that this advice was inconsistent with earlier advice about interchangeability of some of those drugs.

4 Sponsor hearing and consumer comments

Sponsor hearing

4.1 There was no hearing for this item as it was a minor submission.

Consumer comments

4.2 The PBAC noted the input from four health professionals, all of which noted tofacitinib is not a biologic agent and is unique as an oral treatment, which has a different mechanism of action to any available biologics for RA, PsA or MSUC. The input from health professionals also noted that as a small molecule therapy, tofacitinib does not carry any of risks of immunogenicity or development of anti-drug antibodies associated with use of biologics. The PBAC also noted the input from Crohn's and Colitis Australia, which highlighted the equity benefits of oral treatment options for MSUC for patients living in rural and remote areas.

5 PBAC Outcome

5.1 The PBAC deferred the matter of the interchangeability of tofacitinib under Section 101(3BA) of the *National Health Act 1953* to a future meeting to obtain further information and allow further deliberation of the request prior to providing advice.

Outcome:
Deferred

6 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.

7 Sponsor's Comment

Pfizer recognises that this important issue of interchangeability of drugs on an individual patient basis (as opposed to a population basis) necessitates a thorough

consideration by the PBAC and looks forward to receiving a timely and transparent recommendation in due course.