

## 5.16 METHOTREXATE

**Solution for subcutaneous injection, pre-filled syringe,  
7.5 mg/0.15 mL, 10 mg/0.2 mL, 15 mg/0.3 mL, 20 mg/0.4 mL,  
25 mg/0.5 mL**

**Trexject®, Link Medical Products Pty Ltd**

### 1 Purpose of Application

- 1.1 The minor submission requested listing of methotrexate pre-filled syringe (with embedded needle) on the PBS for the treatment of rheumatoid arthritis or psoriasis when methotrexate oral tablet is unsuitable.

### 2 Requested listing

- 2.1 The submission requested the following new listing (p 13-14 of the submission):

| Name, Restriction,<br>Manner of administration and form | Max.<br>Qty | No. of<br>Rpts | Dispensed<br>Price for<br>Max. Qty | Proprietary Name and<br>Manufacturer |
|---|-------------|----------------|------------------------------------|--------------------------------------|
| METHOTREXATE  |             |                |                                    | Trexject® Link Medical Products      |
| 7.5 mg/0.15 mL injection, 1 x 0.15 mL syringe           | 4           | 5              | \$ [REDACTED]                      |                                      |
| 10 mg/0.2 mL injection, 1 x 0.2 mL syringe              | 4           | 5              | \$ [REDACTED]                      |                                      |
| 15 mg/0.3 mL injection, 1 x 0.3 mL syringe              | 4           | 5              | \$ [REDACTED]                      |                                      |
| 20 mg/0.4 mL injection, 1 x 0.4 mL syringe              | 4           | 5              | \$ [REDACTED]                      |                                      |
| 25 mg/0.5 mL injection, 1 x 0.5 mL syringe              | 4           | 5              | \$ [REDACTED]                      |                                      |

|                             |  |
|-----------------------------|--|
| Category / Program          | GENERAL – General Schedule (Code GE)   |
| Prescriber type:            | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists<br><input type="checkbox"/> Midwives  |
| Episodicity:                | Chronic treatment  |
| Severity:                   | Severe, recalcitrant, active   |
| Condition:                  | Rheumatoid arthritis   |
| PBS Indication:             | For the treatment of rheumatoid arthritis when the oral tablet form of methotrexate is unsuitable  |
| Treatment phase:            | Initial and continuing   |
| Restriction Level / Method: | <input checked="" type="checkbox"/> Restricted benefit<br><input type="checkbox"/> Authority Required - In Writing<br><input type="checkbox"/> Authority Required - Telephone<br><input type="checkbox"/> Authority Required – Emergency<br><input type="checkbox"/> Authority Required - Electronic<br><input type="checkbox"/> Streamlined |
| Clinical criteria:          | The condition must not be responding to, or intolerant of, an adequate trial of NSAIDs and one or more disease modifying drugs   |
| Population criteria:        | The patient must be adult.<br>The solid dose form of methotrexate must be unsuitable for the patient.  |

|                             |  |
|-----------------------------|--|
| Category / Program          | GENERAL – General Schedule (Code GE)   |
| Prescriber type:            | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists<br><input type="checkbox"/> Midwives  |
| Episodicity:                | Chronic treatment  |
| Severity:                   | Severe, recalcitrant, disabling  |
| Condition:                  | Psoriasis  |
| PBS Indication:             | For the treatment of psoriasis when the oral tablet form of methotrexate is unsuitable   |
| Treatment phase:            | Initial and continuing   |
| Restriction Level / Method: | <input checked="" type="checkbox"/> Restricted benefit<br><input type="checkbox"/> Authority Required - In Writing<br><input type="checkbox"/> Authority Required - Telephone<br><input type="checkbox"/> Authority Required – Emergency<br><input type="checkbox"/> Authority Required - Electronic<br><input type="checkbox"/> Streamlined |
| Clinical criteria:          | Patient must have severe, recalcitrant, disabling psoriasis which is not adequately responsive to other forms of treatment   |
| Population criteria:        | The patient must be adult.<br>The solid dose form of methotrexate must be unsuitable for the patient.  |

2.2 The Pre-PBAC response acknowledged that parenteral methotrexate has broad application in medicine and expressed a willingness to discuss the most appropriate restriction level.

### 3 Background

3.1 Methotrexate pre-filled syringe is TGA registered for the following indications:

- Rheumatoid arthritis therapy: Management of severe, recalcitrant, active rheumatoid arthritis in adults not responding to, or intolerant of, an adequate trial of NSAIDs and one or more disease modifying drugs.
- Psoriasis therapy: May be of value in the symptomatic control of severe, recalcitrant, disabling psoriasis in adults which is not adequately responsive to other forms of treatment.

3.2 Methotrexate pre-filled syringe has not previously been considered by PBAC.

3.3 Methotrexate vials for injection, the nominated comparator, were granted a substantial price increase under the PBS in December 2015 based on an annual PBS price review (ex-manufacturer price increased from \$[REDACTED] to \$[REDACTED]).

3.4 The Pre-PBAC response noted the price increase of the nominated comparator and presented updated economic analysis and financial estimates.

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

#### **4 Clinical place for the proposed therapy**

- 4.1 Rheumatoid arthritis is a chronic, inflammatory condition that primarily affects synovial joints. Symptoms develop gradually and may include joint pain, stiffness and swelling. Severe rheumatoid arthritis may cause progressive joint destruction with different grades of deformity and functional disability.
- 4.2 Psoriasis is a chronic, inflammatory skin disorder typically characterised by patches of red, itchy and scaly skin. Severity can range from a few isolated plaques to widespread inflammation with pustules and systemic symptoms.
- 4.3 The submission positioned methotrexate pre-filled syringes as an alternative to other parenteral methotrexate formulations for patients in whom the oral tablet formulation was unsuitable (p 19-20 of the submission).
- 4.4 The submission stated that patients may switch from oral to parenteral formulations for a variety of reasons including:
- Gastric intolerance;
  - Bioavailability issues with oral tablets resulting in reduced efficacy;
  - Inability to swallow oral tablets.
- 4.5 The submission claimed that methotrexate pre-filled syringes offered advantages compared to other parenteral formulations due to its ease of use and ability to be self-administered by patients/carers.
- 4.6 The submission also claimed that the fixed dose formulation of the pre-filled syringes reduced the potential for overdose or mis-dose due to measurement error (a potential risk with drawing up a dose from the methotrexate vials). The submission also argued that the ready-prepared nature of the pre-filled syringe reduces unnecessary cytotoxic exposure.
- 4.7 The most commonly co-administered drug is folic acid for the reduction of toxicities associated with methotrexate treatment. Other concomitant therapies include various disease-modifying antirheumatic drugs (DMARDs) and biological disease-modifying antirheumatic drugs (bDMARDs) such as leflunomide, adalimumab, etanercept and infliximab.

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

#### **5 Comparator**

- 5.1 The submission nominated other parenteral methotrexate formulations as the main comparator on the basis that methotrexate pre-filled syringes will most likely substitute for these therapies (p 17-18 of the submission). The comparator was considered appropriate.
- 5.2 The submission claimed that methotrexate 50 mg/2 mL vials for injection are the most comparable presentation as the injection volume is small enough to allow for

subcutaneous or intramuscular injection at standard dose ranges for rheumatoid arthritis and psoriasis. This argument appeared reasonable.

5.3 Table 1 summarises the key differences between methotrexate pre-filled syringe and methotrexate 50 mg/2 mL vials.

Table 1: Summary of the main differences between methotrexate pre-filled syringe and methotrexate vial

|                         | Methotrexate pre-filled syringe   | Methotrexate vial  |
|-------------------------|---|--|
| Presentation            | Pre-filled syringe (7.5 mg, 10 mg, 15 mg, 20 mg, 25 mg) with an embedded needle   | Vial (50 mg), requires separate syringe  |
| Indications             | Rheumatoid arthritis: Management of severe, recalcitrant, active rheumatoid arthritis<br><br>Psoriasis: Symptomatic control of severe, recalcitrant, disabling psoriasis in adults which is not adequately responsive to other forms of treatment | Rheumatoid arthritis: Not TGA registered but currently recommended for moderate-to-severe rheumatoid arthritis (AMH, 2016; eTG 2015)<br><br>Psoriasis: Symptomatic control of severe, recalcitrant, disabling psoriasis in adults which is not adequately responsive to other forms of treatment<br><br>TGA registered for antineoplastic chemotherapy and various oncology indications. Also currently recommended for use in various autoimmune diseases (AMH, 2016; eTG 2015) |
| PBS restriction         | Restricted benefit: Severe, recalcitrant, active rheumatoid arthritis or psoriasis [Requested listing]  | Unrestricted   |
| Route of administration | Subcutaneous injection<br><br>If the clinical situation permits, the treating physician can delegate administration to the patient or caregiver   | Intramuscular, intravenous, intra-arterial, intrathecal injection. Subcutaneous dosing is not included in the product information but is an accepted route of administration (AMH, 2016; eTG 2015)<br><br>Should only be administered by a healthcare professional   |
| Dose                    | Product information<br>Rheumatoid arthritis: 7.5-25 mg per week (should not typically exceed 20 mg)<br>Psoriasis: 7.5-25 mg per week (should not typically exceed 20 mg)  | Product information<br>Rheumatoid arthritis: NA<br>Psoriasis: 10-50 mg per week (should not typically exceed 25 mg)<br><br>Australian Medicines Handbook 2016<br>Rheumatoid arthritis: 5-25 mg per week<br>Psoriasis: 7.5-30 mg per week (should not typically exceed 15 mg)<br><br>Therapeutic guidelines 2015:<br>Rheumatoid arthritis: 5-25 mg per week<br>Psoriasis: 5-20 mg per week  |

Abbreviations: AMH, Australian Medicines Handbook; NA, not applicable; PBS, Pharmaceutical Benefits Scheme; TGA, Therapeutic Goods Administration

Source: Table 4 (p 21-22) of the submission; Australian Medicines Handbook ([www.amh.net.au](http://www.amh.net.au), accessed 1 February 2016), Electronic Therapeutic Guidelines ([www.etg.hcn.com.au](http://www.etg.hcn.com.au), accessed 1 February 2016; Trexject® product information and Methacord® product information

- 5.4 Overall, methotrexate pre-filled syringes appeared to offer improved convenience to both patients and physicians at the cost of reduced dosing flexibility compared to methotrexate vials.

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

## 6 Consideration of the evidence

### **Sponsor hearing**

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

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from health care professionals (4) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with parenteral methotrexate including decreasing nausea and gastrointestinal upsets for those patients who cannot tolerate the oral form and making the treatment process easier in the context of self-administration. The comments also noted that consideration would need to be given to the appropriate method of disposal for the pre-filled syringes.

### **Clinical trials**

- 6.3 The submission was based on a bioequivalence study comparing subcutaneous (10 mg/mL) and intramuscular (10 mg/mL) methotrexate injections (Study MC-MTX.7/PH) as well as an observational study that assessed patient preference, satisfaction and usability of methotrexate pre-filled syringes in patients, physicians and nurses (Striesow & Brandt, 2012). The submission also provided a brief summary of the other clinical studies included in the registration dossier as well as specific studies from the published literature. Study MC-MTX.9/PH was considered in further detail in the evaluation as it compared the bioequivalence of high concentration methotrexate injections (50 mg/mL, same as marketed presentation) with low concentration injections (10 mg/mL).
- 6.4 Publication details of the included studies are provided in the table below.

Table 2: Clinical studies presented in the submission

| Trial ID                 | Protocol title/ Publication title  | Publication citation                 |
|--------------------------|--|--------------------------------------|
| MC-MTX.5/RH              | Not reported   | Internal study report (not provided) |
| MC-MTX.6/RH (Braun 2008) | Not reported   | Internal study report (not provided) |
|                          | Braun et al (2008). Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis | Arthritis & Rheumatism, 58(1):73-81  |
| MC-MTX.7/PH              | Not reported   | Internal study report (not provided) |
| MC-MTX.9/PH              | Not reported   | Internal study report (not provided) |

| Trial ID               | Protocol title/ Publication title  | Publication citation                                      |
|------------------------|--|---|
| MC-MTX.10/RH           | Not reported   | Internal study report (not provided)                      |
| Casalan 2013           | Casalan et al (2013). Prevalence of methotrexate intolerance in rheumatoid arthritis and psoriatic arthritis   | Arthritis Research & Therapy, 15(6):R217                  |
| Schiff 2014            | Schiff et al (2014). Head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses $\geq 15$ mg may be overcome with subcutaneous administration | Annals of the Rheumatic Diseases, 73(8):1549-51           |
| Scott 2014             | Scott et al (2014). Retrospective evaluation of continuation rates following a switch to subcutaneous methotrexate in rheumatoid arthritis patients failing to respond to or tolerate oral methotrexate: the MENTOR study  | Scandinavian Journal of Rheumatology, 43(6):470-6         |
| Tymms 2014             | Tymms et al (2014). Barriers to optimal disease control for rheumatoid arthritis patients with moderate and high disease activity  | Arthritis Care & Research, 66(2):190-6                    |
| Littlejohn 2013        | Littlejohn et al (2013). A multi-center, observational study shows high proportion of Australian rheumatoid arthritis patients have inadequate disease control   | International Journal of Rheumatic Diseases, 16:532-538   |
| Littlejohn 2015        | Littlejohn et al (2015). Patients with rheumatoid arthritis in the Australian OPAL cohort show significant improvement in disease activity over 5 years: a multicenter observational study   | The Journal of Rheumatology, 42(9):1603-9                 |
| Striesow & Brandt 2012 | Striesow & Brandt (2012). Preference, satisfaction and usability of subcutaneously administered methotrexate for rheumatoid arthritis or psoriatic arthritis: results of a postmarketing surveillance study  | Therapeutic Advances in Musculoskeletal Disease, 4(1):3-9 |

Source: Table 5 (p 24) and Table 6 (p 25) of the submission

### Comparative effectiveness

- 6.5 Study MC-MTX.7/PH was a phase 1, open-label, single-phase crossover study comparing single dose (15 mg) intramuscular and subcutaneous methotrexate using the 10 mg/mL injection solution in healthy adults (N=16). A summary of pharmacokinetic parameter results are presented in Table 3.

Table 3: Primary pharmacokinetic parameter results for Study MC-MTX.7/PH

| Parameter                   | Subcutaneous methotrexate | Intramuscular methotrexate | Geometric mean ratio (%) | 90% CI       |
|-----------------------------|---------------------------|----------------------------|--------------------------|--------------|
| t <sub>max</sub> , h        | 1.03 (1.7)                | 0.54 (1.7)                 | -                        | -            |
| AUC <sub>0-t</sub> (µg*h/L) | 1020.79 (1.23)            | 1043.33 (1.18)             | 97.84                    | 91.07-105.11 |
| AUC <sub>0-∞</sub> (µg*h/L) | 1058.89 (1.22)            | 1088.86 (1.18)             | 97.25                    | 91.00-103.92 |
| C <sub>max</sub> (µg/L)     | 221.76 (1.39)             | 381.28 (1.37)              | 58.16                    | 47.61-71.06  |

Source: Table 8 (p 28) of the submission; p 5 of the MC-MTX.7/PH trial report

Abbreviations: AUC, area under the plasma concentration time curve; C<sub>max</sub>, maximum plasma concentration; CI, confidence interval; t<sub>max</sub>, time of maximum concentration

Intramuscular injections were associated with a higher maximum concentration (C<sub>max</sub>) at an earlier time point (T<sub>max</sub>) compared to subcutaneous injections. Both routes of administration were bioequivalent in terms of extent of drug exposure (AUC).

- 6.6 Study MC-MTX.9/PH was a phase 1, open-label, two-phase crossover study comparing single dose (15 mg) methotrexate injections using high concentration

(50 mg/mL) or low concentration (10 mg/mL) solution in healthy adults (N=24). Half the subjects received subcutaneous injections while the other half received intramuscular injections (crossover by solution concentration not route of administration). A summary of pharmacokinetic parameter results are presented in Table 4.

Table 4: Primary pharmacokinetic parameter results for Study MC-MTX.9/PH

| Comparison                                      | Geometric mean ratio (%) | 90% CI       |
|---|--------------------------|--------------|
| <b>AUC<sub>0-∞</sub> (µg*h/L)</b>               |                          |              |
| 50 mg/mL SC injection vs. 10 mg/mL SC injection | 97.56                    | 89.90-105.88 |
| 50 mg/mL IM injection vs. 10 mg/mL IM injection | 91.85                    | 84.63-99.68  |
| 50 mg/mL SC injection vs. 50 mg/mL IM injection | 124.1                    | 112-137      |
| 10 mg/mL SC injection vs. 10 mg/mL IM injection | 117.0                    | 104-131      |
| <b>AUC<sub>0-t</sub> (µg*h/L)</b>               |                          |              |
| 50 mg/mL SC injection vs. 10 mg/mL SC injection | 98.07                    | 90.42-106.37 |
| 50 mg/mL IM injection vs. 10 mg/mL IM injection | 91.90                    | 84.73-99.68  |
| 50 mg/mL SC injection vs. 50 mg/mL IM injection | 123.9                    | 112-137      |
| 10 mg/mL SC injection vs. 10 mg/mL IM injection | 116.1                    | 104-130      |
| <b>C<sub>max</sub> (µg/L)</b>                   |                          |              |
| 50 mg/mL SC injection vs. 10 mg/mL SC injection | 114.93                   | 90.96-145.22 |
| 50 mg/mL IM injection vs. 10 mg/mL IM injection | 120.67                   | 95.51-152.48 |
| 50 mg/mL SC injection vs. 50 mg/mL IM injection | 69.2                     | 53-90        |
| 10 mg/mL SC injection vs. 10 mg/mL IM injection | 72.6                     | 58-90        |

Source: Table 2 (p 14) and Table 4 (p 15) of the TGA clinical evaluators report

Abbreviations: AUC, area under the plasma concentration time curve; C<sub>max</sub>, maximum plasma concentration; CI, confidence interval; IM, intramuscular; SC, subcutaneous;

- 6.7 High concentration injection solution was associated with a numerically higher maximum concentration (C<sub>max</sub>) compared to low concentration solution but these differences were not significant. Both solution concentrations were bioequivalent in terms of extent of drug exposure (AUC).
- 6.8 Between group comparisons suggest that intramuscular injections were associated with a higher maximum concentration (C<sub>max</sub>) but a lower extent of exposure (AUC) compared to subcutaneous injections (although these estimates may be confounded by subject differences and period effects).
- 6.9 The ACPM considered that small differences between pharmacokinetic parameters between routes of administration and solution concentrations were not likely to be of clinical significance (ACPM minutes, June 2015).
- 6.10 Striesow & Brandt (2012) reported on an observational post-marketing surveillance study of patients with rheumatoid arthritis and psoriatic arthritis who were selected by physicians to trial self-administration with methotrexate 50 mg/mL pre-filled syringes (N=403). Patients, physicians and study nurses were assessed for preference, satisfaction and usability. A summary of study results are presented in Table 5.

Table 5: Preference, satisfaction and usability results for pre-filled syringes (Striesow & Brandt 2012)

| Subjective assessment  | Patients | Physicians/<br>Study nurses |
|--|----------|-----------------------------|
| Overall assessment 'very good' and 'good', %                               | 87.6     | 92.8                        |
| Availability and usability of pre-attached needle 'advantageous' and 'very | 91.8     | 88.8                        |

| Subjective assessment   | Patients | Physicians/<br>Study nurses |
|---|----------|-----------------------------|
| advantageous, % (Subgroup with previous experience of MTX 10 mg/mL; N=109)                                      |          |                             |
| Preference for MTX 50 mg/mL formulation in future, % (Subgroup with previous experience of MTX 10 mg/mL; N=109) | 94.5     | -                           |
| Tolerable/comfortable injection, %  | 96.0     | -                           |
| Self-administration led to feeling more independent, %  | 89.1     | -                           |
| Self-administration improved quality of life, %   | 83.6     | -                           |
| Proportion of patients who met physicians' expectations of benefit of switching to self-administration          | -        | 92.8                        |
| Proportion of patients considered suitable for SC self-administration   | -        | 96.3                        |

Source: p 32 of the submission, Striesow & Brandt 2012 publication

Abbreviations: MTX, methotrexate; SC, subcutaneous

- 6.11 The majority of respondents (both patients and healthcare professionals) reported a favourable perception of methotrexate 50 mg/mL pre-filled syringes for self-administration. Based on the study, the submission claimed that 96.3% of patients were considered suitable for subcutaneous self-administration of methotrexate.
- 6.12 The study was conducted in the German healthcare setting which may not be applicable to the Australian PBS population. In particular, many patients had prior experience with using pre-filled methotrexate injection syringes (10 mg/mL, not available in Australia).
- 6.13 Patients enrolled in the study were selected to trial self-administration. The results indicated that 96.3% of these patients were capable of self-administration. The study results **did not** indicate the proportion of patients using methotrexate pre-filled syringes who are likely to self-administer therapy. In clinical practice, patients may be switched to methotrexate pre-filled syringes for other reasons (e.g. physician preference due to ease of use compared to other parenteral formulations). It is unclear what proportion of patients would self-administer methotrexate in practice.
- 6.14 Table 6 provides a brief overview of the other clinical studies identified in the submission.

Table 6: Other clinical studies

| Trial ID     | Description   |
|--------------|---|
| Casalan 2013 | <p><b>Design:</b> Multi-centre, cross-sectional, observational study</p> <p><b>Population:</b> Patients with rheumatoid arthritis and psoriatic arthritis who attended outpatient wards in hospitals (N=291)</p> <p><b>Comparison:</b> Single arm observation with patients receiving oral and parenteral methotrexate</p> <p><b>Primary outcome:</b> Prevalence of methotrexate intolerance due to gastrointestinal adverse effects</p> <p><b>Key finding:</b> Methotrexate intolerance was reported in 11% of patients. Intolerance was higher in patients treated with parenteral methotrexate (20.6%) compared to oral methotrexate (6.2%).</p> |

|                 |  |
|-----------------|--|
| Schiff 2014     | <p><b>Design:</b> Phase 2, randomised, multi-centre, open-label, three-way crossover study</p> <p><b>Population:</b> Patients with rheumatoid arthritis who have received methotrexate treatment <math>\geq 3</math> months (N=50)</p> <p><b>Comparison:</b> Methotrexate 10 mg, 15 mg, 20 mg and 25 mg weekly in a random sequence of oral, SC into the abdomen and SC into the thigh</p> <p><b>Primary outcome:</b> Pharmacokinetic parameters for methotrexate via oral, SC into the abdomen and SC into the thigh routes of administration</p> <p><b>Key finding:</b> Systemic exposure of oral methotrexate plateaued at doses <math>\geq 15</math> mg/week. In contrast, SC methotrexate demonstrated a linear increase in systemic exposure that was greater than oral methotrexate at each dose. No unexpected adverse events were noted for either formulation.</p>   |
| Scott 2014      | <p><b>Design:</b> Retrospective observational study</p> <p><b>Population:</b> Patients with rheumatoid arthritis who were prescribed SC methotrexate following oral methotrexate (N=196)</p> <p><b>Comparison:</b> Single arm observation of patients receiving SC methotrexate after treatment failure (due to efficacy or adverse events) with oral methotrexate</p> <p><b>Primary outcome:</b> Continuation rates after 1 year of SC methotrexate therapy, tolerance and reasons for treatment failure, the number of patients on biologics at initiation of SC methotrexate and the number prescribed biologics at initiation of SC methotrexate</p> <p><b>Key finding:</b> Patients were changed from oral to SC methotrexate because of lack of efficacy (50.5%), adverse events (43.9%), or other/unknown reasons (5.6%). High continuation rates were reported at 1 year (83.0%), 2 years (75.2%) and 5 years (47.0%). Less than 10% of patients using SC methotrexate required the use of an additional biologic due to lack of efficacy</p>  |
| Tymms 2014      | <p><b>Design:</b> Multi-centre, cross-sectional observational study</p> <p><b>Population:</b> Patients with rheumatoid arthritis with moderate to high disease activity with a recorded barrier to disease control (N=714) [subset of the OPAL, Optimising Patient outcomes in Australian Rheumatology study]</p> <p><b>Comparison:</b> Patients with unmodified DMARD therapy vs patients with modified DMARD therapy</p> <p><b>Primary outcome:</b> Identification of barriers to disease control in patients with rheumatoid arthritis with suboptimal control</p> <p><b>Key finding:</b> Barriers to disease control include irreversible joint damage (19.7%), patient-driven preference (14.7%), non-inflammatory musculoskeletal pain (9.2%), insufficient time to assess the effect of recently initiated DMARDs (9.2%), safety concerns (7.5%), comorbidities (6.5%), resistant disease (6.3%), and other less common reasons.</p>  |
| Littlejohn 2013 | <p><b>Design:</b> Multi-centre, cross-sectional observational study</p> <p><b>Population:</b> Patients with rheumatoid arthritis with a recorded visit to a rheumatology clinic within 12 months (N=5685) [subset of the OPAL, Optimising Patient outcomes in Australian Rheumatology study]</p> <p><b>Comparison:</b> Single arm observation of patients classified as low, moderate and high disease activity</p> <p><b>Primary outcome:</b> Proportion of patients with rheumatoid arthritis who have achieved disease remission and identification of the pharmacological interventions used to achieve remission</p> <p><b>Key finding:</b> The study reported 41.6% of patients in remission, 18.6% with low disease activity, 31.6% moderate disease activity and 8.2% high disease activity.</p> <ul style="list-style-type: none"> <li>- Of those in remission, 17% received a bDMARD, 73% methotrexate, 19% leflunomide and 28% prednisolone.</li> <li>- Of those with moderate disease activity, 20% received a bDMARD, 76% methotrexate, 24% leflunomide and 39% prednisolone</li> <li>- Of those with high disease activity, 27% received a bDMARD, 78% methotrexate 31% leflunomide and 60% prednisolone.</li> </ul> |

|                             |   |
|-----------------------------|---|
| Littlejohn 2015             | <p><b>Design:</b> Multi-centre, cross-sectional, observational study<br/> <b>Population:</b> Patients with rheumatoid arthritis who were receiving treatment at a rheumatology clinic (N=8,998) [subset of the OPAL, Optimising Patient outcomes in Australian Rheumatology study]<br/> <b>Comparison:</b> Single arm observation of patients in 5-year follow-up<br/> <b>Primary outcome:</b> Assessment of disease activity trends over time<br/> <b>Key finding:</b> The frequency of remission increased significantly from 36.7% in 2009 to 53.5% in 2014, and that of moderate disease activity decreased from 33% in 2009 to 22.2% in 2014. The use of bDMARDs for patients in remission increased from 17% in 2009 to 36.9% in 2014</p>   |
| MC-MTX.5/RH                 | <p><b>Design:</b> Phase 2, open-label, single-arm trial<br/> <b>Population:</b> Patients with rheumatoid arthritis who were receiving a stable weekly dose of 15-25 mg of methotrexate (oral or parenteral) (N=69)<br/> <b>Comparison:</b> Single arm receiving 15-25 mg methotrexate weekly using 10 mg/mL pre-filled syringe (mix of self-administration and health professional administration)<br/> <b>Primary outcome:</b> Local tolerability of repeat SC methotrexate injections<br/> <b>Key finding:</b> The majority of patients reported mild or no local tolerability issues (89.9%). One patient reported severe redness, six patients reported moderate redness, itching or pain. The majority of patients were satisfied with self-administration (94.2%). Most patients were willing to continue therapy without weekly physician visits (87.0%). Physicians considered that patients were suitable for continued self-administration in 97.1% of cases.</p> |
| MC-MTX.6/RH<br>(Braun 2008) | <p><b>Design:</b> Phase 4, double-blind, multi-centre RCT<br/> <b>Population:</b> Methotrexate-naïve patients with active rheumatoid arthritis (N=384)<br/> <b>Comparison:</b> 15 mg (10 mg/mL) SC injection methotrexate once weekly vs 15 mg oral methotrexate once weekly<br/> <b>Primary outcome:</b> Percentage of patients with an ACR20 response at week 24<br/> <b>Key finding:</b> At week 24, significantly more patients treated with SC methotrexate than with oral methotrexate showed ACR20 (78% versus 70%) and ACR70 (41% versus 33%) responses. At week 16, 14% of patients were classified as ACR20 non-responders and were switched treatment from oral to SC treatment (with a 30% response rate) or were switched from standard SC dose to high SC dose (with a 23% response rate). The rate of adverse events was similar in all groups.</p>  |
| MC-MTX.10/RH                | <p><b>Design:</b> Phase 3, open-label, controlled trial<br/> <b>Population:</b> Patients with active rheumatoid arthritis (N=128)<br/> <b>Comparison:</b> Weekly SC methotrexate 20 mg given as 2mL of 10 mg/mL vs 0.4mL of 50 mg/mL (mix of self-administration and health professional administration)<br/> <b>Primary outcome:</b> Patient's preference between 10 mg/mL vs 50 mg/mL strengths of pre-filled syringe<br/> <b>Key finding:</b> Patients and physicians indicated a strong preference for the smaller 50 mg/mL syringe with embedded needle compared to 10 mg/mL syringe (&gt; 87.5% of respondents).</p>  |

Source: TGA clinical evaluation report, Table 5, p24 of the submission

Abbreviations: ACR20, American College of Rheumatology criteria for 20% improvement, ACR70, American College of Rheumatology criteria for 70% improvement; AUC, area under the curve; BMI, body mass index; bDMARD, biological disease-modifying antirheumatic drugs; DMARD, disease-modifying antirheumatic drugs; IM, intramuscular; RCT, randomised controlled trial; SC, subcutaneous

### Comparative harms

- 6.15 Insufficient data were presented to support a comparison of safety between 50 mg/mL pre-filled syringes and other parenteral methotrexate formulations.
- 6.16 The TGA did not identify any major safety concerns with the new presentation of methotrexate.

- 6.17 There may be potential safety concerns with self-administration of injectable methotrexate outside the clinic setting.

***Clinical claim***

- 6.18 The submission claimed bioequivalence between methotrexate pre-filled syringe and other parenteral formulations of methotrexate (p 34 of the submission). This claim appeared reasonable.
- 6.19 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.20 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

**Economic analysis**

- 6.21 The submission presented a cost-minimisation analysis (drug, injection and administration costs) based on the claim of bioequivalence.
- 6.22 The submission assumed that methotrexate pre-filled syringe and other parenteral formulations of methotrexate have the same equi-effective doses. In pragmatic terms, the submission assumed that one methotrexate pre-filled syringe (7.5 mg, 10 mg, 15 mg, 20 mg, 25 mg dose strengths available) was equivalent to one methotrexate 50 mg vial for injection (which could be used to prepare an equivalent dose, with the remainder lost as wastage). This assumption appeared reasonable.
- 6.23 Estimated drug costs are summarised in Table 7.

Table 7: Drug costs – submission estimates

| PBS Item                                     | DPMQ/DPMA (5 vials) | Licensed compounder | Total for 5 injections | Cost per dose | Weighting |
|--|---------------------|---------------------|------------------------|---------------|-----------|
| <b>Methotrexate 50 mg vial for injection</b> |                     |                     |                        |               |           |
| 1818Q (GS, RA) <sup>a</sup>                  | \$ [REDACTED]       | \$ [REDACTED]       | \$ [REDACTED]          | \$ [REDACTED] | 1%        |
| 2395C (GS, RA) <sup>a</sup>                  | \$ [REDACTED]       | \$ [REDACTED]       | \$ [REDACTED]          | \$ [REDACTED] | 65%       |
| 7250N (EFC, RA) <sup>b</sup>                 | \$ [REDACTED]       | \$ [REDACTED]       | \$ [REDACTED]          | \$ [REDACTED] | 20%       |
| 2395C (GS, PSO) <sup>a</sup>                 | \$ [REDACTED]       | \$ [REDACTED]       | \$ [REDACTED]          | \$ [REDACTED] | 9%        |
| 7250N (EFC, PSO) <sup>b</sup>                | \$ [REDACTED]       | \$ [REDACTED]       | \$ [REDACTED]          | \$ [REDACTED] | 5%        |
| <b>Weighted cost of drug acquisition</b>     |                     |                     |                        |               |           |
| Total (DPMQ)                                 | -                   | -                   | -                      | \$10.84       | -         |

Abbreviations: DPMQ, dispensed price per maximum quantity; DPMA, dispensed price per maximum amount; EFC, efficient funding of chemotherapy program; GS, general schedule; PSO, psoriasis; RA, rheumatoid arthritis

Source: Table 12 (p 37) of the submission

<sup>a</sup> There is a difference in the DPMQ for item 1818Q and 2395C due to differences in the handling of mark-ups which are applied at the individual vial level for 1818Q but applied to a pack of 5 vials for item 2395C

<sup>b</sup> The submission inappropriately calculated the cost of methotrexate vials under the Efficient Funding of Chemotherapy program. The PBS only subsidises the actual mg dispensed and the use of compounding pharmacies will reduce the impact of wastage (i.e. multiple injections can be made from one vial). Therefore, the submission has overestimated the cost of methotrexate vials under the chemotherapy program

- 6.24 The inclusion of chemotherapy items in the calculation of drug prices was inadequately justified. The efficient funding of chemotherapy program is used by oncologists to prescribe chemotherapy and other supportive treatments for the management of cancer in hospital settings. Use of methotrexate in these populations most likely represents its use as an antineoplastic treatment rather than as a treatment for rheumatoid arthritis or psoriasis. Chemotherapy items were excluded from alternative drug price estimates calculated for the evaluation.
- 6.25 The submission did not use the current PBS price of methotrexate 50 mg vial for injection. The PBS price for the 50 mg vial increased from DPMQ \$ [REDACTED] (Proportional Ex-manufacturer Price (PEMP) \$ [REDACTED]) in November 2015 to DPMQ \$ [REDACTED] (PEMP \$ [REDACTED]) in December 2015 based on an annual PBS price review. The updated methotrexate price was used in the alternative estimates presented in the evaluation. The pre-PBAC response acknowledged the price increase in 50 mg vial and supplied updated estimates.
- 6.26 Comparisons of drug costs between treatments should be based on PEMP values rather than DPMQ values as any offset due to other non-drug costs will be applied to

the ex-manufacturer price. Alternative drug price calculations presented in the evaluation were based on ex-manufacturer prices. Alternative drug cost estimates calculated for the evaluation were summarised in Table 8.

Table 8: Drug costs – alternative estimates

| PBS Item                                     | PEMP <sup>a</sup><br>(5 vials) | Licensed<br>compounder | Total for 5<br>injections | Cost per<br>dose | Weighting |
|--|--------------------------------|------------------------|---------------------------|------------------|-----------|
| <b>Methotrexate 50 mg vial for injection</b> |                                |                        |                           |                  |           |
| 1818Q (GS, RA)                               | \$ [REDACTED]                  | \$ [REDACTED]          | \$ [REDACTED]             | \$ [REDACTED]    | 1%        |
| 2395C (GS, RA)                               | \$ [REDACTED]                  | \$ [REDACTED]          | \$ [REDACTED]             | \$ [REDACTED]    | 87%       |
| 2395C (GS, PSO)                              | \$ [REDACTED]                  | \$ [REDACTED]          | \$ [REDACTED]             | \$ [REDACTED]    | 12%       |
| <b>Weighted cost of drug acquisition</b>     |                                |                        |                           |                  |           |
| Total (AEMP)                                 | -                              | -                      | -                         | \$ [REDACTED]    | -         |

Abbreviations: AEMP, approved ex-manufacturer price; PEMP, proportional ex-manufacturer price; GS, general schedule; PSO, psoriasis; RA, rheumatoid arthritis

Source: calculated during evaluation using the cost analysis spreadsheet provided with the submission

<sup>a</sup> Using updated methotrexate price from December 2015 PBS schedule

- 6.27 The submission claimed a reduction in injection costs with the new methotrexate presentation, which is supplied as a pre-filled syringe with embedded needle, compared to the current vials that require the separate purchase of additional needles/syringes. The submission proxied the cost of additional needles/syringes based on the advertised price of insulin needles/syringes (which are a similar size) from an Australian online supplier (Medshop Australia).
- 6.28 Syringe costs appeared reasonable. Needle costs only apply to compounded methotrexate injections dispensed under the Efficient Funding of Chemotherapy (EFC) program and were therefore not directly relevant to the cost-minimisation analysis.
- 6.29 Estimated injection costs are summarised in Table 9.

Table 9: Injection costs

| Item   | Cost          | Units | Cost per dose | Weighting |
|--|---------------|-------|---------------|-----------|
| <b>Methotrexate 50 mg vial for injection</b> |               |       |               |           |
| BD Micro-fine pen needles                    | \$ [REDACTED] | 100   | \$ [REDACTED] | 25%       |
| BD Ultra-fine insulin syringes               | \$ [REDACTED] | 100   | \$ [REDACTED] | 75%       |
| <b>Weighted cost of injections</b>           |               |       |               |           |
| Total  | -             | -     | \$ [REDACTED] | -         |

Source: Table 12 (p 37) of the submission

- 6.30 The submission also claimed a reduction in administration costs with the new methotrexate presentation that can be self-administered by a patient/carer compared to the current vials that are administered by a healthcare professional (requiring weekly visits).
- 6.31 The submission estimated that 96.3% of patients using the methotrexate pre-filled syringe would self-administer treatment and therefore require no additional visits for administration. The remaining 3.7% of patients using methotrexate pre-filled syringe were assumed to require weekly visits for administration. These estimates were based on the proportion of patients considered suitable for self-administration by physicians in a post-marketing study of methotrexate pre-filled syringe in clinical practice (Striesow & Brandt, 2012).

- 6.32 While the claim of reduced healthcare visits appeared plausible the submission has inadequately quantified the potential reduction. The 96.3% estimate used in the submission relates to the proportion of patients selected to trial self-administration who were considered capable of self-administration. There was no estimate of the proportion of patients using methotrexate pre-filled syringes who are likely to self-administer.
- 6.33 The approach used in the submission assumed that patients visit healthcare professionals for the sole purpose of methotrexate injections. In practice, patients may have multiple morbidities/co-administered medications addressed at a single visit.
- 6.34 Other formulations of methotrexate have a wide number of indications (primarily autoimmune disease and oncology) and have unrestricted listings on the PBS. Use of methotrexate pre-filled syringes for indications outside the requested restriction may not be associated with the same savings in administration costs claimed for rheumatoid arthritis and psoriasis.
- 6.35 The PBAC did not consider that the use of the estimate of people willing to self-inject to apportion a reduction in physician visits was reasonable. It is highly likely that the submission has overestimated the proportion of healthcare visits avoided with methotrexate pre-filled syringes versus methotrexate vials.
- 6.36 The submission acknowledged that methotrexate administration may occur in a variety of healthcare settings but for simplicity assumed that the cost of methotrexate administration by a healthcare professional could be represented by MBS item 23 (Level B GP visit, less than 20 minutes). It is unclear which MBS items are being used for the administration of methotrexate in clinical practice.
- 6.37 Estimated administration costs are summarised in Table 10.

Table 10: Administration costs

| Item   | Cost          | Patients with methotrexate administered by healthcare professional (%) | Cost per dose |
|--|---------------|--|---------------|
| <b>Methotrexate 50 mg vial for injection</b> |               |  |               |
| MBS 23 (Level B GP visit)                    | \$ [REDACTED] | 100%   | \$ [REDACTED] |
| <b>Methotrexate pre-filled syringe</b>       |               |  |               |
| MBS 23 (Level B GP visit)                    | \$ [REDACTED] | 3.7%   | \$ [REDACTED] |

Source: p 38 of the submission

- 6.38 The cost minimisation analysis presented in the submission is summarised in Table 11. The Pre-PBAC response (page 4) presented an updated cost minimisation analysis that accounts for the price increase of the comparator presents the AEMP drug cost and separates out the cost of compounding EFC items.

Table 11: Cost minimisation analysis

|  | 1 dose        | 4 doses       |
|--|---------------|---------------|
| <b>Methotrexate 50 mg vial for injection</b> |               |               |
| Drug acquisition costs (DPMQ)                | \$ [REDACTED] | -             |
| Injection costs                              | \$ [REDACTED] | -             |
| Administration costs                         | \$ [REDACTED] | -             |
| Total cost                                   | \$ [REDACTED] | -             |
| <b>Methotrexate pre-filled syringe</b>       |               |               |
| Total cost                                   | \$ [REDACTED] | \$ [REDACTED] |
| Administration costs                         | \$ [REDACTED] | \$ [REDACTED] |
| Injection costs                              | \$ [REDACTED] | \$ [REDACTED] |
| Drug acquisition costs (DPMQ)                | \$ [REDACTED] | \$ [REDACTED] |
| Drug acquisition costs (AEMP) <sup>a</sup>   | \$ [REDACTED] | \$ [REDACTED] |

Abbreviations: AEMP, approved ex-manufacturer price; DPMQ, dispensed price per maximum quantity

Source: Table 13 (p 39) of the submission

<sup>a</sup> Back-calculated based on dispensing fee \$6.93, AHL fee \$3.49 and wholesaler mark-up 1.0752

Table 12: Revised Cost minimisation analysis

|  | 1 dose        | 4 doses       |
|--|---------------|---------------|
| <b>Methotrexate 50 mg vial for injection</b> |               |               |
| Drug acquisition costs (AEMP)                | \$ [REDACTED] | -             |
| Compounding costs <sup>1</sup>               | \$ [REDACTED] | -             |
| Injection costs                              | \$ [REDACTED] | -             |
| Administration costs                         | \$ [REDACTED] | -             |
| Total cost                                   | \$ [REDACTED] | -             |
| <b>Methotrexate pre-filled syringe</b>       |               |               |
| Total cost                                   | \$ [REDACTED] | \$ [REDACTED] |
| Administration costs <sup>2</sup>            | \$ [REDACTED] | \$ [REDACTED] |
| Injection costs                              | \$ [REDACTED] | \$ [REDACTED] |
| Drug acquisition costs (AEMP)                | \$ [REDACTED] | \$ [REDACTED] |
| Drug acquisition costs (DPMQ)                | -             | \$ [REDACTED] |

Source: Table 1 (p4) of the Pre-PBAC response

- 6.39 The submission proposed a flat price of \$ [REDACTED] (DPMQ) for all strengths of methotrexate pre-filled syringe based on the presented cost minimisation analysis.
- 6.40 The analysis presented in the submission was also re-calculated during the evaluation using the revised drug cost estimates (shown in Table 12).
- 6.41 The impact of varying the number of healthcare visits avoided was assessed in sensitivity analyses ranging from 0 (no difference) to 4 (all patients switch to self-administration) visits avoided per 28 days.
- 6.42 The impact of using different healthcare visit costs was assessed in sensitivity analyses using MBS item 3 (Level A GP visit, straightforward issue) and MBS item 105 (subsequent specialist visit).

Table 13: Alternative cost minimisation analysis

|  | 1 dose        | 4 doses       |
|--|---------------|---------------|
| <b>Methotrexate 50 mg vial for injection</b>                     |               |               |
| Drug acquisition costs (AEMP)                                    | \$ [REDACTED] | -             |
| Injection costs  | \$ [REDACTED] | -             |
| Administration costs   | \$ [REDACTED] | -             |
| Total cost   | \$ [REDACTED] | -             |
| <b>Methotrexate pre-filled syringe</b>                           |               |               |
| Total cost   | \$ [REDACTED] | \$ [REDACTED] |
| Administration costs   | \$ [REDACTED] | \$ [REDACTED] |
| Injection costs  | \$ [REDACTED] | \$ [REDACTED] |
| Drug acquisition costs (AEMP)                                    | \$ [REDACTED] | \$ [REDACTED] |
| Drug acquisition costs (DPMQ) <sup>a</sup>                       | \$ [REDACTED] | \$ [REDACTED] |
| <b>Sensitivity analyses (AEMP)</b>                               |               |               |
| 0 healthcare visits avoided with methotrexate pre-filled syringe | \$ [REDACTED] | \$ [REDACTED] |
| 1 healthcare visits avoided with methotrexate pre-filled syringe | \$ [REDACTED] | \$ [REDACTED] |
| 2 healthcare visits avoided with methotrexate pre-filled syringe | \$ [REDACTED] | \$ [REDACTED] |
| 3 healthcare visits avoided with methotrexate pre-filled syringe | \$ [REDACTED] | \$ [REDACTED] |
| 4 healthcare visits avoided with methotrexate pre-filled syringe | \$ [REDACTED] | \$ [REDACTED] |
| Healthcare visit costs based on MBS item 3 (\$16.95)             | \$ [REDACTED] | \$ [REDACTED] |
| Healthcare visit costs based on MBS item 105 (\$43.00)           | \$ [REDACTED] | \$ [REDACTED] |

Abbreviations: AEMP, approved ex-manufacturer price; DPMQ, dispensed price per maximum quantity

Source: Constructed during evaluation

<sup>a</sup> Wholesaler mark-up 1.0752, AHI fee \$ [REDACTED] + 1.035 for PIP cost over \$ [REDACTED] and dispensing fee \$ [REDACTED]

- 6.43 Using the revised drug cost estimates outlined in Table 8 results in a slightly higher price of \$ [REDACTED] (DPMQ).
- 6.44 The estimated cost-minimised price for methotrexate pre-filled syringe was highly sensitive to the estimated number of healthcare visits avoided as well as the cost of each healthcare visit.

**Drug cost/patient/year: \$2,432**

- 6.45 The estimated annual cost of methotrexate pre-filled syringes was \$ [REDACTED] (proposed DPMQ / 4 syringes x 52 weeks). In comparison, the estimated annual cost of methotrexate vials was \$ [REDACTED] (current DPMQ / 5 vials x 52 weeks).

**Estimated PBS usage & financial implications**

- 6.46 The submission used a mixed market share/epidemiology approach to estimate the utilisation/financial implications associated with the PBS listing of methotrexate pre-filled syringe. Market share data were primarily derived from the 10% Medicare analysis. Epidemiology data were derived from a number of published sources (see Table 19 of the submission).

Table 14: Estimated utilisation and financial implications of listing methotrexate pre-filled syringes

|  | Year 2<br>(Apr 2016-<br>Mar 2017) | Year 3<br>(Apr 2017-<br>Mar 2018) | Year 4<br>(Apr 2018-<br>Mar 2019) | Year 5<br>(Apr 2019-<br>Mar 2020) | Year 6<br>(Apr 2020-<br>Mar 2021) |
|--|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| <b>Substitution from methotrexate vials</b>                            |                                   |                                   |                                   |                                   |                                   |
| <i>Methotrexate vial scripts<br/>(1818Q, 2395C, 7250N)<sup>a</sup></i> | ██████                            | ██████                            | ██████                            | ██████                            | ██████                            |
| General schedule RA scripts  | ██████                            | ██████                            | ██████                            | ██████                            | ██████                            |
| Uptake rate of pre-filled MTX syringe                                  | 25%                               | 30%                               | 35%                               | 40%                               | 45%                               |
| Equivalent pre-filled MTX scripts (1.25 pack adjustment)               | ██████                            | ██████                            | ██████                            | ██████                            | ██████                            |
| EFC RA scripts   | ██████                            | ██████                            | ██████                            | ██████                            | ██████                            |
| Uptake rate of pre-filled MTX syringe                                  | 90%                               | 95%                               | 95%                               | 95%                               | 95%                               |
| Equivalent pre-filled MTX scripts (1.25 pack adjustment)               | ██████                            | ██████                            | ██████                            | ██████                            | ██████                            |
| General schedule PSO scripts   | ██████                            | ██████                            | ██████                            | ██████                            | ██████                            |
| Uptake rate of pre-filled MTX syringe                                  | 25%                               | 30%                               | 35%                               | 40%                               | 45%                               |
| Equivalent pre-filled MTX scripts (1.25 pack adjustment)               | ██████                            | ██████                            | ██████                            | ██████                            | ██████                            |
| EFC PSO scripts  | ██████                            | ██████                            | ██████                            | ██████                            | ██████                            |
| Uptake rate of pre-filled MTX syringe                                  | 90%                               | 95%                               | 95%                               | 95%                               | 95%                               |
| Equivalent pre-filled MTX scripts (1.25 pack adjustment)               | ██████                            | ██████                            | ██████                            | ██████                            | ██████                            |
| <b>Substitution from oral methotrexate</b>                             |                                   |                                   |                                   |                                   |                                   |
| RA patients  | ██████                            | ██████                            | ██████                            | ██████                            | ██████                            |
| RA patients taking MTX (78%)   | ██████                            | ██████                            | ██████                            | ██████                            | ██████                            |
| RA MTX patients intolerant to oral form (5%)                           | 3,686                             | 3,737                             | 3,790                             | 3,843                             | 3,896                             |
| RA intolerant patients already using parenteral formulations           | -503                              | -508                              | -513                              | -518                              | -523                              |
| RA intolerant patients not using parenteral formulations               | 3,183                             | 3,229                             | 3,277                             | 3,325                             | 3,373                             |
| Potential number of weekly doses                                       | 165,505                           | 167,927                           | 170,384                           | 172,876                           | 175,404                           |
| Uptake of pre-filled MTX syringe in doses (5%)                         | 8,275                             | 8,396                             | 8,519                             | 8,644                             | 8,770                             |
| Pre-filled MTX syringe scripts (4 doses per script)                    | ██████                            | ██████                            | ██████                            | ██████                            | ██████                            |
| <b>Total</b>   |                                   |                                   |                                   |                                   |                                   |
| Total pre-filled MTX scripts   | ██████                            | ██████                            | ██████                            | ██████                            | ██████                            |
| Cost of pre-filled MTX scripts at proposed DPMQ                        | \$ ██████                         | \$ ██████                         | \$ ██████                         | \$ ██████                         | \$ ██████                         |
| Patient co-payments <sup>b</sup>                                       | -\$ ██████                        | -\$ ██████                        | -\$ ██████                        | -\$ ██████                        | -\$ ██████                        |
| Total cost less co-payments  | -\$ ██████                        | -\$ ██████                        | -\$ ██████                        | -\$ ██████                        | -\$ ██████                        |
| Savings due to substitution <sup>c</sup>                               | -\$ ██████                        | -\$ ██████                        | -\$ ██████                        | -\$ ██████                        | -\$ ██████                        |
| <b>Net cost to PBS/RPBS</b>  | -\$ ██████                        | -\$ ██████                        | -\$ ██████                        | -\$ ██████                        | -\$ ██████                        |
| MBS savings due to reduced administration costs                        | -\$ ██████                        | -\$ ██████                        | -\$ ██████                        | -\$ ██████                        | -\$ ██████                        |
| <b>Net cost to government</b>  | \$ ██████                         | \$ ██████                         | \$ ██████                         | \$ ██████                         | \$ ██████                         |

Public Summary Document – March 2016 PBAC Meeting

Abbreviations: DPMQ, dispensed price per maximum quantity; EFC, efficient funding of chemotherapy program; MBS, Medicare Benefits Schedule; MTX, methotrexate; PBS, Pharmaceutical Benefits Scheme; PSO, psoriasis; RA, rheumatoid arthritis; RPBS, Repatriation Pharmaceutical Benefits Scheme

Source: Table 18 (p 43), Table 20 (p 44), Table 21 (p 45), Table 22 (p 45), Table 24 (p 46), Table 25 (p 46), Table 26 (p 47), Table 27 (p 47), Table 30 (p 49), Table 31 (p 49), Table 32 (p 50), Table 33 (p 50), Table 34 (p 50), Table 38 (p 52), Table 39 (p 53) of the submission

<sup>a</sup> Not estimated in submission. Approximated for the overview based on date-of-processing data for 1818Q (675 scripts) and 2395C (19,960 scripts) as well as PBS item statistic data for 7250N (15,648 scripts) from April 2014-March 2015. Extrapolated to later years using a 1% growth rate

<sup>b</sup> Error in the application of RPBS co-payments to PBS scripts

<sup>c</sup> Based on November 2015 methotrexate pricing

The redacted table above shows that by year 6, the estimated number of scripts would be less than 10,000 and the net cost to PBS less than \$10 million.

- 6.47 The Pre-PBAC response presented revised financial estimates that corrected an error in application of RPBS co-payments to PBS scripts and included the additional compounding fee for EFC items. This is summarised in table 15. The response noted that the revised financial analysis projected a lower overall net cost to Government than presented in the submission and asserted that this net cost should be considered in the context of a significant improvement in quality use of medicines by reducing the risk of dose error, reducing cytotoxic exposure, and a considerable improvement to patient convenience.

Table 15: Updated financial estimates

|                              | Year 2<br>(Apr 2016-<br>Mar 2017) | Year 3<br>(Apr 2017-<br>Mar 2018) | Year 4<br>(Apr 2018-<br>Mar 2019) | Year 5<br>(Apr 2019-<br>Mar 2020) | Year 6<br>(Apr 2020-<br>Mar 2021) |
|------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Overall net cost to the PBS  | \$ [REDACTED]                     | \$ [REDACTED]                     | \$ [REDACTED]                     | \$ [REDACTED]                     | \$ [REDACTED]                     |
| Overall net cost to the RPBS | \$ [REDACTED]                     | \$ [REDACTED]                     | \$ [REDACTED]                     | \$ [REDACTED]                     | \$ [REDACTED]                     |
| Overall net cost for MBS     | -\$ [REDACTED]                    | -\$ [REDACTED]                    | -\$ [REDACTED]                    | -\$ [REDACTED]                    | -\$ [REDACTED]                    |
| Net cost to government       | \$ [REDACTED]                     | \$ [REDACTED]                     | \$ [REDACTED]                     | \$ [REDACTED]                     | \$ [REDACTED]                     |

Source: Table 2 (page 4) of the Pre-PBAC response

The redacted table above shows that by year 6, net cost to PBS less than \$10 million.

- 6.48 The save to the MBS was driven entirely by reduction in GP visits. While a reduction in GP visits can be included in the calculation in the economic impact of listing a new medicine, it is not a valid offset in the financial modelling. The GP system operates at capacity at all times; if visits are reduced for one group, their consultations will be utilised by other demand within the community. Table 16 presents the revised financial estimates excluding the MBS savings associated with reduced GP visits.

Table 16: Updated financial estimates excluding MBS savings

|                              | Year 2<br>(Apr 2016-<br>Mar 2017) | Year 3<br>(Apr 2017-<br>Mar 2018) | Year 4<br>(Apr 2018-<br>Mar 2019) | Year 5<br>(Apr 2019-<br>Mar 2020) | Year 6<br>(Apr 2020-<br>Mar 2021) |
|------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Overall net cost to the PBS  | \$ [REDACTED]                     | \$ [REDACTED]                     | \$ [REDACTED]                     | \$ [REDACTED]                     | \$ [REDACTED]                     |
| Overall net cost to the RPBS | \$ [REDACTED]                     | \$ [REDACTED]                     | \$ [REDACTED]                     | \$ [REDACTED]                     | \$ [REDACTED]                     |
| Net cost to government       | \$ [REDACTED]                     | \$ [REDACTED]                     | \$ [REDACTED]                     | \$ [REDACTED]                     | \$ [REDACTED]                     |

The redacted table above shows that by year 6, net cost to PBS less than \$10 million.

6.49 According to the revised financial estimates (excluding reduction in GP visits), the net cost of listing pre-filled methotrexate syringes on the PBS/RPBS for rheumatoid arthritis and psoriasis was estimated to be up to \$■ million in the fifth year of listing, and the estimated cumulative net cost to the PBS/RPBS over five years was \$■ million.

6.50 The main issues of uncertainty associated with the utilisation estimates were:

- Whether use of methotrexate pre-filled syringe under the PBS would be restricted to patients with rheumatoid arthritis and psoriasis in clinical practice.
- Whether differences between methotrexate pre-filled syringe and other parenteral methotrexate formulations (ease of use, potential for self-administration) were likely to grow the market particularly utilisation captured from oral methotrexate and private scripts for methotrexate vials.
- The likely uptake rate of methotrexate pre-filled syringe in clinical practice given its perceived advantages against other parenteral formulations.
- Whether administration costs could be reliably estimated given that both the number of GP visits for methotrexate administration and the costs of each visit were highly uncertain due to limited data on current practice and likely changes with the introduction of methotrexate pre-filled syringes in the Australian clinical setting.

6.51 Additional issues identified in the evaluation included:

- Poor documentation of the assignment of scripts to indications with particular concern regarding the assignment of dominant indication. Without further validation the assignment of rheumatoid arthritis and psoriasis as the dominant indication in patients receiving treatment under the efficient funding of chemotherapy program was questionable. Additionally, the assumption that patients were receiving treatment with methotrexate for their dominant indication was not adequately supported (e.g. methotrexate use for osteoarthritis).
- Script and patient estimates from different sources did not align.
- The projected market being smaller than the actual market due to use of an inappropriate upscaling factor to adjust concessional scripts to a total PBS script estimate.
- Inadequate justification for methotrexate pre-filled syringe capturing market share from oral tablets in rheumatoid arthritis but not psoriasis.
- Cost of EFC methotrexate vials not consistently estimated between the cost minimisation analysis and budget impact analysis.
- Inadequate accounting for variable dosing with oral methotrexate and methotrexate vials dispensed under the efficient funding of chemotherapy program.
- Growth rates that do not align with historical growth of the methotrexate market (growth rate varies for different formulations and subsidy programs).

- Inappropriate assumption of 100% adherence used to calculate utilisation estimates and used to switch between patient, script and weekly dose estimates.

6.52 Given the uncertainty with the budget impact model presented in the submission, a simple sensitivity analysis was conducted for the evaluation assuming that methotrexate pre-filled syringe would capture 50% or 100% of the general schedule utilisation of methotrexate vials (based on actual utilisation in April 2014-March 2015), using current prices (December 2015) and assuming all treatments have the same distribution across beneficiary categories.

6.53 The sensitivity analysis was summarised in Table 17.

Table 17: Budget impact sensitivity analyses

| Descriptor   | Value |
|--|-------|
| Scripts for methotrexate vials (1818Q, 2395C); April 2014-March 2015; date-of-processing |       |
| <b>Pre-filled methotrexate syringe capture 50% of methotrexate vial market</b>           |       |
| Uptake rate (50%), scripts   |       |
| Adjustment factor for difference in pack size (1.25), scripts                            |       |
| Cost at DPMQ (\$187.06)  | \$    |
| Patient co-payments (avg. \$20.44)   | -\$   |
| Total cost less co-payments  | \$    |
| Cost of substituted vials (DPMQ \$50.31 – avg co-pay \$20.44)                            | -\$   |
| Net cost to PBS/RPBS   | \$    |
| <b>Pre-filled methotrexate syringe capture 100% of methotrexate vial market</b>          |       |
| Uptake rate (100%), scripts  |       |
| Adjustment factor for difference in pack size (1.25), scripts                            |       |
| Cost at DPMQ (\$187.06)  | \$    |
| Patient co-payments (avg. \$20.44)   | -\$   |
| Total cost less co-payments  | \$    |
| Cost of substituted vials (DPMQ \$50.31 – avg. co-pay \$20.44)                           | -\$   |
| Net cost to PBS/RPBS   | \$    |

Abbreviations: DPMQ, dispensed price per maximum quantity; PBS, Pharmaceutical Benefits Scheme; PSO, psoriasis; RA, rheumatoid arthritis; RPBS, Repatriation Pharmaceutical Benefits Scheme  
Source: Constructed during evaluation

6.54 The results of the sensitivity analyses indicated that the budget impact associated with listing methotrexate pre-filled syringes on the PBS/RPBS may be substantially higher than estimated in the submission.

6.55 The Pre-PBAC response stated (page 2) that patients who had received methotrexate vial scripts under the EFC program, and were coded to RA or psoriasis, were unlikely to have been receiving methotrexate as an antineoplastic treatment. The response estimated that 25% of methotrexate vials (50 mg/2 mL) used in RA or psoriasis had been claimed under the EFC program. The response presented an additional sensitivity analysis around this estimate.

Table 18: Further sensitivity analyses (EFC)

| Sensitivity analyses (AEMP)                      |  |      |      |
|--|--|------|------|
| EFC items comprise 25% of use; 75% self-inject   |  | \$\$ | \$\$ |
| EFC items comprise 10% of use; 96.3% self-inject |  | \$\$ | \$\$ |
| EFC items comprise 10% of use; 75% self-inject   |  | \$\$ | \$\$ |

Source: Table 1 (page 4) of the Pre-PBAC response

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

## 7 PBAC Outcome

- 7.1 The PBAC did not recommend the PBS listing of methotrexate pre-filled syringe for the treatment of rheumatoid arthritis or psoriasis when methotrexate oral tablets are unsuitable. The PBAC considered that while a clinical need existed for pre-filled syringes, uncertainty remained around key inputs into the cost-minimisation analysis.
- 7.2 The PBAC agreed that parenteral methotrexate formulations were the appropriate comparator.
- 7.3 The PBAC noted that the submission's claim of bioequivalence was based on a bioequivalence study comparing subcutaneous (10 mg/mL) and intramuscular (10 mg/mL) methotrexate injections as well as an observational study that assessed patient preference, satisfaction and usability of methotrexate pre-filled syringe in patients, physicians and nurses. Based on this evidence, the PBAC accepted that the pre-filled syringe subcutaneous injection was bioequivalent to the intramuscular injection.
- 7.4 The PBAC noted that there may be potential safety concerns with self-administration of injectable methotrexate outside the clinic setting. In this context, the PBAC considered that the health and safety risk of self-injection, including disposal of the used syringe, had not been adequately addressed by the submission.
- 7.5 The PBAC noted the updated cost-minimisation analysis presented in the Pre-PBAC response, however considered that substantial issues remained, namely the inclusion of EFC items and the estimation of the proportion of patients who would self-inject.
- 7.6 The PBAC noted that the inclusion of chemotherapy items in the calculation of drug prices was inadequately justified and agreed that the use of methotrexate in these populations most likely represents its use as an antineoplastic treatment rather than as a treatment for rheumatoid arthritis or psoriasis. The PBAC did not accept the Pre-PBAC response's argument that patients who had received methotrexate vial scripts under the EFC program, and were coded to RA or psoriasis, were unlikely to have been receiving methotrexate as an antineoplastic treatment. The PBAC considered the inclusion of the EFC items was not appropriate.
- 7.7 The PBAC considered that the estimated proportion of patients who would self-inject may be overestimated, noting that the 96.3% estimate was based on patients who were considered suitable for subcutaneous self-administration of methotrexate, not

patients who were likely to self-administer. The PBAC considered that sensitivity analyses around this estimate would be helpful.

- 7.8 The PBAC noted that substantial leakage outside the requested indications was likely, and considered that a Risk Share Arrangement based on projected usage in rheumatoid arthritis and psoriasis, would be needed to mitigate the costs to government.
- 7.9 The PBAC considered that a future submission would need to provide clarity around the proportion of patients likely to self-administer with the associated decrease in GP visits, and should also address the health and safety concerns associated with self-administration. The PBAC considered that the outstanding data requests could only be met in the form of a Major submission to the PBAC.
- 7.10 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

**8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**9 Sponsor's Comment**

The sponsor had no comment.