# 6.13 UPADACITINIB, Tablet 15 mg, Tablet 30 mg, Tablet 45 mg, Rinvoq®, AbbVie Pty Ltd

## 1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule, Authority Required (written) listing of upadacitinib for the treatment of severe Crohn disease (CD) under the same restrictions and clinical criteria as the other PBS-listed biologics. The submission was provided for consideration at the March 2023 meeting; however, it was considered at the July 2023 meeting.

1.2 Listing was requested on the basis of a cost-minimisation approach versus adalimumab.

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

| Component | Description |
|---|---|
| Population | Adults with severe Crohn disease who have failed to achieve an adequate response, or are contraindicated, to prior systemic therapy |
| Intervention | Induction regimen: upadacitinib 45 mg oral modified release tablet once daily for 12 weeks<br>Maintenance regimen: upadacitinib 15 mg or 30 mg oral tablet once daily thereafter |
| Comparator | As there is no pharmacological analogue, infliximab, adalimumab, vedolizumab, ustekinumab and risankizumab are all relevant comparators |
| Outcomes [a] | Clinical remission, clinical response, safety |
| Clinical claim | Upadacitinib is non-inferior to infliximab, adalimumab, vedolizumab, ustekinumab and risankizumab at achieving clinical response and clinical remission and non-inferior in terms of safety |

Source: Table 1-1, pp13-14 of the submission.
[a] Outcomes defined as follows: Clinical response: CDAI reduction of ≥100 points from baseline; Clinical remission: CDAI <150.
CDAI= Crohn's Disease Activity Index.

## 2 Background

### *Registration status*

2.1 **TGA status at time of PBAC consideration:** The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration in July 2023, the proposed Product Information document, Delegate's Overview and ACM advice were available.

2.2 The indication proposed in the draft Product Information provided prior to PBAC consideration is as follows:

'RINVOQ is indicated for the treatment of adult patients with moderately to severely active Crohn's disease, who have had an inadequate response, lost response or where intolerant to either conventional therapy or a biological medicine'.

2.3 Upadacitinib is currently TGA registered for five indications: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, atopic dermatitis, and ulcerative colitis.

### *Previous PBAC consideration*

2.4 Upadacitinib has not previously been considered for severe CD.

2.5 Upadacitinib is PBS listed for severe active rheumatoid arthritis, severe psoriatic arthritis, ankylosing spondylitis, chronic severe atopic dermatitis and moderate to severe ulcerative colitis.

## 3 Requested listing

3.1 The requested abridged listing for severe CD is provided below.

| MEDICINAL PRODUCT medicinal product pack | Dispensed Price for Max. Qty | Max. qty packs | Max. qty units | №. of Rpts | Available brands |
|---|---|---|---|---|---|
| **UPADACITINIB** | | | | | |
| **Initial** | | | | | |
| Upadacitinib, 45 mg, oral tablet | $2,716.07 published price | 1 | 28 | 2 | RINVOQ |
| **Initial treatment- dose change** | | | | | |
| Upadacitinib, 30 mg, oral tablet | $2,076.38 published price | 1 | 28 | 0 | |
| Upadacitinib, 15 mg, oral tablet | $1,271.40 published price | 1 | 28 | 0 | |
| **Continuing treatment** | | | | | |
| Upadacitinib, 30 mg, oral tablet | $2,076.38 published price | 1 | 28 | 5 | |
| Upadacitinib, 15 mg, oral tablet | $1,271.40 published price | 1 | 28 | 5 | |
| **Continuing treatment- dose change** | | | | | |
| Upadacitinib, 30 mg, oral tablet | $2,076.38 published price | 1 | 28 | 4 | |
| Upadacitinib, 15 mg, oral tablet | $1,271.40 published price | 1 | 28 | 4 | |

| |
|---|
| **Category / Program:** Section 85- General Schedule |
| **Prescriber type:** Medical Practitioners |
| **Restriction type:** Authority Required- In Writing |
| **Severity:** Severe |
| **Condition:** Crohn disease |
| **Indication:** Severe Crohn disease |
| **Treatment criteria:** Must be treated by a gastroenterologist or consultant physician [specialising in gastroenterology] |
| **Population criteria:** Patient must be aged 18 years or older |
| *The above criteria apply to all treatment phases outlined below:* |

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| **Treatment Phase: Initial treatment 1 (new patient, or change or re-commencement of treatment after break > 5 years)** |
| **Clinical criteria:** |
| Patient must have confirmed severe Crohn disease<br>AND<br>Patient must have failed to achieve an adequate response to prior systemic therapy (corticosteroids and at least 3 months of immunosuppressive therapy)<br>AND<br>Patient must have severity of disease activity with CDAI ≥300; OR CDAI ≥220 with extensive small intestine disease |

| |
|---|
| AND<br>Evidence of intestinal inflammation; OR in high faecal output state; OR require surgery or total parenteral nutrition as the next therapeutic option<br>AND<br>The treatment must not exceed 12 weeks under this restriction<br>**Restriction type:** Authority Required- In Writing |
| **Prescribing Instructions:**<br>A maximum quantity and number of repeats to provide for an initial 12 week course of this drug will be authorised under this item code. A further 4 week course of treatment can be accessed under the balance of supply criteria.<br>The assessment of the patient's response to this initial course of treatment, including the balance of supply, must be made following a minimum of 12 weeks of therapy so that there is adequate time for a response to be demonstrated.<br>It is recommended that an application for continuing treatment is posted to the Department of Human Services at the time of the 12 week assessment, to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug |

| **Treatment Phase: Initial treatment 2 (change or re-commencement of treatment after break < 5 years)** |
|---|
| **Clinical criteria:** |
| Patient must have received prior PBS-subsidised treatment with a biologic for this condition in this treatment cycle<br>AND<br>Patient must not have failed PBS-subsidised therapy with this drug for this condition more than once in the current treatment cycle<br>AND |
| The treatment must not exceed 12 weeks under this restriction |
| **Restriction type:** Authority Required- In Writing |
| **Prescribing Instructions:** As per initial treatment 1 |

| **Treatment Phase: Initial treatment- balance of supply** |
|---|
| **Clinical criteria:** Patient must have received insufficient therapy under Initial 1/2/3 scripts |
| **Restriction type:** Authority Required- In Writing |
| **Prescribing Instructions:** Balance must provide no more than 12 weeks of therapy under Initial 1/2/3 |

| **Treatment Phase: Initial treatment 3 (transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements)** |
|---|
| **Clinical criteria:** |
| Patient must have received treatment with this drug for this PBS indication prior to [PBS listing date]<br>AND<br>Patient must have confirmed severe Crohn disease<br>AND<br>Patient must have, prior to initiating treatment with this drug for this condition, failed to achieve an adequate response to prior systemic therapy (corticosteroids and at least 3 months of immunosuppressive therapy)<br>AND<br>Patient must have had, prior to initiating treatment with this drug for this condition, severity of disease activity with CDAI ≥300; OR CDAI ≥220 with extensive small intestine disease<br>AND<br>Evidence of intestinal inflammation; OR in high faecal output state; OR require surgery or total parenteral nutrition as the next therapeutic option |
| **Restriction type:** Authority Required- In Writing |
| **Prescribing Instructions:** As per initial treatment 1 |

| **Treatment Phase: Initial treatment 1, 2, 3 – balance of supply** |
|---|
| **Clinical criteria:** |
| Patient must have received insufficient therapy with this drug for this condition under the Initial 1/2/3 restriction to complete 16 weeks treatment<br>AND |

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|---|
| The treatment must not exceed a total of 4 weeks |
| **Restriction type:** ☒Authority Required- In Writing<br>☒Authority Required- Telephone<br>☒Authority Required- Electronic |
| **Prescribing Instructions:**<br>A maximum quantity to provide for a 4 week course of treatment can be accessed under this criteria. The initial 12 week treatment course should be requested under the Initial treatment item code<br>The assessment of the patient's response to this initial course of treatment, including the balance of supply, must be made following a minimum of 12 weeks of therapy so that there is adequate time for a response to be demonstrated<br>It is recommended that an application for continuing treatment is posted to the Department of Human Services at the time of the 12 week assessment, to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug |

| **Treatment Phase: Continuing treatment** |
|---|
| **Clinical criteria:** |
| Patient must have previously received PBS-subsidised treatment with this drug for this condition<br>AND<br>Patient must have shown adequate response as CDAI <150; OR show an improvement of intestinal inflammation/ reversal of high faecal output state/avoidance of TPN<br>AND<br>Patient must not receive >24 weeks of treatment |
| **Restriction type:** Authority Required- In Writing |
| **Prescribing Instructions:**<br>Each application for subsequent continuing treatment with this drug must include an assessment of the patient's response to the prior course of therapy. |
| If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition within this treatment cycle. |

| **Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply - Grandfather arrangements** |
|---|
| **Clinical criteria:** |
| Patient must have received treatment with this drug for this PBS indication prior to [PBS listing date]<br>AND<br>Patient must have confirmed severe Crohn disease<br>AND<br>Patient must have, prior to initiating treatment with this drug for this condition, failed to achieve an adequate response to prior systemic therapy (corticosteroids and at least 3 months of immunosuppressive therapy)<br>AND<br>Patient must have had, prior to initiating treatment with this drug for this condition, severity of disease activity with CDAI ≥300; OR CDAI ≥220 with extensive small intestine disease<br>AND<br>Evidence of intestinal inflammation; OR in high faecal output state; OR require surgery or total parenteral nutrition as the next therapeutic option<br>AND<br>Patient must have shown adequate response as CDAI <150; OR show an improvement of intestinal inflammation/reversal of high faecal output state/avoidance of TPN<br>AND<br>Patient must not receive >24 weeks of treatment |
| **Restriction type:** Authority Required- In Writing |
| **Prescribing Instructions:** As per continuing |

| **Treatment Phase: Dose change – increasing to the 30 mg dose or decreasing to the 15 mg dose in the continuation phase** |
|---|
| **Clinical criteria:** |

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|---|
| Patient must be undergoing existing PBS-subsidised treatment with this therapy where each of the following is true: (i) there is a change in daily dose, (ii) any remaining PBS repeat prescriptions for the strength that the patient is changing from, is marked as 'cancelled' |
| **Restriction type:** Authority Required- Telephone |
| **Prescribing Instructions:** None |

Source: Tables 1-7 to 1-10, pp 26-29 of the submission.
CDAI= Crohn's Disease Activity Index; PBS= Pharmaceutical Benefits Scheme; TPN= Total Parenteral Nutrition.

3.2 Similar to its listing for moderate to severe ulcerative colitis (MSUC), the maintenance dosing of upadacitinib is variable, with dosing at either 15 mg or 30 mg daily following an induction period of 12 weeks at 45 mg. The requested listings allow for flexibility to move between 15 mg and 30 mg doses via the proposed balance of supply restrictions (see Section 8 'Recommended listing').

3.3 The submission requested an increase to the number of therapies in a treatment cycle for severe CD to account for the addition of a new mechanism of action [Janus kinase (JAK) inhibitors], as the current PBS restriction allows patients with severe CD to trial and fail a maximum of three classes of biologic agents (TNFα, α4β7 integrin and interleukin 12/23 inhibitors) in a 5-year treatment cycle. The Secretariat noted that upadacitinib is the only targeted synthetic disease modifying anti-rheumatic drug (tsDMARD) agent for severe CD that is available in oral tablet form. The other PBS-listed biologics either require an intravenous infusion or subcutaneous self-injection. Minor flow-on changes to the restrictions of the other agents were proposed to facilitate the listing of upadacitinib.

3.4 A Special Pricing Agreement (SPA) was requested for upadacitinib.

3.5 The submission requested a grandfather clause be incorporated in the listing to allow approximately < 500 patients from a planned upadacitinib Product Familiarisation Program (PFP) and < 500 patients enrolled in the upadacitinib open-label extension trial to transition to PBS-subsidised upadacitinib.

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

# 4 Population and disease

4.1 CD and ulcerative colitis are two conditions commonly referred to as inflammatory bowel disease. They are immunologically mediated inflammatory diseases that can affect any portion of the gastrointestinal tract from the mouth to the perianal area. CD runs a relapsing and remitting course. It is a progressive disorder with no cure, and despite optimal therapy, most patients have a poor quality of life. CD can cause debilitating pain, rectal bleeding, diarrhoea, fatigue, and weight loss due to malnutrition. Some patients who develop complications require surgery, such as surgical resection.

4.2 The submission positioned upadacitinib as an additional treatment option to other biologics for patients with severe CD on the PBS. These biologics (adalimumab, infliximab, vedolizumab and ustekinumab) were recently considered as alternative therapies (ustekinumab was the nominated main comparator) by the PBAC for

risankizumab (Paragraph 7.3, Risankizumab, Public Summary Document (PSD), July 2022 PBAC meeting).

4.3 Upadacitinib is an orally administered, small-molecule inhibitor of a class of JAK enzymes (JAK1, JAK2, and JAK3), which are involved in the process of immune-mediated inflammatory diseases.

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

# 5 Comparator

5.1 The submission nominated all PBS-listed bDMARDs (adalimumab, infliximab, vedolizumab and ustekinumab) and recently recommended risankizumab (November 2022 PBAC meeting outcomes) as comparators.

5.2 Although all biologics were included as relevant comparators in the clinical and financial analyses, the submission only undertook a cost minimisation approach versus adalimumab. The submission claimed that adalimumab was selected as the appropriate comparator due to the high market share, and like adalimumab, upadacitinib is expected to be used exclusively in the community setting.

5.3 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, 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 adalimumab, infliximab, vedolizumab, ustekinumab and risankizumab.

*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 noted the increasing incidence/prevalence of IBD conditions in Australia, expected to reach 1% in the next decade and described the high rates of failure of conventional therapies and current biologics (as high as 30-50%), with particularly high rates of discontinuation of TNF inhibitors. The clinician noted that upadacitinib is a highly effective oral agent which offers advantages of being a small molecule which works on multiple cytokine pathways and has no risk of immunogenicity associated with biologics.

## *Consumer comments*

6.2 The PBAC noted and welcomed the input from organisations (1) via the Consumer Comments facility on the PBS website. The PBAC noted the advice received from

Crohn's and Colitis Australia, which highlighted the value of a first oral therapy for the treatment of severe Crohn's disease and additional choice for patients.

## *Clinical trials*

6.3 There were no head-to-head trials comparing upadacitinib with adalimumab, risankizumab, infliximab, vedolizumab and ustekinumab for severe CD. The submission was based on indirect comparisons of three upadacitinib trials and 18 comparator trials.

6.4 The three upadacitinib randomised controlled trials (RCTs) included two phase 3 induction trials and one phase 3 maintenance trial. These are:

- U-EXCEED (induction trial): comparing upadacitinib 45 mg daily dose (QD) with placebo (N=495). Patients were randomised 2:1 to (double-blind) upadacitinib 45 mg QD (N=324) or matching placebo (N=171) for a 12-week induction period.
- U-EXCEL (induction trial): comparing upadacitinib 45 mg QD with placebo (N=526). Patients were randomised 2:1 to (double-blind) upadacitinib 45 mg QD (N=350) or matching placebo (N=176) for a 12-week induction period.
- U-ENDURE (maintenance trial): a total of 502 patients were included in Cohort 1 and randomised to receive either upadacitinib 15 mg QD (N=169), upadacitinib 30 mg QD (N=168) or a matching placebo (N=165).

6.5 The submission presented a series of indirect comparisons using data from 18 randomised placebo-controlled comparator trials. Further details of the comparator trials are presented in Table 2 below.

- Five RCTs of adalimumab versus placebo – CLASSIC I (N=299), CLASSIC II (N=55), GAIN (N=325), CHARM (N=778) and Watanabe 2012 (N=90 (induction); N=50 (maintenance)).
- Four RCTs of risankizumab versus placebo – M15-993 (N=121), ADVANCE (N=931), MOTIVATE (N=618) and FORTIFY (N=542).
- Two RCTs of infliximab versus placebo – T16 (N=108) and ACCENT I (N=573).
- Four RCTs of vedolizumab versus placebo – Watanabe 2020 (N=157 (induction); N= 24 (maintenance)), VISIBLE 2 (N=410 (vedolizumab SC)), GEMINI II (induction phase N= 368, maintenance phase N = 461), and GEMINI III (N=416).
- Three RCTs of ustekinumab versus placebo – UNITI-I (N=741), UNITI-II (N=628) and IM-UNITI (N=397).

6.6 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 |
|---|---|---|
| **Upadacitinib** | | |
| U-EXCEED (M14-431)<br>NCT03345836 | A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or are Intolerant to Biologic Therapy. | 21 March 2022. |
| U-EXCEL (M14-433)<br>NCT03345849 | A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or are Intolerant to Conventional and/or Biologic Therapies. | 23 May 2022. |
| U-ENDURE (M14-430)<br>NCT03345823 | A Multicenter, Randomized, Double-Blind, Placebo-Controlled Maintenance and Long-Term Extension Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects with Crohn's Disease Who Completed the Studies M14-431 or M14-433. | 27 June 2022. |
| **Adalimumab** | | |
| CLASSIC I<br>NCT00055523 | Hanauer, S. B., Sandborn, W. J., Rutgeerts, P., Fedorak, R. N., Lukas, M., MacIntosh, D., Panaccione, R., Wolf, D., and Pollack, P. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: The CLASSIC-I trial. | Gastroenterology. 2006 Feb;130(2):323-33; quiz 591. doi: 10.1053/j.gastro.2005.11.030. PMID: 16472588. |
| CLASSIC II<br>NCT00055497 | Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG, Panaccione R, Wolf D, Kent JD, Bittle B, Li J, Pollack PF. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. | Gut. 2007 Sep;56(9):1232-9. doi: 10.1136/gut.2006.106781. Epub 2007 Feb 13. PMID: 17299059; PMCID: PMC2701613. |
| CHARM<br>NCT00077779 | Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, Schreiber S, Byczkowski D, Li J, Kent JD, Pollack PF. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. | Gastroenterology. 2007 Jan;132(1):52-65. doi: 10.1053/j.gastro.2006.11.041. Epub 2006 Nov 29. PMID: 17241859. |
| GAIN<br>NCT00105300 | Sandborn, W. J., Rutgeerts, P., Enns, R., Hanauer, S. B., Colombel, J. F., Panaccione, R., D'Haens, G., Li, J., Rosenfeld, M. R., Kent, J. D., and Pollack, P. F. Adalimumab induction therapy for Crohn disease previously treated with infliximab: A randomized trial. | Annals of Internal Medicine 2007; 146 (12): 829-838. |
| | Panaccione R, Sandborn WJ, D'Haens G, Wolf DC, Berg S, Maa JF, Petersson J, Robinson AM. Clinical Benefit of Long-Term Adalimumab Treatment in Patients With Crohn's Disease Following Loss of Response or Intolerance to Infliximab: 96-Week Efficacy Data From GAIN/ADHERE Trials. | J Crohns Colitis. 2018 Jul 30;12(8):930-938. doi: 10.1093/ecco-jcc/jjy050. PMID: 29697818; PMCID: PMC6065484. |
| Watanabe 2012<br>NCT00445939 | Watanabe M, Hibi T, Lomax KG, Paulson SK, Chao J, Alam MS, Camez A; Study Investigators. Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease. | J Crohns Colitis. 2012 Mar;6(2):160-73. doi: 10.1016/j.crohns.2011.07.013. Epub 2011 Aug 26. PMID: 22325170. |

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|---|
| **Risankizumab** | | |
| M15-993<br>NCT02031276 | Feagan, Sandborn, W. J., D'Haens, G., Panés, J., Kaser, A., Ferrante, M., Louis, E., Franchimont, D., Dewit, O., Seidler, U., Kim, K.-J., Neurath, M. F., Schreiber, S., Scholl, P., Pamulapati, C., Lalovic, B., Visvanathan, S., Padula, S. J., Herichova, I., … Böcher, W. O. (2017). Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomized, double-blind, placebo-controlled phase 2 study. | The Lancet (British Edition), 389(10080), 1699–1709. https://doi.org/10.1016/S0140-6736(17)30570-6. |
| | Feagan BG, Panés J, Ferrante M, Kaser A, D'Haens GR, Sandborn WJ, Louis E, Neurath MF, Franchimont D, Dewit O, Seidler U, Kim KJ, Selinger C, Padula SJ, Herichova I, Robinson AM, Wallace K, Zhao J, Minocha M, Othman AA, Soaita A, Visvanathan S, Hall DB, Böcher WO. Risankizumab in patients with moderate to severe Crohn's disease: an open-label extension study. | Lancet Gastroenterol Hepatol. 2018 Oct;3(10):671-680. doi: 10.1016/S2468-1253(18)30233-4. Epub 2018 Jul 25. PMID: 30056030. |
| | Ferrante M, Feagan BG, Panés J, Baert F, Louis E, Dewit O, Kaser A, Duan WR, Pang Y, Lee WJ, Gustafson D, Liao X, Wallace K, Kalabic J, D'Haens GR. Long-Term Safety and Efficacy of Risankizumab Treatment in Patients with Crohn's Disease: Results from the Phase 2 Open-Label Extension Study. | J Crohns Colitis. 2021 Dec 18;15(12):2001-2010. doi: 10.1093/ecco-jcc/jjab093. PMID: 34077509; PMCID: PMC8684487. |
| | Feagan BG, Sandborn WJ, D'Haens G, Panés J, Kaser A, Ferrante M, Louis E, Franchimont D, Dewit O, Seidler U, Kim KJ, Neurath MF, Schreiber S, Scholl P, Pamulapati C, Lalovic B, Visvanathan S, Padula SJ, Herichova I, Soaita A, Hall DB, Böcher WO. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomized, double-blind, placebo-controlled phase 2 study. | Lancet. 2017 Apr 29;389(10080):1699-1709. doi: 10.1016/S0140-6736(17)30570-6. Epub 2017 Apr 12. PMID: 28411872. |
| ADVANCE<br>NCT03105128 | D'Haens G, Panaccione R, Baert F, Bossuyt P, Colombel JF, Danese S, Dubinsky M, Feagan BG, Hisamatsu T, Lim A, Lindsay JO, Loftus EV Jr, Panés J, Peyrin-Biroulet L, Ran Z, Rubin DT, Sandborn WJ, Schreiber S, Neimark E, Song A, Kligys K, Pang Y, Pivorunas V, Berg S, Duan WR, Huang B, Kalabic J, Liao X, Robinson A, Wallace K, Ferrante M. Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. | Lancet. 2022 May 28;399(10340):2015-2030. doi: 10.1016/S0140-6736(22)00467-6. PMID: 35644154. |
| MOTIVATE<br>NCT03104413 | Joint ADVANCE and MOTIVATE publication citation above. | |
| FORTIFY<br>NCT03105102 | Ferrante M, Panaccione R, Baert F, Bossuyt P, Colombel JF, Danese S, Dubinsky M, Feagan BG, Hisamatsu T, Lim A, Lindsay JO, Loftus EV Jr, Panés J, Peyrin-Biroulet L, Ran Z, Rubin DT, Sandborn WJ, Schreiber S, Neimark E, Song A, Kligys K, Pang Y, Pivorunas V, Berg S, Duan WR, Huang B, Kalabic J, Liao X, Robinson A, Wallace K, D'Haens G. Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomized, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. | Lancet. 2022 May 28;399(10340):2031-2046. doi: 10.1016/S0140-6736(22)00466-4. PMID: 35644155. |

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|---|
| **Infliximab** | | |
| T16<br>NCT00269854 | Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, DeWoody KL, Schaible TF, Rutgeerts PJ. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. | N Engl J Med. 1997 Oct 9;337(15):1029-35. doi: 10.1056/NEJM199710093371502. PMID: 9321530. |
| ACCENT I<br>NCT00207662 | Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. | Lancet. 2002 May 4;359(9317):1541-9. doi: 10.1016/S0140-6736(02)08512-4. PMID: 12047962. |
| **Ustekinumab** | | |
| UNITI-I<br>NCT01369329 | Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. | New England Journal of Medicine. 2016;375(20):1946-60. |
| UNITI-II<br>NCT01369342 | Sandborn WJ, Rutgeerts P, Gasink C, Jacobstein D, Zou B, Johanns J, Sands BE, Hanauer SB, Targan S, Ghosh S, de Villiers WJS, Colombel JF, Feagan BG. Long-term efficacy and safety of ustekinumab for Crohn's disease through the second year of therapy. | Aliment Pharmacol Ther. 2018 Jul;48(1):65-77. doi: 10.1111/apt.14794. Epub 2018 May 24. PMID: 29797519; PMCID: PMC6032827. |
| IM-UNITI<br>NCT01369355 | Hanauer SB, Sandborn WJ, Feagan BG, Gasink C, Jacobstein D, Zou B, Johanns J, Adedokun OJ, Sands BE, Rutgeerts P, de Villiers WJS, Colombel JF, Ghosh S. IM-UNITI: Three-year Efficacy, Safety, and Immunogenicity of Ustekinumab Treatment of Crohn's Disease. | J Crohns Colitis. 2020 Jan 1;14(1):23-32. doi: 10.1093/ecco-jcc/jjz110. PMID: 31158271. |
| | Sandborn WJ, Rebuck R, Wang Y, Zou B, Adedokun OJ, Gasink C, Sands BE, Hanauer SB, Targan S, Ghosh S, de Villiers WJS, Colombel JF, Feagan BG, Lynch JP. Five-Year Efficacy and Safety of Ustekinumab Treatment in Crohn's Disease: The IM-UNITI Trial. | Clin Gastroenterol Hepatol. 2022 Mar;20(3):578-590.e4. doi: 10.1016/j.cgh.2021.02.025. Epub 2021 Feb 19. PMID: 33618023; PMCID: PMC8374005. |
| **Vedolizumab** | | |
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| GEMINI III<br>NCT01224171 | Sands BE, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, Sy R, D'Haens G, Ben-Horin S, Xu J, Rosario M, Fox I, Parikh A, Milch C, Hanauer S. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. | Gastroenterology. 2014 Sep;147(3):618-627.e3. doi: 10.1053/j.gastro.2014.05.008. Epub 2014 May 21. PMID: 2459203 |
| VISIBLE 2<br>NCT02611817 | Vermeire S, D'Haens G, Baert F, Danese S, Kobayashi T, Loftus EV, Bhatia S, Agboton C, Rosario M, Chen C, Zhang W, Kisfalvi K, Sandborn WJ. Efficacy and Safety of | J Crohns Colitis. 2022 Jan 28;16(1):27-38. doi: |

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|---|
| | Subcutaneous Vedolizumab in Patients With Moderately to Severely Active Crohn's Disease: Results From the VISIBLE 2 Randomised Trial. | 10.1093/ecco-jcc/jjab133. PMID: 34402887; PMCID: PMC8797168. |
| Watanabe 2020 NCT02038920 | Watanabe K, Motoya S, Ogata H, Kanai T, Matsui T, Suzuki Y, Shikamura M, Sugiura K, Oda K, Hori T, Araki T, Watanabe M, Hibi T. Effects of vedolizumab in Japanese patients with Crohn's disease: a prospective, multicenter, randomized, placebo-controlled Phase 3 trial with exploratory analyses. | J Gastroenterol. 2020 Mar;55(3):291-306. doi: 10.1007/s00535-019-01647-w. Epub 2019 Dec 13. PMID: 31836930; PMCID: PMC7026209. |

Source: Table 2.3, p36 of the submission.

6.7 The key features of the randomised trials included in the submission are summarised in Table 3.

**Table 3: Key features of the included evidence (upadacitinib and comparator trials)**

| Trial | N | Design | Duration (Assessment of outcomes) | Risk of bias | Patient population | Outcome(s) |
|---|---|---|---|---|---|---|
| **Upadacitinib vs placebo** | | | | | | |
| U-EXCEED | 495 | Phase 3, MC, R, DB | IP: 12 weeks | Low | Bio-experienced and inadequate response/ intolerant biologic therapy | CDAI clinical remission [a, b] CDAI clinical response [c] |
| U-EXCEL | 526 | | | Low | Bio-naïve (inadequate response or intolerance to conventional therapies but had not failed biologic therapy) and bio-experienced patients (inadequate response/ intolerant to biologic therapy) | |
| U-ENDURE | 502 | | MP: 52 weeks | Low | Patients that completed the U-EXCEED or U-EXCEL trials and achieved SF/APS clinical response, defined as ≥30% decrease in average daily SF and/or ≥30% decrease in APS. | |
| **Adalimumab vs placebo** | | | | | | |
| CLASSIC I | 299 | Phase 3, R, DB, PC, MC | IP: 4 weeks | Low | TNF naïve | Proportion of patients with remission defined as a CDAI <150 |
| GAIN | 325 | | | Low | TNF-experienced (infliximab) – intolerant or lost response | |
| CHARM | 778 | Phase 3, R, OL for IP, DB for MP, PC, MC | IP: 4 weeks MP: 56 weeks | Low | TNF-naïve and TNF-experienced (non-refractory) | |
| CLASSIC II | 55 | Phase 3, MC R, DB | | Low | Patients who achieved clinical response | |
| Watanabe 2012 | 90 | Phase 2/3, R, DB | IP:8 weeks | Low | TNF-naïve and TNF-experienced. non-responders to prior anti-TNF therapy were excluded | |
| | 50 | | MP: 52 weeks | Low | TNF-experienced and achieving a clinical response in the induction phase | |
| **Risankizumab vs placebo** | | | | | | |

| Trial | N | Design | Duration (Assessment of outcomes) | Risk of bias | Patient population | Outcome(s) |
|---|---|---|---|---|---|---|
| M15-993 | 121 | Phase 2, R, DB, PC, MC | IP: 12 weeks | Low | Bio-naïve and experienced patients | CDAI clinical remission [a, b] CDAI clinical response [c] |
| ADVANCE | 931 (926 random-ised) | Phase 3, R, DB, PC, MC | | Low | | |
| MOTIVATE | 618 (605 random-ised) | | | Low | Bio-experienced and inadequate response/intolerant only | |
| FORTIFY | 542 | Phase 2, R, DB, PC, MC | MP: 64 weeks [d] | Low | Responders from the ADVANCE and MOTIVATE trials (≥30% decrease in SF and/or ≥30% decrease in average daily AP score, and both not worse than the baseline of induction) | |
| **Infliximab vs placebo** | | | | | | |
| T16 | 108 | MC, R, DB | IP: 12 weeks | Low | TNF antagonist naïve patients | Reduction in CDAI score of 70 or more at 4-week s |
| ACCENT 1 | 573 | Phase 3, MC, R, DB | MP: 54 weeks | Low | Patients who had a clinical response to IFX at 2 weeks during induction therapy | Clinical remission at week 30 (defined as a CDAI < 150) |
| **Vedolizumab vs placebo** | | | | | | |
| GEMINI II | 368 | Phase 3, MC, R, DB | IP:6 weeks | Low | TNF antagonist naïve or experienced intolerant or no response | Clinical remission (CDAI score of ≤150 points) and CDAI-100 response (≥100-point decrease |
| GEMINI II | 461 | | MP: 52 weeks | Low | | |
| GEMINI III | 416 | | IP: 10 weeks | Low | TNF antagonist naïve or experienced intolerant or no response | Clinical remission defined as a CDAI score ≤150 at week 6 restricted to patients with prior TNF antagonist failure |
| Watanabe 2020 | 157 | Phase 3, R, DB | IP: 14 weeks | Low | TNF antagonist naïve or experienced intolerant or lost or inadequate response | Clinical remission is defined as a ≥150-point decrease in the CDAI score |
| | 24 | | MP: 60 weeks | Low | TNF experienced intolerant or lost or inadequate response | |
| Visible 2 | 410 | Phase 3, MC, | MP: 52 weeks | Low | TNF experienced intolerant | |

| Trial | N | Design | Duration (Assessment of outcomes) | Risk of bias | Patient population | Outcome(s) |
|---|---|---|---|---|---|---|
| (VDZ SC) | | R, DB | | | or lost or inadequate response | |
| **Ustekinumab vs placebo** | | | | | | |
| UNITI-I | 741 | Phase 3, R, DB, PC, MC | IP: 8 weeks | Low | TNF antagonist refractory | CDAI clinical response [b, c] CDAI clinical remission [a] |
| UNITI-II | 628 | | | Low | TNF naïve and TNF experienced (but non-refractory) | |
| IM-UNITI | 397 | Phase 3, R, DB, PC, MC | MP: 52 weeks [d] | Low | Patients with a response (CR-100) to UST induction at W8 of UNITI-I or UNITI-II | |

Source: Compiled during the evaluation from Table 1 and Table 4 of Attachment 2.5 of the submission and Table 2.6, p50 of the submission.
AP= abdominal pain; CDAI= Crohn's Disease Activity Index; CR-100= clinical response as defined by attaining; DB= double blind; IFX= infliximab; IP= induction phase; MC= multicentre, MP= maintenance phase; PC= placebo-controlled; R= randomised; SC= subcutaneous; SF= stool frequency; TNF= tumour necrosis factor; UST= ustekinumab; VDZ= vedolizumab.
[a] CDAI clinical remission was classified as CDAI < 150.
[b] Denotes the primary trial outcome.
[c] CDAI clinical response defined by a CDAI ≥ 100 point reduction from baseline.
[d] Counted from the start of induction therapy.

6.8 The upadacitinib trials were double-blind, all efficacy analyses were based on the intention-to-treat population, and loss to follow-up across trials was minimal (< 2%) and balanced. The submission described upadacitinib trials as having a low risk of bias.

6.9 The PBAC previously considered the low risk of bias in the adalimumab (CLASSIC I, GAIN, Watanabe 2012, CLASSIC II, CHARM), ustekinumab (UNITI-I, UNITI-II, IM-UNITI), infliximab (T16, ACCENT I), and vedolizumab (GEMINI II, GEMINI III) trials (Paragraph 6.11, Ustekinumab, PSD, March 2017 PBAC meeting). The risankizumab trials (M15, ADVANCE, MOTIVATE, FORTIFY) were also considered to be at low risk of bias by the PBAC (Paragraph 6.10, Risankizumab, PSD, July 2022 PBAC meeting).

6.10 The PBAC had not previously considered the VISIBLE 2 and Watanabe 2020 trials of vedolizumab. The submission considered low risk of bias for the VISIBLE 2 and Watanabe 2020 trials.

6.11 Overall, the risk of bias was low across all trials, however some trials included open label components (see Table 3).

6.12 The mean CDAI scores in the upadacitinib trials range from 292 to 312. The proposed PBS listing is for severe CD (CDAI score ≥ 300 or CDAI ≥ 220 with extensive small intestine disease), and CDAI scores > 450[1] define severely active disease. Therefore, the upadacitinib trials were likely to include moderate CD patients not eligible for the proposed PBS indication and excluded severe CD patients who may be treated with upadacitinib under the PBS. The Pre-Sub-Committee Response (PSCR) claimed that post-hoc analyses of the adalimumab, risankizumab and upadacitinib studies demonstrated that the U-EXCEL and U-EXCEED inclusion criteria were met by 85-92%

[1] Paragraph 6.11. Risankizumab, Public Summary Document, July 2022 PBAC meeting.

of patients with a baseline CDAI of 220 to 450. The PBAC has previously considered trials that included moderate to severe CD (CDAI score of ≥ 220 and ≤ 450) to support the clinical and safety claims for severe CD for risankizumab, ustekinumab and vedolizumab (paragraph 6.11, risankizumab PSD, July 2022 PBAC meeting).

6.13 Some noticeable differences between the upadacitinib and comparator trials that may affect transitivity in the indirect comparisons were:

- Prior medication: The U-EXCEL trial included patients who showed an inadequate response to one or more conventional therapies or biologics. In contrast, the U-EXCEED trial only included patients with an inadequate response or intolerance to biologics. Comparator trials used a mix of naïve, non-responsive or intolerant to ≥ 1 anti-TNF patients (M15-993), intolerant/inadequate response to ≥ 1 biologic (ADVANCE, MOTIVATE), refractory or intolerant to ≥ 1 anti-TNF (UNITI-I), refractory or intolerant to immunomodulators (UNITI-II). Consequently, the proportion of patients with no TNF failure in the upadacitinib trials ranges from 4.1% to 57.4%. The U-EXCEL trial included significantly more non-TNF failure patients compared to the trials of risankizumab (3.2% to 7.3%).
- Therapies used at baseline: Corticosteroids were used by approximately 33.3% to 36.4% of patients at baseline in the upadacitinib trials, compared to 17.6% to 53.0% in the comparator trials. Immunomodulator use was reported in 1.7% to 7.6% of patients in the upadacitinib trials at baseline, compared to between 18.8% to 51.0% in the comparator trials. The proportion of patients using prednisone was higher in the U-ENDURE trial arms (treatment 37.5% and placebo 37.3%) compared to the U-EXCEED (treatment 14.8% and placebo 17.5%) and U-EXCEL (treatment 16.6% and placebo 14.8%) trial arms, which the ESC considered was clinically inconsistent with the other outcomes, however noted the results reported in the U-ENDURE clinical study report were not the same as reported in the submission The Pre-PBAC Response clarified the issue raised by the ESC and presented additional information to incorporate time of entry into the U-ENDURE (maintenance) study, and reported the proportions using prednisone was 6.5% in the upadacitinib 30 mg arm, 4.1% in the 15 mg and 4.8% in the placebo arm.
- Duration of drug exposure: The mean duration for drug exposure in the U-EXCEED and U-EXCEL trials (induction) was 84 days. In some of the comparator trials, the mean duration of drug exposure was shorter (CLASSIC I and GAIN: 28 days; UNITI-I and UNITI-II: 56 days; GEMINI III: 70 days) than in upadacitinib trials in the induction phase. The mean duration for drug exposure in the U-ENDURE trials (maintenance) was 56 weeks (337 days for upadacitinib 30 mg and 288 days for upadacitinib 15 mg). In some of the comparator trials, the mean duration for drug exposure was longer (CHARM: 392 days; Watanabe 2020: 420 days; VISIBLE 2: 392 days; M15-993 trial: 469 days) than upadacitinib in the maintenance phase. The ESC considered the impact was unclear, noting different trial durations within studies of the same drug.

- Duration of follow-up: The follow-up duration in the upadacitinib trials (52 weeks plus 30 days after the last dose of the study drug) was shorter than the proposed PBS restriction. In addition, the duration of follow-up was longer in the adalimumab (52 weeks plus 70 days from the last dose of the study drug), risankizumab (52 weeks plus 140 days after the last dose of the study drug), ustekinumab (40 weeks plus 140 days from induction dose) and vedolizumab (60 weeks plus 112 days after the last dose) trials compared to the upadacitinib trials. The ESC noted the likely impact of the half-life of the medications (bDMARDs vs tsDMARD) on follow up, however considered these differences were unlikely to be impactful on the exchangeability of the clinical trials.
- Concomitant therapies: Across the trials, there were differences in the protocols on use of concomitant treatments, particularly in the time when tapering or adjustments were allowed. The ESC agreed with the evaluation that this could impact the comparability between trials, but the direction of impact is unclear.
- Definition of clinical response: The definition of clinical response varied between trials, with the upadacitinib and risankizumab trials defining response as ≥ 30% decrease in average daily stool frequency and/or ≥ 30% decrease in abdominal pain score. IM-UNITI defined clinical response as a decrease from baseline in CDAI score ≥ 100 points or a total CDAI of < 150. All other trials defined clinical response as a decrease from baseline CDAI of ≥ 70 points. Clinical remission in CLASSIC II was described as a CDAI score of fewer than 150 points.
- Timing of assessment: The timing of assessment differed between upadacitinib and comparator trials. For induction, upadacitinib assessment was at week 12, and ustekinumab was at week 8. For maintenance, upadacitinib was at week 52, risankizumab assessment was at week 64 and ustekinumab at week 52. The ESC agreed with the evaluation that this could impact the comparability between trials; however, the direction of impact is unclear.

6.14 No non-inferiority margin or minimal clinically important difference (MCID) was nominated by the submission to assist with the interpretation of the efficacy evidence. The PSCR acknowledged these issues and agreed there was uncertainty with the indirect comparison results presented, however noted the PBAC's previous consideration of risankizumab also highlighted transitivity issues including prior exposure to biologics, concomitant use of other therapies, differences in placebo response rates and differences in primary outcome measures, which the PBAC considered and was of the view the analyses in that submission were generally reliable for informing a comparison of risankizumab and ustekinumab. On that basis, the PSCR argued the indirect comparisons in the upadacitinib submission should also be considered generally reliable for informing a comparison of upadacitinib and the nominated comparison.

## *Comparative effectiveness*

6.15 The submission nominated clinical remission (defined by CDAI < 150) as the primary outcome for the induction and maintenance phases. This outcome definition is consistent with the continuation criteria for PBS treatment. The submission also reported the outcome of clinical response defined by the reduction of > 100 points in CDAI score from baseline. The PBAC previously considered these outcomes in the March 2017 submission for ustekinumab and July 2022 submission for risankizumab.

6.16 Indirect comparisons were performed using the Bucher single pairwise method.

Efficacy: clinical remission

6.17 Table 4 and Table 5 present the results for clinical remission across the trials for the induction and maintenance phases, respectively. Meta-analysed (pooled) results for the induction trials and results of the indirect comparisons between upadacitinib and comparators are also included in the tables.

**Table 4: Clinical remission, induction phase: trial and indirect comparison results of upadacitinib vs comparators**

| Intervention / Trial ID | Active treatment n/N (%) | PBO n/N (%) | OR (95% CI), result >1 favours intervention | RR (95% CI), result >1 favours intervention | RD (95% CI), result >0 favours intervention |
|---|---|---|---|---|---|
| **UPA (45 mg) vs PBO– week 12 results** | | | | | |
| U-EXCEED | 126/324 (38.9) | 36/171 (21.1) | **2.39 (1.55, 3.67)[a]** | **1.85 (1.34, 2.55)** | **0.18 (0.10, 0.26)** |
| U-EXCEL | 173/350 (49.5) | 51/176 (29.1) | **2.40 (1.63, 3.53)[a]** | **1.71 (1.32, 2.20)** | **0.20 (0.12, 0.29)** |
| Pooled | 299/674 (44.4) | 87/347 (25.1)[a] | **2.39 (1.79, 3.19)** | **1.76 (1.44, 2.15)** | **0.19 (0.13, 0.25)** |
| **ADA (week 0: 160 mg, week 2: 80 mg) vs PBO– week 4 results** | | | | | |
| CLASSIC I | 27/76 (35.5) | 9/74 (12.2) | **3.98 (1.72, 9.22)** | **2.92 (1.48, 5.78)** | **0.23 (0.10, 0.36)** |
| GAIN | 34/159 (21.4) | 12/166 (7.2) | **3.49 (1.73, 7.02)** | **2.96 (1.59, 5.51)** | **0.14 (0.07, 0.22)** |
| Watanabe 2012 | 11/33 (33.3) | 3/23 (13.0) | 3.33 (0.81, 13.69) | 2.56 (0.80, 8.15) | 0.20 (-0.01, 0.41) |
| Pooled | 72/268 (26.9) | 24/263 (9.1) | **3.63 (2.20, 6.01)** | **2.89 (1.88, 4.42)** | **0.17 (0.11, 0.23)** |
| **RISA (600 mg) vs PBO- week 12 results** | | | | | |
| M15-993 | 15/41 (36.6) | 6/39 (15.4) | **3.17 (1.08, 9.32)** | **2.38 (1.03, 5.50)** | **0.21 (0.03, 0.40)** |
| ADVANCE | 152/336 (45.2) | 43/175 (24.6) | **2.54 (1.69, 3.80)** | **1.84 (1.38, 2.45)** | **0.21 (0.12, 0.29)** |
| MOTIVATE | 80/191 (41.9) | 37/187 (19.8) | **2.92 (1.84, 4.63)** | **2.12 (1.52, 2.95)** | **0.22 (0.13, 0.31)** |
| Pooled | 247/568 (43.5) | 86/401 (21.4) | **2.73 (2.04, 3.66)** | **1.98 (1.6, 2.44)** | **0.21 (0.16, 0.27)** |
| **IFX (week 0: 5mg/kg) – week 4 results** | | | | | |
| T16 | 13/27 (48.1) | 1/24 (4.2) | **21.36 (2.51,181.4)** | **11.56 (1.63,81.89)** | **0.44 (0.24, 0.64)** |
| **VDZ (week 0: 300mg, week2:300mg) vs PBO – week 6 results** | | | | | |
| GEMINI II | 32/220 (14.5) | 10/148 (6.8) | **2.35 (1.12, 4.94)** | **2.15 (1.09, 4.24)** | **0.08 (0.02, 0.14)** |
| GEMINI III | 40/209 (19.1) | 25/207 (12.1) | 1.72 (1.00, 2.96) | 1.58 (1.00, 2.51) | 0.07 (0.00, 0.14) |
| Watanabe 2020 | 14/79 (17.7) | 8/78 (10.3) | 1.88 (0.74, 4.79) | 1.73 (0.77, 3.89) | 0.07 (-0.03, 0.18) |
| Pooled | 86/508 (16.9) | 43/433 (9.9) | **1.92 (1.30, 2.86)** | **1.76 (1.25, 2.49)** | **0.07 (0.03, 0.12)** |
| **UST (week 0: tiered dose/kg) vs PBO – week 8 results** | | | | | |
| UNITI-I | 52/249 (20.9) | 18/247 (7.3) | **3.36 (1.90, 5.93)** | **2.87 (1.73, 4.75)** | **0.14 (0.08, 0.20)** |
| UNITI-II | 84/209 (40.2) | 41/209 (19.6) | **2.77 (1.79, 4.30)** | **2.05 (1.49, 2.82)** | **0.21 (0.12, 0.29)** |
| Pooled | 136/458 (29.7) | 59/456 (12.9) | **2.98 (2.10, 4.21)** | **2.30 (1.75, 3.02)** | **0.17 (0.12, 0.22)** |
| **Indirect comparisons: UPA vs comparators** | | UPA vs ADA | 0.66 (0.37, 1.18) | **0.61 (0.38, 0.98)** | 0.02 (-0.0, 0.11) |
| | | UPA vs RISA | 0.88 (0.58, 1.32) | 0.89 (0.66, 1.19) | -0.02 (-0.10,0.06) |
| | | UPA vs IFX | **0.11 (0.01, 0.97)** | 0.15 (0.02, 1.09) | **-0.25 (-0.46,-0.04)** |
| | | UPA vs VDZ | 1.24 (0.76, 2.03) | 1.00 (0.67, 1.49) | **0.18 (0.11, 0.26)** |
| | | UPA vs UST | 0.80 (0.51, 1.26) | 0.77 (0.55, 1.07) | 0.02 (-0.06, 0.10) |

Source: Table 2.23, p134 of the submission.

ADA= adalimumab; CI= confidence interval; IFX= infliximab; kg= kilogram; mg= milligram; n= number of participants with event; N= total participants in group; NR= not reported; OR= odds ratio; PBO= placebo; RD= risk difference; RISA= risankizumab; RR= relative risk; UST= ustekinumab; UPA= upadacitinib; VDZ= vedolizumab; vs= versus.

**BOLD** values mean statistically significant results. **RED** means values significantly favour comparators.

[a] Corrected values were calculated during the evaluation.

**Table 5: Clinical remission, maintenance phase: trial and indirect comparison results of upadacitinib vs comparators**

| Intervention / Trial ID | Active treatment n/N (%) | PBO n/N (%) | OR (95% CI), result >1 favours intervention | RR (95% CI), result >1 favours intervention | RD (95% CI), result >0 favours intervention |
|---|---|---|---|---|---|
| **UPA (30 / 15 mg) – week 52 results** | | | | | |
| U-ENDURE (30 mg) | 63/169 (37.3)<br>80/168 (47.6)[a] | 25/165 (15.1) | **5.09 (3.02, 8.58)** | **3.14 (2.12, 4.66)** | **0.32 (0.23, 0.42)** |
| U-ENDURE (15 mg) | 80/168 (47.6)<br>63/169 (37.3)[a] | 25/165 (15.1) | **3.33 (1.96, 5.64)** | **2.46 (1.63, 3.71)** | **0.22 (0.13, 0.31)** |
| U-ENDURE (30/15 mg) | 143/337 (42.4) | 25/165 (15.1) | **4.13 (2.56, 6.65)** [a] | **2.80 (1.91, 4.10)** | **0.27 (0.20, 0.35)** |
| **ADA (40mg q2w) – week 52 or 56 (excl. IP)** | | | | | |
| CLASSIC II (CDAI<150 week 4& 8 IP)[b] | 15/19 (78.9) | 8/18 (44.4) | **4.69 (1.11, 19.83)** | **1.78 (1.01, 3.13)** | **0.35 (0.05, 0.64)** |
| CHARM (CR-70 week 4 IP)[c] | 62/172 (36.0) | 20/170 (11.8) | **4.23 (2.41, 7.41)** | **3.06 (1.94, 4.84)** | **0.24 (0.16, 0.33)** |
| Watanabe 2012 (CR-70 week 4 IP)[d] | 8/21 (38.1) | 2/22 (9.1) | **6.15 (1.12, 33.67)** | 4.19 (1.00,17.5) | **0.29 (0.05, 0.53)** |
| Pooled | 85/212 (40.1) | 30/210 (14.3) | **4.43 (2.69, 7.29)** | **2.54 (1.61, 4.01)** | **0.26 (0.18, 0.33)** |
| **RISA (360 mg) – week 64 results** | | | | | |
| M16-000 (FORTIFY) | 74/141 (52.5) | 67/164 (40.9) | **1.60 (1.02, 2.52)** | **1.28 (1.1, 1.64)** | 0.12 (0.00, 0.23) |
| **IFX (5mg/kg week 2, week 6, q8w) – week 56 results (incl. IP)** | | | | | |
| ACCENT I (CR-70 week2 IP)[e] | 32/113 (28.0) | 15/110 (13.7) | **2.50 (1.27, 4.94)** | **2.08 (1.19, 4.01)** | **0.15 (0.04, 0.25)** |
| **VDZ (300mg q8w) – week 52 results (incl. IP)** | | | | | |
| GEMINI II (CR-70 week 6 IP)[f] | 60/154 (39.0) | 33/153 (21.6) | **2.32 (1.4, 3.84)** | **1.81 (1.26, 2.59)** | **0.17 (0.07, 0.27)** |
| Watanabe 2020 (CR-70 week10)[g] | 5/12 (41.7) | 2/12 (16.7) | 3.57 (0.53, 23.95) | 2.50 (0.60,10.4) | 0.25 (-0.10, 0.60) |
| Pooled | 65/166 (39.2) | 35/165 (21.2) | **2.39 (1.47, 3.89)** | **1.85 (1.30, 2.62)** | **0.18 (0.08, 0.28)** |
| **VDZ SC (108mg q2w) – week 52 results** | | | | | |
| VISIBLE 2 (CR-70 week 6)[f] | 132/275 (48.0) | 46/164 (34.3) | **2.37 (1.56, 3.58)**[a] | **1.71 (1.30, 2.25)**[a] | **0.14 (0.04, 0.24)** |
| **UST (90mg q8w) – week 52 results (incl. IP)** | | | | | |
| IM-UNITI (CR-100 week 8 IP)[h] | 68/128 (53.1) | 47/131 (35.9) | **2.03 (1.23, 3.33)** | **1.48 (1.12, 1.96)** | **0.17 (0.05, 0.29)** |
| **Indirect comparison: UPA 15 mg vs comparators** | | UPA vs. ADA | 1.15 (0.56, 2.37) | 1.13 (0.66, 1.92) | 0.06 (-0.06, 0.19) |
| | | UPA vs. RISA | **3.18 (1.59, 6.36)** | **2.45 (1.54, 3.89)** | **0.21 (0.06, 0.35)** |
| | | UPA vs. IFX | 2.03 (0.86, 4.80) | 1.51 (0.77, 2.99) | **0.18 (0.04, 0.32)** |
| | | UPA vs. VDZ | **2.13 (1.04, 4.35)** | **1.70 (1.00, 2.88)** | **0.14 (0.01, 0.28)** |
| | | UPA vs. VDZ SC | **2.15 (1.10, 4.19)**[a] | **1.84 (1.14, 2.97)**[a] | **0.19 (0.05, 0.32)** |
| | | UPA vs. UST | **2.51 (1.22, 5.17)** | **2.12 (1.31, 3.44)** | 0.15 (0.00, 0.30) |
| **Indirect comparison: UPA 30 mg vs comparators** | | UPA vs. ADA | 0.75 (0.36, 1.55) | 0.88 (0.51, 1.52) | -0.04 (-0.16, 0.08) |
| | | UPA vs. RISA | **2.08 (1.04, 4.18)** | **1.92 (1.19, 3.08)** | 0.10 (-0.04, 0.25) |
| | | UPA vs. IFX | 1.33 (0.56, 3.15) | 1.18 (0.59, 2.36) | 0.07 (-0.06, 0.21) |
| | | UPA vs. VDZ | 1.39 (0.68, 2.85) | 1.33 (0.78, 2.28) | 0.04 (-0.09, 0.18) |
| | | UPA vs. VDZ SC | 1.41 (0.72, 2.75)[a] | 1.44 (0.88, 2.36)[a] | 0.08 (-0.05, 0.22) |
| | | UPA vs. UST | 1.64 (0.80, 3.39) | **1.66 (1.01, 2.73)** | 0.05 (-0.10, 0.20) |

| Intervention / Trial ID | Active treatment n/N (%) | PBO n/N (%) | OR (95% CI), result >1 favours intervention | RR (95% CI), result >1 favours intervention | RD (95% CI), result >0 favours intervention |
|---|---|---|---|---|---|
| **Indirect comparison: UPA 30/15 mg vs comparators** | | UPA vs. ADA | 0.93 (0.47, 1.86) | 1.00 (0.59, 1.69) | 0.01 (-0.10, 0.12) |
| | | UPA vs. RISA | **2.58 (1.34, 4.99)** | **2.18 (1.39, 3.43)** | **0.16 (0.02, 0.29)** |
| | | UPA vs. IFX | 1.65 (0.72, 3.79) | 1.35 (0.69, 2.64) | 0.13 (0.00, 0.26) |
| | | UPA vs. VDZ | 1.73 (0.87, 3.41) | 1.51 (0.90, 2.54) | 0.09 (-0.03, 0.22) |
| | | UPA vs. VDZ SC | 1.74 (0.93, 3.28)[a] | **1.64 (1.02, 2.62)[a]** | **0.14 (0.01, 0.26)** |
| | | UPA vs. UST | **2.04 (1.02, 4.06)** | **1.89 (1.18, 3.04)** | 0.10 (-0.04, 0.24) |

Source: Table 2.24, p137 of the submission.

ADA= adalimumab; biologic; CI= confidence interval; INF= infliximab; IP= induction phase; kg= kilogram; mg= milligram; n= number of participants with event; N= total participants in group; NR= not reported; OR= odds ratio; PBO= placebo; RD= risk difference; RISA= risankizumab; RR= relative risk; SC= subcutaneous; Q8W= 8-weekly; Q2W= 2-weekly; UST= ustekinumab; UPA= upadacitinib; VDZ= vedolizumab; vs= versus.

Note: In Table 2.24, the submission reported UPA 15 mg active treatment n/N (%) values for UPA 30 mg and vice versa**.** Correct values for indirect comparisons have been presented in this table based on Table 2.15, p 120 of the submission.

**Bold** values represent statistically significant results.

[a] Corrected values were calculated during the evaluation.

[b] CDAI< 150 'remission' at week 4 and week 8 following induction with either 160/80 mg, 80/40 mg, 40/20 mg or placebo at week 0 and week 2 (in CLASSIC I) then 40 mg at week 4 and week 6 (Open label phase in CLASSIC II)

[c] CR-70 responders at week 4 following induction with 80/40 mg at week 0 and week 2

[d] CR-70 responders at week 4 following induction with either 160/80 mg, 80/40 mg or placebo at week 0 or week 2

[e] CR-70 responders at week 2 following induction with 5 mg/kg at week 0

[f] CR-70 responders at week 6 following induction with 300 mg at week 0 and week 2

[g] CR-70 responders at week 10 following induction with 300 mg at week 0, week 2 and week 6

[h] CR-100 responders at week 8 following induction with either 130 mg, weight-based dose or placebo at week 0 (UNITI-I or UNITI-II).

6.18 A significantly greater proportion of patients treated with upadacitinib compared to placebo achieved clinical remission in all upadacitinib trials in the induction and maintenance phases. The pooled results for comparator trials also showed significant clinical remission compared with the corresponding placebo controls.

6.19 Induction phase: Results for the indirect comparison of upadacitinib with comparators showed that upadacitinib demonstrated significantly higher rates of achieving clinical remission in comparison to vedolizumab on risk difference (RD) but not for the relative risk (RR) or odds ratio (OR). Upadacitinib demonstrated significantly lower clinical rates of achieving remission compared to adalimumab (only for RR, but not OR RD) and infliximab (based on OR and RD but not RR) (Table 4). Clinical remission rates were lower in upadacitinib trials than in the risankizumab and ustekinumab trials, but the results were not statistically significant.

6.20 Maintenance phase: Indirect comparison results showed significantly higher clinical remission for upadacitinib (15 mg) versus risankizumab (based on OR, RR and RD), infliximab (only for RD), vedolizumab IV (only for the OR and RD but not RR), vedolizumab subcutaneous (based on OR, RR, RD) and ustekinumab (based on OR, RR, RD) (Table 5). A higher dose of upadacitinib (30 mg) resulted in significantly higher clinical remission versus risankizumab (for OR and RR but not RD), vedolizumab subcutaneous (only for RR) and ustekinumab (only for RR).

6.21 The U-ENDURE clinical study report (CSR) noted that 'A clear treatment effect was observed between the two doses, with a larger treatment effect in the 30 mg dose

arm noted in subgroups of subjects with CDAI > 300, and hsCRP [high sensitivity C-reactive protein] and FCP [faecal calprotectin] above the upper limit of normal at baseline or with prior failure to a biologic.' (p96 of the U-ENDURE CSR). Otherwise, there was consistent treatment effects across the other subgroups explored.

Efficacy: clinical response

6.22 Table 6 and Table 7 present the clinical response results across the trials for the induction and maintenance phases, respectively. It also includes meta-analysed (pooled) results for the induction trials and results of the indirect comparisons between upadacitinib and comparators.

**Table 6: Clinical response, induction phase: trial and indirect comparison results of upadacitinib vs comparators**

| Intervention / Trial ID | Active treatment n/N (%) | PBO n/N (%) | OR (95% CI), result >1 favours intervention | RR (95% CI), result >1 favours intervention | RD (95% CI), result >0 favours intervention |
|---|---|---|---|---|---|
| **UPA (45 mg) – week 12 results** | | | | | |
| U-EXCEED | 164/324 (50.6) | 47/171 (27.5) | **2.70 (1.81, 4.04)** | **1.84 (1.41, 2.40)** | **0.23 (0.15, 0.32)** |
| U-EXCEL | 198/350 (62.6)<br>(56.6)[a] | 66/176 (58.5)<br>(37.5)[a] | **2.17 (1.50, 3.15)** | **1.51 (1.22, 1.86)** | **0.19 (0.10, 0.28)** |
| Pooled | 362/674 (53.7) | 113/317 (32.6)<br>113/347 (33)[a] | **2.41 (1.83, 3.16)** | **1.65 (1.39, 1.94)** | **0.21 (0.15, 0.27)** |
| **ADA (week 0: 160 mg, week 2: 80 mg) – week 4 results** | | | | | |
| CLASSIC I | 38/76 (50) | 19/74 (25) | **2.89 (1.45, 5.76)** | **1.95 (1.24, 3.05)** | **0.24 (0.09, 0.39)** |
| GAIN | 61/159 (38) | 41/166 (25) | **1.90 (1.18, 3.05)** | **1.55 (1.12, 2.16)** | **0.14 (0.04, 0.24)** |
| Watanabe 2012 | 15/33 (46) | 4/23 (15) | **3.96 (1.10, 14.20)** | 2.61 (0.99, 6.87) | **0.28 (0.05, 0.51)** |
| Pooled | 114/268 (42.5) | 64/263 (24.3) | **2.30 (1.59, 3.34)** | **1.75 (1.35, 2.26)** | **0.18 (0.10, 0.26)** |
| **RISA (150 mg)- week 12 results** | | | | | |
| M15-993 | 17/41 (41.5) | 9/39 (23.1) | 2.36 (0.90, 6.23) | 1.80 (0.91, 3.54) | 0.18 (-0.02, 0.38) |
| ADVANCE | 201/336 (59.8) | 64/175 (36.6) | **2.58 (1.77, 3.77)** | **1.64 (1.32, 2.03)** | **0.23 (0.14, 0.32)** |
| MOTIVATE | 114/191 (59.7) | 56/187 (29.9) | **3.46 (2.26, 5.30)** | **1.99 (1.55, 2.55)** | **0.30 (0.20, 0.39)** |
| Pooled | 332/568 (58.5) | 129/401 (32.2) | **2.89 (2.20, 3.79)** | **1.78 (1.52, 2.08)** | **0.25 (0.19, 0.32)** |
| **IFX (week 0: 5mg/kg) – week 4 results** | | | | | |
| T16[†] | 22/27 (82) | 4/24 (17) | **22 (5.17, 93.56)** | **4.89 (1.96, 12.18)** | **0.65 (0.44, 0.86)** |
| **VDZ (week 0: 300mg, week2:300mg) – week 6 results** | | | | | |
| GEMINI II | 69/220 (31.4) | 38/148 (25.7) | 1.32 (0.83, 2.11) | 1.22 (0.87, 1.71) | 0.06 (-0.04, 0.15) |
| GEMINI III | 82/209 (39.2) | 47/207 (22.7) | **2.20 (1.43, 3.37)** | **1.73 (1.28, 2.34)** | **0.17 (0.08, 0.25)** |
| Watanabe 2020 | 21/79 (26.6) | 13/78 (16.7) | 1.81 (0.83, 3.94) | 1.59 (0.86, 2.96) | 0.10 (-0.03, 0.23) |
| Pooled | 172/508 (33.9) | 98/433 (22.6) | **1.75 (1.31, 2.34)** | **1.49 (1.21, 1.84)** | **0.11 (0.06, 0.17)** |
| **UST (week 0: tiered dose/kg) – week 8 results** | | | | | |
| UNITI-I | 94/249 (37.8) | 50/247 (20.2) | **2.39 (1.60, 3.57)** | **1.86 (1.39, 2.50)** | **0.18 (0.10, 0.25)** |
| UNITI-II | 121/209 (57.9) | 67/209 (32.1) | **2.91 (1.95, 4.35)** | **1.81 (1.44, 2.27)** | **0.26 (0.17, 0.35)** |
| Pooled | 215/458 (46.9) | 117/456 (25.7) | **2.64 (1.99, 3.50)** | **1.83 (1.53, 2.20)** | **0.21 (0.15, 0.27)** |
| **Indirect comparisons: UPA vs comparators** | | UPA vs. RISA | 0.83 (0.57, 1.23) | 0.93 (0.74, 1.17) | -0.04 (-0.13, 0.05) |
| | | UPA vs. ADA | 1.05 (0.66, 1.66) | 0.94 (0.69, 1.28) | 0.03 (-0.07, 0.13) |
| | | UPA vs. IFX | **0.11 (0.03, 0.48)** | **0.34 (0.13, 0.85)** | **-0.44 (-0.66, -0.22)** |
| | | UPA vs. VDZ | 1.38 (0.92, 2.05) | 1.11 (0.85, 1.45) | **0.10 (0.02, 0.18)** |
| | | UPA vs. UST | 0.91 (0.62, 1.35) | 0.90 (0.70, 1.15) | 0.00 (-0.08, 0.08) |

Source: Table 2.25, p142 of the submission.

ADA= adalimumab; CI= confidence interval; IFX= infliximab; kg= kilogram; mg= milligram; n= number of participants with event; N= total participants in group; OR= odds ratio; PBO= placebo; RD= risk difference; RISA= risankizumab; RR= relative risk; UPA= upadacitinib; UST=

ustekinumab; VDZ= vedolizumab; vs= versus.
Note: These estimates were calculated as per Section 2.5 of the evaluation.
**BOLD** values mean statistically significant results. **RED** indicates significant results favouring comparators.
[a] Corrected values were calculated during the evaluation.

**Table 7: Clinical response, maintenance phase: trial and indirect comparison results of upadacitinib vs comparators**

| Intervention / Trial ID | Active treatment n/N (%) | PBO n/N (%) | OR (95% CI), result >1 favours intervention | RR (95% CI), result >1 favours intervention | RD (95% CI), result >0 favours intervention |
|---|---|---|---|---|---|
| **UPA (30 / 15 mg) – week 52 results** | | | | | |
| U-ENDURE (30 mg) | 86/168 (51.2) | 25/165 (15.2) | **5.87 (3.48, 9.90)** | **2.73 (1.83, 4.09)**<br>**3.38 (2.29, 4.99)[a]** | **0.36 (0.27, 0.45)** |
| U-ENDURE (15 mg) | 70/169 (41.4) | 25/165 (15.2) | **3.96 (2.34, 6.69)** | **3.38 (2.29, 4.99)**<br>**2.73 (1.83, 4.09)[a]** | **0.26 (0.17, 0.35)** |
| U-ENDURE (30/15 mg) | 156/337(46.3) | 25/165 (15.2) | **4.66 (2.89, 7.50)**<br>**4.83 (3.00, 7.77) [a]** | **3.00 (2.05, 4.38)** | **0.30 (0.23, 0.38)** |
| **ADA (40mg q2w) – week 52 or 56 (excl. IP)** | | | | | |
| CLASSIC II[b] | 15/19 (79) | 10/18 (56) | **3.00 (0.71, 12.69)** | **2.51 (1.71, 3.67)** | 0.23 (-0.06, 0.53) |
| CHARM[c] | 71/172 (41.3) | 28/170 (16.5) | **3.57 (2.15, 5.92)** | 1.42 (0.88, 2.28) | **0.25 (0.16, 0.34)** |
| Pooled | 86/191 (45.0) | 38/188 (20.2) | **3.50 (2.17, 5.64)** | **2.22 (1.62, 3.04)** | **0.25 (0.16, 0.33)** |
| **RISA (150 mg) – week 64 results** | | | | | |
| FORTIFY | 87/141 (61.7) | 79/164 (48.2) | **1.73 (1.10, 2.74)** | **1.28 (1.1, 1.64)** | **0.14 (0.02, 0.25)** |
| **VDZ (300mg q8w) – week 52 results (incl. IP)** | | | | | |
| GEMINI II[f] | 67/154 (43.5) | 46/153 (30.1) | **1.79 (1.12, 2.87)** | **1.45 (1.07, 1.96)** | **0.13 (0.03, 0.24)** |
| Watanabe 2020[g] | 7/12 (58.3) | 1/12 (12.5) | **15.4 (1.47,1 60.97)** | **7.0 (1.01, 48.54)** | **0.50 (0.18, 0.82)** |
| Pooled | 74/166 (44.6) | 47/165 (28.5) | **2.01 (1.27, 3.16)** | **1.56 (1.16, 2.11)** | **0.16 (0.06, 0.26)** |
| **UST (90mg q8w) – week 52 results (incl. IP)** | | | | | |
| IM-UNITI[a] | 76/128 (59.4) | 58/131 (44.3) | **1.84 (1.12, 3.01)** | **1.34 (1.06, 1.70)** | **0.15 (0.03, 0.27)** |
| **Indirect comparison: UPA 15 mg vs comparators** | | UPA vs. ADA | 1.13 (0.56, 2.30) | 1.23 (0.74, 2.05) | 0.01 (-0.11, 0.14) |
| | | UPA vs. RISA | **2.28 (1.14, 4.58)** | **2.13 (1.36, 3.36)** | 0.13 (-0.02, 0.27) |
| | | UPA vs. VDZ | 1.97 (0.98, 3.95) | **1.75 (1.06, 2.90)** | 0.10 (-0.03, 0.24) |
| | | UPA vs. UST | **2.15 (1.05, 4.42)** | **2.04 (1.28, 3.26)** | 0.11 (-0.04, 0.26) |
| **Indirect comparison: UPA 30 mg vs comparators** | | UPA vs. ADA | 1.68 (0.83, 3.40) | 1.52 (0.92, 2.51) | 0.11 (-0.02, 0.24) |
| | | UPA vs RISA | **3.39 (1.69, 6.78)** | **2.64 (1.70, 4.10)** | **0.23 (0.08, 0.37)** |
| | | UPA vs. VDZ | **2.92 (1.46, 5.84)** | **2.17 (1.32, 3.54)** | **0.20 (0.06, 0.34)** |
| | | UPA vs. UST | **3.19 (1.56, 6.55)** | **2.52 (1.59, 0.98)** | **0.21 (0.06, 0.36)** |
| **Indirect comparison: UPA 30/15 mg vs comparators** | | UPA vs ADA | 1.38 (0.70, 2.71) | 1.38 (0.84, 2.25) | 0.06 (-0.05, 0.18) |
| | | UPA vs. RISA | **2.78 (1.44, 5.39)** | **2.39 (1.55, 3.67)** | **0.18 (0.04, 0.31)** |
| | | UPA vs UST | **2.40 (1.24, 4.64)** | **1.96 (1.21, 3.17)** | **0.15 (0.03, 0.28)** |
| | | UPA vs VDZ | **2.62 (1.32, 5.21)** | **2.28 (1.45, 3.57)** | **0.16 (0.02, 0.30)** |

Source: Table 2.26, p145 of the submission.
ADA= adalimumab; biologic; CI= confidence interval; IFX= infliximab; IP= induction phase; mg= milligram; n= number of participants with event; N= total participants in group; NR= not reported; OR= odds ratio; PBO= placebo; Q8W= 8-weekly; Q2W= 2-weekly; RD= risk

difference; RISA= risankizumab; RR= relative risk; SC= subcutaneous; UST= ustekinumab; UPA= upadacitinib; VDZ= vedolizumab; vs= versus.
Note: The submission did not report indirect comparisons for upadacitinib vs infliximab. The PBAC previously noted that the trial data for the comparator infliximab had extremely wide confidence intervals and small patient numbers making the indirect comparison unreliable (Paragraph 7.8, Vedolizumab, PSD, March 2015 PBAC meeting).
**BOLD** values mean statistically significant results.
[a] CR-100 responders at week 8 following induction with either 130 mg, weight-based dose or placebo at week 0 (UNITI-I or UNITI-II).
[b] CDAI< 150 'remission' at week 4 and week 8 following induction with either 160/80 mg, 80/40 mg, 40/20 mg or placebo at week 0 and week 2 (in CLASSIC I) then 40 mg at week 4 and week 6 (Open label phase in CLASSIC II).
[c] CR-70 responders at week 4 following induction with 80/40 mg at week 0 and week 2.
[d] CR-70 responders at week 4 following induction with either 160/80 mg, 80/40 mg or placebo at week 0 or week 2.
[e] CR-70 responders at week 2 following induction with 5 mg/kg at week 0.
[f] CR-70 responders at week 6 following induction with 300 mg at week 0 and week 2.
[g] CR-70 responders at week 10 following induction with 300 mg at week 0, week 2 and week 6.

6.23 A statistically significant greater proportion of patients treated with upadacitinib compared to placebo achieved clinical response in all upadacitinib trials (induction and maintenance phases). Similar results were observed in the comparator trials, with the treatment arm achieving a better clinical response than the placebo arm.

6.24 Induction phase: The indirect comparisons showed statistically significant results favouring infliximab over upadacitinib (in terms of OR, RR and RD) (Table 6). Adalimumab and vedolizumab also achieved higher clinical response rates than upadacitinib, but the results were not statistically significant.

6.25 Maintenance phase: Three doses of upadacitinib were indirectly compared with the comparators: 15 mg, 30 mg, and pooled 15/30 mg data (Table 7). Upadacitinib 15 mg patients had a significantly higher clinical response compared to risankizumab and ustekinumab (for OR and RR) and vedolizumab (for RR only). Upadacitinib 30 mg patients had significantly higher clinical response compared to risankizumab, vedolizumab and ustekinumab (in terms of OR, RR and RD).

6.26 The submission did not report an indirect comparison for upadacitinib vs infliximab in the maintenance phase. The PBAC previously noted that the trial data for the comparator infliximab had extremely wide confidence intervals and small patient numbers making the indirect comparison unreliable (Paragraph 7.8, Vedolizumab, PSD, March 2015 PBAC meeting).

## *Comparative harms*

Safety: induction phase

6.27 Table 8 presents a summary of the safety results for the induction phase.

**Table 8: Safety summary, induction phase: trial and indirect comparison results**

| Trial type or estimate | Trial ID | Active Treatment n/N (%) | PBO n/N (%) | OR (95% CI) Results <1 favours intervention | RR (95% CI) Results <1 favours intervention | RD (95% CI) Results <0 favours intervention |
|---|---|---|---|---|---|---|
| **Any AE** | | | | | | |
| UPA vs PBO | U-EXCEED | 221/324 (68.2) | 112/171 (65.5) | 1.13 (0.76,1.67) | 1.04 (0.91,1.19) | 0.03 (-0.06, 0.11) |
| | U-EXCEL | 219/350 (62.6) | 103/176 (58.5) | 1.18 (0.82,1.72) | 1.07 (0.92,1.24) | 0.04 (-0.05, 0.13) |
| | Pooled | 440/674 (65.2) | 215/317 (62.0)<br>215/347 (62.0)[a] | 1.16 (0.89,1.52) | 1.05 (0.96,1.16) | 0.03 (-0.03, 0.10) |
| **Indirect comparisons: UPA vs comparators** | | | UPA vs ADA | **1.81 (1.15, 2.85)** | **1.22 (1.05, 1.42)** | **0.13 (0.03, 0.23)** |
| | | | UPA vs RISA | **1.59 (1.09, 2.31)** | **1.19 (1.03, 1.38)** | **0.10 (0.01, 0.19)** |
| | | | UPA vs UST | 1.10 (0.76, 1.61) | 1.03 (0.90, 1.18) | 0.02 (-0.07, 0.11) |
| | | | UPA vs VDZ | 1.35 (0.91, 1.99)<br>1.23 (0.84,1.78)[a] | 1.12 (0.96, 1.30) | 0.07 (-0.03, 0.17) |
| **Serious AEs** | | | | | | |
| UPA vs PBO | U-EXCEED | 30/324 (9.3) | 17/171 (9.9) | 0.93 (0.53, 1.64) | 0.92 (0.49, 1.73) | -0.01 (-0.06, 0.05) |
| | U-EXCEL | 24/350 (6.9) | 12/176 (6.8) | 1.01 (0.52, 1.96) | 1.01 (0.49, 2.06) | 0.00 (-0.05, 0.05) |
| | Pooled | 54/674 (8.0) | 29/347 (8.4) | 0.96 (0.62, 1.48) | 0.96 (0.60, 1.54) | 0.00 (-0.04, 0.03) |
| **Indirect comparisons: UPA vs comparators** | | | UPA vs ADA | 2.23 (0.75, 6.66) | 2.18 (0.76, 6.24) | 0.03 (-0.02, 0.08) |
| | | | UPA vs RISA | **2.67 (1.39, 5.10)** | **2.40 (1.33, 4.33)** | **0.09 (0.04, 0.14)** |
| | | | UPA vs UST | 1.10 (0.53, 2.30) | 1.09 (0.55, 2.17) | -0.03 (-0.09,0.03) |
| | | | UPA vs VDZ | 0.88 (0.43, 1.81) | 0.89 (0.45, 1.74) | -0.01 (-0.06, 0.04) |
| **Serious infections** | | | | | | |
| UPA vs PBO | U-EXCEED | 9/324 (2.8) | 3/171 (1.8) | 1.58 (0.43, 5.77) | 1.60 (0.43, 5.99) | 0.01 (-0.02, 0.04) |
| | U-EXCEL | 4/350 (1.1) | 3/176 (1.7) | 0.67 (0.15, 2.96) | 0.67 (0.15, 3.01) | -0.01 (-0.03, 0.02) |
| | Pooled | 13/674 (1.9) | 6/347 (1.7) | 1.12 (0.43, 2.92) | 1.13 (0.42, 2.98) | 0.00 (-0.02, 0.02) |
| **Indirect comparisons: UPA vs comparators** | | | UPA vs ADA | 1.88 (0.33,10.88) | 1.84 (0.32,10.48) | 0.01 (-0.02, 0.04) |
| | | | UPA vs RISA | **4.35 (1.10, 17.20)** | **4.15 (1.10, 15.63)** | **0.03 (0.01, 0.06)** |
| | | | UPA vs UST | 1.03 (0.13, 8.44) | 0.85 (0.20, 3.53) | 0.00 (-0.03, 0.03) |
| | | | UPA vs VDZ | 0.99 (0.15, 6.44) | 0.98 (0.16, 6.06) | 0.00 (-0.02, 0.02) |
| **AEs leading to discontinuations** | | | | | | |
| UPA vs PBO | U-EXCEED | 18/324 (5.6) | 7/171 (4.1) | 1.36 (0.58, 3.19) | 1.38 (0.56, 3.37) | 0.01 (-0.02, 0.05) |
| | U-EXCEL | 15/350 (4.3) | 10/176 (5.7) | 0.75 (0.35, 1.64) | 0.74 (0.33, 1.69) | -0.01 (-0.05, 0.03) |
| | Pooled | 33/674 (4.9) | 17/347 (4.9) | 1.00 (0.57, 1.77) | 1.00 (0.55, 1.82) | 0.00 (-0.03, 0.03) |
| **Indirect comparisons: UPA vs comparators** | | | UPA vs ADA | 2.33 (0.56, 9.60) | 2.27 (0.56, 9.26) | 0.02 (-0.02, 0.06) |
| | | | UPA vs RISA | **3.85 (1.23, 11.98)** | **3.57 (1.49, 8.56)** | 0.03 (-0.01, 0.07) |
| | | | UPA vs UST | NR | NR | NR |
| | | | UPA vs VDZ | 2.04 (0.52, 8.02)<br>**3.03 (1.06, 8.63)** | 2.00 (0.65, 6.13) | 0.02 (-0.02, 0.06) |

Source: Table 2.29, p148 of the submission.

ADA= adalimumab; AE= adverse event; AT= active treatment; CI= confidence interval; IFX= infliximab; ITC= indirect trial comparison; n= number of participants with event; N= total participants in group; NR= not reported; OR= odds ratio; PBO= placebo; Ph= phase; RD= risk difference; RISA= risankizumab; RR= relative risk; UPA= upadacitinib; UST= ustekinumab; VDZ= vedolizumab; vs= versus.

Note: The submission did not report indirect comparisons for upadacitinib vs infliximab. The PBAC previously noted that the trial data for the comparator infliximab had extremely wide confidence intervals and small patient numbers making the indirect comparison unreliable (Paragraph 7.8, Vedolizumab, PSD, March 2015 PBAC meeting).

**BOLD** values represent statistically significant results. **RED** indicates significant results in favour of comparators.

[a] Corrected values were calculated during the evaluation.

[b] Pooled Adalimumab trials: CLASSIC I, GAIN, Watanabe 2012; Pooled RISA trials: M15-993 (Ph 2), ADVANCE, MOTIVATE; Pooled Infliximab trial: T16; Pooled Vedolizumab trials: GEMINI II, GEMINI III, Watanabe 2020; Pooled Ustekinumab trials: UNITI-I, UNITI-II.

6.28 The indirect comparisons reported significantly greater rates of any AE with upadacitinib compared with adalimumab and risankizumab (in terms of OR, RR and RD) (Table 8). For serious AEs and serious infections, upadacitinib reported a significantly greater number of events in comparison to risankizumab only (in terms of OR, RR and RD). In addition, significantly more upadacitinib patients experienced AEs leading to discontinuation compared to risankizumab (in terms of OR and RR) and vedolizumab (in terms of OR only).

6.29 No other significant differences between upadacitinib and comparators were observed in the induction phase. However, compared to patients treated with adalimumab, risankizumab, vedolizumab, and ustekinumab, a numerically higher proportion of patients in upadacitinib trials reported AEs, serious AEs, serious infections and AEs leading to discontinuation.

Safety: maintenance phase

6.30 Table 9 summarises the safety results (trial and indirect comparisons) of upadacitinib with comparators for the maintenance phase.

**Table 9: Safety summary, maintenance phase: trial and indirect comparison results**

| Trial type or estimate | Result type | Active treatment n/N (%) | PBO n/N (%) | OR (95% CI) Results <1 favours intervention | RR (95% CI) Results <1 favours intervention | RD (95% CI) Results <0 favours intervention |
|---|---|---|---|---|---|---|
| **Any AEs** | | | | | | |
| UPA vs PBO | *Pooled results of the trials* [b] | 341/450 (75.8) | 169/223 (75.8) | 1.00 (0.69, 1.45) | 1.00 (0.91, 1.09) | 0.00 (-0.07, 0.07) |
| **Indirect comparisons: UPA 15 mg vs comparators** [c] | | | UPA vs ADA | 0.80 (0.42, 1.51) | 0.97 (0.85, 1.09) | -0.03 (-0.13, 0.06) |
| | | | UPA vs RISA | 1.01 (0.53, 1.89) | 1.00 (0.85, 1.18) | 0.00 (-0.12, 0.12) |
| | | | UPA vs IFX | NR | NR | NR |
| | | | UPA vs UST | 1.07 (0.49, 2.30) | 1.01 (0.86, 1.17) | 0.01 (-0.12, 0.13) |
| | | | UPA vs VDZ | 0.93 (0.53, 1.65) | 0.99 (0.86, 1.12) | -0.01 (-0.11, 0.09) |
| | | | UPA vs VDZ SC | 1.08 (0.57, 2.07) | 1.02 (0.87, 1.20) | 0.02 (-0.10, 0.14) |
| **Indirect comparisons: UPA 30 mg vs comparators** [c] | | | UPA vs ADA | 0.90 (0.48, 1.70) | 0.99 (0.88, 1.12) | -0.01 (-0.10, 0.08) |
| | | | UPA vs RISA | 1.13 (0.60, 2.14) | 1.03 (0.88, 1.21) | 0.02 (-0.10, 0.14) |
| | | | UPA vs IFX | NR | NR | NR |
| | | | UPA vs UST | 1.20 (0.56, 2.59) | 1.04 (0.89, 1.21) | 0.03 (-0.09, 0.15) |
| | | | UPA vs VDZ | 1.05 (0.59, 1.86) | 1.01 (0.89, 1.15) | 0.01 (-0.09, 0.11) |
| | | | UPA vs VDZ SC | 1.22 (0.64, 2.33) | 1.05 (0.90, 1.23) | 0.04 (-0.08, 0.16) |
| **SAE** | | | | | | |
| UPA vs PBO | *Pooled results of the trials* [b] | 50/450 (11.1) | 31/223 (13.9) | 0.77 (0.48, 1.25) | 0.8 (0.53, 1.21) | -0.03 (-0.08,0.03) |
| **Indirect comparisons: UPA 15 mg vs comparators** [c] | | | UPA vs ADA | 1.59 (0.75, 3.35) | 1.51 (0.78, 2.93) | 0.05 (-0.03, 0.13) |
| | | | UPA vs RISA | 0.89 (0.38, 2.06) | 0.90 (0.43, 1.89) | -0.01 (-0.11,0.08) |
| | | | UPA vs IFX | 0.88 (0.43, 1.79) | 0.88 (0.49, 1.58) | -0.01 (-0.12,0.10) |
| | | | UPA vs UST | 1.33 (0.52, 3.36) | 1.28 (0.57, 2.90) | 0.03 (-0.07, 0.13) |
| | | | UPA vs VDZ | 0.84 (0.41, 1.72) | 0.86 (0.47, 1.60) | -0.02 (-0.10,0.06) |
| | | | UPA vs VDZ SC | 1.06 (0.43, 2.58) | 1.06 (0.48, 2.35) | 0.00 (-0.09, 0.09) |
| **Indirect comparisons: UPA 30 mg vs comparators** [c] | | | UPA vs ADA | 1.39 (0.66, 2.96) | 1.35 (0.69, 2.63) | 0.04 (-0.04 ,0.11) |
| | | | UPA vs RISA | 0.78 (0.33, 1.82) | 0.80 (0.38, 1.69) | -0.03 (-0.12,0.06) |
| | | | UPA vs IFX | 0.77 (0.38, 1.59) | 0.79 (0.44, 1.43) | -0.02 (-0.13,0.09) |
| | | | UPA vs UST | 1.16 (0.46, 2.97) | 1.14 (0.50, 2.60) | 0.02 (-0.08 ,0.12) |
| | | | UPA vs VDZ | 0.74 (0.36, 1.52) | 0.77 (0.41, 1.44) | -0.03 (-0.11,0.04) |
| | | | UPA vs VDZ SC | 0.93 (0.38, 2.28) | 0.94 (0.42, 2.11) | -0.01 (-0.10,0.07) |
| **Serious infection** | | | | | | |
| UPA vs PBO | *Pooled results of the trials* [b] | 18/450 (4) | 9/223 (4.0) | 0.99 (0.44, 2.24) | 0.99 (0.45, 2.17) | 0.00 (-0.03, 0.03) |
| **Indirect comparisons: UPA 15 mg with comparators** [c] | | | UPA vs ADA | 1.08 (0.28, 4.22) | 1.08 (0.29, 4.02) | 0.00 (-0.04, 0.05) |
| | | | UPA vs RISA | 0.66 (0.16, 2.79) | 0.67 (0.17, 2.68) | -0.02 (-0.07, 0.04) |
| | | | UPA vs IFX | 0.80 (0.19, 3.30) | 0.81 (0.21, 3.15) | -0.01 (-0.06, 0.05) |
| | | | UPA vs UST | 0.77 (0.11, 5.15) | 0.77 (0.12, 4.94) | -0.01 (-0.06, 0.04) |
| | | | UPA vs VDZ | 1.20 (0.32, 4.52) | 1.19 (0.33, 4.22) | 0.00 (-0.04, 0.04) |
| | | | UPA vs VDZ SC | 2.47(0.48,12.60) | 2.42 (0.50,11.74) | 0.02 (-0.03, 0.07) |
| **Indirect comparisons: UPA 30 mg with comparators** [c] | | | UPA vs ADA | 1.67 (0.46, 6.03) | 1.63 (0.47, 5.64) | 0.02 (-0.03, 0.07) |
| | | | UPA vs RISA | 1.01 (0.26, 4.00) | 1.01 (0.27, 3.77) | 0.00 (-0.05, 0.06) |
| | | | UPA vs IFX | 1.23 (0.32, 4.74) | 1.22 (0.34, 4.44) | 0.01 (-0.05, 0.06) |
| | | | UPA vs UST | 1.18 (0.19, 7.53) | 1.17 (0.19, 7.10) | 0.01 (-0.04, 0.06) |
| | | | UPA vs VDZ | 1.85 (0.53, 6.45) | 1.80 (0.55, 5.90) | 0.02 (-0.03, 0.06) |
| | | | UPA vs VDZ SC | 3.81(0.79,18.27) | 3.66 (0.80,16.70) | 0.04 (-0.02, 0.09) |

| Trial type or estimate | Result type | Active treatment n/N (%) | PBO n/N (%) | OR (95% CI) Results <1 favours intervention | RR (95% CI) Results <1 favours intervention | RD (95% CI) Results <0 favours intervention |
|---|---|---|---|---|---|---|
| **AEs leading to discontinuation** | | | | | | |
| UPA vs PBO | *Pooled results of the trials* | 29/450 (6.4) | 8/223 (3.6) | 1.85 (0.83, 4.12) | 1.8 (0.84, 3.86) | 0.03 (0, 0.06) |
| **Indirect comparisons: UPA 15 mg with comparators** [c] | | | UPA vs ADA | **4.88 (1.74, 13.65)** | **4.29 (1.63, 11.33)** | **0.12 (0.05, 0.18)** |
| | | | UPA vs RISA | 3.09 (0.66, 14.57) | 2.94 (0.66, 13.17) | 0.05 (-0.01, 0.10) |
| | | | UPA vs IFX | 0.32 (0.09, 1.19) | 0.36 (0.10, 1.24) | -0.09 (-0.16, - 0.02) |
| | | | UPA vs UST | NR | NR | NR |
| | | | UPA vs VDZ | **4.66 (1.20, 18.14)** | **4.12 (1.17, 14.52)** | **0.07 (0.01, 0.12)** |
| | | | UPA vs VDZ SC | **4.50 (1.32, 15.33)** | **4.14 (1.30, 13.19)** | **0.08 (0.01, 0.15)** |
| **Indirect comparisons: UPA 30 mg with comparators** [c] | | | UPA vs ADA | **3.76 (1.31, 10.80)** | **3.37 (1.24, 9.14)** | **0.10 (0.04, 0.16)** |
| | | | UPA vs RISA | 2.39 (0.50, 11.43) | 2.31(0.51,10.52) | 0.03 (-0.02, 0.08) |
| | | | UPA vs IFX | **0.25 (0.07, 0.94)** | **0.28 (0.08, 0.99)** | **-0.10 (-0.17, - 0.04)** |
| | | | UPA vs UST | NR | NR | NR |
| | | | UPA vs VDZ | 3.59 (0.91, 14.27) | 3.23 (0.90, 11.64) | 0.05 (0.00, 0.11) |
| | | | UPA vs VDZ SC | 3.47 (1.00, 12.08) | 3.25 (1.00, 10.59) | 0.06 (0.00, 0.13) |

Source: Table 2.31, p155 of the submission.

ADA= adalimumab; AE= adverse event; AT= active treatment; CI= confidence interval; IFX= infliximab; ITC= indirect trial comparison; mg= milligram; n= number of participants with event; N= total participants in group; NA= not applicable; NR= not reported; OR= odds ratio; PBO= placebo; RD= risk difference; RISA= Risankizumab; RR= relative risk; SAE= serious adverse event; SC= subcutaneous; UPA= upadacitinib; UST= ustekinumab; VDZ= vedolizumab; vs= versus.

**BOLD** values mean significant results. **RED** indicates significant results in favour of comparators.

[a] Corrected values were calculated during the evaluation.

[b] Pooled Adalimumab trials: CLASSIC II, CHARM, Watanabe 2012; Pooled RISA trial: FORTIFY; Pooled Infliximab trial: ACCENT I; Pooled Vedolizumab trials: GEMINI II, Watanabe 2020; Vedolizumab SC trial: VISIBLE 2; Pooled Ustekinumab trial: IM-UNITI.

[c] Indirect comparisons were shown separately for 30 mg and 15 mg doses of upadacitinib because of the variability in the effect sizes. For example, UPA vs VDZ indirect comparisons were only significant with the 15 mg dose for AEs resulting in discontinuation.

6.31 Overall, the maintenance phase indirect treatment results did not show statistically significant differences between upadacitinib and the comparators, except for the AEs leading to discontinuation. Patients in the upadacitinib 15 mg group had a significantly higher proportion of patients discontinuing due to AEs compared to adalimumab, vedolizumab and vedolizumab SC (in terms of OR, RR and RD). Patients in the upadacitinib 30 mg group had a significantly higher proportion of patients discontinuing due to AEs compared to adalimumab (in terms of OR, RR and RD). Conversely, significantly fewer patients discontinued due to AEs on upadacitinib 30 mg than infliximab (in terms of OR, RR and RD).

6.32 Overall, the safety results trended toward favouring comparators over upadacitinib over a period of 73 weeks in the induction and maintenance phases.

6.33 The safety profile observed in patients with CD treated with upadacitinib was broadly consistent with the known safety profile of upadacitinib in other indications (pp18-38, Upadacitinib Australian Product Information, September 2022). The PBAC previously noted that upadacitinib was included in the TGA Black Triangle Scheme and subject to additional post-market surveillance (Paragraph 7.4, Upadacitinib PSD, March 2021 PBAC meeting). The PBAC also previously noted this issue was being monitored in multiple jurisdictions and may be a class effect for the Janus kinase inhibitor family.

## *Benefits/harms*

6.34 A benefits and harms table is not presented as the submission made a claim of non-inferiority. The indirect nature of the comparisons and exchangeability issues with the clinical trials presented in the submission did not allow for a reliable comparison of the benefits and harms of upadacitinib vs comparators.

## *Clinical claim*

6.35 The submission claimed that upadacitinib is non-inferior in terms of effectiveness and safety compared with adalimumab, risankizumab, infliximab, ustekinumab and vedolizumab.

6.36 The evaluation considered the non-inferior effectiveness claim may not be adequately supported due to the following concerns:

- No head-to-head trials comparing upadacitinib with any of the comparators were presented.
- The upadacitinib trials likely included moderate CD patients who were not eligible for the proposed PBS indication and excluded severe CD patients who may be treated with upadacitinib under the PBS. Subgroup analysis suggested a larger proportion of patients with a baseline Crohn's Disease Activity Index (CDAI) > 300 achieved clinical remission in the 30 mg dose arm compared to placebo in the maintenance phase (U-ENDURE trial). Consequently, the applicability of the trials to the PBS population is reduced. The ESC noted that there were some differences in longer term outcomes based on induction dose and the subgroup baseline characteristics appeared fairly balanced.
- Several transitivity issues related to prior medication, therapies used at baseline, duration of drug exposure, duration of follow-up, concomitant therapies, the definition of clinical response, and the timing of assessment create substantial uncertainty in indirect comparisons. The ESC agreed with the PSCR's claim that transitivity issues for Crohn's disease have been previously considered by the PBAC (paragraph 6.10 refers). The ESC considered the trial populations were sufficiently exchangeable for decision-making and noted the subgroup analysis by baseline CDAI did not suggest reduced efficacy in patients with CDAI > 300 vs < 300 in subgroup analyses.

- Compared to risankizumab, ustekinumab, and vedolizumab trials, the placebo response rate was lower in the upadacitinib trials during the maintenance phase and greater during the induction phase. The difference in the placebo response rate may reflect differences in the populations recruited or how the trials were conducted and introduces further additional uncertainty to the indirect comparisons, especially for the results expressed in terms of relative risk and risk difference. This is likely to bias the results against upadacitinib in the induction phase and bias against risankizumab, ustekinumab and vedolizumab in the maintenance analysis.
- Results for the indirect comparisons of upadacitinib with the comparators did not show a clear pattern due to the variability in the results versus the nominated comparators.
- No non-inferiority margin or MCID was nominated to assist with the interpretation of the efficacy evidence. For vedolizumab, the PBAC raised concern about the claim of non-inferiority in the absence of a pre-specified non-inferiority margin (Paragraph 6.22, Vedolizumab, PSD, March 2015 PBAC meeting). Nonetheless, the lack of non-inferiority margin and MCID has been considered by the PBAC for severe CD in the vedolizumab (Paragraph 7.1, Vedolizumab, PSD, March 2015 PBAC meeting), ustekinumab (Paragraph 7.1, Ustekinumab, PSD, March 2017 PBAC meeting) and risankizumab (Paragraph 6.31, Risankizumab, PSD, July 2022 PBAC meeting) submissions.

6.37 Given the identified transitivity issues and variable nature of the indirect comparison results (with some favouring comparators) the evaluation considered the results should be interpreted with caution.

6.38 The non-inferior safety claim may not be adequately supported due to similar reasons noted above, as well as:

- A significantly greater number of upadacitinib patients experienced AEs, serious AEs, serious infections, and AEs leading to discontinuations than adalimumab risankizumab, vedolizumab and ustekinumab patients in the induction phase.
- AE leading to discontinuation was significantly higher for upadacitinib than adalimumab, vedolizumab and vedolizumab SC in the maintenance phase.

6.39 The ESC noted the transitivity issues and their potential influence on the certainty of the clinical claims, and considered that these were similar to issues previously considered for this indication. On balance, the ESC considered the evidence presented likely supported the clinical claims of non-inferior efficacy.

6.40 The evaluation considered the safety profile observed in patients with CD treated with upadacitinib was broadly consistent with the known safety profile of upadacitinib in other indications. The ESC considered the safety profile of upadacitinib was generally well-characterised and the results versus placebo were consistent with that profile;

however also considered the results of some of the induction phase indirect comparisons may merit further consideration.

6.41 The Pre-PBAC Response argued the indirect comparisons for the safety of upadacitinib in MSUC were limited as they did not control for any between trial differences that may explain differences in the outcomes and further argued that no statistically significant differences between upadacitinib and the comparators were found in maintenance therapy.

6.42 The PBAC considered that the claim of non-inferior comparative effectiveness was likely to be adequately supported, noting the transitivity issues identified and the impact on the indirect comparisons are not unique to upadacitinib.

6.43 The PBAC considered that the claim of non-inferior comparative safety was on balance, likely supported by the data. The PBAC noted the safety results in the upadacitinib trials are consistent with the established safety profile in other indications.

## *Economic analysis*

6.44 The submission presented a cost-minimisation approach comparing upadacitinib with adalimumab. The key components and assumptions are summarised in Table 10. The evaluation considered the claim of non-inferior effectiveness and safety of upadacitinib compared with adalimumab may not be adequately supported by the clinical evidence presented in the submission. Therefore, the cost-minimisation approach is only appropriate if the clinical claims are accepted.

6.45 The submission stated that adalimumab was an appropriate comparator due to its high market share and that it is exclusively used in the community setting, where upadacitinib was also anticipated to be used.

**Table 10: Key components and assumptions of the cost-minimisation approach**

| Component | Claim or assumption |
|---|---|
| Therapeutic claim: effectiveness | Based on the clinical evidence, the effectiveness of upadacitinib is assumed to be non-inferior compared with adalimumab. This may not be appropriate. See comparative effectiveness section for further discussion. |
| Therapeutic claim: safety | Based on the clinical evidence, the safety of upadacitinib is assumed to be non-inferior compared with adalimumab. This may not be appropriate. See comparative effectiveness section for further discussion. |
| Evidence base | The evidence for the effectiveness and safety of upadacitinib compared with infliximab, adalimumab, vedolizumab, ustekinumab and risankizumab was informed by an indirect comparison via placebo using the Bucher methodology based on:<br>• Three randomised controlled trials of upadacitinib versus placebo – U-EXCEED, U-EXCEL and U-ENDURE.<br>• Four randomised controlled trials of risankizumab versus placebo – M15-993, ADVANCE, MOTIVATE and FORTIFY.<br>• Four randomised controlled trials of vedolizumab versus placebo – GEMINI II & III, Watanabe 2020 and VISIBLE 2.<br>• Three randomised controlled trials of ustekinumab versus placebo – UNITI-I& II and, IM-UNITI.<br>• Five randomised controlled trials of adalimumab versus placebo – CLASSIC I & II, GAIN, CHARM and Watanabe 2012.<br>• Two randomised controlled trials of infliximab versus placebo – T16 and ACCENT I. |
| Equi-effective doses | Upadacitinib 45 mg for the first 12 weeks (i.e., initiation phase) followed by upadacitinib 30 mg or 15 mg thereafter (i.e. continuation phase), modified release oral tablet, once daily<br>=<br>Adalimumab 160 mg at week 0 followed by 80 mg at week 2 and 40 mg every two weeks thereafter subcutaneous injection.<br><br>The dose regimens are aligned with the proposed (upadacitinib) and approved (adalimumab) TGA Product Information. |
| Direct medicine costs | Drug costs and MBS item codes associated with injection assistance were presented. Costing was done based on the published pricing information. The data source is appropriate. The published price of adalimumab used in the cost-minimisation analysis is appropriate. |
| Other costs or cost offsets | The submission assumed that other potential healthcare resource utilisation such as periodic face-to-face special consultation visits and associated monitoring would occur equally with each treatment. The assumption may not be reasonable in terms of adverse events. |

Source: Table 3-1, p167 of the submission.
MBS= Medicare Benefits Schedule; mg= milligram; TGA= Therapeutic Goods Administration
Note: Continuing phase is subject to PBS restriction criteria outlined in Section 1.4.3, pp28-29 of the submission.

6.46 The submission proposed that upadacitinib 45 mg tablet once daily for 12 weeks, followed by either 15 mg or 30 mg tablet once daily thereafter, is equi-effective to adalimumab 160 mg on Day 0 administered as four 40 mg/0.4 mL subcutaneous injections, followed by 80 mg on Day 14 administered as two 40 mg/0.4 mL subcutaneous injections and then 40 mg/0.4 mL subcutaneous injections administered on Day 28 dosed fortnightly thereafter. The use of upadacitinib matches the dosing, frequency of use, continuation or cessation rules in the draft TGA Product Information (Upadacitinib (Rinvoq) TGA draft Product Information, September 2022). They are also consistent with the dosing and frequency of use in the trial arms presented in the clinical evidence to support the clinical claims.

6.47 The submission assumed that 10% of patients receiving adalimumab would require injection assistance, and MBS item 23 was applied, updated on 1 July 2022 to $39.75. The submission claimed that this assumption was in line with the previous biologic

submissions where the PBAC considered it appropriate to include the associated costs for injection assistance as a visit to a doctor (Paragraph 7.16, Vedolizumab PSD, November 2020 PBAC meeting).

6.48 The submission assumed that potential healthcare resource utilisation, such as periodic face-to-face specialist consultation visits and associated monitoring, would occur equally with each treatment. A similar assumption was previously considered in the case of risankizumab (Paragraph 6.65, Risankizumab, PSD, July 2022 PBAC meeting).

6.49 The submission used the published AEMP ($818.54) for adalimumab when originally submitted to the March 2023 PBAC meeting. The PBAC noted the price of some brands of adalimumab had reduced between the March 2023 and July 2023 meetings, however the proposed cost minimisation approach was not updated prior to consideration.

6.50 Results of the cost-minimisation approach of upadacitinib versus adalimumab using the published AEMP for adalimumab are presented in Table 11.

**Table 11: Cost-minimisation approach of upadacitinib versus adalimumab over 24 months of treatment based on the published ex-manufacturer price of adalimumab**

| Row | Component | UPA | ADA | Source / calculation |
|---|---|---|---|---|
| A | Treatment duration, years | 2 | 2 | Reported by the submission |
| **Drug costs** | | | | |
| *B* | Dosing details | Initial therapy: 45 mg tablet once daily for 12 weeks<br><br>Continuing therapy: 30 mg or 15 mg tablet once daily | Initial therapy: 160 mg on Day 0, 80 mg on day 14<br><br>Continuing therapy: 40 mg SC injection starting Day 28 and continuing fortnightly | Reported by the submission (equi-effective doses) |
| C | AEMP per pack | $883.36[a, b] | $818.54 (published) | Reported by the submission |
| D | Medical assistance with injections | $0 | $3.98[c] | |
| E | Unit volume | 45 mg, 30 mg and 15 mg oral tablets | 160 mg and 80 mg PFS, Pen | |
| F | Number of packs first year | 13 | 16 | |
| G | Number of packs second year | 13 | 12 | |
| H | Packs utilised over two years | 26 | 28 | F+G |
| I | Total drug costs over two years | $23,030.42 | $23,030.42 | (C+D)*H |
| J | Difference in cost over two years [published AEMP] | $0 | | UPA Row I- ADA Row I |

Source: Compiled during the evaluation based on Table 3-4, p169 of the submission and Sheets Cost-min UPA vs AD and Dosing per week, Section 3 Workbook.

ADA= Adalimumab; AEMP= approved ex-manufacturer's price; PFS= pre-filled syringe; SC= subcutaneous; UPA= Upadacitinib.

[a] Indicative cost-minimised price based on the published price of adalimumab. This figure was estimated by dividing AEMP by the total number of packs, i.e., $23,030.42/26.07.

[c] 10% of the MBS item for doctor visit (item 23) of $39.75 added to the total costs associated with adalimumab treatment.

## *Drug cost/patient/year*

6.51 Based on the published AEMP, the cost per patient per year is $11,515.21.

## *Estimated PBS usage & financial implications*

6.52 The submission was not considered by the DUSC. The submission used a market share approach to estimate the use and financial impact of listing upadacitinib for adult patients with severe CD.

6.53 Table 12 summarises the key inputs used to calculate the financial estimates.

**Table 12: Key inputs for financial estimates**

| Data | Value applied and source | Comment |
|---|---|---|
| **Treatment utilisation** | | |
| Market growth without the listing of UPA | Functional form: Linear<br>Source: The submission assumed a linear trend of growth in Year 1 to 6 following the listing reflecting the 2017-2021 usage, and each modelled list item was projected individually. | The linear trend lines predicted from the 2017-2021 usage data are correct. It may be reasonable to assume linear growth of IFX, UST and VDZ based on the 2017-2021 usage data. However, the usage of ADA initiation therapy fluctuates, and it is uncertain if it follows a linear trend. Assuming a linear trend likely overestimated the usage for ADA. |
| Substitution rates of UPA | Year 1: 5%<br>Year 2: 7%<br>Year 3: 9%<br>Year 4: 11%<br>Year 5: 13%<br>Year 6: 15%<br>Source: Assumed | The substitution rates were unsupported and are uncertain. Upadacitinib may have a higher substitution rate compared to all comparators given it will be the only oral medicine available to treat severe CD if listed. Sensitivity analysis conducted during the evaluation found that this parameter had a large impact on the results. |
| Market growth due to PBS listing of UPA (additional growth/UPA uptake on the PBS) | 0%<br>Source: Assumed | This assumption is uncertain, and there is a possibility of additional market growth as a result of patients who are refractory or intolerant to currently listed biologics returning for treatment. |
| Script equivalence vs UPA | **Initiation** / **Continuation**<br>UPA: Reference / Reference<br>ADA: 5:3-UPA 45mg 1:0.3-UPA 30mg 1:0.7-UPA 15mg / 1:0.3-UPA 30mg 1:0.7-UPA 15mg<br>IFX[a]: 1:1 UPA 45mg 1:0.3 UPA 30mg 1.0.7 UPA 15mg / 1:0.6-UPA 30mg 1:1.4-UPA 15mg<br>UST: 1:3-UPA 45mg 1:0.3-UPA 30mg 1:0.7-UPA 15mg / 1:0.6-UPA 30mg 1:1.4-UPA 15mg<br>VDZ[b]: 1:1 UPA 45mg 1:0.3 UPA 30mg 1.0.7 UPA 15mg / 1:0.6-UPA 30mg 1:1.4-UPA 15mg<br>Source: Assumed | The estimation of the script equivalence is correct based on the estimates provided in Section 4 Workbook. However, the source of the proposed dosing regimens is unclear as the submission assumed that 70% of the total continuation scripts would be a 15 mg regimen (thus 30% for the 30 mg regimen). |
| UPA | **Treatment** / **DPMQ** / **Source**<br>UPA 45 mg / $2,716.13 / Proposed DPMQs based on publicly available prices<br>UPA 30 mg / $2,076.44<br>UPA 15 mg / $1,271.46 | Also, the proposed published DPMQs differ from the published prices proposed in Section 1 of the submission (UPA 45mg: $2,716.07, UPA 30mg: $2,076.38, and UPA 15mg: $1,271.40). |
| Comparators | **Treatment** / **DPMQ (weighted[c])** | |

| Data | Value applied and source | | Comment |
|---|---|---|---|
| | UST 130 mg/26 mL injection, 26 mL vial - Initiating | $12,465.68[d] | The assumption of the average vial number (3.27) per script is reasonable.<br><br>The weighted price used in the analysis is appropriate |
| | UST 45 mg/0.5 mL injection, 0.5 mL vial - Initiating/continuing | $7,779.38[e] | This is appropriate. |
| | ADA 40 mg x 2 injections (script equivalence matched) – Initiating & continuing | $885.50[f] | |
| | IFX 100 mg injection, 1 vial - Initiating/continuing | $1,413.67[g] | The assumptions of the average vial number per script (4.34 for initiating/continuing and 4.54 for no max qty- continuing) are reasonable.<br><br>The submission did not justify why the UST data rather than the IFX data was used to inform the public vs. private split. The proportion of s100 public of all PBS items related to IFX IV during 2017-2021 was 62.94% (estimated during the evaluation). The submission may have slightly underestimated the financial implication weighting by the UST service split. Sensitivity analysis conducted during the evaluation found that this parameter had minimal impact on the results. |
| | IFX 100 mg injection, 1 vial (no Max Qty) – Continuing | $1,477.22[g] | |
| | IFX 100mg injection, 1 vial (Max Qty = 5) - Continuing | $1,623.87[g] | |
| | VDZ 300mg injection, 1 vial – Initiating/continuing | $2,970.25[h] | The submission did not justify why the UST data rather than the VDZ data was used to inform the public vs. private split. The proportion of s100 public of VDZ (10390W/10415E) during the 2017-2021 period was 64.26% (estimated during the evaluation). The submission may have slightly underestimated the financial implication weighting by the UST service split. Sensitivity analysis conducted during the evaluation found that this parameter had minimal impact on the results. |
| IV administration for UST/VDZ | $81.05<br>Source: MBS item 116 | | This is appropriate. |
| IV administration for IFX | $103.55<br>MBS item 14245 | | This is appropriate. |
| MBS costs: Administration fee for ADA and UST SC | $39.75<br>MBS item 23<br>Source: Assumed based on Paragraph 6.48, PSD, Vedolizumab, November 2020 PBAC meeting and Paragraph 10, PSD, Golimumab, March 2010 PBAC meeting. | | The inclusion of MBS item 23 is not be appropriate and would overestimate the net reduction to MBS-funded procedures due to the listing of upadacitinib. In this regard, the ESC noted that "…MBS items for general practice should not be included in the estimated financial implications as these costs/savings to Government will not be realised in clinical practice" (Paragraph 6.63, Cabotegravir/Cabotegravir and Rilpivirine, PSD, |

| Data | Value applied and source | Comment |
|---|---|---|
| | | November 2021 PBAC meeting). |

Source: Compiled during the evaluation based on Attachment 4- upadacitinib Section 4 workbook of the submission and Tables 4-3-4-6, 4-8, 4-9, 4-11, 4-13-4-14,4-17-4-18, pp176-180, 183, 185 of the submission.
ADA= adalimumab; AHI= Administration, handling and infrastructure; DPMQ= dispensed price for maximum quantity; IV= intravenous; IFX: infliximab; Max Qty= maximum quantity; MBS= Medicare Benefits Schedule; PBS= Pharmaceutical Benefits Scheme; PSD= Public Summary Document; SC= subcutaneous; UPA= upadacitinib; UST= ustekinumab; VDZ= vedolizumab.
[a] IV formulations were reflected in the current market share analysis (SC formulation usage captured within).
[b] Script equivalence for vedolizumab subcutaneous, initiation/continuation/balance of supply (PBS items 12620F/12638E/12654B) was done by dividing its usage by 2.
[c] Weighted based on s100 public and S100 private services split, where applicable.
[d] DPMQ (public) determined using the following formula in the Section 4 Workbook: AEMP of $3,809.08* 3.27 vials = $12,445.36; DPMQ (private) determined using the following formula in the Section 4 Workbook: AEMP of $3,809.08* 3.27 vials + AHI mark-up of $40 + dispensing fee of $7.78. Note: Current (from 1 July 2022) dispensing fee= $7.82.
[e] Current DPMQ of UST 45mg/0.5 mL injection, 0.5 mL vial= $7,779.44
[f] Current DPMQ of ADA 40mg x 2 injections= $885.56
[g] Used AEMP of $320.71 to calculate DPMQs. Current AEMP= $253.52; Used in the submission: $320.71.
[h] DPMQ for 10415E (i.e. s100 private) = $2997.75; Used in the submission: $2,997.71; the difference was due to the inclusion of dispensing fee of $7.78 instead of the current dispensing fee of $7.82.
Note: The submission noted that the 2021 ustekinumab IV data were used for the Section 100 public vs private split (i.e., 57.96% vs. 42.04%). However, it used 2017-2021 ustekinumab IV data in the calculations.

6.54 The estimated use and financial implications of upadacitinib for severe CD are presented in Table 13.

**Table 13: Estimated use and financial implications (using published prices)**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|---|---|---|---|---|---|
| **Estimated extent of use** | | | | | | |
| Number of scripts[a] dispensed | 1 | 2 | 2 | 3 | 4 | 5 |
| **Estimated financial implications of UPA** | | | | | | |
| Net cost to PBS/RPBS[b]($) | 6 | 7 | 8 | 9 | 10 | 11 |
| **Estimated financial implications for ADA, IFX, UST and VDZ** | | | | | | |
| Net cost PBS/RPBS[c]($) | 12 | 12 | 12 | 12 | 12 | 12 |
| **Net financial implications** | | | | | | |
| Net cost to PBS/RPBS (published DPMQ)($) | 12 | 12 | 12 | 12 | 12 | 12 |
| Net cost to MBS (MBS items 23, 116 and 14245)[d] ($) | 12 | 12 | 12 | 12 | 12 | 12 |
| Net cost to MBS excluding MBS item 23 ($) | 12 | 12 | 12 | 12 | 12 | 12 |
| Net cost savings to MBS due to the inclusion of MBS item 23 ($) | 13 | 13 | 13 | 13 | 13 | 13 |

Source: Compiled during the evaluation based on Tables 4-19-4-20, 4-22, 4-23, pp186-188 of the submission and Section 3 Workbook; Table 4-24, p189 of the submission and Sheet 7. Net changes - MBS, Section 4 Workbook.
ADA= adalimumab; CMA=cost-minimisation analysis; IFX= infliximab; PBS= Pharmaceutical Benefits Scheme; RPBS= Repatriations Pharmaceutical Benefits Scheme; UPA= upadacitinib; UST= ustekinumab; VDZ= vedolizumab
[a] Includes scripts for upadacitinib 45mg, initiation, upadacitinib 30mg, balance of supply, upadacitinib 15 mg, balance of supply, upadacitinib 30 mg, continuing and upadacitinib 15 mg, continuing.
[b] Cost to PBS – less co-payments
[c] There were errors in Table 4-22, p187 of the submission. They were corrected in the table above based on the source cited in the submission (Sheet 4b. Impact – affected (pub), Section 4 Workbook). The cost-savings were largely driven by ustekinumab. Cost-savings due to ustekinumab alone ranged between 65% in year 1 and 73% in year 6 (based on calculations done in sheet 4b. Impact – affected (pub), Section 4 Workbook).
[d] As presented in the submission, which included MBS items 23, 116 and 14245. Excluding MBS item 23 would result in 9% less MBS savings in all years.

*The redacted values correspond to the following ranges:*
*[1] 5,000 to < 10,000*
*[2] 10,000 to < 20,000*
*[3] 20,000 to < 30,000*
*[4] 30,000 to < 40,000*
*[5] 40,000 to < 50,000*
*[6] $10 million to < $20 million*
*[7] $20 million to < $30 million*
*[8] $30 million to < $40 million*
*[9] $40 million to < $50 million*
*[10] $50 million to < $60 million*
*[11] $60 million to < $70 million*
*[12] net cost saving*
*[13] $0 to < $10 million*

6.55 The total cost to the PBS/RPBS of listing upadacitinib was estimated to be $60 million to < $70 million in Year 6, and a total of $200 million to < $300 million in the first 6 years of listing based on the published DPMQ, however after accounting for the replacement of other medicines, the submission estimated a net save to the PBS.

6.56 The results should be considered with caution because:

- The substitution rates were unsupported and are uncertain. Upadacitinib may replace the alternatives at a higher rate, given it will be the only oral medicine available to treat severe Crohn disease if listed. It may also grow the market due to patients who are refractory or intolerant to currently listed biologics returning for treatment. The ESC considered additional market growth is likely and noted this was acknowledged by the PSCR.
- The submission identified MBS items 23 (category 1- professional attendance), 14245 (immunomodulating agent, administration of, by intravenous infusion for at least two hours duration) and 116 (professional attendance by a general practitioner at consulting rooms other than a service to which other items would apply, lasting less than 20 minutes). The inclusion of MBS items 14245 and 116 was considered appropriate in previous submissions (Paragraph 6.46 and 6.54, Vedolizumab, PSD, November 2020 PBAC meeting;). However, the inclusion of MBS item 23 (professional attendance by a general practitioner; cost: $39.75 with 10% of patients assumed to require such attendance) is not be appropriate and would overestimate the net reduction to MBS-funded procedures due to the listing of upadacitinib. The ESC previously noted that MBS items for general practice should not be included in the estimated financial implications as these costs/savings to Government will not be realised in clinical practice (Paragraph 6.63, Cabotegravir/Cabotegravir and Rilpivirine, PSD, November 2021 PBAC meeting). Overall, it would have a minimal financial impact, with an overestimated MBS savings of around 9% in all years.

6.57 The submission did not present sensitivity analyses on the financial implication estimates. The sensitivity analyses indicated that the net financial impacts are most sensitive to the substitution rates of upadacitinib and substitution rates with adalimumab relative to other comparator treatments. However, if listed on a cost

minimisation basis with the least costly alternative, UPA will only substitute for medicines that are the same or less costly.

### *Quality Use of Medicines*

6.58 The submission noted that the sponsor has a risk management plan, including an Australian-specific annex submitted to the TGA as part of the regulatory dossier. A patient support program was proposed to support prescribers and patients regarding using upadacitinib. No post-marketing surveillance study was proposed in the submission.

### *Financial Management – Risk Sharing Arrangements*

6.59 The submission did not identify any risk of usage beyond the restriction, and no risk-sharing arrangements were proposed. There are no risk-sharing arrangements in place for the comparator treatments for severe CD. There is a potential risk of upadacitinib leakage to less severe patients given a non-inferior clinical claim and that it will be the only oral medicine available to treat severe CD if listed, while all its comparators involve IV infusions and/or subcutaneous injections.

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

## 7 PBAC Outcome

7.1 The PBAC recommended the General Schedule listing of upadacitinib for the treatment of severe Crohn's disease (CD). The PBAC's recommendation was based on, among other matters, its assessment the cost-effectiveness of upadacitinib would be acceptable if it were cost minimised to the least costly alternative therapy of adalimumab, infliximab, vedolizumab, ustekinumab. The Committee noted risankizumab was recommended for listing at its November 2022 meeting but was not yet listed on the PBS, however considered risankizumab was also an alternative therapy.

7.2 The Committee considered the equi-effective doses of upadacitinib and the alternative therapies could be derived with reference to the therapeutic relativity sheets and relevant Product Information documents, noting the equi-effective dose component includes treatment with upadacitinib 45 mg once daily for 12 weeks in induction therapy, followed by either 15 mg or 30 mg once daily thereafter for maintenance therapy and a split of 70% use of 15 mg and 30% use of 30 mg (per Table 12) was likely to be reasonable.

7.3 The PBAC considered it was reasonable for the listing of upadacitinib to be consistent with other biologic or targeted synthetic disease modifying anti-rheumatic drugs (bDMARDs/tsDMARDs), with prescribing limited to eligible medical practitioners, an induction treatment period of 12 weeks, followed by maintenance therapy with re-assessment at 24-week intervals. The Committee noted the flow-on changes to other CD listings to include upadacitinib in the list of eligible therapies.

7.4 The submission nominated all currently listed (or recommended) bDMARDs for Crohn's disease as comparators, including adalimumab, infliximab, vedolizumab, ustekinumab and risankizumab. The PBAC considered the nominated comparators were reasonable, however noted the submission also argued adalimumab should be the primary comparator as upadacitinib would similarly be predominantly used in the community setting. The PBAC considered upadacitinib would replace all the alternative therapies in practice.

7.5 The PBAC noted no direct trials comparing upadacitinib to the alternatives were presented and the submission relied on indirect treatment comparisons (ITCs) supported by 3 upadacitinib trials (2 induction, 1 maintenance) and 18 comparator trials. The Committee also noted the results of the trials showed upadacitinib achieved statistically significantly higher rates of response and remission in induction and maintenance therapy over placebo. With respect to the ITCs, the PBAC noted some inconsistency with the results, with some analyses showing statistically significant differences selectively based on odds ratio, relative risk or risk difference, with some favouring upadacitinib and others a comparator drug. The PBAC further considered there were transitivity issues which impacted interpretation of the ITCs and considered it was appropriate to consider the totality of the available evidence. Overall, the PBAC considered there was no clear directionality with results of the ITCs and no clear indication of a difference in effectiveness between upadacitinib and any of the comparators, in either induction or maintenance therapy and considered that the claim of non-inferior comparative effectiveness to the nominated comparators was, on balance, likely to be supported.

7.6 The submission presented many ITCs for adverse events, serious adverse events, serious infections and adverse events leading to discontinuation. The PBAC noted, for induction therapy, upadacitinib was associated with statistically significantly worse results versus risankizumab for most of these outcomes, with inconsistent results versus other comparators but most not reaching statistical significance. The PBAC noted for maintenance therapy the results were generally similar with inconsistent results but most not reaching statistical significance. The PBAC considered that overall, the safety profile of upadacitinib in Crohn's disease appears to be consistent with its known safety profile in other indications and that a claim of non-inferior comparative safety to the nominated comparators was, on balance, likely to be reasonable.

7.7 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 upadacitinib. The PBAC considered the cost of upadacitinib should be no greater than the alternative therapies, accounting for the proportional split of 70% use of 15 mg and 30% use of 30 mg in maintenance therapy (see Table 12 and paragraph 7.2).

7.8 The PBAC noted the utilisation and financial estimated a net save to the PBS/RPBS over 6 years. The PBAC considered the large estimated net save was driven by using published prices for some bDMARDs/tsDMARDs, while the requested price was based

on adalimumab which is in the F2 formulary and is less costly. The PBAC considered given the use of published prices in the utilisation and financial estimates, the projected save will not be realised. Furthermore, the PBAC considered as a first oral agent there is a risk upadacitinib will grow the market, but the extent of which would be difficult to predict. Overall, given its recommendation was on a cost minimisation basis to the least costly alternative bDMARD/tsDMARD, the PBAC considered the listing of upadacitinib is, as it will replace therapies that are either of equivalent cost or more expensive.

7.9 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because upadacitinib is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over the alternative therapies, 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.

7.10 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 indication as follows, subject to alignment with final TGA approved Product Information dosing directions for severe active Crohn disease (expected late July 2023):

| **Category / Program:** GENERAL – General Schedule (Code GE) | | | | | | |
|---|---|---|---|---|---|---|
| **MEDICINAL PRODUCT medicinal product pack** | | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of Rpts** | **Available brands** |
| UPADACITINIB | | | | | | |
| upadactinib 45 mg modified release tablet, 28 | | NEW 1 MP | 1 | 28 | 2 | Rinvoq |
| | | | | | | Safety Net Rule Penalty Applies? Yes |
| | | | | | | |
| Prescribi | | **Administrative Advice:** *insert updated long administrative 'NOTE' here (shown at the end of the restrictions)* | | | | |
| | | **Administrative Advice:** No increase in the maximum quantity or number of units may be authorised. | | | | |
| | | **Administrative Advice:** No increase in the maximum number of repeats may be authorised. | | | | |

| | | |
|---|---|---|
| | | **Administrative Advice:**<br>Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).<br><br>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au<br><br>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos<br>Or mailed to:<br>Services Australia<br>Complex Drugs<br>Reply Paid 9826<br>HOBART TAS 7001 |
| | | **Administrative Advice:**<br>The prescriber completing this authority application must be a specialist medical practitioner of the type specified in the restriction. |
| | | |
| **Restriction Summary / Treatment of Concept:: Authority Required** | | |
| | | **Indication:** Severe Crohn disease |
| | | |
| | | **Treatment Phase:** Initial 1 (induction treatment covering the first 12 weeks in a patient untreated with biological medicine) |
| | | |
| | | **Treatment criteria:** |
| | | Must be treated by a gastroenterologist (code 87); or |
| | | Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; or |
| | | Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)] |
| | | |
| | | **Population criteria:** |
| | | Patient must be at least 18 years of age |
| | | |
| | | **Clinical criteria:** |
| | | Patient must have confirmed severe Crohn disease, defined by standard clinical, endoscopic and/or imaging features, including histological evidence, with the diagnosis confirmed by a gastroenterologist or a consultant physician |
| | | **AND** |
| | | **Clinical criteria:** |
| | | Patient must have failed to achieve an adequate response to prior systemic therapy with a tapered course of steroids, starting at a dose of at least 40 mg prednisolone (or equivalent), over a 6 week period |
| | | **AND** |
| | | **Clinical criteria:** |
| | | Patient must have failed to achieve adequate response to prior systemic immunosuppressive therapy with azathioprine at a dose of at least 2 mg per kg daily for 3 or more consecutive months; or |
| | | Patient must have failed to achieve adequate response to prior systemic immunosuppressive therapy with 6-mercaptopurine at a dose of at least 1 mg per kg daily for 3 or more consecutive months; or |
| | | Patient must have failed to achieve adequate response to prior systemic immunosuppressive therapy with methotrexate at a dose of at least 15 mg weekly for 3 or more consecutive months |
| | | **AND** |
| | | **Clinical criteria:** |
| | | Patient must have a Crohn Disease Activity Index (CDAI) Score greater than or equal to 300 as evidence of failure to achieve an adequate response to prior systemic therapy; or |
| | | Patient must have short gut syndrome with diagnostic imaging or surgical evidence, or have had an ileostomy or colostomy; and must have evidence of intestinal inflammation; and must have evidence of failure to achieve an adequate response to prior systemic therapy as specified below; or |
| | | Patient must have extensive intestinal inflammation affecting more than 50 cm of the small intestine as evidenced by radiological imaging; and must have a Crohn Disease Activity Index (CDAI) Score greater than or equal to 220; and must have evidence of failure to achieve an adequate response to prior systemic therapy as specified below |
| | | |

| | |
|---|---|
| | **Prescribing Instructions:**<br>The authority application must be made in writing and must include:<br>(1) a completed authority prescription form; and<br>(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). |
| | **Prescribing Instructions:**<br>Evidence of failure to achieve an adequate response to prior therapy must include at least one of the following:<br>(a) patient must have evidence of intestinal inflammation;<br>(b) patient must be assessed clinically as being in a high faecal output state;<br>(c) patient must be assessed clinically as requiring surgery or total parenteral nutrition (TPN) as the next therapeutic option, in the absence of this drug, if affected by short gut syndrome, extensive small intestine disease or is an ostomy patient.<br><br>Evidence of intestinal inflammation includes:<br>(i) blood: higher than normal platelet count, or, an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour, or, a C-reactive protein (CRP) level greater than 15 mg per L; or<br>(ii) faeces: higher than normal lactoferrin or calprotectin level; or<br>(iii) diagnostic imaging: demonstration of increased uptake of intravenous contrast with thickening of the bowel wall or mesenteric lymphadenopathy or fat streaking in the mesentery. |
| | **Prescribing Instructions:**<br>All assessments, pathology tests and diagnostic imaging studies must be made within 4 weeks of the date of application and should be performed preferably whilst still on conventional treatment, but no longer than 4 weeks following cessation of the most recent prior treatment. |
| | **Prescribing Instructions:**<br>If treatment with any of the specified prior conventional drugs is contraindicated according to the relevant TGA-approved Product Information, please provide details at the time of application. |
| | **Prescribing Instructions:**<br>If intolerance to treatment develops during the relevant period of use, which is of a severity necessitating permanent treatment withdrawal, details of this toxicity must be provided at the time of application. |
| | **Prescribing Instructions:**<br>Details of the accepted toxicities including severity can be found on the Services Australia website. |
| | **Prescribing Instructions:**<br>Any one of the baseline criteria may be used to determine response to an initial course of treatment and eligibility for continued therapy, according to the criteria included in the continuing treatment restriction. However, the same criterion must be used for any subsequent determination of response to treatment, for the purpose of eligibility for continuing PBS-subsidised therapy. |
| | |
| **Restriction Summary / Treatment of Concept: Authority Required** | |
| | **Indication:** Severe Crohn disease |
| | |
| | **Treatment Phase:**<br>Initial treatment – Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) |
| | |
| | **Treatment criteria:** |
| | Must be treated by a gastroenterologist (code 87); or |
| | Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; or |
| | Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)] |
| | |
| | **Clinical criteria:** |
| | Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition in this treatment cycle |
| | **AND** |
| | **Clinical criteria:** |
| | The treatment must not have on a previous occasion failed to provide the patient with an adequate response during the current treatment cycle |
| | |
| | **Population criteria:** |
| | Patient must be at least 18 years of age |

| | |
|---|---|
| | |
| | **Prescribing Instructions:**<br>The authority application must be made in writing and must include:<br>(1) a completed authority prescription form; and<br>(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). |
| | **Prescribing Instructions:**<br>In relation to the biological medicine prescribed immediately before this one, provide at least one of the following which is not more than 4 weeks from the last administered dose:<br>(i) the Crohn Disease Activity Index (CDAI) score, including the date the score was calculated on; or<br>(ii) the unique serial/identifying number and date(s) of pathology or diagnostic imaging test(s) used to assess response to therapy for patients with short gut syndrome, extensive small intestine disease or an ostomy, if relevant; or<br>(iii) confirmation that a severe intolerance occurred that resulted in the cessation of treatment. |
| | |
| **Restriction Summary / Treatment of Concept: Authority Required** | |
| | **Indication:** Severe Crohn disease |
| | |
| | **Treatment Phase:** Initial treatment - Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) |
| | |
| | **Treatment criteria:** |
| | Must be treated by a gastroenterologist (code 87); or |
| | Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; or |
| | Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)] |
| | |
| | **Clinical criteria:** |
| | Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have had a break in treatment of 5 years or more from the most recently approved PBS-subsidised biological medicine for this condition |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have confirmed severe Crohn disease, defined by standard clinical, endoscopic and/or imaging features, including histological evidence, with the diagnosis confirmed by a gastroenterologist or a consultant physician |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have a Crohn Disease Activity Index (CDAI) Score of greater than or equal to 300 that is no more than 4 weeks old at the time of application; or |
| | Patient must have a documented history of intestinal inflammation and have diagnostic imaging or surgical evidence of short gut syndrome if affected by the syndrome or has an ileostomy or colostomy; or |
| | Patient must have a documented history and radiological evidence of intestinal inflammation if the patient has extensive small intestinal disease affecting more than 50 cm of the small intestine, together with a Crohn Disease Activity Index (CDAI) Score greater than or equal to 220 and that is no more than 4 weeks old at the time of application |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have evidence of intestinal inflammation; or |
| | Patient must be assessed clinically as being in a high faecal output state; or |
| | Patient must be assessed clinically as requiring surgery or total parenteral nutrition (TPN) as the next therapeutic option, in the absence of this drug, if affected by short gut syndrome, extensive small intestine disease or is an ostomy patient |
| | |
| | **Population criteria:** |
| | Patient must be at least 18 years of age |
| | |

| | |
|---|---|
| | **Prescribing Instructions:**<br>The authority application must be made in writing and must include:<br>(1) a completed authority prescription form; and<br>(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). |
| | **Prescribing Instructions:**<br>Provide at least one of the following:<br>(i) the current Crohn Disease Activity Index (CDAI) score, including the date this score was calculated on;<br>(ii) confirmation that there is a documented history of intestinal inflammation plus diagnostic imaging/surgical evidence of at least one of: (a) short gut syndrome, (b) ileostomy, (c) colostomy;<br>(iii) confirmation that there is a documented history and radiological evidence of intestinal inflammation from extensive small intestinal disease affecting more than 50 cm of the small intestine where the CDAI score is at least 220, but below 300 |
| | **Prescribing Instructions:**<br>Evidence of intestinal inflammation includes:<br>(i) blood: higher than normal platelet count, or, an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour, or, a C-reactive protein (CRP) level greater than 15 mg per L; or<br>(ii) faeces: higher than normal lactoferrin or calprotectin level; or<br>(iii) diagnostic imaging: demonstration of increased uptake of intravenous contrast with thickening of the bowel wall or mesenteric lymphadenopathy or fat streaking in the mesentery. |
| | **Prescribing Instructions:**<br>Any one of the baseline criteria may be used to determine response to an initial course of treatment and eligibility for continued therapy, according to the criteria included in the continuing treatment restriction. However, the same criterion must be used for any subsequent determination of response to treatment, for the purpose of eligibility for continuing PBS-subsidised therapy. |
| | |
| **Restriction Summary / Treatment of Concept:: Authority Required** | |
| | **Indication:** Severe Crohn disease |
| | |
| | **Treatment Phase:** Transitioning from non-PBS to PBS-subsidised supply – 'grandfather' arrangements |
| | |
| | **Clinical criteria:** |
| | Patient must have commenced non-PBS supply prior to [insert listing date here] |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have confirmed severe Crohn disease, defined by standard clinical, endoscopic and/or imaging features, including histological evidence, with the diagnosis confirmed by a gastroenterologist or a consultant physician |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have failed to achieve an adequate response to prior systemic therapy with a tapered course of steroids, starting at a dose of at least 40 mg prednisolone (or equivalent), over a 6 week period |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have failed to achieve adequate response to prior systemic immunosuppressive therapy with azathioprine at a dose of at least 2 mg per kg daily for 3 or more consecutive months; or |
| | Patient must have failed to achieve adequate response to prior systemic immunosuppressive therapy with 6-mercaptopurine at a dose of at least 1 mg per kg daily for 3 or more consecutive months; or |
| | Patient must have failed to achieve adequate response to prior systemic immunosuppressive therapy with methotrexate at a dose of at least 15 mg weekly for 3 or more consecutive months |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have had a Crohn Disease Activity Index (CDAI) Score of greater than or equal to 300 prior to commencing treatment with this drug; or |
| | Patient must have a documented history of intestinal inflammation and have diagnostic imaging or surgical evidence of short gut syndrome if affected by the syndrome or has an ileostomy or colostomy; or |
| | Patient must have a documented history and radiological evidence of intestinal inflammation if the patient has extensive small intestinal disease affecting more than 50 cm of the small intestine. |

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| | **Treatment criteria:** |
| | Must be treated by a gastroenterologist (code 87); or |
| | Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; or |
| | Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)] |
| | |
| | **Population criteria:** |
| | Patient must be at least 18 years of age |
| | |
| | **Prescribing Instructions:**<br>The authority application must be made in writing and must include:<br>(1) a completed authority prescription form; and<br>(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). |
| | **Prescribing Instructions:**<br>Evidence of failure to achieve an adequate response to prior therapy must include at least one of the following:<br>(a) patient must have evidence of intestinal inflammation;<br>(b) patient must be assessed clinically as being in a high faecal output state;<br>(c) patient must be assessed clinically as requiring surgery or total parenteral nutrition (TPN) as the next therapeutic option, in the absence of this drug, if affected by short gut syndrome, extensive small intestine disease or is an ostomy patient.<br><br>Evidence of intestinal inflammation includes:<br>(i) blood: higher than normal platelet count, or, an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour, or, a C-reactive protein (CRP) level greater than 15 mg per L; or<br>(ii) faeces: higher than normal lactoferrin or calprotectin level; or<br>(iii) diagnostic imaging: demonstration of increased uptake of intravenous contrast with thickening of the bowel wall or mesenteric lymphadenopathy or fat streaking in the mesentery. |
| | **Prescribing Instructions:**<br>All assessments, pathology tests and diagnostic imaging studies were to have been within 4 weeks leading up to commencing the non-PBS subsidised supply of this drug and should have been performed preferably whilst still on conventional treatment, but no longer than 4 weeks following the last dose of conventional treatment.<br><br>Where extensive small intestinal disease affecting more than 50 cm of the small intestine applies, the CDAI must have been at least 220 prior to commencing the non-PBS subsidised supply of this drug. |
| | **Prescribing Instructions:**<br>If treatment with any of the specified prior conventional drugs is contraindicated according to the relevant TGA-approved Product Information, please provide details at the time of application. |
| | **Prescribing Instructions:**<br>If intolerance to treatment develops during the relevant period of use, which is of a severity necessitating permanent treatment withdrawal, details of this toxicity must be provided at the time of application. |
| | **Prescribing Instructions:**<br>Details of the accepted toxicities including severity can be found on the Services Australia website. |
| | **Prescribing Instructions:**<br>Any one of the baseline criteria may be used to determine response to an initial course of treatment and eligibility for continued therapy, according to the criteria included in the continuing treatment restriction. However, the same criterion must be used for any subsequent determination of response to treatment, for the purpose of eligibility for continuing PBS-subsidised therapy. |
| | |
| | **Administrative advice:**<br>Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria. |
| | **Administrative advice:**<br>This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria. |
| | **Administrative advice:**<br>Where prior systemic treatments are specified in this restriction, this is in the context of the time period leading up to the initiation of non-PBS subsidised supply of this drug. |
| | |
| **Restriction Summary / Treatment of Concept:: Authority Required** | |

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|---|---|
| | **Indication:** Severe Crohn disease |
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| | **Treatment Phase:** Balance of supply for Initial (induction) treatment phases |
| | |
| | **Treatment criteria:** |
| | Must be treated by a gastroenterologist (code 87); or |
| | Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; or |
| | Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)] |
| | |
| | **Clinical criteria:** |
| | The treatment must have been prescribed in a quantity in the most recent prescription which did not seek the full quantity available in regards to any of: (i) the quantity per dispensing, (ii) repeat prescriptions |
| | **AND** |
| | **Clinical criteria:** |
| | The treatment must provide no more than the balance available under the treatment phase from which the immediately preceding supply was obtained under |
| | |
| | **Administrative Advice:**<br>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). |
| | **Administrative Advice:**<br>Initial (induction) treatment phases and 'Extended induction' treatment phases for this benefit aim to provide 12 weeks treatment duration. |

| **Category / Program:** GENERAL – General Schedule (Code GE) | | | | | |
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| **MEDICINAL PRODUCT**<br>**medicinal product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of Rpts** | **Available brands** |
| UPADACITINIB | | | | | |
| upadactinib 30 mg modified release tablet, 28 | NEW<br>MP | 1 | 28 | 2 | Rinvoq |
| | | | | | Safety Net Rule Penalty Applies: Yes |

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| **Restriction Summary / Treatment of Concept: : Authority Required** | |
| | **Indication:** Severe Crohn disease |
| | |
| | **Treatment Phase:** Extended induction period (optional) from weeks 12 to 24 |
| | |
| | **Treatment criteria:** |
| | Must be treated by a gastroenterologist (code 87); or |
| | Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; or |
| | Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)] |
| | |
| | **Clinical criteria:** |
| | Patient must have experienced an inadequate therapeutic benefit following at least one of: (i) dosing with 45 mg daily in the initial 12-week induction period, (ii) dosing with 15 mg daily |
| | |
| | **Population criteria:** |
| | Patient must be at least 18 years of age |
| | |
| | **Administrative Advice:**<br>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). |
| | **Administrative Advice:** No increase in the maximum quantity or number of units may be authorised. |
| | **Administrative Advice:** No increase in the maximum number of repeats may be authorised. |

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| | **Administrative Advice:**<br>The prescriber completing this authority application must be a specialist medical practitioner of the type specified in the restriction. |

| **Category / Program:** GENERAL – General Schedule (Code GE) | | | | | |
|---|---|---|---|---|---|
| **MEDICINAL PRODUCT**<br>**medicinal product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of Rpts** | **Available brands** |
| UPADACITINIB | | | | | |
| upadactinib 30 mg modified release tablet, 28 | NEW<br>MP | 1 | 28 | 5 | Rinvoq |
| | | | | | Safety Net Rule Penalty Applies: Yes |

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| | **Administrative Advice:**<br>*insert updated long administrative 'NOTE' (currently concept 27712) here (shown at the end of the restrictions)* |
| | **Administrative advice:** No increase in the maximum quantity or number of units may be authorised. |
| | **Administrative advice:** No increase in the maximum number of repeats may be authorised. |
| | **Administrative Advice:**<br>Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).<br>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au<br>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos<br>Or mailed to:<br>Services Australia<br>Complex Drugs<br>Reply Paid 9826<br>HOBART TAS 7001 |
| | **Administrative Advice:**<br>The prescriber completing this authority application must be a specialist medical practitioner of the type specified in the restriction. |
| | |
| **Restriction Summary / Treatment of Concept:: Authority Required** | |
| | **Indication:** Severe Crohn disease |
| | |
| | **Treatment Phase:** Continuing (maintenance) treatment |
| | |
| | **Treatment criteria:** |
| | Must be treated by a gastroenterologist (code 87); or |
| | Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; or |
| | Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)] |
| | |
| | **Clinical criteria:** |
| | Patient must have received this drug as their most recent course of PBS-subsidised biological medicine treatment for this condition |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have an adequate response to this drug defined as a reduction in Crohn Disease Activity Index (CDAI) Score to a level no greater than 150 if assessed by CDAI or if affected by extensive small intestine disease; or |
| | Patient must have an adequate response to this drug defined as (a) an improvement of intestinal inflammation as demonstrated by: (i) blood: normalisation of the platelet count, or an erythrocyte sedimentation rate (ESR) level no greater than 25 mm per hour, or a C-reactive protein (CRP) level no greater than 15 mg per L; or (ii) faeces: normalisation of lactoferrin or calprotectin level; or (iii) evidence of mucosal healing, as demonstrated by diagnostic imaging findings, compared to the baseline assessment; or (b) reversal of high faecal output state; or (c) avoidance of the need for surgery or total parenteral nutrition (TPN), if affected by short gut syndrome, extensive small intestine or is an ostomy patient; or |
| | The condition must have not met the improvements specified above due to the prescribed dose being too low – this authority application seeks higher dosing |

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| | **Population criteria:** |
| | Patient must be at least 18 years of age |
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| | **Prescribing Instructions:**<br>The authority application must be made in writing and must include:<br>(1) a completed authority prescription form; and<br>(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). |
| | **Prescribing Instructions:**<br>In relation to the immediately preceding supply of this biological medicine, provide at least one of the following which is not more than 4 weeks from the last administered dose:<br>(i) the Crohn Disease Activity Index (CDAI) score, including the date the score was calculated on; or<br>(ii) the unique serial/identifying number and date(s) of pathology or diagnostic imaging test(s) used to assess response to therapy for patients with short gut syndrome, extensive small intestine disease or an ostomy, if relevant; |
| | |
| **Restriction Summary / Treatment of Concept; Authority Required** | |
| | **Indication:** Severe Crohn disease |
| | |
| | **Treatment Phase:** Transitioning from non-PBS to PBS-subsidised supply – 'grandfather' arrangements |
| | |
| | **Clinical criteria:** |
| | Patient must have commenced non-PBS supply prior to [insert listing date here] |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have confirmed severe Crohn disease, defined by standard clinical, endoscopic and/or imaging features, including histological evidence, with the diagnosis confirmed by a gastroenterologist or a consultant physician |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have failed to achieve an adequate response to prior systemic therapy with a tapered course of steroids, starting at a dose of at least 40 mg prednisolone (or equivalent), over a 6 week period |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have failed to achieve adequate response to prior systemic immunosuppressive therapy with azathioprine at a dose of at least 2 mg per kg daily for 3 or more consecutive months; or |
| | Patient must have failed to achieve adequate response to prior systemic immunosuppressive therapy with 6-mercaptopurine at a dose of at least 1 mg per kg daily for 3 or more consecutive months; or |
| | Patient must have failed to achieve adequate response to prior systemic immunosuppressive therapy with methotrexate at a dose of at least 15 mg weekly for 3 or more consecutive months |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have had a Crohn Disease Activity Index (CDAI) Score of greater than or equal to 300 prior to commencing treatment with this drug; or |
| | Patient must have a documented history of intestinal inflammation and have diagnostic imaging or surgical evidence of short gut syndrome if affected by the syndrome or has an ileostomy or colostomy; or |
| | Patient must have a documented history and radiological evidence of intestinal inflammation if the patient has extensive small intestinal disease affecting more than 50 cm of the small intestine. |
| | |
| | **Treatment criteria:** |
| | Must be treated by a gastroenterologist (code 87); or |
| | Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; or |
| | Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)] |
| | |
| | **Population criteria:** |
| | Patient must be at least 18 years of age |

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| | **Prescribing Instructions:**<br>The authority application must be made in writing and must include:<br>(1) a completed authority prescription form; and<br>(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). |
| | **Prescribing Instructions:**<br>Evidence of failure to achieve an adequate response to prior therapy must include at least one of the following:<br>(a) patient must have evidence of intestinal inflammation;<br>(b) patient must be assessed clinically as being in a high faecal output state;<br>(c) patient must be assessed clinically as requiring surgery or total parenteral nutrition (TPN) as the next therapeutic option, in the absence of this drug, if affected by short gut syndrome, extensive small intestine disease or is an ostomy patient.<br><br>Evidence of intestinal inflammation includes:<br>(i) blood: higher than normal platelet count, or, an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour, or, a C-reactive protein (CRP) level greater than 15 mg per L; or<br>(ii) faeces: higher than normal lactoferrin or calprotectin level; or<br>(iii) diagnostic imaging: demonstration of increased uptake of intravenous contrast with thickening of the bowel wall or mesenteric lymphadenopathy or fat streaking in the mesentery. |
| | **Prescribing Instructions:**<br>All assessments, pathology tests and diagnostic imaging studies were to have been within 4 weeks leading up to commencing the non-PBS subsidised supply of this drug and should have been performed preferably whilst still on conventional treatment, but no longer than 4 weeks following the last dose of conventional treatment.<br><br>Where extensive small intestinal disease affecting more than 50 cm of the small intestine applies, the CDAI must have been at least 220 prior to commencing the non-PBS subsidised supply of this drug. |
| | **Prescribing Instructions:**<br>If treatment with any of the specified prior conventional drugs is contraindicated according to the relevant TGA-approved Product Information, please provide details at the time of application. |
| | **Prescribing Instructions:**<br>If intolerance to treatment develops during the relevant period of use, which is of a severity necessitating permanent treatment withdrawal, details of this toxicity must be provided at the time of application. |
| | **Prescribing Instructions:**<br>Details of the accepted toxicities including severity can be found on the Services Australia website. |
| | **Prescribing Instructions:**<br>Any one of the baseline criteria may be used to determine response to an initial course of treatment and eligibility for continued therapy, according to the criteria included in the continuing treatment restriction. However, the same criterion must be used for any subsequent determination of response to treatment, for the purpose of eligibility for continuing PBS-subsidised therapy. |
| | |
| | **Administrative advice:**<br>Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria. |
| | **Administrative advice:**<br>This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria. |
| | **Administrative advice:**<br>Where prior systemic treatments are specified in this restriction, this is in the context of the time period leading up to the initiation of non-PBS subsidised supply of this drug. |
| | |
| **Restriction Summary / Treatment of Concept:: Authority Required** | |
| | **Indication:** Severe Crohn disease |
| | |
| | **Treatment Phase:** Balance of supply for the Continuing (maintenance) treatment phase |
| | |
| | **Treatment criteria:** |
| | Must be treated by a gastroenterologist (code 87); or |
| | Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; or |
| | Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)] |

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| | **Clinical criteria:** |
| | The treatment must have been prescribed in a quantity in the most recent prescription which did not seek the full quantity available in regards to any of: (i) the quantity per dispensing, (ii) repeat prescriptions |
| | **AND** |
| | **Clinical criteria:** |
| | The treatment must provide no more than the balance available under the treatment phase from which the immediately preceding supply was obtained under |
| | |
| | **Administrative Advice:**<br>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). |
| | **Administrative Advice:** Continuing (maintenance) treatment aims to provide 24 weeks. |

| **Category / Program:** GENERAL – General Schedule (Code GE) | | | | | |
|---|---|---|---|---|---|
| **MEDICINAL PRODUCT**<br>**medicinal product pack** | **PBS item code** | **Max. qty packs** | **Max. qty units** | **№.of Rpts** | **Available brands** |
| UPADACITINIB | | | | | |
| upadactinib 15 mg modified release tablet, 28 | NEW<br>MP | 1 | 28 | 5 | Rinvoq |
| | | | | | Safety Net Rule Penalty Applies: Yes |

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| | **Administrative Advice:**<br>*Insert updated long administrative 'NOTE' (currently concept 27712) here (shown at the end of the restrictions)* |
| | **Administrative advice:** No increase in the maximum quantity or number of units may be authorised. |
| | **Administrative advice:** No increase in the maximum number of repeats may be authorised. |
| | **Administrative Advice:**<br>Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).<br><br>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au<br><br>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos<br>Or mailed to:<br>Services Australia<br>Complex Drugs<br>Reply Paid 9826<br>HOBART TAS 7001 |
| | **Administrative Advice:**<br>The prescriber completing this authority application must be a specialist medical practitioner of the type specified in the restriction. |
| | |
| **Restriction Summary / Treatment of Concept: : Authority Required** | |
| | **Indication:** Severe Crohn disease |
| | |
| | **Treatment Phase:** Continuing treatment (maintenance treatment) |
| | |
| | **Treatment criteria:** |
| | Must be treated by a gastroenterologist (code 87); or |
| | Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; or |
| | Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)] |
| | |
| | **Clinical criteria:** |

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|---|---|
| | Patient must have received this drug as their most recent course of PBS-subsidised biological medicine treatment for this condition |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have an adequate response to this drug defined as a reduction in Crohn Disease Activity Index (CDAI) Score to a level no greater than 150 if assessed by CDAI or if affected by extensive small intestine disease; or |
| | Patient must have an adequate response to this drug defined as (a) an improvement of intestinal inflammation as demonstrated by: (i) blood: normalisation of the platelet count, or an erythrocyte sedimentation rate (ESR) level no greater than 25 mm per hour, or a C-reactive protein (CRP) level no greater than 15 mg per L; or (ii) faeces: normalisation of lactoferrin or calprotectin level; or (iii) evidence of mucosal healing, as demonstrated by diagnostic imaging findings, compared to the baseline assessment; or (b) reversal of high faecal output state; or (c) avoidance of the need for surgery or total parenteral nutrition (TPN), if affected by short gut syndrome, extensive small intestine or is an ostomy patient; |
| | |
| | **Population criteria:** |
| | Patient must be at least 18 years of age |
| | |
| | **Prescribing Instructions:**<br>The authority application must be made in writing and must include:<br>(1) a completed authority prescription form; and<br>(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). |
| | **Prescribing Instructions:**<br>In relation to the immediately preceding supply of this biological medicine, provide at least one of the following which is not more than 4 weeks from the last administered dose:<br>(i) the Crohn Disease Activity Index (CDAI) score, including the date the score was calculated on; or<br>(ii) the unique serial/identifying number and date(s) of pathology or diagnostic imaging test(s) used to assess response to therapy for patients with short gut syndrome, extensive small intestine disease or an ostomy, if relevant; |
| | |
| **Restriction Summary / Treatment of Concept: : Authority Required** | |
| | **Indication:** Severe Crohn disease |
| | |
| | **Treatment Phase:** Transitioning from non-PBS to PBS-subsidised supply – 'grandfather' arrangements |
| | |
| | **Clinical criteria:** |
| | Patient must have commenced non-PBS supply prior to [insert listing date here] |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have confirmed severe Crohn disease, defined by standard clinical, endoscopic and/or imaging features, including histological evidence, with the diagnosis confirmed by a gastroenterologist or a consultant physician |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have failed to achieve an adequate response to prior systemic therapy with a tapered course of steroids, starting at a dose of at least 40 mg prednisolone (or equivalent), over a 6 week period |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have failed to achieve adequate response to prior systemic immunosuppressive therapy with azathioprine at a dose of at least 2 mg per kg daily for 3 or more consecutive months; or |
| | Patient must have failed to achieve adequate response to prior systemic immunosuppressive therapy with 6-mercaptopurine at a dose of at least 1 mg per kg daily for 3 or more consecutive months; or |
| | Patient must have failed to achieve adequate response to prior systemic immunosuppressive therapy with methotrexate at a dose of at least 15 mg weekly for 3 or more consecutive months |
| | **AND** |
| | **Clinical criteria:** |
| | Patient must have had a Crohn Disease Activity Index (CDAI) Score of greater than or equal to 300 prior to commencing treatment with this drug; or |
| | Patient must have a documented history of intestinal inflammation and have diagnostic imaging or surgical evidence of short gut syndrome if affected by the syndrome or has an ileostomy or colostomy; or |
| | Patient must have a documented history and radiological evidence of intestinal inflammation if the patient has extensive small intestinal disease affecting more than 50 cm of the small intestine. |

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| | **Treatment criteria:** |
| | Must be treated by a gastroenterologist (code 87); or |
| | Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; or |
| | Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)] |
| | |
| | **Population criteria:** |
| | Patient must be at least 18 years of age |
| | |
| | **Prescribing Instructions:**<br>The authority application must be made in writing and must include:<br>(1) a completed authority prescription form; and<br>(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). |
| | **Prescribing Instructions:**<br>Evidence of failure to achieve an adequate response to prior therapy must include at least one of the following:<br>(a) patient must have evidence of intestinal inflammation;<br>(b) patient must be assessed clinically as being in a high faecal output state;<br>(c) patient must be assessed clinically as requiring surgery or total parenteral nutrition (TPN) as the next therapeutic option, in the absence of this drug, if affected by short gut syndrome, extensive small intestine disease or is an ostomy patient.<br><br>Evidence of intestinal inflammation includes:<br>(i) blood: higher than normal platelet count, or, an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour, or, a C-reactive protein (CRP) level greater than 15 mg per L; or<br>(ii) faeces: higher than normal lactoferrin or calprotectin level; or<br>(iii) diagnostic imaging: demonstration of increased uptake of intravenous contrast with thickening of the bowel wall or mesenteric lymphadenopathy or fat streaking in the mesentery. |
| | **Prescribing Instructions:**<br>All assessments, pathology tests and diagnostic imaging studies were to have been within 4 weeks leading up to commencing the non-PBS subsidised supply of this drug and should have been performed preferably whilst still on conventional treatment, but no longer than 4 weeks following the last dose of conventional treatment.<br><br>Where extensive small intestinal disease affecting more than 50 cm of the small intestine applies, the CDAI must have been at least 220 prior to commencing the non-PBS subsidised supply of this drug. |
| | **Prescribing Instructions:**<br>If treatment with any of the specified prior conventional drugs is contraindicated according to the relevant TGA-approved Product Information, please provide details at the time of application. |
| | **Prescribing Instructions:**<br>If intolerance to treatment develops during the relevant period of use, which is of a severity necessitating permanent treatment withdrawal, details of this toxicity must be provided at the time of application. |
| | **Prescribing Instructions:**<br>Details of the accepted toxicities including severity can be found on the Services Australia website. |
| | **Prescribing Instructions:**<br>Any one of the baseline criteria may be used to determine response to an initial course of treatment and eligibility for continued therapy, according to the criteria included in the continuing treatment restriction. However, the same criterion must be used for any subsequent determination of response to treatment, for the purpose of eligibility for continuing PBS-subsidised therapy. |
| | |
| | **Administrative advice:**<br>Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria. |
| | **Administrative advice:**<br>This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria. |
| | **Administrative advice:**<br>Where prior systemic treatments are specified in this restriction, this is in the context of the time period leading up to the initiation of non-PBS subsidised supply of this drug. |
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| **Restriction Summary / Treatment of Concept: : Authority Required** | |
| | **Indication:** Severe Crohn disease |

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| | **Treatment Phase:** Balance of supply for the Continuing (maintenance) treatment phase |
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| | **Treatment criteria:** |
| | Must be treated by a gastroenterologist (code 87); or |
| | Must be treated by a consultant physician [internal medicine specialising in gastroenterology (code 81)]; or |
| | Must be treated by a consultant physician [general medicine specialising in gastroenterology (code 82)] |
| | |
| | **Clinical criteria:** |
| | The treatment must have been prescribed in a quantity in the most recent prescription which did not seek the full quantity available in regards to any of: (i) the quantity per dispensing, (ii) repeat prescriptions |
| | **AND** |
| | **Clinical criteria:** |
| | The treatment must provide no more than the balance available under the treatment phase from which the immediately preceding supply was obtained under |
| | |
| | **Administrative Advice:**<br>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). |
| | **Administrative Advice:** Continuing (maintenance) treatment aims to provide 24 weeks. |

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| | **Administrative Advice:**<br>**SEVERE CROHN DISEASE – TREATMENT PHASES AND CYCLES**<br>The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of benefits that contain the words: 'severe Crohn disease' in the stated PBS indication. Some of these benefits are not biological medicines, but are small molecules (e.g. a Janus-kinase inhibitor). Where the term 'biological medicine' appears in the restriction, it includes such benefits for PBS administrative purposes.<br><br>A patient is eligible for PBS-subsidised treatment with only one PBS-subsidised biological medicine at any one time.<br><br>Treatment cycle:<br>A treatment cycle begins when an authority application is approved under an Initial 1 or Initial 3 type restriction. Once commenced, where biological medicine fails to provide the patient with an adequate response on 3 occasions, the current treatment cycle ends and there must be an absence of PBS-subsidy for a period of 5 years. The 5 year break is measured from the date of the last approval for PBS-subsidised biological medicine treatment in the most recent cycle to the date of the first application for initial treatment with a biological medicine under the new treatment cycle.<br><br>An exception to this 5 year break clause applies where:<br>(i) since the commencement of the break, an additional biological medicine has since become PBS-listed with a different pharmacological mechanism of action (i.e. the newly listed biological medicine) relative to those available on the PBS at the time of commencing the 5 year break; and<br>(ii) the patient has never been prescribed the newly listed biological medicine; and<br>(iii) the prescribed biological medicine is the newly listed biological medicine.<br>Prescribing of the newly listed biological medicine is to occur through the 'Initial 2' treatment phase listing and the patient will not be in a new treatment cycle (i.e. where this newly listed biological medicine fails to provide an adequate response, the current treatment cycle ends and there must be an absence of PBS-subsidised biological medicine for a period of 5 years unless the exception outlined above is triggered again).<br><br>Within the same treatment cycle, the same PBS-subsidised biological medicine cannot continue to be subsidised where it has resulted in an inadequate response. An inadequate response is one which does not meet the minimum improvements in disease measures stated in the Continuing treatment restriction. A serious adverse reaction leading to treatment discontinuation will be exempted from being counted as an inadequate response.<br><br>There is no limit to the number of treatment cycles a patient may undertake in their lifetime.<br><br>Treatment phases:<br>(a) Initial 1<br>Apply through this treatment phase where the patient has never been treated with PBS-subsidised biological medicine for this indication. |

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| | (b) Initial 2<br>Apply through this treatment phase where the prescribed treatment is changing (other than dose/form), or, where there has been a break in therapy of less than 5 years and treatment is resuming; authority applications through this treatment phase do not require prior response to conventional therapies to be re-established and do not require baseline disease activity to be re-demonstrated. An assessment of response to the preceding supply must be provided – where it is not, it will be assumed that the preceding supply provided an inadequate response.<br><br>(c) Initial 3<br>Apply through this treatment phase where treatment is resuming after an absence of PBS-subsidy for at least 5 years; authority applications through this treatment phase do not require a re-trial of conventional therapies.<br><br>(d) Continuing treatment<br>Apply through this treatment phase where an adequate response to the preceding supply is observed (or where the dose is increasing where multiple strengths exist). It is recommended that a patient be reviewed in the 4 weeks prior to exhausting the current supply to ensure uninterrupted supply. Continuing treatment authority applications are not to be made on the same day as Initial treatment authority applications.<br><br>(e) Balance of supply<br>Apply through this type of treatment phase only where the benefit was not requested in the full amount available in the preceding supply – this may be because the maximum quantity was not prescribed and/or the full number of repeat prescriptions was not prescribed. The intent of this treatment phase listing is to: (i) provide the balance of what could have been obtained had the full quantity and number of repeats been prescribed in the preceding authority application, (ii) allow further time for an adequate response to treatment to be demonstrated where it may not have already, and (iii) provide more immediate access to PBS-subsidy via a telephone/online authority application relative to an 'in-writing only' application where the preceding supply was obtained through such. |

**27712 Concept lineage (as at 1 December 2022):**

**PBS item code / medicinal product pack:**

9188N / adalimumab 40 mg/0.8 mL injection, 2 x 0.8 mL syringes
9189P / adalimumab 40 mg/0.8 mL injection, 2 x 0.8 mL syringes
9190Q / adalimumab 40 mg/0.8 mL injection, 2 x 0.8 mL pen devices
9191R / adalimumab 40 mg/0.8 mL injection, 2 x 0.8 mL pen devices
12419P / adalimumab 80 mg/0.8 mL injection, 0.8 mL pen device
12372E / adalimumab 80 mg/0.8 mL injection, 0.8 mL syringe
12352D / adalimumab 40 mg/0.8 mL injection, 2 x 0.8 mL pen devices
12402R / adalimumab 40 mg/0.8 mL injection, 2 x 0.8 mL pen devices
12437N / adalimumab 40 mg/0.8 mL injection, 2 x 0.8 mL syringes
12345R / adalimumab 40 mg/0.4 mL injection, 2 x 0.4 mL pen devices
12389C / adalimumab 40 mg/0.4 mL injection, 2 x 0.4 mL pen devices
12451H / adalimumab 40 mg/0.4 mL injection, 2 x 0.4 mL syringes
12410E / adalimumab 40 mg/0.4 mL injection, 2 x 0.4 mL syringes
12387Y / adalimumab 40 mg/0.8 mL injection, 2 x 0.8 mL syringes
12433J / adalimumab 40 mg/0.4 mL injection, 2 x 0.4 mL pen devices
12453K / adalimumab 40 mg/0.4 mL injection, 2 x 0.4 mL syringes

5754W / infliximab 100 mg injection, 1 vial
9613Y / infliximab 100 mg injection, 1 vial
11400B / infliximab 100 mg injection, 1 vial
11396T / infliximab 100 mg injection, 1 vial
11389K / infliximab 100 mg injection, 1 vial
11399Y / infliximab 100 mg injection, 1 vial
12551N / infliximab 120 mg/mL injection, 1 mL pen device
12585J / infliximab 120 mg/mL injection, 1 mL syringe
12560C / infliximab 120 mg/mL injection, 1 mL pen device
12586K / infliximab 120 mg/mL injection, 1 mL syringe
12567K / infliximab 120 mg/mL injection, 1 mL pen device
12597B / infliximab 120 mg/mL injection, 1 mL syringe

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| 11182M / ustekinumab 130 mg/26 mL injection, 26 mL vial<br>11164N / ustekinumab 130 mg/26 mL injection, 26 mL vial<br>11178H / ustekinumab 45 mg/0.5 mL injection, 0.5 mL vial<br><br>10390W / vedolizumab 300 mg injection, 1 vial<br>10415E / vedolizumab 300 mg injection, 1 vial<br>12638E / vedolizumab 108 mg/0.68 mL injection, 2 x 0.68 mL pen devices<br>12654B / vedolizumab 108 mg/0.68 mL injection, 2 x 0.68 mL pen devices<br>12620F / vedolizumab 108 mg/0.68 mL injection, 2 x 0.68 mL pen devices |

***This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed***.

# 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

The sponsor had no comment.