

7.04 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 resubmission requested an Authority Required (Streamlined) listing of methotrexate pre-filled syringe (with embedded needle) for the treatment of rheumatoid arthritis or psoriasis when methotrexate oral tablets are unsuitable. The pre-filled syringe is proposed for subcutaneous (SC) administration. The proposed drug is referred to as SC methotrexate in this document.

2 Requested listing

2.2 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough. In the Pre-Sub-Committee Response (PSCR), the sponsor agreed that the changes suggested by the Secretariat were appropriate.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty* [^]	Proprietary Name and 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]	

*Corrected using Tier 1 AHJ fees. The DPMQ includes a wholesale mark-up of 7.52%; plus Tier 1 AHJ of \$3.54 per prescription plus dispensing fee of \$7.02 per prescription.

[^] Revised DPMQ of \$ [REDACTED] was presented in the Pre-PBAC Response.

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 <input type="checkbox"/> Midwives
Episodicity:	Chronic treatment
Severity:	Severe, recalcitrant, active
Condition:	Rheumatoid arthritis
PBS Indication:	For the treatment of Severe, recalcitrant, active rheumatoid arthritis when the oral tablet form of methotrexate is unsuitable
Treatment phase:	Initial and continuing

Public Summary Document – March 2017 PBAC Meeting

Restriction Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>The condition must be not responding to, or intolerant of, an adequate trial of NSAIDs and one or more disease modifying drugs, OR <i>The condition must be intolerant of an adequate trial of NSAIDs and one or more disease modifying drugs,</i></p> <p>AND</p> <p><i>Patient must be unsuitable for administration of an oral form of methotrexate for this condition.</i></p>
Population criteria:	<p>The p Patient must be an adult. The solid dose form of methotrexate must be unsuitable for the patient.</p>

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 <input type="checkbox"/> Midwives
Episodicity:	Chronic treatment
Severity:	Severe, recalcitrant, disabling
Condition:	Psoriasis
PBS Indication:	Severe, recalcitrant, disabling For the treatment of psoriasis when the oral tablet form of methotrexate is unsuitable
Treatment phase:	Initial and continuing
Restriction Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have severe, recalcitrant, disabling psoriasis which is not <i>The condition must not be</i> adequately responsive to other forms of treatment,</p> <p>AND</p> <p><i>The patient must be unsuitable for administration of an oral form of methotrexate for this condition.</i></p>
Population criteria:	<p>The p Patient must be an adult. The solid dose form of methotrexate must be unsuitable for the patient.</p>

2.3 The resubmission changed the proposed restriction level from Restricted Benefit to Authority Required (Streamlined) to help minimise potential use outside the requested indications. This was to address the PBAC’s concerns (from its previous consideration) that substantial leakage outside the requested indications was likely. Apart from this, the wording of the proposed restriction was unchanged from the previous submission.

- 2.4 The resubmission presented a cost-minimisation analysis that compared SC methotrexate with other parenteral methotrexate.
- 2.5 The PBAC noted that the proposed PBS indications were aligned with the TGA indications (“severe, recalcitrant, active rheumatoid arthritis” and “severe, recalcitrant, disabling psoriasis”). However, the PBAC viewed that these criteria were sufficiently captured by the clinical criteria under the restriction, and considered that PBS indications of “severe rheumatoid arthritis” and “severe psoriasis” would be sufficient to identify the appropriate patient population.
- 2.6 The PBAC noted that the proposed RA listing required that patients have failed, or be intolerant to NSAIDs or one or more disease modifying drugs prior to commencing therapy with methotrexate SC. The PBAC considered that this was not aligned with current clinical practice and did not recommend inclusion of this criterion in the listing. For the psoriasis listing, the PBAC advised that the clinical criteria should specify that “the condition must not have adequately responded to topical treatment”. Finally, the PBAC was of the view that an age requirement was unnecessary for either listing, as the prescribing clinician would be responsible for ensuring that methotrexate SC was only prescribed for suitable patients.

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

3 Background

- 3.1 **TGA status at time of PBAC consideration:** SC methotrexate was TGA registered on 25 August 2015 for the following indications:
 - Management of severe, recalcitrant, active rheumatoid arthritis in adults not responding to, or intolerant of, an adequate trial of non-steroidal anti-inflammatory drugs (NSAID) and one or more disease-modifying antirheumatic drugs (DMARD); and
 - 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 The PBAC previously considered SC methotrexate as a minor submission at the March 2016 meeting. The PBAC rejected the submission on the basis that uncertainty remained around key inputs into the cost-minimisation analysis. The PBAC considered that a future submission would need to provide clarity around the proportion of patients likely to self-inject with the associated decrease in general practitioner (GP) visits, and should also address the health and safety concerns associated with self-injection.
- 3.3 A summary of the comparison of the previous submission and this resubmission is outlined in Table 1.

Table 1: Summary of the previous submission and current resubmission

	Methotrexate March 2016	Current re-submission																
Requested PBS listing	Restricted Benefit listing for: •Severe, recalcitrant, active rheumatoid arthritis when the oral tablet form is unsuitable. •Severe, recalcitrant, disabling psoriasis which is not adequately responsive to other forms of treatment and the oral tablet form is unsuitable. PBAC Comment: substantial leakage outside the requested indications likely (Para 7.8).	Authority Required (Streamlined) listing for same conditions.																
Requested price (DPMQs)	\$ [REDACTED] for all strengths	\$ [REDACTED] for all strengths (corrected to \$ [REDACTED] during evaluation, to account for appropriate fees)																
Main comparator	Other parenteral methotrexate formulations. PBAC Comment: The PBAC agreed that other parenteral methotrexate formulations were the appropriate comparator (Para 7.2)	Main comparator: unchanged Supplementary comparator: oral MTX																
Clinical evidence	2 bioequivalence studies: - SC MTX vs IM MTX: MC MTX.7/PH (N=16) - SC MTX (high vs low concentration) vs IM MTX: MC-MTX.9/PH (N=24). 1 patient preference study: Striesow & Brandt (2012), (N=403).	3 new bioequivalence studies: SC MTX vs IM MTX: Jundt (1993), (N=12); Brookes (1990), (N=5); NCT01737944 (N=36). Study MC MTX.7/PH (N=16) re-presented.																
Key effectiveness data	<p>Study MC-MTX.7/PH: 15 mg SC vs 15 mg IM MTX</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Geometric mean ratio (90% CI)</th> </tr> </thead> <tbody> <tr> <td>AUC_{0-t} (µg*h/L)</td> <td>97.8% (91.1, 105.1)</td> </tr> <tr> <td>AUC_{0-∞} (µg*h/L)</td> <td>97.3% (91.0, 103.9)</td> </tr> <tr> <td>C_{max} (µg/L)</td> <td>58.2% (47.6, 71.1)</td> </tr> </tbody> </table> <p>Study MC-MTX.9/PH: IM MTX had higher C_{max} lower AUC but this was not considered clinically significant by ACPM. Striesow & Brandt (2012) patient preference study: majority of patients and healthcare professionals reported a favourable perception of SC MTX. PBAC Comment: PBAC accepted pre-filled syringe SC injection was bioequivalent to the IM injection. (Para 7.3)</p>	Parameter	Geometric mean ratio (90% CI)	AUC _{0-t} (µg*h/L)	97.8% (91.1, 105.1)	AUC _{0-∞} (µg*h/L)	97.3% (91.0, 103.9)	C _{max} (µg/L)	58.2% (47.6, 71.1)	<p>Study NCT01737944: SC MTX with auto-injector vs SC MTX without auto-injector vs IM MTX. Doses of 10 mg, 15 mg, 20 mg or 25 mg were used, based on the patient's baseline MTX dose and disease status. The study used a crossover design (single administration of each product) and the patient's dose was the same for the entire study.</p> <p>Results SC MTX (with auto-injector) vs IM MTX</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Geometric mean ratio (90% CI)</th> </tr> </thead> <tbody> <tr> <td>AUC_{0-∞} (ng*hr/mL/mg)</td> <td>101.3% (97.2, 105.6)</td> </tr> <tr> <td>AUC₀₋₂₄ (ng*hr/mL/mg)</td> <td>101.1% (97.0, 105.4)</td> </tr> <tr> <td>C_{max} (ng/mL/mg)</td> <td>89.8% (81.6, 98.8)</td> </tr> </tbody> </table> <p>90% CI for AUC within 80% to 125% prespecified range required to demonstrate bioequivalence.</p>	Parameter	Geometric mean ratio (90% CI)	AUC _{0-∞} (ng*hr/mL/mg)	101.3% (97.2, 105.6)	AUC ₀₋₂₄ (ng*hr/mL/mg)	101.1% (97.0, 105.4)	C _{max} (ng/mL/mg)	89.8% (81.6, 98.8)
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Key safety data	Limited safety data was presented in the submission. The TGA did not identify any safety concerns. PBAC Comment: PBAC considered that the health and safety risks of self-injection outside clinic setting, including disposal of used syringes, had not been adequately addressed. (Para 7.4)	<ul style="list-style-type: none"> • Naïve indirect comparison of adverse events from a range of studies. • Results from post-marketing study of proposed drug (Striesow and Brandt (2012)) that showed no serious adverse events and few (5%) administration errors. • Outlined QUM activities: patient education and provision of free cytotoxic sharps container. 																

Public Summary Document – March 2017 PBAC Meeting

	Methotrexate March 2016	Current re-submission
Clinical claim	Claimed bioequivalence and non-inferior comparative safety between MTX pre-filled syringe and other parenteral formulations of MTX. PBAC Comment: Non-inferior comparative effectiveness was reasonable. Non-inferior comparative safety was not adequately supported. (Para 6.19)	Unchanged
Economic evaluation	Cost-minimisation including administration costs: <ul style="list-style-type: none"> • One MTX pre-filled syringe (7.5 mg, 10 mg, 15 mg, 20 mg, 25 mg dose strengths) was equivalent to one MTX 50 mg vial for injection; • Parenteral MTX listings for chemotherapy (EFC listings) were included; • 96.3% of patients would self-inject SC MTX; • MBS item 23 (\$37.05) used as administration cost of parenteral MTX administration; • Cost of needles and syringes for IM MTX: \$0.25. PBAC Comment: Equivalent dosing considered appropriate. Inclusion of EFC MTX listings inappropriate. Overestimation of patients suitable for self-injection. PBAC requested a suitable estimate and sensitivity analyses. (Para 6.22, 6.35, 7.5, 7.7)	Cost-minimisation including administration costs: <ul style="list-style-type: none"> • Equi-effective doses unchanged; • EFC items removed; • 85.5% of patients would self-inject based on clinician survey (N=48); • MBS Item 23 (\$37.05) and \$0.25 in supplies will be used for IM injection (unchanged); • Supplementary cost-utility analysis: SC MTX vs oral MTX. SC MTX dominant.
Number of patients	No patient numbers calculated.	Less than 10,000 in Year 1 increasing to less than 10,000 in Year 5.
Number of prescriptions	Less than 10,000 in Year 1 increasing to less than 10,000 in Year 5, based on market share approach.	10,000 – 50,000 in Year 1 increasing to 10,000 – 50,000 in Year 5, based on epidemiological approach.
Estimated total cost to PBS/RPBS (net)	Less than \$10 million in Year 1 increasing to less than \$10 million in Year 5 for a total of less than \$10 million over the first 5 years of listing. PBAC Comment: There is a substantial risk of leakage outside requested indications. A risk share arrangement would be needed to mitigate costs. (Para 7.8)	Less than \$10 million in Year 1 increasing to less than \$10 million in Year 5 for a total of \$10 - 20 million over the first 5 years of listing (updated for corrected DPMQ during the evaluation). Increase in costs was due to epidemiological method resulting in larger number of estimated prescriptions compared to predominantly market share approach in previous submission.
PBAC decision	•Reject. Future submission should clarify proportion of patients who will self-administer and address health and safety concerns with self-administration. (Para 7.9)	-

Source: Compiled during the evaluation

ACPM = Advisory Committee of Prescription Medicines; AUC = area under the plasma concentration time curve; C_{max} = maximum plasma concentration; CI = confidence interval; DPMQ = dispensed price for maximum quantity; EFC = Efficient Funding of Chemotherapy; IM = intramuscular; MBS = Medicare Benefits Schedule; MTX = methotrexate; Para = paragraph; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; QUM = quality use of medicines; SC = subcutaneous; TGA = Therapeutic Goods Administration; vs = versus

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

4 Clinical place for the proposed therapy

- 4.1 Methotrexate is a folic acid antagonist that has immunosuppressant and anti-inflammatory effects. It is used in doses up to 25 mg weekly for the treatment of rheumatoid arthritis and psoriasis.
- 4.2 The resubmission proposed that SC methotrexate would be an alternative to other parenteral methotrexate formulations for patients with rheumatoid arthritis and psoriasis who are unable to use methotrexate tablets. Patients may be unable to use methotrexate tablets due to gastrointestinal adverse events, poor oral bioavailability and poor efficacy at higher doses, and an inability to swallow tablets. This was appropriate and unchanged from the previous submission.
- 4.3 The resubmission requested that SC methotrexate pre-filled syringes be determined as an item exempt from statutory price reductions in accordance with Section 84AH of the *National Health Act 1953*. For this to apply, among other criteria, the Minister must be satisfied, having regard to advice (if any) by the PBAC, that:
- (i) the listed drug in the relevant item represents suitable therapy for a particular patient population; and
 - (ii) the relevant item is suitable for use by a particular subgroup of that population because of either or both of the form and manner of administration of the drug in the item; and
 - (iii) no other pharmaceutical item that has that drug is suitable for use by that subgroup because of either or both of the form and manner of administration of the drug in that other item.
- 4.4 The Revised Explanatory Memorandum of the *National Health Amendment (Pharmaceutical Benefits Scheme) Bill 2007* details that the intention of exemption is to encourage the availability of certain pharmaceutical items with particular formulations of drugs that are used by a demographic subgroup (e.g. children or geriatric patients) for whom other formulations of the drug are not suitable. The Explanatory Memorandum goes on to say that subgroups identified on the grounds of their disease characteristics will not qualify.
- 4.5 The proposed item is the only brand of injectable methotrexate that is TGA registered for SC administration injection. It is also the only injectable methotrexate that is TGA registered for use in rheumatoid arthritis. The resubmission:
- (i) stated that SC methotrexate is a suitable therapy for patients with rheumatoid arthritis and psoriasis;
 - (ii) stated that SC methotrexate is intended for use by a subgroup of patients, namely those for whom the oral form of methotrexate is unsuitable. This constitutes a subgroup identified on the grounds of its disease characteristics, rather than a demographic subgroup; and
 - (iii) did not provide a rationale as to why no other pharmaceutical item would be suitable for use by that subgroup. The identified subgroup may be able to use methotrexate 50 mg in 2 mL glass vials.
- 4.6 The PSCR argued that the patients who are unsuitable for the oral tablet form of methotrexate may present clinical features which are not necessarily disease

characteristics. The ESC advised that these clinical features do not appear to represent a demographic subgroup.

- 4.7 The ESC advised that the resubmission did not adequately address the last two criteria (i.e. whether there were demographic subgroups for whom SC methotrexate was the only formulation suitable).
- 4.8 The Pre-PBAC Response stated that may not be viable for the sponsor to supply SC methotrexate to the PBS should the presentation be subject to ongoing fluctuations in the pricing of methotrexate vials.

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

5 Comparator

- 5.1 The comparator was parenteral methotrexate in the form of methotrexate 50 mg in 2 mL glass vials. The resubmission assumed the glass vials were generally given as an intramuscular (IM) injection. The PBAC reaffirmed that this was the appropriate comparator.
- 5.2 In the supplementary economic evaluation, the resubmission nominated oral methotrexate as a comparator. The resubmission claimed that parenteral methotrexate was currently underutilised and that listing a "convenient" dose form may result in additional patients switching from oral methotrexate to parenteral methotrexate. The resubmission further claimed that this would delay patients progressing to biological DMARDs (bDMARD). This was not appropriate; because the resubmission only sought listing in patients who are unsuitable for oral methotrexate, not those who would prefer a SC formulation; and the presented evidence (Hazelwood et al, 2015) found that there was no statistically significant difference between SC and oral administrations of methotrexate at one year in terms of progression to a bDMARD. Further, the resubmission did not present any evidence that methotrexate was currently underutilised, nor that the availability of SC methotrexate would increase utilisation of methotrexate. The ESC considered that this comparison was inappropriate, but noted that it was provided for information only in the supplementary cost-effectiveness context and did not impact the clinical claim (non-inferiority to parenteral methotrexate) nor the price requested.
- 5.3 The PBAC did not consider the supplementary comparison as relevant to the requested PBS population.

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.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (21), health care professionals (29) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with SC methotrexate pre-filled syringes including improved dosing accuracy, ease of administration, lack of wastage compared to vials, improved compliance and enhanced quality of life. It was also noted that the availability of pre-filled syringes could potentially delay or remove the need for patients to transition to more expensive biologic therapies. The PBAC also noted the comments that the TGA registration of SC methotrexate pre-filled syringes had led to some compounding pharmacists stopping production of pre-filled syringes, which had increased administrative burdens for those patients who now have to see their GP for injections.
- 6.3 The comments from Creaky Joints Australia and the Young Women's Arthritis Support Group also highlighted that the pre-filled syringes provided convenience in the administration of methotrexate, particularly as patients with RA may have limited dexterity and be unable to administer other forms of injectable methotrexate. The PBAC welcomed the patient comments compiled by Creaky Joints Australia. These comments reiterated the range of benefits experienced using SC methotrexate pre-filled syringes.
- 6.4 The PBAC also noted the correspondence from Monash Rheumatology at Monash Health, strongly in support of PBS listing of methotrexate SC pre-filled syringes. This correspondence viewed that the listing would increase the uptake of injectable methotrexate treatments in Australia, resulting in improved efficacy and improved quality of life, and delay or reduce the uptake of biological therapies for RA. The correspondence also stated that significant numbers of patients at Monash had been successfully treated with SC methotrexate after an inadequate response to oral methotrexate.

Clinical trials

- 6.5 At its March 2016 meeting, the PBAC considered that SC methotrexate pre-filled syringes were non-inferior to IM methotrexate. To further support this, the resubmission presented three new studies and re-presented one study from the previous submission (MC MTX.7/PH).
- 6.6 Two of the newly identified studies (Jundt (1993) and Brooks (1990)) were excluded during the evaluation as they did not include the relevant outcomes. The studies did not report the geometric mean ratio between pharmacokinetic parameters. Thus, the evaluation was based on two pharmacokinetic studies (n = 52).
- 6.7 Additionally, the resubmission presented one randomised trial (n = 375) and one observational study (n = 666) that compared SC methotrexate with oral methotrexate to support the supplementary comparison against oral methotrexate. The PBAC did not consider the comparison informative to its decision-making for the requested PBS listing.

6.8 Details of the studies presented in the resubmission are provided in the table below.

Table 2: Trials and associated reports presented in the re-submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Pharmacokinetic studies		
MC-MTX.7/PH	Clinical study to evaluate the pharmacokinetic characteristics and the rate and extent of absorption of 16.5 mg methotrexate disodium salt as an aqueous solution corresponding to 15.0 mg methotrexate when given subcutaneously as compared to an equal dose after intramuscular administration as reference in 16 healthy male volunteers.	Not published
Jundt 1993	A comparison of low dose methotrexate bioavailability: oral solution, oral tablet, subcutaneous and intramuscular injection.	Journal of Rheumatology 1993; 20:1845-49.
Brooks 1990	Pharmacokinetics of methotrexate administered by intramuscular and subcutaneous injections in patients with rheumatoid arthritis.	Arthritis and rheumatism 1990; 33(1): 91-4.
NCT01737944	Exposure Study Comparing 3 Routes of Methotrexate Administration	Not published
Supplementary comparison		
MC-MTX.6/RH	Double-blind, multicentric, randomized clinical trial phase IV to evaluate efficacy of subcutaneous administered methotrexate (Metex®) in comparison with oral treatment in patients with active rheumatoid arthritis	Clinical Study Report MC-MTX.6/RH 16 January 2007
	Braun et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis.	Arthritis and rheumatism, 2008; 58(1):73-81.
Hazelwood 2015	Hazelwood et al. The comparative effectiveness of oral versus subcutaneous methotrexate for the treatment of early rheumatoid arthritis.	Annals of the Rheum Diseases, 2016; 75(6):1003-8.(Published online May 2015)

Source: Table 11, p43 of the resubmission; Study MC-MTX.7/PH study report, p1; Jundt (1993); Brooks (1990); NCT01737944; and constructed during the evaluation.

6.9 The key features of the included studies in the main comparison are summarised in the table below.

Table 3: Key features of the included evidence: SC MTX versus IM MTX

Study	N	Design/ duration	Risk of bias	Patient population	Therapies compared	In previous submission?
MC-MTX.7/PH	16	OL, two period, single dose random sequence, crossover study	Low	Healthy males	- 15 mg IM MTX - 15 mg SC MTX	Yes
NCT01737944	36	R, OL, crossover Single administration of each study drug	Low	RA pts receiving MTX 10-25 mg weekly	- SC MTX (with PFS auto-injector device) ^a - SC MTX (without PFS auto-injector device) - IM MTX MTX doses of 10 mg, 15 mg, 20 mg and 25mg were used. The patient's dose was the same for the entire study	No

Source: Compiled during evaluation

IM = intramuscular; MTX = methotrexate; OL = open label; PFS = pre-filled syringe; pts = patients; R = randomised. RA = rheumatoid arthritis; SC = subcutaneous

^a This was a propriety auto-injector device (i.e. not the same PFS as that proposed for listing)

6.10 Study NCT01737944 was the only new study included in the evaluation. This was a randomised, open label, crossover study with three arms: SC methotrexate administered with a pre-filled syringe auto-injector device; SC methotrexate administered without a device; and IM methotrexate. It was conducted in patients with rheumatoid arthritis who were on methotrexate. Methotrexate doses of 10 mg, 15 mg, 20 mg and 25 mg were used. Each patient's dose was determined by the investigator based on the dose at baseline and disease status. The study had a crossover design wherein each patient received all three formulations, and the patient's dose was the same for the entire study.

Comparative effectiveness

6.11 Table 4 presents the key pharmacokinetic outcomes from study NCT01737944.

Table 4: Results of pharmacokinetic outcomes from NCT01737944 (dose normalised^a)

Parameter	SC MTX with device (SD)	SC MTX without device (SD)	IM MTX (SD)	Geometric mean ratio, % (90% CI)	
				SC MTX with device vs IM MTX ^b	SC MTX with device vs SC MTX without device
AUC _{0-∞} (ng*hr/mL/mg)	118.1 (42.3)	122.6 (40.6)	116.7 (41.4)	101.3% (97.2, 105.6)	96.2% (92.3, 100.3)
AUC ₀₋₂₄ (ng*hr/mL/mg)	116.6 (41.0)	121.1 (39.4)	122.6 (40.6)	101.1% (97.0, 105.4)	96.2% (92.3, 100.3)
C _{max} (ng/mL/mg)	21.4 (8.3)	22.4 (10.3)	23.4 (7.2)	89.8% (81.6, 98.8)	96.8% (87.9, 106.5)

Source: Table 16, pp53-4 of the resubmission

AUC_{0-∞} = area under the curve extrapolated to infinity; AUC₀₋₂₄ = area under the curve from zero to 24 hours post dose; CI = confidence interval; IM = intramuscular; MTX = methotrexate; PFS = pre-filled syringe; SC = subcutaneous; SD = standard deviation

^a The pharmacokinetic parameter was divided by the dose administered.

^b This was a propriety auto-injector device (i.e. not the same PFS as that proposed for listing). As this was a pharmacokinetic study in a clinic setting, differences between types of pre-filled syringes would be unlikely to affect outcomes.

- 6.12 The 90% confidence interval of the ratio of the geometric least square means of the area under the curve (AUC) of SC methotrexate with the administration device versus IM methotrexate was fully contained within the pre-specified 80% to 125% range. This supported the PBAC's previous conclusion (from March 2016) of non-inferiority between SC methotrexate and IM methotrexate.
- 6.13 The Advisory Committee on Prescription Medicines (ACPM) considered that small differences in pharmacokinetic parameters between IM and SC methotrexate administration seen in study MC-MTX.7/PH were not likely to be of clinical significance (ACPM minutes, June 2015).

Comparative harms

Comparative safety (versus IM methotrexate)

- 6.14 In its previous consideration, the PBAC stated that the claim of non-inferior comparative safety was not adequately supported by the data. To address this, the resubmission presented a naïve comparison of safety outcomes of SC versus IM methotrexate (in patients with rheumatoid arthritis) using single arm studies or studies with different comparators. There was significant heterogeneity between the studies in terms of the patient populations (e.g. different severity of arthritis), the doses of methotrexate given (which ranged from 2 mg weekly to 15 mg weekly), and the reporting of adverse events. The outcomes of the two most similar studies (MC-MTX.6/RH and Rau (1997)) are presented in Table 5. MC-MTX.6/RH compared 15 mg SC methotrexate (could be increased to 20 mg after 16 weeks) with oral methotrexate in methotrexate-naïve patients. Rau (1997) compared IM methotrexate (7.5 mg for the first two weeks, 15 mg thereafter) and IM gold in patients with erosive rheumatoid arthritis.

Table 5: Naïve comparison of safety outcomes between SC and IM methotrexate

Trial ID	SC MTX MC-MTX.6/RH; n = 193 ^a	IM MTX Rau 1997; n = 87
All AEs (patients)	66.3%	66.7%
Grade 3/4 AEs (events)	-	16%
SAE (patients) ^b	5.7%	-
AEs leading to discontinuation	9.3%	6.9%

Source: Table 17, p56 and Table 18, p60 of the submission; Rau (1997); pp108-109 of MC-MTX.6/RH CSR; Table 12.2.3.2, p106, Table 14.3.1.1A, p322 and pp100-101 of MC-MTX.6/RH CSR; and Braun (2008)

AE = adverse event, IM = intramuscular; MTX = methotrexate; SAE = serious adverse event; SC= subcutaneous

^a Safety population

^b Any event that resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, or was a congenital anomaly or birth defect.

Note: Grade3/4 adverse events reported in Rau (1997) are not comparable with SAEs reported in MC-MTX.6/RH.

- 6.15 There was significant heterogeneity between the two studies; however, the naïve comparison showed broadly similar rates of adverse events between SC and IM methotrexate.

Safety of self-administration in the community

- 6.16 In its previous consideration, the PBAC noted that there may be potential health and safety concerns with self-administration of injectable methotrexate outside the clinic setting. To address this, the resubmission presented a range of information including data regarding the use of SC methotrexate in the community (including Striesow (2012)); and details regarding Quality Use of Medicines activities.
- 6.17 The most relevant study presented to support the safety of self-administration of SC methotrexate in the community setting was a post-marketing surveillance study by Striesow (2012). The study assessed preference, satisfaction, usability, and tolerability of SC methotrexate pre-filled syringes in 403 patients with rheumatoid arthritis or psoriatic arthritis. Patients received six doses: the first dose was administered by a clinician, the second and sixth doses were self-administered with clinician supervision and the remaining three doses were self-administered. The findings were:
- no serious adverse events were reported in the study;
 - 5% of participants reported administration errors relating to administration site and disinfection; and,
 - 87.6% of patients assessed the SC methotrexate pre-filled syringes as ‘very good’ or ‘good’;
- The results of the Striesow (2012) showed no serious adverse events and few administration errors.
- 6.18 During the evaluation, guidance from the Australian Rheumatology Association was identified regarding the handling of low dose methotrexate. The guidance stated that methotrexate “is not absorbed through the skin in tablet or liquid forms: the tablets and injections can be handled without absorption through contact.” Further, it stated that “high dose (1,000-2,000 mg) contamination studies have shown no methotrexate in air samples – gloves and masks are certainly not required when handling the lower doses.” (Australian Rheumatology Association, 2015).

- 6.19 To address the PBAC's concerns from the March 2016 meeting regarding disposal of used syringes, the resubmission stated that the sponsor would provide education material relating to the appropriate use and disposal of SC methotrexate. This would include free provision of a cytotoxic sharps container bin through online order or a Reply Paid Card included in the educational materials. This appeared to place the responsibility on the patient to source the cytotoxic sharps container, and may result in patients receiving the sharps container weeks after starting SC methotrexate. Distribution through pharmacies (e.g. via wholesalers) or rheumatologists/prescribers (e.g. as part of the educational material) may provide easier and more timely access to the sharps container. Further, the education materials state that sharps containers can be requested with the patient's first prescription. However, replacements would be required on an ongoing basis.
- 6.20 The patient education materials stated that patients should seek advice from their doctor, pharmacist, local council or hospital for advice on disposal of the full sharps container. The Return of Unwanted Medicines project (in community pharmacies) website stated that it does not collect sharps or liquid cytotoxic products.

Clinical claim

- 6.21 The resubmission described SC methotrexate pre-filled syringes as non-inferior and bioequivalent in terms of comparative effectiveness and non-inferior in terms of comparative safety over methotrexate glass vials injected intramuscularly. The PBAC had previously accepted the claim of non-inferior comparative effectiveness over IM methotrexate and the new clinical data supported the PBAC's previous conclusion.
- 6.22 The PBAC considered that the claim of non-inferior comparative safety was reasonable, and viewed that the resubmission had adequately addressed the PBAC's previous concerns about the safety of methotrexate self-injection outside the clinic setting.
- 6.23 The following health and safety risks of self-injection in the community setting were adequately addressed:
- methotrexate is only minimally absorbed through skin and not detected in air samples, minimising the risk of inadvertent exposure through spills;
 - SC methotrexate pre-filled syringes have been available internationally since 2009 and, at 30 June 2016, are registered in 34 countries. No specific safety problems have been identified with respect to the safety of self-administration, including in patient preference studies and post-marketing surveillance activities; and
 - the sponsor has developed an education program on appropriate handling of SC methotrexate. This included provision of free cytotoxic sharps containers.

Economic analysis

- 6.24 The resubmission presented a cost-minimisation analysis versus methotrexate glass vials including drug, injection and administration costs (a cost-analysis). This included reduced healthcare visits for weekly self-administration of methotrexate. Table 6 summarises the key differences compared with the previous submission.

Table 6: Comparison of the economic evaluation in the previous submission and the current resubmission

Issue	Previous submission March 2016	Previous PBAC/evaluator comments March 2016	Resubmission
Equi-effective doses	One SC MTX PFS equivalent to one 50 mg/2 mL vial.	Reasonable (Para 6.22)	Unchanged. This was appropriate
EFC MTX items	Included in drug price calculations.	Inappropriate and inadequately justified. (Para 7.6)	Excluded. This was appropriate
% of pts self-injecting MTX PFS	96.3%	Overestimated. The estimate was based on patients considered suitable for self-injection (Para 7.7)	85.5% based on a clinician survey (n=48) The clinician survey was generally well conducted but did not include patients and GPs.
% of pts self-injecting MTX glass vials	0%	-	10%. The basis was unclear. Likely overestimated but conservative.
Cost of MTX administration	MBS Item 23 (Level B GP, \$37.05)	Unclear which MBS items are being used in clinical practice (Para 6.36)	Unchanged, stating use of MBS Item 3 (Level A GP) is very low.
% of visits to GPs solely for MTX injection	100% of attendances assumed to be solely for MTX administration	Pts may have multiple morbidities/ co-administered medications addressed in a single visit (Para 6.33).	Unchanged. This may not be appropriate.

Source: Compiled during evaluation based on pp73-74 of the resubmission

EFC = efficient funding of chemotherapy; GP = General Practitioner; IM = intramuscular; MBS = Medicare Benefits Schedule; MTX = methotrexate; Para = paragraph; PFS = pre-filled syringe; pts = patients; SC = subcutaneous

- 6.25 The resubmission assumed SC methotrexate pre-filled syringes and other forms of parenteral methotrexate had the same equi-effective dosing. In pragmatic terms, the resubmission assumed that one SC 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 glass vial for injection (which could be used to prepare an equivalent dose, with the remainder lost as wastage). This was unchanged from the previous submission. This approach was considered reasonable by the PBAC.
- 6.26 A key difference compared with the previous submission was that the proportion of patients who would self-inject SC methotrexate was updated as requested by the PBAC. The resubmission included a survey of rheumatologists and dermatologists conducted to quantify the proportion of patients who were likely to self-inject SC methotrexate. A total of 48 clinicians provided evaluable responses (31 rheumatologists, 14 dermatologists and 3 rheumatology nurses) and the response rate was 41% (based on evaluable responses, calculated during evaluation to exclude nil or incomplete responses). Overall, clinicians considered that 85.5% (range 30% to 100%) of patients prescribed SC methotrexate would be likely to self-inject. The range indicated a high variation in responses, although most clinicians (90%) indicated that 70% or more of patients would be likely to self-inject. Overall, the survey appeared to have been reasonably well conducted. However, it was unclear how clinicians were selected to participate, and the survey did not include patients or General Practitioners (GP) (who would be responsible for the day-to-day management of patients with rheumatoid arthritis).
- 6.27 To further support this estimate, the resubmission noted that the PBAC had previously accepted that 10% of patients would require assistance with SC administration of golimumab, a bDMARD (March 2010). The resubmission did not

consider whether the rates of self-injection would differ between cytotoxic and non-cytotoxic medicines.

- 6.28 The resubmission included an estimate that 10% of patients currently self-inject parenteral methotrexate from the 50 mg in 2 mL glass vials. This was not included in the previous submission and no evidence was provided to support this. However, this assumption was conservative in nature (reduced the price of SC methotrexate).
- 6.29 The re-submission assumed that patients not self-injecting methotrexate would require a Level B GP consult (MBS Item 23, less than 20 minutes) once weekly for administration. This was unchanged from the previous submission. This assumed that each visit was for the sole purpose of methotrexate injection. The previous consideration stated that patients may have multiple morbidities and/or co-administered medications addressed at a single visit (Paragraph 6.33, March 2016 PSD). Further, there may be some administration by practice nurses. Thus, the use of one Level B GP consult for every non-self-administered injection may overestimate the administration costs of methotrexate glass vials.
- 6.30 As shown in Table 7, the resubmission proposed an ex-manufacturer price of \$ [redacted] per syringe (dispensed price maximum quantity (DPMQ) = \$ [redacted] for 4 syringes). The Pre-PBAC Response revised this price to \$ [redacted] per syringe (DPMQ = \$ [redacted] for 4 syringes), to address the ESC's advice that the cost offsets for administration of glass vials were likely overestimated.

Table 7: Cost-minimisation analysis

Type of resource item	MTX vials		SC MTX	
	Per dose	Total per month ^a	Per dose	Total per month ^a
Drug costs per injection (AEMP)	\$3.13/vial	\$12.52	-	-
Administration costs				
Level B GP attendance	\$37.05/consult	\$133.38	\$37.05/consult	\$21.49
% patients who require weekly consult	90% (10% self-inject)		14.5% (85.5% self-inject)	
Needles and syringes	\$0.25/injection	\$1.00	-	-
Total administration cost	\$33.60^b	\$134.38^b	\$5.37	\$21.49
Total cost MTX vial	\$36.73	\$146.90	-	-
Total cost SC MTX (AEMP)	-	-	\$ [redacted] ^c	\$ [redacted]
Total cost SC MTX (DPMQ)	-	-	-	\$ [redacted] ^d

Source: Table 20, pp76-77 of the resubmission; and corrected during evaluation

AEMP = approved ex-manufacturer price; AHI = Administration, Handling and Infrastructure; DPMQ = dispensed price for maximum quantity; GP = General practitioner; MBS = Medicare Benefits Schedule; MTX = methotrexate; NA = not applicable; PBS = Pharmaceutical Benefits Scheme; SC= subcutaneous

^a 4 weeks

^b Calculated as \$37.05 (MBS fee) × 90% per dose + \$0.25/injection for needles and syringes.

^c Derived by subtracting the SC MTX administration cost per dose (\$ [redacted]) from the total cost of MTX vial (\$ [redacted]).

^d Corrected during evaluation, using Tier 1 AHI fees. The DPMQ includes a wholesale mark-up of 7.52%; plus Tier 1 AHI of \$3.54 per prescription plus dispensing fee of \$7.02 per prescription.

- 6.31 The results of sensitivity analyses undertaken during the evaluation are presented in Table 8.

Table 8: Results of sensitivity analyses undertaken during evaluation

Sensitivity analyses	DPMQ
Base case	\$ [REDACTED] ^a
% self-injection	
0% self-injection of glass vials (Base case = 10%)	\$ [REDACTED]
80% self-injection of SC methotrexate (38% of clinicians surveyed estimated that ≤ 80% patients would be likely to self-inject) (Base case = 85.5%)	\$ [REDACTED]
70% self-injection of SC methotrexate (Base case = 85.5%)	\$ [REDACTED]
MBS item for methotrexate administration	
85% of consults for methotrexate administration only, with remainder administered by practice nurse or as part of another consult (Base case = 100% of patients who do not self-inject require a GP consult for each weekly administration)	\$ [REDACTED] ^b

Source: Section D spreadsheet; and calculated during the evaluation

DPMQ = dispensed price for maximum quantity; MBS = Medicare Benefits Schedule; PFS = pre-filled syringe; SC = subcutaneous

^a Pricing mark-ups recalculated during the evaluation.

^b In total, 77% of IM methotrexate vials would be associated with a GP visit (90% * 85%) and 12% of SC methotrexate vials would be associated with a GP visit (14.5% * 85%)

- 6.32 The cost-minimisation analysis was most sensitive to the proportion of patients self-administering methotrexate and the proportion of GP consults that were solely for the purpose of methotrexate administration. The revised price in the Pre-PBAC response was intended to account for the sensitivity analysis in the table above where 85% of GP consults are for methotrexate administration only.

Drug cost/patient/year: \$ [REDACTED]. Revised in Pre-PBAC Response to \$ [REDACTED].

- 6.33 The proposed cost was \$ [REDACTED] per patient per year, compared with \$ [REDACTED] for 50 mg in 2 mL methotrexate glass vials. The cost of the proposed drug was based on DPMQ of \$ [REDACTED] (for four doses) and [REDACTED] prescriptions per year (95% compliance). The revised cost was \$ [REDACTED] (based on a DPMQ of \$ [REDACTED] and 12.4 prescriptions). The cost of the methotrexate glass vials was based on a DPMQ of \$ [REDACTED] (for five vials) and [REDACTED] prescriptions per year (95% compliance).

Estimated PBS usage & financial implications

- 6.34 This resubmission was not considered by DUSC. The resubmission presented revised estimates of use and financial implications. An epidemiological approach was used to derive the estimates. This approach and the estimated utilisation differed substantially from the previous submission, which was predominantly based on a market-share approach.
- 6.35 Table 9 summarises the estimated utilisation and financial implications associated with PBS listing of SC methotrexate. The previous submission (March 2016) estimates are included for comparison.

Table 9: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Eligible population					
Treated patients					
Prescriptions					
Prescriptions - March 2016 ^a					
Cost to PBS/RPBS					
Cost to PBS/RPBS for SC MTX (no offsets) ^b	\$	\$	\$	\$	\$
Reduced cost of MTX glass vials	-\$	-\$	-\$	-\$	-\$
Reduced cost of oral MTX (as proxy for other DMARDs)	-\$	-\$	-\$	-\$	-\$
Estimated total net cost to PBS/RPBS					
Net cost to PBS/RPBS ^b	\$	\$	\$	\$	\$
Net cost to PBS/RPBS excluding oral MTX cost offsets	\$	\$	\$	\$	\$
Net cost to PBS/RPBS - March 2016	\$	\$	\$	\$	\$

Source: Table 16, p18 of PBAC PSD, March 2016; compiled during the evaluation; and corrected during the evaluation

DPMQ = dispensed price maximum quantity; PBS= Pharmaceutical Benefits Scheme; RPBS= Repatriation Pharmaceutical Benefits Scheme; SC= subcutaneous

^a The previous submission did not estimate the number of patients likely to utilise SC methotrexate.

^b Recalculated during the evaluation using the corrected DPMQ of \$

- 6.36 The resubmission estimated that the cost to the PBS/RPBS would be \$10 - 20 million in the first five years of listing. This was compared with less than \$10 million in the previous submission. The resubmission estimated that at year 5, the number of treated patients would be less than 10,000 per year.
- 6.37 The evaluation considered that the cost to the PBS/RPBS could be higher or lower than presented in the resubmission because:
- the number of patients with moderate-to-severe rheumatoid arthritis (or severe psoriasis) on methotrexate was underestimated (75%). This was because patients with moderate-to-severe rheumatoid arthritis (or severe psoriasis) were assumed to have the same rate of use of methotrexate as all patients with rheumatoid arthritis (or psoriasis), regardless of disease severity (likely underestimated the eligible population);
 - the proportion of patients with rheumatoid arthritis who are unsuitable for oral methotrexate (22.5%) was overestimated because it was based on a study that used a treatment strategy that was not applicable to Australian clinical practice (likely overestimated the eligible population). This differed substantially from the previous submission which estimated 5% of rheumatoid arthritis patients were unsuitable for oral methotrexate;
 - the proportion of patients with psoriasis who are unsuitable for oral methotrexate (5%) was poorly justified;
 - uptake from oral methotrexate was used as a proxy for uptake from other DMARDs. It may be reasonable to assume that SC methotrexate might grow the market for parenteral methotrexate and there may be substitution from other DMARDs. However, the inclusion of cost offsets for substitution of oral methotrexate was not appropriate because other DMARDs are more costly than methotrexate (underestimated cost offsets); and
 - the uptake rates were poorly justified (unknown impact).

- 6.38 The resubmission assumed that uptake of SC methotrexate would be from two sources:
- methotrexate vials, with 95% substitution assumed.
 - oral methotrexate (as a proxy for other DMARDs and delayed use of bDMARDs). The resubmission base case stated that uptake was likely to be more gradual, with 10% uptake in Year 1 increasing linearly to 50% in Year 5. No basis was provided for this uptake rate.
- 6.39 The Pre-PBAC Response presented revised financial estimates and additional sensitivity analysis, shown in the table below. The PBAC noted that the sensitivity analysis that removed the cost offsets for substitution of oral methotrexate had incorrectly included co-payments for oral methotrexate (revised below).

Table 10: Pre-PBAC Response revised financial implications and sensitivity analyses

Net cost to Government for listing of Trexject	Year 1	Year 2	Year 3	Year 4	Year 5
Base case (DPMQ \$ [redacted])	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Sensitivity analyses					
1. Higher methotrexate use (79%, Nash 2013)	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
2. Lower unsuitable for oral methotrexate (16%, Braun 2008)	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
3. Lower uptake from eligible pool not using vials (10-30% over 5 years)	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
4. Removal of cost offsets for substitution	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
1 and 2 and 3 and 4	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Revised – without co-payments for oral methotrexate					
4. Removal of cost offsets for substitution	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
1 and 2 and 3 and 4	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]

Source: Pre-PBAC Response

The redacted table shows that, for each of the sensitivity analyses, the net cost to Government for listing of Trexject is less than \$10 million per year in each of the first five years.

- 6.40 The PSCR stated that “the Evaluator erroneously refers to patients with moderate to severe RA [rheumatoid arthritis] [COM.46], where in fact both the TGA indication and the proposed PBS listing limit the eligible patient pool to patients with severe disease.” The Pre-PBAC Response stated that the ESC advice had reiterated “erroneous references to patients moderate to severe RA”, where the TGA indication and proposed PBS listing are limited to patients with severe disease.

- 6.41 In the financial estimates, the disease severity was based on the proportion of patients in the OPAL database with moderate or severe disease activity, 22.2% and 6.8% respectively (p2 of Littlejohn et al, 2015). That is, the resubmission used the combined total of patients with moderate or severe disease activity (29%) to derive the eligible patient population. This was then multiplied by the proportion of patients taking methotrexate and those under specialist care. The Pre-PBAC response confirmed that the resubmission had applied the proportion of patients with moderate to severe disease activity on DAS-28 in the OPAL database as an approximation of patients who could be described as having severe disease.

Quality Use of Medicines

- 6.42 The resubmission claimed that the availability of SC methotrexate as a pre-filled syringe formulation would reduce dosing errors that may occur when drawing up the correct dose from a 50 mg in 2 mL glass vial and may also reduce healthcare practitioners' exposure to methotrexate.
- 6.43 Further, the resubmission stated the sponsor would provide education materials for patients and clinicians that would include dummy syringes to assist in training patients to self-inject. There may be scope to provide home sharps containers within the proposed education materials to ensure access for all patients self-injecting.

Financial Management – Risk Sharing Arrangements

- 6.44 In its consideration of the previous submission, 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.
- 6.45 The resubmission stated that the sponsor would consider a Risk Sharing Arrangement to mitigate the risk of use outside the TGA-registered indications of rheumatoid arthritis and psoriasis.
- 6.46 The resubmission claimed that the Authority Required (Streamlined) listing may reduce the risk of leakage. An Authority Required (Streamlined) listing may not prevent use outside the restrictions. Clinicians may still use SC methotrexate in conditions such as juvenile idiopathic arthritis and psoriatic arthritis where similar doses of methotrexate would be used.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the General Schedule Authority Required (Streamlined) listing of methotrexate pre-filled syringe (with embedded needle) for subcutaneous administration for the treatment of rheumatoid arthritis or psoriasis when methotrexate oral tablets are unsuitable, on a cost-minimisation basis with methotrexate 50 mg vial, taking into account the offsets associated with reduced administration costs.

- 7.2 The PBAC noted that the equi-effective doses were unchanged from the previous submission which stated that one methotrexate pre-filled syringe (7.5 mg, 10 mg, 15 mg, 20 mg, 25 mg dose strengths) was equivalent to one methotrexate 50 mg vial for injection. The PBAC reaffirmed that this was appropriate.
- 7.3 The PBAC reaffirmed that there was a clinical need for this presentation of methotrexate.
- 7.4 The PBAC considered that PBS indications of “severe active rheumatoid arthritis” and “severe psoriasis” would be sufficient to identify the appropriate patient population. The PBAC noted that the proposed RA listing required that patients have failed, or be intolerant to NSAIDs or one or more disease modifying drugs prior to commencing therapy with methotrexate SC. The PBAC considered that this was not aligned with current clinical practice and did not recommend inclusion of this criterion in the listing. For the psoriasis listing, the PBAC advised that the clinical criteria should specify that “the condition must not have adequately responded to topical treatment”. In addition, the PBAC was of the view that an age requirement was unnecessary for either listing, as the prescribing clinician would be responsible for ensuring that methotrexate SC was only prescribed for suitable patients.
- 7.5 The Committee reaffirmed its view from the March 2016 meeting that the claim of non-inferior comparative effectiveness was reasonable.
- 7.6 The PBAC was satisfied that the comparison showed broadly similar rates of adverse events between SC versus IM methotrexate. In terms of the safety of SC methotrexate in the community setting, the PBAC was satisfied that the resubmission had presented sufficient data to support its use in this setting, and details regarding its proposed Quality Use of Medicines activities. Thus, the PBAC considered that the claim of non-inferior comparative safety was reasonable.
- 7.7 In terms of the economic evaluation, the PBAC recalled its uncertainty around key inputs into the original cost-minimisation analysis. In this resubmission, the PBAC noted that the proportion of patients who would self-inject SC methotrexate was updated from 96.3% to 85.5%, based on a clinician survey (n=48), which was considered a more reasonable estimate. However, the resubmission did not revise its assumption that 100% of patients not self-injecting methotrexate would require a Level B GP consult (MBS Item 23, less than 20 minutes) once weekly for administration, which the PBAC continued to view as an overestimate of the administration costs of methotrexate glass vials. The Pre-PBAC Response acknowledged the ESC’s advice that the cost offsets for administration of glass vials were therefore overestimated, and proposed a new DPMQ of \$ [REDACTED] for four syringes (or \$ [REDACTED] per syringe), based on an assumption that 85% of GP consults would be for methotrexate administration only. The PBAC noted that there are likely benefits of a subcutaneous form of methotrexate, and requested that the Department negotiate with the sponsor in relation to the offsets associated with reduced administration costs.
- 7.8 The PBAC noted the concerns raised during the evaluation and ESC meeting about the uncertainty of the estimated utilisation and financial impact of listing SC methotrexate (see paragraph 6.39). The PBAC also noted the revised financial implications presented in the Pre-PBAC Response. Overall, the PBAC viewed that

the financial estimates presented in the submission were likely an overestimate of the cost to the PBS. In particular, the PBAC noted that the uptake estimates for SC methotrexate were underpinned by an assumption that some patients being prescribed oral methotrexate would then switch to SC methotrexate. The PBAC noted that this assumption was not supported by evidence, and it was not considered plausible.

- 7.9 Finally, the PBAC noted that the resubmission requested that SC methotrexate pre-filled syringes be determined as a pharmaceutical item exempt from statutory price reductions in accordance with Section 84AH of the *National Health Act 1953* (the *Act*). The PBAC noted that SC methotrexate is suitable therapy for patients with rheumatoid arthritis and psoriasis (in accordance with the circumstance specified under 101(4AB – a) of the *Act*.) However, the PBAC considered that patients who are unsuitable for the oral tablet form of methotrexate do not represent an alternative, demographically based subgroup of patients as set out in subsection 101 (4AB – b) of the *Act*. Moreover, as the identified subgroup can use methotrexate 50 mg in 2 mL glass vials, the PBAC also considered that the resubmission did not provide justification that the circumstance specified under 101(4AB –c) of the *Act* exists in relation to SC methotrexate. Therefore, the PBAC had no reason to advise the Minister under section 101(4AB) of the *Act* that the relevant circumstances exist for SC methotrexate to be determined as an item exempt from statutory price reductions.
- 7.10 The PBAC advised that SC methotrexate is not suitable for prescribing by nurse practitioners under the PBS.
- 7.11 The PBAC advised that SC methotrexate pre-filled syringes should not be exempt from the Early Supply Rule.
- 7.12 The PBAC noted that this submission was not eligible for Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Manufacturer	Name and
METHOTREXATE			Trexject®	Link Medical Products
7.5 mg/0.15 mL injection, 1 x 0.15 mL syringe	4	5		
10 mg/0.2 mL injection, 1 x 0.2 mL syringe	4	5		
15 mg/0.3 mL injection, 1 x 0.3 mL syringe	4	5		
20 mg/0.4 mL injection, 1 x 0.4 mL syringe	4	5		
25 mg/0.5 mL injection, 1 x 0.5 mL syringe	4	5		

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 <input type="checkbox"/> Midwives
Severity:	Severe
Condition:	Rheumatoid arthritis
PBS Indication:	Severe active rheumatoid arthritis
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must be unsuitable for administration of an oral form of methotrexate for this condition.

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 <input type="checkbox"/> Midwives
Severity:	Severe
Condition:	Psoriasis
PBS Indication:	Severe psoriasis
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	The condition must not have adequately responded to topical treatment, AND Patient must be unsuitable for administration of an oral form of methotrexate for this condition.

9 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.

10 Sponsor's Comment

Link welcomes the recommendation by the PBAC for PBS listing of Trexject for patients with rheumatoid arthritis or psoriasis. Disappointingly, although the PBAC recommended the listing of Trexject (7.1 above) “on a cost-minimisation basis with methotrexate 50 mg vial, taking into account the offsets associated with reduced administration costs”, the Department of Health has advised Link that it does not accept the cost offsets associated with reduced administration costs, and will not progress the listing of Trexject at the requested price. Link continues to work with the Department on this issue, noting that it is not commercially viable for Link to import and supply Trexject to the Australian market unless the listed price is aligned with the recommendation of the PBAC.