

An addendum has been included at the end of the Public Summary Document (PSD).

5.16 CARMELLOSE WITH GLYCEROL AND HYALURONIC ACID,

Eye drops containing carmellose sodium 5 mg per mL with glycerol 9 mg per mL and sodium hyaluronate

1 mg per mL, 10 mL,

Optive Fusion[®],

Allergan Australia Pty Ltd

1 Purpose of Submission

- 1.1 The Category 3 submission sought to list carmellose sodium 0.5% + glycerol 0.9% + hyaluronate sodium 0.1% (herein referred to as CGH) multidose preservative-containing (PC) eye drops (Optive Fusion[®]) as a General Schedule Restricted Benefit listing for the treatment of severe dry eye syndrome.

2 Background

- 2.1 CGH is a 10 mL multidose combination of carmellose sodium 0.5%, glycerol 0.9% and hyaluronate sodium 0.1% used for the treatment of severe dry eye syndrome. The recommended dosage of CGH is 1-2 drops into the affected eye(s) as required.

Registration status

- 2.2 CGH was TGA registered on 13 March 2019 as a Class III medical device.

Previous PBAC consideration

- 2.3 CGH has not been considered by the PBAC previously as a combination product, however, the active components have been listed separately on the PBS as carmellose sodium 0.5% with glycerin 0.9% (Optive[®]), and hyaluronate sodium (HS) 0.1% (Hilo-Fresh[®]). The only other PBS listed form of hyaluronate sodium is HS 0.2% (Hilo-Forte[®]).

3 Requested listing

3.1 The submission requested the following new listing:

MEDICINAL PRODUCT Medicinal Product Pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
CARMELOSE SODIUM + GLYCEROL + HYALURONATE SODIUM carmellose sodium 0.5% + glycerol 0.9% + hyaluronate sodium 0.1% eye drops, 10 mL	New	1	1	5	Optive Fusion

3.2 Restriction Summary / Treatment of Concept

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input checked="" type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method: <input type="checkbox"/> Unrestricted benefit <input checked="" type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Authority Required – Streamlined
Condition: Severe dry eye syndrome
Indication: Severe dry eye syndrome

3.3 The submission requested a restricted benefit listing for the treatment of severe dry eye syndrome, consistent with the authority level of other PC ocular lubricants listed on the PBS and the PBS listed indication for HS. However, the PBAC noted that other PC ocular lubricants with restricted benefit listings have the indication ‘Severe dry eye syndrome, including Sjogren’s syndrome’, and there appeared to be an inconsistency with the application of this indication across the different PBS listings of ocular lubricants.

3.4 Unlike the listing of HS 0.1% and 0.2%, the clinical criterion ‘Patient must be sensitive to preservatives in multi-dose eye drops’ was not included as the formulation of CGH includes a preservative, purite 0.01% (Clinical Evaluation Report within the main body of submission). The PBAC noted that PF ocular lubricants are Authority Required (STREAMLINED).

4 Comparator

4.1 The submission nominated HS 0.1% as the main comparator, stating that HS is the key component of CGH and therefore CGH is most likely to substitute for other HS containing products. This was appropriate, however all PBS-listed ocular lubricants may also be relevant comparators (see paragraph 5.16).

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 presented one phase IV randomised clinical trial to demonstrate the comparative efficacy and safety of CGH (outlined in Table 1). This trial was sponsored by Allergan plc.

Table 1: Trial presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
NCT02117687/Labetoulle (2017)	Labetoulle, M, Chiambaretta, F, Shirlaw, A, Leaback, R, Baudouin, C. Osmoprotectants, carboxymethylcellulose and hyaluronic acid multi-ingredient eye drop: a randomised controlled trial in moderate to severe dry eye.	<i>Official Journal of the Royal College of Ophthalmologists</i> 2017 31(10):1409-1416E

Source: Table 2-4 of the submission

5.4 The Labetoulle 2017 study compared CGH with HS 0.18% (Vismed® Multi) to demonstrate the comparative efficacy. Patients were instructed to instil 1-2 drops into each eye, 2-6 times a day for 3 months. The primary outcome was change in Global Ocular Staining Score (GOSS) from baseline in the study eye at day 35, with the secondary outcome being change from baseline after 3 months.

5.5 The proposed PBS population is patients with severe dry eye syndrome. As the PBS criteria does not specify clinical criteria for the severity of ‘severe’ dry eye, patients in the trials were required to have symptoms of moderate to severe dry eye syndrome.

5.6 The Labetoulle study used HS 0.18% as a proxy for the efficacy of the PBS listed formulations of HS. While HS 0.18% is not PBS listed, the PBAC noted it had previously accepted the approach of using non-PBS listed ocular lubricants as a proxy for PBS-listed ocular lubricants (paragraph 5.6, Cationorm PSD, July 2020 PBAC Meeting).

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

Comparative effectiveness

5.8 Non inferiority of CGH compared with HS 0.18% was tested in the per-protocol (PP) population (i.e., all randomised patients who received ≥ 1 dose of study treatment, had ≥ 1 follow-up visit, and no major protocol violations) as well as in the intent to treat (ITT) population. A two-sided 95% confidence interval (CI) of the treatment difference at day 35 was determined, based on a two-way analysis of covariance (ANCOVA) model with change from baseline as main effect, and site and baseline GOSS as covariates. If the upper limit was less than or equal to the prespecified

two-grade margin, CGH was considered non-inferior to HS 0.18%. The results of the study are presented in Table 2.

Table 2: Change in GOSS from baseline in the study eye

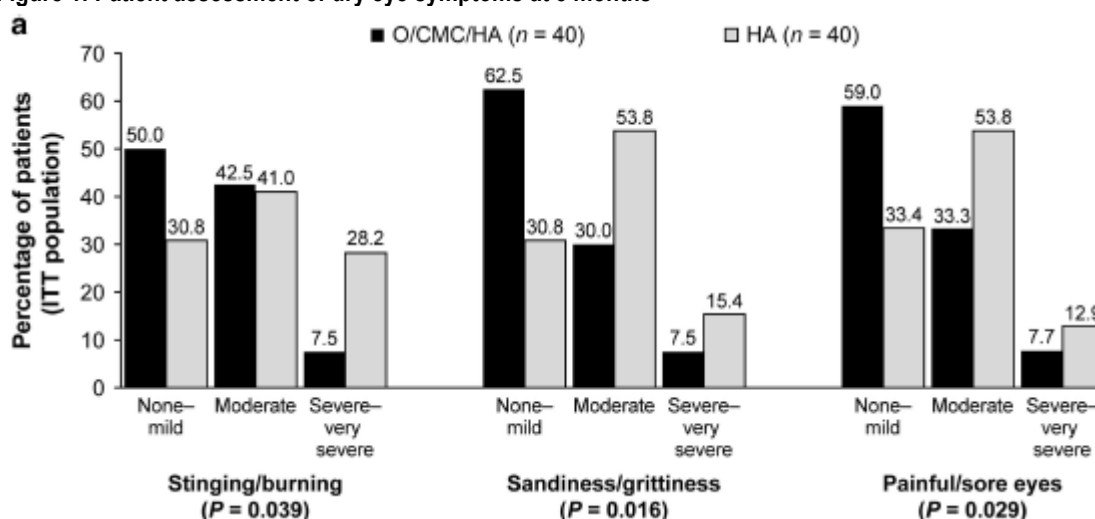
PP population					
Timepoint	Measure	CGH (n=35)	HS 0.18% (n=31)	Between-treatment Difference	P value
Day 35	Mean (SD)	-1.5 (1.5)	-1.6 (1.5)	0.1	0.778
	95% CI	-4.6 to 1.5	-4.7 to 1.4	-0.5 to 0.7	
Month 3	Mean (SD)	-2.5 (2.2)	-2.4 (2.2)	-0.3	0.480
	95% CI	-6.9 to 1.8	-6.8 (2.0)	-1.1 to 0.5	
ITT population					
Timepoint	Measure	Optive Fusion (n=40)	HA 0.18% (n=39)	Between-treatment Difference	P value
Day 35	Mean (SD)	-1.3 (1.7)	-1.6 (1.7)	0.3	0.300
	95% CI	-4.7 to 2.1	-4.8 to 1.7	-0.3 to 0.8	
Month 3	Mean (SD)	-2.3 (2.4)	-2.3 (2.2)	0.1	0.780
	95% CI	-7.0 to 2.5	-6.7 to 2.0	-0.7 to 0.9	

Source: Table 2-5 of the submission

5.9 The submission noted that there was no statistically significant difference between CGH and HS 0.18% for the mean change in GOSS scores in both the PP and ITT populations, which supported a non-inferiority claim for efficacy.

5.10 The submission also presented results from a five-point Likert Scale, bilateral assessment of the dry eye symptoms, ranging from 0 (no discomfort) to 4 (very severe). The results showed that patients using CGH after 3 months experienced less severe symptoms than patients using HS 0.18%. The results are shown in figure 1.

Figure 1: Patient assessment of dry eye symptoms at 3 months



Source: Figure 2-2 of the submission

Comparative safety

5.11 The clinical claim for safety was measured by the proportion of patients who experienced treatment-related adverse events (TRAEs). A total of 16 TRAEs were reported by 9 patients (5/40 taking CGH, and 4/40 taking HS 0.18%). The submission claimed that all were mild or moderate in severity and the results suggest that CGH has a similar safety profile to HS 0.18%. The claim of non-inferiority is uncertain given the small sample size.

Clinical claim

5.12 The submission claimed the non-inferior comparative effectiveness and non-inferior comparative safety of CGH compared with HS 0.1%.

5.13 The PBAC considered that the claim of non-inferior comparative effectiveness and non-inferior comparative safety was reasonably supported by the data.

Economic analysis

5.14 The submission did not provide a cost-minimisation approach or an equi-effective dose. If the PBAC accepts non-inferiority based on the results of the Labetoulle study then it is reasonable to conclude that one drop of CGH is equivalent to one drop of HS 0.18%, and therefore by extension, one drop of HS 0.1%.

5.15 The submission proposed an AEMP of \$16.46 for CGH and a DPMQ of \$29.84. The AEMP of HS 0.1% was \$20.90 with a DPMQ of \$34.61 as at February 2023.

5.16 The PBAC first recommended the listing of hyaluronate based ocular lubricants on the PBS at its July 2012 meeting, and these listed on the PBS in December 2012. The PBAC subsequently 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 (paragraph 3.1, ocular lubricants PSD, November 2014 PBAC meeting).

5.17 The Secretariat has presented a cost-minimisation analysis in Table 3 using CGH as the intervention, HS 0.1%/0.2% as the main comparators, and polyethylene glycol 400 4 mg with propylene glycol 3 mg (Systane® Original) as a proxy for the lowest cost ocular lubricant.

Table 3: Cost minimisation analysis

	CGH	HS 0.1%/0.2%	Systane Original
Quantity per prescription			
Volume per pack (mL)	10	10	15
Drops per pack	300 ^a	300 ^b	300 ^c
Treatments per pack	150 [300 / 2 drops]	150 [300 / 2 drops]	150 [300 / 2 drops]
Cost per treatment			
AEMP per pack	\$16.46	\$20.90	\$2.31
AEMP per treatment	\$0.110 [\$16.46 / 150]	\$0.139 [\$20.90 / 150]	\$0.0154 [\$2.31 / 150]

^a The pre-PBAC response clarified that one pack of CGH supplies 300 drops.

^b Source: <https://www.aftpharm.com/product/hylo-fresh-au/>

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

Estimated PBS utilisation and financial implications

- 5.18 The submission adopted a market share approach, claiming that the addition of CGH to the PBS is unlikely to increase the use of HS formulations on the PBS but rather will substitute their use. This claim was based on a DUSC utilisation review of ocular lubricants in February 2021 that found that there was a significant increase in multidose PF ocular lubricant prescriptions which was almost entirely attributable to an increasing use of multidose PF HS (HS 0.1% or HS 0.2%). Even if the substitution is within the existing market, as the ocular lubricants do not have the same price, substitution patterns will determine whether there is a cost to the PBS.
- 5.19 The base case of the financial model assumes that CGH will substitute HS 0.1% on a one-to-one basis with a peak market share of 30% (10% in year 1, 20% in year 2, 30% in years 3-6). The pre-PBAC response justifies this assumption using the February 2021 DUSC Analysis which shows that the increase in the use of PF ocular lubricants over PC ocular lubricants correlated with the introduction of products containing HS. The response therefore suggested that the introduction of an alternative multi-dose HS containing product will shift the market share and that it is unlikely CGH will substitute for HS-free ocular lubricants any more than the HS containing ocular lubricants would.
- 5.20 Table 4 presents the estimated use and the financial implications of CGH to the PBS/RPBS.

Table 4: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of CGH scripts dispensed	1	2	3	3	4	4
Number of HA 0.1% scripts dispensed	-1	-2	-3	-3	-4	-4
Estimated financial implications						
Cost to PBS/RPBS less co-payment of CGH (\$)	5	5	5	5	5	5
Cost to PBS/RPBS less co-payment of HA 0.1% (\$)	6	6	6	6	6	6
Net financial implications						
Net cost to PBS/RPBS (\$)	6	6	6	6	6	6

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

Source: Impact Net' OPTIVE FUSION Section 4 Utilisation Workbook

The redacted values correspond to the following ranges:

¹ 5,000 to < 10,000

² 20,000 to < 30,000

³ 30,000 to < 40,000

⁴ 40,000 to < 50,000

⁵ \$0 to < \$10 million

⁶ net cost saving

- 5.21 Using the proposed price, the submission estimated that the listing of CGH will result in net cost savings from year 1 to year 6 with a total estimated saving of \$0 to < \$10 million over the first 6 years. A sensitivity analysis was conducted using

the price of the lowest cost ocular lubricant and the savings over the first 6 years increased to \$0 to < \$10 million.

- 5.22 A sensitivity analysis was also provided to include HS 0.2% substitution. This resulted in estimated net cost savings from year 1 to year 6 with a total estimated saving of \$0 to < \$10 million over the first 6 years.
- 5.23 As a Category 3 submission, neither the economic analysis nor the financial estimates analysis have been independently evaluated.

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

- 6.1 The PBAC deferred making a recommendation to list CGH for the treatment of severe dry eye syndrome to undertake further analysis of the cost effectiveness of ocular lubricants in Australia.
- 6.2 The PBAC recalled that in its July 2020 consideration of Cationorm it considered the cost minimisation comparison of Hyaluronate 0.1/0.2% to Cationorm was appropriate, advising that “all preservative free, multi-dose ocular lubricants currently listed on the PBS were appropriate comparators for Cationorm” (paragraph 6.2, Cationorm PSD, July 2020 PBAC Meeting).
- 6.3 The PBAC also recalled its advice in 2014 that all ocular lubricants should be considered equivalent for pricing purposes, inclusive of hyaluronate based ocular lubricants. However, the PBAC acknowledged that over time prices have diverged due to different formulary allocations, notwithstanding that the listings were on a cost minimisation basis.
- 6.4 The PBAC considered that the cost-effectiveness of PF ocular lubricants in relation to PC ocular lubricants was uncertain. The PBAC considered that CGH, a PC ocular lubricant, demonstrated non-inferior comparative effectiveness and safety to the nominated comparator, which is a PF ocular lubricant, suggesting that there is no added benefit to PF hyaluronate based ocular lubricants.
- 6.5 The PBAC sought to further review the cost effectiveness of ocular lubricants prior to making a recommendation.
- 6.6 The PBAC requested that a literature review and economic analysis be undertaken, along with obtaining clinical advice, to confirm whether any products are superior and the appropriate therapeutic relativities for ocular lubricants.
- 6.7 The PBAC noted that the submission assumed that CGH will substitute HS 0.1% on a one-to-one basis with a peak market share of 1% (1% in year 1, 1% in year 2, 1% in years 3-6). The PBAC also noted a DUSC utilisation review of ocular lubricants in February 2021 had found that there has been an increase in the use of PF ocular lubricants over PC ocular lubricants. The PBAC considered that the submission may have overestimated utilisation, however, the financial impact would be clarified once

the therapeutic relativities of the PBS listed ocular lubricants are confirmed. The PBAC also noted that the market share estimates may be impacted by the listing of hyaluronic acid with polyethylene glycol 400 with propylene glycol with hydroxypropyl guar (Systane® Hydration) were it to be recommended.

- 6.8 The PBAC also advised that it is not necessary to make explicit mention of Sjogren's syndrome in the indications of ocular lubricants as this indication is encompassed within the indication of severe dry eye syndrome. The PBAC considered that its presence in some but not all restrictions of ocular lubricants used for severe dry eye syndrome may suggest that not all these ocular lubricants are suitable for Sjogren's syndrome, which is not the case. The PBAC therefore advised that the listings of all ocular lubricants used for severe dry eye syndrome be revised to remove any reference to Sjogren's syndrome.

Outcome:

Deferred

7 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.

8 Sponsor's Comment

Allergan is disappointed by the PBAC's decision to defer making a recommendation on CGH until a cost effectiveness review of all ocular lubricants has been conducted.

Addendum to the March 2023 PBAC PSD:

4.02 CARMELLOSE WITH GLYCEROL AND HYALURONIC ACID,

Eye drops containing carmellose sodium 5 mg per mL with glycerol 9 mg per mL and sodium hyaluronate

1 mg per mL, 10 mL,

Optive Fusion[®],

Allergan Australia Pty Ltd

9 Purpose

- 9.1 To determine the appropriate comparator for the listing of CGH multidose PC eye drops (Optive Fusion) as a General Schedule Restricted Benefit listing for the treatment of severe dry eye syndrome.

10 Background

- 10.1 The PBAC considered the listing of CGH at its March 2023 meeting and deferred making a recommendation to undertake further analysis of the cost effectiveness of ocular lubricants in Australia.
- 10.2 The PBAC had advised that it considered the submission's claim of non-inferior comparative effectiveness and non-inferior comparative safety to HS 0.1% was reasonably supported by the submission data. The PBAC had noted that the nominated comparator, HS 0.1%, is a PF ocular lubricant, whereas CGH is a PC ocular lubricant, and therefore considered that the data presented demonstrated that there was no added benefit to PF ocular lubricants over PC ocular lubricants.
- 10.3 Furthermore, the PBAC had recalled its advice in 2014 that all ocular lubricants should be considered equivalent for pricing purposes, inclusive of hyaluronate based ocular lubricants. At the March 2023 meeting, the PBAC had considered that Systane Hydration multi-dose PF eye drops were non-inferior in comparative effectiveness and comparative safety when compared with HS 0.1%, HS 0.2%, and Cationorm respectively, noting that Systane Hydration does not contain hyaluronate.

11 PBAC Outcome

- 11.1 The PBAC recommended the listing of CGH multidose PC eye drops for the treatment of severe dry eye syndrome on a cost-minimisation basis to the lowest cost PBS listed ocular lubricant.
- 11.2 The PBAC noted that under section 101(3B) of the Act, for a therapy to be substantially more costly than an alternative therapy or alternative therapies, it must, for some

patients, provide a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies. The PBAC considered that CGH multidose PC eye drops do not provide a significant improvement in efficacy or reduction of toxicity over other PC ocular lubricants and reaffirmed its previous 2014 advice that hyaluronate based PF eye drops are considered to be non-inferior in effectiveness and safety to other PBS listed ocular lubricants. Specifically, the PBAC considered that PF ocular lubricants do not provide a significant reduction in toxicity over PBS listed PC ocular lubricants and that hyaluronate based ocular lubricants do not provide a significant improvement in efficacy over other PBS listed ocular lubricants.

- 11.3 The PBAC considered that the financial estimates would be acceptable once cost-minimised to the lowest cost ocular lubricant.
- 11.4 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because CGH 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 an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 11.5 The PBAC advised that under Section 101(3BA) of the *National Health Act 1953* CGH should be treated as interchangeable with other PBS-listed ocular lubricants on an individual patient basis.
- 11.6 The PBAC advised that CGH is suitable for prescribing by nurse practitioners and optometrists, which aligns with other PBS-listed ocular lubricants.
- 11.7 The PBAC advised that CGH should be exempt from the Early Supply Rule as it currently does not apply to other PBS-listed ocular lubricants.
- 11.8 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

12 Recommended listing

12.1 Add new listing:

MEDICINAL PRODUCT Medicinal Product Pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
CARMELLOSE SODIUM + GLYCEROL + HYALURONATE SODIUM carmellose sodium 0.5% + glycerol 0.9% + hyaluronate sodium 0.1% eye drops, 10 mL	New	1	1	5	Optive Fusion

Restriction Summary / Treatment of Concept

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input checked="" type="checkbox"/> Optometrists
Restriction Level / Method: <input checked="" type="checkbox"/> Restricted benefit
Condition: Severe dry eye syndrome
Indication: Severe dry eye syndrome

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

13 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.

14 Sponsor's Comment

The sponsor had no comment.