

5.21 PROPYLENE GLYCOL

Eye drops 60 micrograms per mL, 10 mL, Systane® Balance, ALCON LABORATORIES (AUSTRALIA) PTY LTD

1 Purpose of Submission

- 1.1 The Category 3 submission requested a General Schedule, Restricted Benefit listing for propylene glycol multi-dose preservative-containing (MDPC) eye drops 60 micrograms per mL, 10 mL (Systane® Balance) for the treatment of severe dry eye syndrome.

2 Background

- 2.1 Systane Balance is an emulsion containing propylene glycol 0.6%w/v, hydroxypropyl guar, mineral oil and dimyristoylphosphatidylglycerol, which provides temporary relief of burning and irritation due to dryness of the eye for patients with severe dry eye syndrome.

Registration status

- 2.2 Systane Balance was registered on the Australian Register of Therapeutic Goods (ARTG) on 3 September 2010 as a class IIa medical device for the treatment of patients with severe dry eye syndrome.

Previous PBAC consideration

- 2.3 Systane Balance has not previously been considered by the PBAC for the treatment of severe dry eye syndrome.
- 2.4 During its May 2023 meeting, the PBAC recommended the listing of Systane Hydration® multi-dose preservative-free (MDPF) eye drops on a cost-minimisation basis to the lowest cost PBS listed ocular lubricant, noting that it was not demonstrated that the product provides a significant improvement in efficacy or reduction of toxicity over other PC ocular lubricants. In this context, the PBAC also reaffirmed its previous 2014 consideration that hyaluronate based PF eye drops are considered to be non-inferior in effectiveness and safety to other (PC) PBS listed ocular lubricants (paragraph 11.2, Systane Hydration Public Summary Document (PSD), May 2023 PBAC Meeting).

3 Requested listing

- 3.1 The submission requested the following new listing with the same restrictions as MDPF eye drops currently listed on the PBS. Additions have been marked in italics and omissions with a strikethrough.

MEDICINAL PRODUCT		PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
medicinal product pack PROPYLENE GLYCOL 0.6% eye drops, 10 mL		NEW	1	1	5	Systane Balance
Restriction Summary [NEW] / Treatment of Concept: [NEW]						
Concept ID		Category / Program: GENERAL – General Schedule (Code GE)				
(for internal Dept. use)		Prescriber type <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input checked="" type="checkbox"/> Optometrists				
		Restriction type: <input checked="" type="checkbox"/> Restricted benefit				
Prescribing rule level	New	Administrative Advice: The in-use shelf life of Systane Balance MDPC this product is 6 months from the date of opening				
		Severity: Severe				
		Condition: Dry Eye Syndrome				
		Indication: Severe Dry Eye Syndrome				

3.2 The proposed amendment to the administrative advice was made to align the advice with that of other restrictions.

4 Comparator

4.1 The submission nominated 0.1%/0.2% hyaluronate sodium MDPF eye drops (Hilo-Fresh and Hilo-Forte respectively) as the main comparators as they have the greatest market share for this PBS indication. The submission nominated 0.5% carmellose sodium + glycerol MDPC eye drops (Optive) as a supplementary comparator noting that the PBAC, in its July 2020 consideration of Cationorm, recommended that ‘all preservative free, multi-dose ocular lubricants currently listed on the PBS were appropriate comparators’. The PBAC in its May 2023 consideration of Systane Hydration considered that all PBS-listed ocular lubricants are also relevant comparators (paragraph 11.2, Systane Hydration PSD, May 2023 PBAC Meeting) as it considered that ocular lubricants with and without preservatives were non-inferior in efficacy.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item.

Consumer comments

5.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

5.3 The submission was based on the indirect comparison of two randomised controlled trials (outlined in Table 1) which demonstrated the comparative efficacy and safety of propylene glycol. The Jerkin et al 2020 study (hereafter referred to as the ‘Jerkin

study’) compared propylene glycol with 0.5% carmellose sodium + glycerol PC eye drops. The Baudouin et al 2012 study (hereafter referred to as the ‘Baudouin study’) compared 0.18% hyaluronate sodium PF (hereafter referred to as HSPF) eye drops with 0.5% carmellose sodium + glycerol PC eye drops. The HSPF eye drops was used as a proxy for the efficacy of the PBS-listed formulations of hyaluronate sodium MDPF eye drops (e.g. Hylo-Fresh/Forte). While HSPF is not PBS listed, the PBAC has previously accepted the approach of using non-PBS listed PF eye drops as a proxy for PBS-listed PF eye drops (paragraph 5.6, Cationorm PSD, July 2020 PBAC Meeting).

- 5.4 The proposed PBS population was patients with severe dry eye syndrome. As the PBS restriction does not provide a definition of ‘severe’ dry eye, patients in the trials were required to have symptoms of moderate to severe dry eye syndrome.
- 5.5 The randomised controlled clinical trials that were used to inform the therapeutic conclusions employed a fixed dosing regimen. Patients in the Jerkin study received one drop in each eye four times daily, and in the Baudouin study they received one drop in each eye 3-6 times daily.

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
NCT02776670 / Jerkin (2020)	<i>Jerkin et al. - A Comparison of Efficacy and Safety of Two Lipid-Based Lubricant Eye Drops for the Management of Evaporative Dry Eye Disease.</i>	2020 <i>Clinical Ophthalmology</i> 2020; Vol (14), pp 1665-1673
NCT00987727 / Baudouin (2012)	<i>Baudouin et al - Randomized, phase III study comparing osmoprotective carboxymethylcellulose with sodium hyaluronate in dry eye disease.</i>	2012 <i>European Journal of Ophthalmology</i> 2012; Vol (22): pp 751-761

Source: Table 2.2-3 of the submission.

- 5.6 As a Category 3 submission, no evaluation of the clinical evidence was undertaken.

Comparative effectiveness

- 5.7 The clinical claim for the efficacy of propylene glycol eye drops was based on an indirect comparison of the two randomised control trials (the Jerkin study and the Baudouin study) where 0.5% carmellose sodium + glycerol PC eye drops was the common reference arm, to demonstrate efficacy against propylene glycol and HSPF eye drops, respectively.
- 5.8 The clinical outcome observed was the mean change from baseline in tear break-up time (TBUT) at Day 35. This was the primary outcome in the Jerkin study and an exploratory outcome in the Baudouin study.
- 5.9 In the Jerkin study, non-inferiority was established if the lower limit of the 95% confidence interval (CI) for the treatment difference for TBUT at Day 35 was above - 1.0 second. In the Baudouin study, non-inferiority was established via ANCOVA analysis. A non-inferiority margin was not applied for the indirect comparison of both trials, but instead non-inferiority was based on the absence of a statistically significant

difference between propylene glycol and HSPF eye drops for the mean change in TBUT at Day 35.

- 5.10 The submission stated a modified ITT population and PP population were used to assess the efficacy outcomes in the Baudouin study which consisted of randomised patients who had received at least one dose of treatment and undergone at least one baseline and post-baseline assessment. In the Jerkin study the efficacy outcome was assessed in both the Full Analysis Set (FAS), i.e., randomised patients, and the per protocol (PP) population (patients within the FAS without major protocol deviations).
- 5.11 The submission noted that there was no statistically significant difference between propylene glycol and HSPF eye drops for the mean change in TBUT at Day 35 between the two trials (LSM 0.17, 95% CI: - 0.78, 1.12; $p=0.7244$), which it considered supportive of a non-inferiority claim for efficacy.

Comparative harms

- 5.12 The clinical claim of non-inferior safety between propylene glycol and HSPF eye drops was based on the absence of a statistically significant difference in the proportion of patients experiencing Adverse Events (AEs), Serious Adverse Events (SAEs) or discontinuations due to AEs (DISCAE) up to Day 35 in the Jerkin study and up to 3 months in the Baudouin study. Safety was measured by the proportion of patients who experienced AEs up to Day 35. The evaluation noted the proposed listing would provide up to approximately 6 months of treatment per prescription.
- 5.13 Results for the indirect comparisons showed that there was no statistically significant difference between propylene glycol PC eye drops and HSPF eye drops for any AE (RD 0.10, 95% CI: 0.27, 0.07; $p = 0.2508$), any SAE (RD -0.01, 95% CI: - 0.08, 0.06; $p = 0.7920$) or the DISCAE rate (RD 0, 95% CI: -0.07, 0.07; $p = 1.00$). That is, there was no statistically significant difference between propylene glycol and HSPF eye drops for safety outcomes.

Clinical claim

- 5.14 The submission claimed the non-inferior comparative effectiveness and non-inferior comparative safety of propylene glycol compared with 0.1%/0.2% hyaluronate sodium MDPF eye drops and 0.5% carmellose + glycerol MDPC eye drops.
- 5.15 The PBAC considered that the claims of non-inferior comparative effectiveness and non-inferior comparative safety were reasonable and supported by the data.

Economic analysis

- 5.16 The submission presented two cost-minimisation approaches (CMAs) of propylene glycol. The first was a comparison against 0.1%/0.2% hyaluronate sodium MDPF eye drops and the second, against 0.5% carmellose sodium + glycerol MDPC as presented in Table 2. The equi-effective dose for propylene glycol used was 1:1 for both 0.1%/0.2% hyaluronate sodium MDPF and 0.5% carmellose sodium + glycerol MDPC.

Table 2: CMA 0.1%/0.2% hyaluronate sodium MDPF and 0.5% carmellose sodium + glycerol MDPC

	Propylene glycol MDPC	0.1%/0.2% HA MDPF	Propylene glycol MDPC	0.5% CS + glycerol MDPC
AEMP per pack	\$22.04	\$19.86	\$3.04	\$2.74
Drops per pack	333	300	333*	300
AEMP per drop	\$0.07	0.07 [\$19.86/300]	\$0.01	0.01 [\$2.74/300]
Drop per treatment	2	2	2	2
AEMP per treatment	\$0.132 [2 x \$0.07]	\$0.132	\$0.018	\$0.018 [2 x \$0.01]

Abbreviations: AEMP = approved ex-manufacturer price; MDPF = multi-dose preservative-free; MDPC = multi-dose preservative free; HA = hyaluronate sodium; Tx = treatment, CS = carmellose sodium

Source: Table 3.4.2 of the submission

* This was 300 drops per pack in this section of the submission, however, the pre-PBAC response confirmed this should read 333.

5.17 The submission claimed a PBS listing for propylene glycol is not expected to result in changes in resource use resulting from differences in prescribing or administration profiles, management of adverse events or monitoring requirements. The CMA only includes the cost of medicines with the analysis undertaken on a per treatment basis, defined as 1 drop in each eye.

5.18 The submission proposed a price for propylene glycol of \$13.96. This price was derived from the AEMP of each CMA, which was averaged and weighted using the distribution of MDPC and MDPF eye drop prescriptions processed by Services Australia in the 2023 calendar year as shown in Table 3.

Table 3: Weighted average AEMP based on utilisation of MDPC and MDPF eye drops

	0.1%/0.2% HA MDPF eye drops	0.5% CS + glycerol MDPC eye drops	Propylene glycol MDPC eye drops
Total adjusted services processed*	835,643	699,718	
Distribution	57.47%	42.53%	100%
AEMP per treatment	\$0.132	\$0.018	\$0.084
Weighted average AEMP/treatment	\$0.084		\$0.084

Abbreviations: AEMP = approved ex-manufacturer price; MDPC = multi-dose preservative containing; MDPF = multi-dose preservative free

Source: Table 3.4.3, p74 of the submission

*Values are adjusted for the number of treatments per pack of each ocular lubricant

5.19 Table 4 provides an alternative cost-minimisation analysis developed during the evaluation, in which propylene glycol, both nominated comparators, and a proxy for the lowest cost ocular lubricant (polyethylene glycol 400 4 mg with propylene glycol 3 mg (Systane® Original)) are compared.

Table 4: Alternative CMA (developed during the evaluation)

	Propylene glycol MDPC eye drops	0.1%/0.2% HA MDPF eye drops	0.5% CS + glycerol MDPC eye drops	Systane Original eye drops
Quantity per prescription				
Drops per pack	333 ^a	300 ^a	300 ^a	300 ^b
Treatments per pack	166 [333 / 2 drops]	150 [300 / 2 drops]	150 [300 / 2 drops]	150 [300 / 2 drops]
Cost per treatment				
AEMP per pack	\$13.96	\$20.90	\$2.74	\$2.31
AEMP per treatment	\$0.084 [\$13.96/166]	\$0.139 [\$20.90 / 150]	\$0.0183 [\$2.74 / 150]	\$0.0154 [\$2.31 / 150]

Abbreviations: AEMP = approved ex-manufacturer price; MDPF = multi-dose preservative-free; MDPC = multi-dose preservative free; HA = hyaluronate sodium; Tx = treatment, CS = carmellose sodium

^a Source: Table 3.4.2 of the submission

^b As the number of drops in Systane original is not publicly available, a standard assumption of 20 drops per 1 mL was applied.

- 5.20 Using the AEMP per treatment of Systane Original, the resultant AEMP per pack of propylene glycol would be \$2.56, which is an 81.6% price reduction of the proposed AEMP.
- 5.21 The PBAC has previously advised that all ocular lubricants should be considered equivalent for pricing purposes, including those that contain a preservative, those that are preservative-free, multi-dose products and single dose unit products (November 2014 PSD on ocular lubricants). The PBAC reaffirmed this notion in its most recent recommendation of preservative-free, multi-dose eye drops in May 2023, where the PBAC advised that under Section 101(3BA) of the Act, Systane Hydration should be treated as interchangeable with other PBS-listed ocular lubricants on an individual patient basis (paragraph 11.4, Systane® Hydration PSD, May 2023 PBAC Meeting).
- 5.22 As a Category 3 submission, the economic analysis has not been independently evaluated.

Estimated PBS usage and financial implications

- 5.23 The submission used a market share approach to estimate the predicted use and financial implications to the PBS/RPBS.
- 5.24 The submission claimed that propylene glycol may substitute for any of the current MDPF or MDPC ocular lubricants currently listed on the PBS for the treatment of severe dry eye syndrome. The estimates used to calculate the financial analysis over the forward estimates are shown in Table 5.

Table 5: Variables and data sources used in the analysis

	Value	Source
Prescriptions		
Predicted prescriptions for preservative free and preservative containing multidose eye drops.	Prescriptions 2024: ██████ 1 2025: ██████ 2 2026: ██████ 2 2027: ██████ 2 2028: ██████ 2 2029: ██████ 3	Observed data: Services Australia PBS statistics from January 2013 to December 2023 for Evolve Carmellose (11852T & 11853W), Evolve Hypromellose (11842G & 11849P), Hylo-Fresh (2181T, 2184Y), Hylo-Forte (2171G, 2253N), Novatears (11446K & 11439C), Cationorm (12612T), Refresh Tears Plus (8548X, 9211T & 5507W), Refresh Liquigel (8593G, 9212W & 5508X), Optive (5556K, 9355J, 9356K) Methopt (2956N, 9214Y & 5517J), In a wink moisturising/Genteal/Revive Tears (11625W, 11643T & 11634H), Poly-Tears/Tears Naturale (1509K, 9216C & 5520M) and Systane/Optix (8676P, 9219F & 5524R) ocular lubricants. Extrapolation: Second-order polynomial trend analysis of a 24-month moving average
Changes in utilisation		
Uptake of Systane Balance MDPC (%)	Uptake 2024: ██████ % 2025: ██████ % 2026: ██████ % 2027: ██████ % 2028: ██████ % 2029: ██████ %	Alcon Laboratories anticipated
Treatments per prescription	Treatments/script Evolve Carmellose: 125 Evolve Hypromellose: 125 Hylo-Fresh: 150 Hylo-Forte: 150 Novatears: 140 Cationorm: 193 Refresh Tears Plus: 150 Refresh Liquigel: 150 Optive: 150 Methopt: 150 In a wink moisturising: 100 Poly-Tears: 150 Systane: 150 Systane Balance MDPC: 166	Alcon Laboratories, cationic ophthalmic emulsion PSD July 2020, par. 5.12, Table 3 and Carmellose and Hypromellose PSD July 2019, par.5.6, Table 1 (Appendix 1). Note that where the number of drops per bottle was not available, this was estimated by assuming that 1 mL = 20 drops. (East Surrey CCG et al., 2018)
Cost of medicines		
Systane Balance MDPC, 10 mL x 1	AEMP: \$13.96	Proposed by Alcon Laboratories.
Alternative ocular lubricants	Evolve Carmellose: \$10.74 Evolve Hypromellose: \$10.74 Hylo-Fresh: \$19.86 Hylo-Forte: \$19.86 Novatears: \$20.00	Schedule of Pharmaceutical Benefits, March 2024

Public Summary Document – July 2024 PBAC Meeting

	Value	Source
	Cationorm: \$23.80 Refresh Tears Plus: \$2.74 Refresh Liquigel: \$2.74 Optive: \$2.74 Methopt: \$3.50 In a wink moisturising: \$2.50 Poly-Tears: \$3.50 Systane \$2.31	
Patient co-payments		
Patient co-payments	General ordinary: \$31.60 General safety net: \$7.70 Concessional ordinary: \$7.70 RPBS ordinary: \$7.70	Schedule of Pharmaceutical Benefits, March 2024

Abbreviations: AEMP = Approved Ex-Manufacturer Price; MDPC = multi-dose preservative containing; MDPF = multi-dose preservative-free; PBS = Pharmaceutical Benefits Scheme.

Source: Table 4.1.1 of the submission.

The redacted values correspond to the following ranges

1 1,000,000 to < 2,000,000

2 2,000,000 to < 3,000,000

3 3,000,000 to < 4,000,000

- 5.25 Table 6 presents the estimated extent of use of Propylene glycol and the net financial implications to the PBS/RPBS. The financial impact to Services Australia will be determined by that agency as part of the post-PBAC process.
- 5.26 The submission estimated that 800,000 to < 900,000 prescriptions would be dispensed for Propylene glycol over the first six years of listing (50,000 to < 60,000 in Year 1 to 200,000 to < 300,000 in Year 6).
- 5.27 The submission stated that the estimated net financial impact to the PBS/RPBS for the listing of Propylene glycol would be \$0 to < \$10 million over six years (Year 1: \$0 to < \$10 million; to Year 6: \$0 to < \$10 million), as illustrated in Table 6.

Table 6: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed	1	2	3	3	4	4
Estimated financial implications of Propylene glycol						
Cost to PBS less co-payment	5	5	5	5	5	5
Cost to RPBS less co-payment	5	5	5	5	5	5
Estimated financial implications of other ocular lubricants to the R/PBS						
Cost to PBS less co-payment	6	6	6	6	6	6
Cost to RPBS less co-payment	6	6	6	6	6	6
Net financial implications						
Net cost to PBS/RPBS	5	5	5	5	5	5

Abbreviations: MBS = Medical Benefits Scheme; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

Source: Table 4.41 of the submission.

The redacted values correspond to the following ranges

1 50,000 to < 60,000

2 80,000 to < 90,000

3 100,000 to < 200,000

4 200,000 to < 300,000

5 \$0 to < \$10 million

6 net cost saving

6 PBAC Outcome

- 6.1 The PBAC recommended the listing of propylene glycol (Systane Balance) for the treatment of severe dry eye syndrome on a cost-minimisation basis to the lowest cost PBS-listed ocular lubricant. The PBAC noted that propylene glycol was a PC eye drop and the nominated comparator was PF hyaluronate containing eye drop. The PBAC considered that the submission had demonstrated the non-inferior comparative effectiveness and non-inferior comparative safety of propylene glycol compared with 0.1%/0.2% hyaluronate sodium MDPF eye drops and 0.5% carmellose + glycerol MDPC eye drops. The PBAC therefore reaffirmed its May 2023 advice that all PBS-listed ocular lubricants should be considered as relevant comparators, regardless of whether they contain preservatives or hyaluronate.
- 6.2 The PBAC noted that under Section 101(3B) of the *National Health Act 1953* (“the Act”), when the proposed medicine is substantially more costly than an alternative therapy, the Committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. The PBAC, on this occasion, was not satisfied that propylene glycol provided a significant improvement in efficacy and/or reduction of toxicity over the other PBS-listed ocular lubricants to justify the AEMP requested.
- 6.3 The PBAC noted the financial estimates and considered that listing on a cost minimisation basis to the lowest cost ocular lubricant may result in a potential net saving to Government depending on the proposed substitution rates.

- 6.4 The PBAC advised under s101(3BA) of the Act that propylene glycol should be treated as interchangeable on an individual patient basis with all other PBS-listed ocular lubricants.
- 6.5 The PBAC advised that propylene glycol is suitable for prescribing by nurse practitioners and optometrists.
- 6.6 The PBAC recommended that the Early Supply Rule should apply.
- 6.7 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because propylene glycol is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity over all other ocular lubricants, or not expected to address a high and urgent unmet clinical need given the presence of alternative therapies, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met
- 6.8 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

7 Recommended listing

7.1 Add new item:

MEDICINAL PRODUCT		PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
medicinal product pack						
PROPYLENE GLYCOL 0.6% eye drops, 10 mL		NEW	1	1	5	Systane Balance
Restriction Summary [NEW] / Treatment of Concept: [NEW]						
Concept ID		Category / Program: GENERAL – General Schedule (Code GE)				
(for internal Dept. use)		Prescriber type <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input checked="" type="checkbox"/> Optometrists				
		Restriction type: <input checked="" type="checkbox"/> Restricted benefit				
Prescribing rule level	New	Administrative Advice: The in-use shelf life of this product is 6 months from the date of opening				
		Severity: Severe				
		Condition: Dry Eye Syndrome				
		Indication: Severe Dry Eye Syndrome				

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

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.