7.14 CARMELLOSE

Eye drops containing carmellose sodium 5 mg per mL, 10 mL,
Evolve® carmellose 0.5%,
Contact Lens Centre Australia
HYPROMELLOSE
Eye drops containing hypromellose 3 mg per mL, 10 mL
Evolve® hypromellose 0.3%,
Contact Lens Centre Australia

1 Purpose of Application

1.1 The minor resubmission requested General Schedule, Authority Required (STREAMLINED) listings for carmellose (Evolve® carmellose 0.5%) and hypromellose (Evolve® hypromellose 0.3%), hereafter referred to as carmellose 0.5% and hypromellose 0.3%, in multi-dose eye drops for the treatment of severe dry eye syndrome in patients who are sensitive to preservatives in multi-dose eye drops.

2 Requested listing

2.1 The resubmission proposed no changes to the PBS restriction wording recommended at the July 2018 PBAC meeting, which has the same criteria as other PBS-listed preservative-free ocular lubricants. The PBAC agreed with the Sponsor that there was no need for changes to the restriction wording.

2.2 The Sponsor requested a DPMQ of $29.61, which was lower than the DPMQ requested in the first submission considered in July 2018 ($33.56).

For more details on PBAC's view, see section 6 PBAC Outcome.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
CARMELLOSE SODIUM carmellose sodium 0.5% (5 mg/mL) eye drops, 10 mL	1	5	$29.61	Evolve® carmellose 0.5%	Contact Lens Centre Australia
HYPROMELLOSE hypromellose 0.3% (3 mg/mL) eye drops, 10 mL	1	5	$29.61	Evolve® hypromellose 0.3%	
Category / Program	GENERAL – General Schedule (Code GE)				

Prescriber type:	☒Medical Practitioners ☒Nurse practitioners ☒Optometrists
Severity:	Severe
Condition:	Dry eye syndrome
PBS Indication:	Severe dry eye syndrome
Restriction Level / Method:	☒Streamlined
Clinical criteria:	Patient must be sensitive to preservatives in multi-dose eye drops
Administrative Advice:	The in-use shelf life of Evolve® carmellose 0.5% and Evolve® hypromellose 0.3% is 3 months from the date of opening

3 Background

3.1 Carmellose 0.5% and hypromellose 0.3% were registered on the Australian Register of Therapeutic Goods on 17 October 2017 for use in the relief of discomfort that arises from dry eye sensations.

3.2 This was the PBAC's second consideration of carmellose 0.5% and hypromellose 0.3%. The previous minor submission was considered at the July 2018 meeting, and the Committee recommended that carmellose 0.5% and hypromellose 0.3% should be made available as a pharmaceutical benefit in accordance with Section 101 of the *National Health Act 1953* for the treatment of severe dry eye syndrome in patients who are sensitive to preservatives in multi-dose eye drops.

3.3 In its consideration of carmellose 0.5% and hypromellose 0.3% in July 2018, the PBAC recalled its previous recommendation 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 ocular lubricants). The PBAC noted that the submission did not provide clinical evidence to support a claim of superiority compared to any of the currently PBS-listed ocular lubricants, and therefore advised, under Section 101(3B) of the *National Health Act 1953*, that carmellose 0.5% and hypromellose 0.3% should be cost-minimised against the lowest cost ocular lubricant.

For more details on PBAC's view, see section 6 PBAC Outcome.

4 Current situation

4.1 The minor resubmission indicated that, following the PBAC's July 2018 recommendation, the Sponsor and the Department were unable to reach agreement on the PBAC's intent regarding the appropriate choice of pricing comparator for carmellose 0.5% and hypromellose 0.3%.

4.2 The resubmission sought clarification from the PBAC regarding the appropriate choice of comparator for carmellose 0.5% and hypromellose 0.3%, particularly with reference

to the PBAC's decision to recommend perfluorohexyloctane at its March 2018 meeting on a cost-minimisation basis to other preservative-free multi-dose ocular lubricants.

4.3 The minor resubmission claimed that carmellose 0.5% and hypromellose 0.3% and perfluorohexyloctane all provide a "reduction of toxicity over alternative therapies (i.e. preservative-containing products)" and therefore satisfied the requirements of Section 101(3B) of the *National Health Act 1953*. As such, the Sponsor requested a higher price than the preservative-containing formulations.

4.4 The minor resubmission nominated hyaluronic acid, perfluorohexyloctane and single-dose unit carmellose 0.5% as appropriate comparators (all are preservative-free ocular lubricants).

For more details on PBAC's view, see section 6 PBAC Outcome.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item as it was a minor resubmission.

Consumer comments

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

Interpretation of clinical evidence

5.3 The minor resubmission claimed that carmellose 0.5% and hypromellose 0.3% preservative-free eye drops were clinically equivalent to single-dose carmellose and hypromellose preservative-free eye drops.

5.4 The minor resubmission also claimed that carmellose 0.5% and hypromellose 0.3% preservative-free eye drops had non-inferior efficacy compared with other PBS-listed preservative-free ocular lubricant formulations, such as perfluorohexyloctane (Nova-Tears®) and hyaluronic acid (Hylo-Fresh®/Hylo-Forte®). The basis for this claim was the PBAC's consideration that "no evidence was presented to conclude any difference in patient outcomes between the various ocular lubricants" (November 2014 PSD ocular lubricants). No clinical evidence was presented to support this claim.

5.5 The minor resubmission also claimed that carmellose 0.5% and hypromellose 0.3% preservative-free eye drops have superior safety compared to preservative-containing eye drops for patients who are sensitive to preservatives used in multi-dose eye drop formulations. The basis for this claim presented in the resubmission was:

- trial evidence that preservative-free eye drops may decrease ocular inflammation and increase antioxidant contents in the tears of patients with dry eye syndrome compared with preservative-containing eye drops (Jee et al. 2014);

- preservatives such as benzalkonium chloride cause adverse effects such as keratopathy and eye irritation (as reported in Badouin, 2008 and the 2007 report of the International Dry Eye Workshop);
- preservatives can induce allergic reactions and delayed hypersensitivity reactions (Goh, 1989);
- an epidemiological study of 4,100 glaucoma patients that found those using preservative-containing ocular hypotensives (such as β blockers and α_2 agonists) had a higher prevalence of adverse effects such as discomfort upon instillation, burning-stinging, foreign body sensation, and dry eye sensation, compared to those using preservative-free drops (Pisella et al. 2002); and
- in rare cases, severe systemic reactions including anaphylaxis have been reported (Anderson et al. 2009).

Economic analysis

5.6 A formal economic analysis was not presented in the minor resubmission. A cost comparison of PBS-listed preservative-free ocular lubricants is presented in the table below. At the requested DPMQ of $29.61, carmellose 0.5% and hypromellose 0.3% would be less expensive than the existing single-dose preservative-free ocular lubricants on a cost per treatment basis. The requested price for carmellose 0.5% and hypromellose 0.3% ($0.136 per treatment) were consistent with the cost per treatment for hyaluronic acid ($0.139) and perfluorohexyloctane ($0.143).

Table 1: Cost comparison across PBS listed ocular lubricants (excluding ointments)

Drug LI, Strength (Brand Name)	PBS Item Code	Qty & Presentation	[a]AEMP	DPMQ	[b]Total Treatments per pack	[c]Cost per Treatment (both eyes)
Single-dose unit preservative-free ocular lubricants						
Carbomer, 980 (Viscotears Gel PF)	5504Q, 8578L	3 x 30, Single dose eye drops	$8.00	$37.14	30	$0.267
Carbomer 974, (Poly Gel)	5502N, 8514D	3 x 30, Single dose eye drops	$6.49	$32.28	30	$0.216
[d]Carmellose, 0.5% (Cellufresh, Optifresh Tears)	2338C, 5506T	3 x 30, Single dose eye drops	$5.45	$28.92	30	$0.182
Carmellose, 1% (Celluvisc, Optifresh Plus)	2324H, 5505R	3 x 30, Single dose eye drops	$5.45	$28.92	30	$0.182
[d]Hypromellose with dextran (Bion Tears)	8299T, 5521N	3 x 28 Single dose eye drops	$7.72	$36.24	28	$0.276
Polyethylene glycol 400 with propylene glycol (Systane)	5532E, 9170P	2 x 28, Single dose eye drops	$9.09	$30.87	56	$0.162
Multi-dose preservative-free ocular lubricants						
Carmellose, 0.5% (Evolve)	**N/A**	**1 x 10mL, Multi dose eye drops**	**$17.00**	**$29.61**	**125**	**$0.136**
Hypromellose, 0.3% (Evolve)	**N/A**	**1 x 10mL, Multi dose eye drops**	**$17.00**	**$29.61**	**125**	**$0.136**
[d]Hyaluronic acid (Hylo-Fresh, Hylo-Forte)	2184Y, 2181T, 2171G, 2253N	1 x 10 mL, Multi dose eye drops	$20.90	$33.80	150	$0.139
[d]Perfluorohexyloctane (Novatears)	11446K, 11439C	1 x 3 mL, Multi dose eye drops	$20.00	$32.83	140	$0.143
Soy lecithin (Tearsagain)	5545W, 9448G	2 x 10 mL, Multi dose eye spray	$11.39	$35.83	50	$0.228
Ocular lubricants containing preservatives*						
Carmellose 0.5% (Refresh Tears Plus)	5507W, 8548X, 9211T	1 x 15mL, Multi dose eye drops	$2.74	$14.28		
Carmellose 1% (Refresh Liquigel)	5508X, 8593G, 9212W	1 x 15mL, Multi dose eye drops	$2.74	$14.28		
Hypromellose 0.3% (Genteal, In A Wink)	11643T, 11634H 11625W, 8287E, 5518K, 9213X	1 x 10mL, 1 x 15mL, Multi dose eye drops	$2.08 $3.12	$13.57 $14.68		
Hypromellose 0.5% (Methopt)	2956N, 5517J, 9214Y	1 x 15mL, Multi dose eye drops	$3.12	$14.68		
Hypromellose with dextran (Poly-Tears, Tears Naturale)	1509K, 5520M, 9216C, 1509K, 5520M, 9216C	1 x 15mL, Multi dose eye drops	$3.29	$14.87		
Polyethylene glycol 400 with propylene glycol (Systane)	5524R, 8676P, 9219F	1 x 15mL, Multi dose eye drops	$2.45	$14.29		

2019 prices from May 2019 Pharmaceutical Benefits Schedule

[c] Cost per treatment for both eyes calculated using [a]AEMP divided by [b]Total number of treatments per pack rounded to third decimal.

* For the purposes of comparison, this is not an exhaustive list of all preservative-containing multi-dose eye drops.

[d] All nominated comparators by the Sponsor

Source: Table 3.1 pg.21-22 of the submission and Ex-manufacturer Price List May 2019 from PBS Online.

Estimated PBS usage & financial implications

5.7 The financial estimates in this minor resubmission were not independently evaluated.

5.8 The resubmission used a market share approach which assumed the market for preservative-free ocular lubricants will experience no additional growth as a result of the proposed listing.

5.9 The submission assumed carmellose 0.5% and hypromellose 0.3% would substitute for perfluorohexyloctane (Novatears®), hyaluronic acid (Hylo-Fresh®, Hylo-Forte®), carmellose 0.5% (Cellufresh®, Optifresh Tears®), and hypromellose with dextran (Bion Tears®). It was assumed that only eye drops would be substituted, therefore paraffin ointment (Poly-Visc®) and soy lecithin spray (Tears-Again®) were not included in the estimates.

5.10 The resubmission estimated that carmellose 0.5% would substitute for 46% of the market share of all its comparators combined in Year 1 of listing (2020), increasing to 75% by Year 5. Estimates for hypromellose 0.3% were the same. The majority of substitution was expected to be for single-dose unit carmellose and hypromellose products. The same estimates and assumptions were used in the previous minor submission.

5.11 Table 2 shows the current market share for PBS-listed ocular lubricants as provided in the July 2018 and July 2019 minor (re)submissions. Based on these PBS script data, there had been approximately a 13% increase in PBS services for these items between 2017 and 2018. Between these periods, the greatest rise in services was the uptake of hyaluronic acid products. This could be as a result of the delisting of carmellose 0.25%, patients switching from preservative-containing products, or growth in the market (new patients being prescribed ocular lubricants).

Table 2: Market share figures for comparator ocular lubricants

	PBS Services Feb 2017- Jan 2018		PBS Services Mar 2018- Feb 2019	
Name & Item Code	**Total**	**Market %**	**Total**	**Market %**
Hypromellose + dextran	121,906	29.69%	144,368	31.04%
Carmellose 0.25%	16,356	3.98%	N/A	N/A
Carmellose 0.5%	124,054	30.22%	131,370	28.25%
Carmellose 1%	33,443	8.15%	NP	NP
Perfluorohexyloctane	N/A	N/A	4,774	1.03%
Hyaluronic acid (0.1% + 0.2%)	114,784	27.96%	184,565	39.68%
Total relevant market*	**410,543**		**465,077**	

* Excludes figures for other preservative-free multi-dose lubricants and single-dose lubricants.
NP Not Provided in the submission.
N/A Not applicable as either wasn't listed or no longer listed.
Source: market figures provided in workbooks from July 2018 and July 2019 submissions.

5.12 In its consideration of the previous minor submission in July 2018, the PBAC commented that hyaluronic acid products are multi-dose products that have been listed on the PBS since 2012, and therefore some displacement of single-dose products due to the convenience of multi-dose products would likely have already occurred. The PBAC considered that it was therefore possible that the Sponsor had

overestimated the potential market share for carmellose 0.5% and hypromellose 0.3%, and also overestimated the potential net savings to the PBS. At the July 2019 meeting, the PBAC reiterated that the potential market share and net savings to the PBS may have been overestimated, but accepted that the listing would either be at worst cost-neutral or result in some minor savings to Government.

5.13 The shelf life for the carmellose 0.5% and hypromellose 0.3% is three months after opening, however the submission claimed that multiple drops per eye per day are usually required, therefore the likelihood of wastage is low. The PBAC considered that this was reasonable.

For more details on PBAC's view, see section 6 PBAC Outcome.

Table 3: Estimated use and financial implications

Year 1-5	2020	2021	2022	2023	2024
Estimated extent of use (based on total estimates of displaced drugs[a])					
Estimated number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated number of scripts dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of new listing[b]					
to PBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
to RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
to the PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Less co-payments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
PBS/RPBS less co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated cost of displaced drugs[a]					
to PBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
to RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
to the PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Less co-payments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
PBS/RPBS less co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated net cost of new listing					
to PBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
to RPBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
to the PBS/RPBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Less co-payments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
PBS/RPBS less co-payments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]

[a] Displaced drugs being existing single-dose unit carmellose 0.5% (Cellufresh, Optifresh Tears) and hypromellose (Bion Tears) products, hyaluronic acid (Hylo-Fresh, Hylo-Forte) and perfluorohexyloctane (Novatears) and numbers taken from Table 4.9 of the submission.
[b] Combining estimates for use of both carmellose 0.5% and hypromellose 0.3% from Table 4.8 of the submission.
Source: Table 4.6, 4.7, 4.8, 4.9, 4.10, pg.26-28 of the submission.

The redacted table shows that at Year 6, the estimated number of patients was 10,000 – 50,000, and the estimated net cost to the PBS would be less than $10 million.

6 PBAC Outcome

6.1 The PBAC recommended the listing of carmellose (Evolve® carmellose 0.5%) and hypromellose (Evolve® hypromellose 0.3%) multi-dose preservative-free eye drops on the General Schedule as an Authority Required (STREAMLINED) listing for the treatment of severe dry eye syndrome in patients who are sensitive to preservatives in multi-dose eye drops. Carmellose 0.5% and hypromellose 0.3% were recommended on the basis that the price proposed by the sponsor resulted in a lower cost per treatment compared to other currently listed preservative-free eye drops, however PBAC considered they were at least non-inferior to the lowest cost PBS-listed multi-dose preservative-free eye drop in terms of both safety and effectiveness.

6.2 The PBAC recalled that in July 2018 it recommended the Authority Required (STREAMLINED) listing of carmellose (Evolve® carmellose 0.5%) and hypromellose (Evolve® hypromellose 0.3%) multi-dose preservative-free eye drops on a cost-minimisation basis to the lowest cost ocular lubricant. PBAC noted that following review of further information from the sponsor around the comparative safety of carmellose 0.5% and hypromellose 0.3% when compared to some eye drops that contain preservatives, that carmellose 0.5% and hypromellose 0.3% is likely to have superior safety, although there is no evidence of improvement in efficacy. PBAC therefore accepted that the appropriate comparator is the lowest priced multi-dose preservative-free eye drops.

6.3 The PBAC recommend the same restriction wording as in its July 2018 recommendation.

6.4 The PBAC considered that all preservative-free eye drops were appropriate comparators for carmellose 0.5% and hypromellose 0.3%.

6.5 The PBAC noted that the resubmission had requested a price which would make carmellose 0.5% and hypromellose 0.3% the lowest cost multi-dose preservative-free eye drops on the PBS, and would be less expensive than the existing PBS-listed single-dose preservative-free eye drops on a cost per treatment basis.

6.6 The PBAC reiterated that the potential market share and net savings to the PBS may have been overestimated (paragraph 5.10, July 2018 PSD), but accepted that the listing would either be cost-neutral or result in cost savings to Government.

6.7 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because carmellose 0.5% and hypromellose 0.3% is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over all other preservative-free eye drops, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost*

Recovery) Regulations 2009 for Pricing Pathway A were not met.

6.8 The PBAC reiterated that under Section 101(3BA) of the *National Health Act 1953,* carmellose 0.5% and hypromellose 0.3%, and other PBS-listed preservative-free multi-dose ocular lubricants be treated as interchangeable on an individual patient basis.

6.9 The PBAC reiterated that carmellose 0.5% and hypromellose 0.3% are suitable for prescribing by nurse practitioners and optometrists.

6.10 The PBAC reiterated that the Early Supply Rule currently does not apply to any eye drop formulations and considered that carmellose 0.5% and hypromellose 0.3% should also be exempt.

6.11 The PBAC noted that this resubmission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

7 Recommended listing

7.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
CARMELLOSE SODIUM carmellose sodium 0.5% (5 mg/mL) eye drops, 10 mL	1	5	Evolve® carmellose 0.5%	Contact Lens Centre Australia
HYPROMELLOSE hypromellose 0.3% (3 mg/mL) eye drops, 10 mL	1	5	Evolve® hypromellose 0.3%	

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☒Medical Practitioners ☒Nurse practitioners ☒Optometrists
Severity:	Severe
Condition:	Dry eye syndrome
PBS Indication:	Severe dry eye syndrome
Restriction Level / Method:	☒Streamlined
Clinical criteria:	Patient must be sensitive to preservatives in multi-dose eye drops
Administrative Advice:	The in-use shelf life of Evolve® carmellose 0.5% and Evolve® hypromellose 0.3% is 3 months from the date of opening

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

Corneal Lens Centre Australia welcomes the PBAC's recommendation to list carmellose (Evolve® carmellose 0.5%) and hypromellose (Evolve® hypromellose 0.3%) multi-dose preservative-free eye drops on the PBS.