

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

## **5.17 HYALURONIC ACID WITH POLYETHYLENE GLYCOL 400 WITH PROPYLENE GLYCOL WITH HYDROXYPROPYL GUAR**

**Eye drops containing sodium hyaluronate 1.5 mg per mL with polyethylene glycol 400, propylene glycol and hydroxypropyl guar, 10 mL, Systane® Hydration, Alcon Laboratories (Australia) Pty Ltd**

### **1 Purpose of Submission**

- 1.1 The Category 3 submission requested a General Schedule, Authority Required (STREAMLINED) listing for hyaluronic acid with polyethylene glycol 400 with propylene glycol with hydroxypropyl guar (Systane® Hydration) multi-dose preservative free (MDPF) (herein referred to as Systane Hydration) eye drops for the treatment of severe dry eye syndrome in patients who are sensitive to preservatives in multi-dose eye drops.

### **2 Background**

- 2.1 Systane Hydration contains both hyaluronate sodium and hydroxypropyl guar, which provides a treatment option for patients with severe dry eye syndrome who are sensitive to preservatives in multi-dose eye drops.

#### ***Registration status***

- 2.2 Systane Hydration was registered on the Australian Register of Therapeutic Goods (ARTG) on 10 June 2022 as a Medical Device Class III (Lubricant, eye) for the:
- temporary relief of burning and irritation due to dryness of the eye
  - lubricate and rewet silicone hydrogel and soft (hydrophilic) contact lenses.

#### ***Previous PBAC consideration***

- 2.3 Systane Hydration has not been considered by the PBAC previously.

### 3 Requested listing

3.1 The submission requested the following new listing with the same restrictions as other MDPF eye drops currently listed on the PBS:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
HYALURONATE SODIUM + POLYETHYLENE GLYCOL-400 + PROPYLENE GLYCOL + HYDROXYPROPYL GUAR					
hyaluronate sodium 0.15% + polyethylene glycol-400 + propylene glycol + hydroxypropyl guar eye drops, 10 mL	NEW	1	1	5	Systane Hydration Lubricant
<b>Restriction Summary / Treatment of Concept</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input checked="" type="checkbox"/> Optometrists					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required - Streamlined [new code]					
<b>Administrative Advice:</b> <i>The in-use shelf life of this product is 3 months from the date of opening</i>					
<b>Severity:</b> Severe					
<b>Condition:</b> Dry Eye Syndrome					
<b>Indication:</b> Severe Dry Eye Syndrome					
<b>Clinical criteria:</b> Patient must be sensitive to preservatives in multi-dose eye drops					

3.2 The submission has requested that Systane Hydration be considered as substitutable with other PBS listed MDPF eye drops.

### 4 Comparator

4.1 The submission nominated 0.1/0.2% hyaluronate sodium MDPF eye drops (Hylo-Fresh and Hylo-Forte respectively) as the main comparators noting that they have the greatest market share for this PBS indication. These products have been PBS listed since December 2012. The submission nominated cationic ophthalmic emulsion MDPF eye drops (Cationorm®) 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’. This was considered appropriate, however, the PBAC has previously considered that all PBS-listed ocular lubricants are relevant comparators (see paragraph 5.23).

*For more detail 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.

### Consumer comments

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

### Clinical trials

- 5.3 The submission included two trials to demonstrate the comparative efficacy and safety of Systane Hydration (outlined in Table 1). The Labetoulle et al 2018 study (herein referred to as the ‘Labetoulle study’) compared Systane Hydration with hyaluronate sodium 0.15%, and the Robert, Pierre-Yves et al. 2016 study (herein referred to as the ‘Robert study’) compared hyaluronate sodium 0.18% with Cationorm. The common reference arm between these studies was hyaluronate sodium.
- 5.4 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.
- 5.5 The randomised controlled clinical trials that were used to determine the therapeutic conclusions employed a fixed dosing regimen whereby patients received one drop in each eye four times daily.

**Table 1: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>NCT02470429/ Labetoulle (2018)</b>	Labetoulle et al - <i>Efficacy and safety of dual polymer hydroxypropyl guar- and hyaluronic acid- containing lubricant eyedrops for the management of dry eye disease: a randomised double masked clinical study.</i>	5 December 2018 Clin Ophthalmol 2018; Vol(12.): 2499-2508
<b>NVG11F120/ Robert (2016)</b>	Robert, Pierre-Yves et al. <i>Efficacy and safety of a cationic emulsion in the treatment of moderate to severe dry eye disease: a randomized controlled study.</i>	European Journal of Ophthalmology 2016; 26(6): 546 – 555

Source: Table ES-6 of the submission.

- 5.6 The Labetoulle study used Systane Hydration preservative containing (PC) eye drops (herein referred to as Systane Hydration PC) as a proxy rather than the proposed medicine of Systane Hydration MDPF due to the absence of randomised controlled evidence for the proposed medicine. The PBAC has previously stated that preservative free (PF) eye drops are ‘likely to have superior safety, although there is no evidence of improvement in efficacy’ (paragraph 6.2, Evolve Carmellose 0.5% PSD, July 2019 PBAC Meeting) compared to PC eye drops. The submission therefore claimed that Systane Hydration MDPF eye drops are expected to have the same efficacy, but superior safety compared to Systane Hydration PC eye drops.
- 5.7 The Labetoulle study used 0.15% hyaluronate sodium PF eye drops (Hyabak® 0.15%) as a proxy for the efficacy of the PBS listed formulations of hyaluronate sodium MDPF

eye drops (e.g. Hylo-Fresh/Forte). While Hyabak 0.15% 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).

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

### ***Comparative effectiveness***

- 5.9 The clinical claim for efficacy was based on the primary outcome of the mean change from baseline to day 42 for Systane Hydration vs Hyabak 0.15% in the ocular surface score (OSS).
- 5.10 The clinical claim for efficacy for Systane Hydration MDPF eye drops was based on an indirect comparison of two randomised control trials (the Labetoulle study and the Robert study) where hyaluronate sodium PF eye drops was the common reference arm, to demonstrate the efficacy between Systane Hydration MDPF and Cationorm. Both trials reported the mean change from baseline in the OSS scores as the primary outcome.
- 5.11 The treatment duration was shorter in the Labetoulle study compared to the Robert study, however, the Labetoulle study assessed the outcome at day 42 in the Intention-to-treat (ITT) population, whereas the Robert study assessed at Day 28 in the Full Analysis Set (FAS) despite the total treatment duration being 84 days.
- 5.12 Both trials applied a non-inferiority margin of 2 to the upper limit of the 95% confidence interval for the least square mean (LSM) treatment difference.
- 5.13 The submission stated the ITT population was used to assess efficacy outcomes in the Labetoulle study which consisted of randomised patients. In the Robert study the primary outcome was assessed in both the FAS (randomised patients) and the per protocol (PP) population (patients within the FAS without major protocol deviations). A LSM treatment difference of -0.24 (95% CI: -0.90, 0.42; p=0.476) was observed between Systane Hydration PC and Hyabak, with the upper limit of the 95% CI not exceeding the non-inferiority margin of 2.
- 5.14 The submission noted that there was no statistically significant difference between Systane Hydration PC and Cationorm for the mean change in OSS scores between the two trials (LSM 0.07, 95% CI: - 0.87, 1.01; p=0.8840), which supported a non-inferiority claim for efficacy.

### ***Comparative safety***

- 5.15 The clinical claim for safety was measured by the proportion of patients who experienced treatment-emergent adverse events (TEAEs).
- 5.16 The clinical claim of non-inferior safety between Systane Hydration PC and Hyabak was based on the absence of a statistically significant difference in the proportion of patients experiencing treatment emergent adverse events (TEAEs) up to Day 42 in the Labetoulle study and up to Day 84 in the Robert study.

- 5.17 Results included patients who have experienced ocular TEAEs (RD 0.02, 95% CI: -0.21, 0.25; p=0.8625), any treatment-related ocular TEAE (RD 0.07, 95% CI: -0.11, 0.25; p=0.4380), any ocular TEAE leading to discontinuation (RD -0.02, 95% CI: -0.11, 0.07; p=0.6612), and treatment-related eye irritation (RD 0.06, 95% CI: -0.05, 0.17; p=0.2895).

**Clinical claim**

- 5.18 The submission claimed the non-inferior comparative effectiveness and non-inferior comparative safety of Systane Hydration compared with Hylo-fresh, Hylo-Forte and Cationorm respectively.
- 5.19 The PBAC considered that the claim of non-inferior comparative effectiveness and non-inferior comparative safety was reasonable.

**Economic analysis**

- 5.20 The submission presented a cost-minimisation approach (CMA) comparing Systane Hydration with Hylo-Fresh/Hylo-Forte and Cationorm respectively.
- 5.21 The submission claimed a PBS listing for Systane Hydration is not expected to result in changes in resource use due to differences in prescribing or the administration profiles, adverse events or monitoring requirements. The CMA included the cost of the medicines only and was undertaken on a treatment basis, defined as one drop in both eyes.
- 5.22 The submission claimed that the equi-effective dose for Systane Hydration MDPF eye drops is 1:1 with both 0.1%/0.2% hyaluronate sodium MDPF and Cationorm respectively.

**Table 2: Cost minimisation analysis**

	Systane Hydration MDPF	0.1%/0.2% hyaluronic sodium MDPF	Cationic ophthalmic emulsion MDPF
<b>Quantity per prescription</b>			
Drops per pack	230	300	386
Treatments per pack	115 [230 / 2 drops]	150 [300 / 2 drops]	193 [386 / 2 drops]
<b>Cost per treatment</b>			
AEMP per pack	\$14.18	\$20.90	\$23.80
AEMP per treatment	\$0.123 [\$14.18 / 115]	\$0.139 [\$20.90 / 150]	\$0.123 [\$23.80 / 193]

- 5.23 The submission proposed a price \$14.18 for Systane Hydration with the cost per treatment being \$0.123. This is \$0.016 less than the main comparators yet identical to the price of Cationorm.
- 5.24 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) inclusive of hyaluronate based ocular lubricants.

5.25 As a Category 3 submission, the economic analysis has not been independently evaluated.

**Estimated PBS usage and financial implications**

5.26 The submission used a market share approach to estimate the predicted use and financial implications to the PBS/RPBS.

5.27 The submission estimated a net cost saving to the PBS/RPBS in Year 1 of listing, with a total net saving to the PBS/RPBS of \$0 to < \$10 million over the first 6 years of listing (see Table 3).

**Table 3: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of scripts dispensed	■ <sup>1</sup>	■ <sup>2</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>4</sup>	■ <sup>4</sup>
<b>Estimated financial implications of Systane Hydration</b>						
Cost to PBS/RPBS less co-payment (\$)	■ <sup>5</sup>	■ <sup>5</sup>	■ <sup>5</sup>	■ <sup>5</sup>	■ <sup>5</sup>	■ <sup>5</sup>
<b>Estimated financial implications of PBS listed MDPF ocular lubricants</b>						
Cost to PBS/RPBS less co-payment (\$)	■ <sup>6</sup>	■ <sup>6</sup>	■ <sup>6</sup>	■ <sup>6</sup>	■ <sup>6</sup>	■ <sup>6</sup>
<b>Net financial implications</b>						
Net cost to PBS/RPBS (\$)	■ <sup>6</sup>	■ <sup>6</sup>	■ <sup>6</sup>	■ <sup>6</sup>	■ <sup>6</sup>	■ <sup>6</sup>

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

Source: [Table ES-11], Financial Implications of the submission.

The redacted values correspond to the following ranges:

<sup>1</sup> 50,000 to < 60,000

<sup>2</sup> 80,000 to < 90,000

<sup>3</sup> 100,000 to < 200,000

<sup>4</sup> 200,000 to < 300,000

<sup>5</sup> \$0 to < \$10 million

<sup>6</sup> net cost saving

5.28 A DUSC utilisation review of ocular lubricants in February 2021 found that there had been an increase in the use of PF ocular lubricants over PC ocular lubricants<sup>1</sup>. It seemed to be due to more patients starting on these formulations without any record of trialling a PC ocular lubricant. In 2019, 80% of patients started on a PF ocular lubricant appear to have been directly initiated on a PF ocular lubricant. An analysis of NPS MedicineWise MedicineInsight general practice data found there was little private prescribing of ocular lubricants. Among regularly attending patients to general practice who were initiated on a PF product, 74.9% had no record of previous PC

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<sup>1</sup> Drug Utilisation Sub-Committee Public Release Document, February 2021, ‘Ocular lubricants: Utilisation analysis using PBS data’. Accessed on 9 February 2023 at: <https://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/dusc-utilisation-public-release-docs>

ocular lubricant prescriptions<sup>2</sup>. While the reason for this cannot be established using PBS data it could reflect:

- previous use of over-the-counter or private PC or PF ocular lubricants before a patient is dispensed their first PBS prescription;
- a clinical preference for PF ocular lubricants given difficulties in clearly classifying symptom severity, limited PBS guidance as to what constitutes severe dry eye syndrome, and guidance that states that PF formulations are preferred for patients with severe dry eye syndrome.

*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 Systane Hydration for the treatment of severe dry eye syndrome in patients who are sensitive to preservatives in multi-dose eye drops in order to undertake further analysis of the cost effectiveness of ocular lubricants.
- 6.2 The PBAC recalled that, at 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 2014 advice that all ocular lubricants should be considered equivalent for pricing purposes, which was 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 Furthermore, the PBAC considered that the cost-effectiveness of PF ocular lubricants in relation to PC ocular lubricants was uncertain, noting its consideration at this same meeting (March 2023) that a PC hyaluronate based ocular lubricant (carmellose sodium 0.5% + glycerol 0.9% + hyaluronate sodium 0.1% multidose PC eye drops, Optive Fusion®) demonstrated non-inferiority to PF hyaluronate ocular lubricants listed on the PBS.
- 6.5 While the PBAC was of a mind to recommend the listing of Systane Hydration on a cost minimisation basis to PF hyaluronate containing products listed on the PBS, it sought to further review the cost effectiveness of the more expensive PF ocular

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<sup>2</sup> Drug Utilisation Sub-Committee Public Release Document, February 2021, 'Ocular lubricants: Utilisation analysis using MedicineInsight data'. Accessed on 9 February 2023 at: <https://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/dusc-utilisation-public-release-docs>

lubricants relative to the preservative containing alternatives that are now substantially less costly 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 if the existing utilisation of ocular lubricants is cost effective, and what the appropriate therapeutic relativities may be.

**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**

The sponsor had no comment.

**Addendum to the March 2023 PBAC PSD:**

**4.03 HYALURONIC ACID WITH POLYETHYLENE GLYCOL 400  
WITH PROPYLENE GLYCOL WITH HYDROXYPROPYL  
GUAR**

**Eye drops containing sodium hyaluronate 1.5 mg per  
mL with polyethylene glycol 400, propylene glycol  
and hydroxypropyl guar, 10 mL,  
Systane® Hydration,  
Alcon Laboratories (Australia) Pty Ltd**

**9 Purpose**

- 9.1 To determine the appropriate comparator for the General Schedule, Authority Required (STREAMLINED) listing for Systane Hydration eye drops for the treatment of severe dry eye syndrome in patients who are sensitive to preservatives in multi-dose eye drops.

**10 Background**

- 10.1 The PBAC considered the listing of Systane Hydration 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 0.1%/0.2% hyaluronate sodium MDPF and Cationorm respectively was reasonably supported by the submission data. The PBAC noted that Systane Hydration does not contain hyaluronate sodium. 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.
- 10.3 At the March 2023 meeting, the PBAC also considered that Optive Fusion, a PC based ocular lubricant, had demonstrated non-inferiority to PF ocular lubricants listed on the PBS.

**11 PBAC Outcome**

- 11.1 The PBAC recommended the listing of Systane Hydration for the treatment of severe dry eye syndrome in patients who are sensitive to preservatives in multi-dose eye drops 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 Systane Hydration does 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 noted that its recommendation was on a cost-minimisation basis and advised that, because Systane Hydration 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.
- 11.4 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.
- 11.5 The PBAC advised that Systane Hydration is suitable for prescribing by nurse practitioners and optometrists, which aligns with other PBS-listed ocular lubricants.
- 11.6 The PBAC advised that Systane Hydration should be exempt from the Early Supply Rule as it currently does not apply to other PBS-listed ocular lubricants.
- 11.7 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	№.of Rpts	Available brands
HYALURONATE SODIUM + POLYETHYLENE GLYCOL-400 + PROPYLENE GLYCOL + HYDROXYPROPYL GUAR					
hyaluronate sodium 0.15% + polyethylene glycol-400 + propylene glycol + hydroxypropyl guar eye drops, 10 mL	NEW	1	1	5	Systane Hydration Lubricant
<b>Restriction Summary / Treatment of Concept</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input checked="" type="checkbox"/> Optometrists					
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required - Streamlined [new code]					
<b>Administrative Advice:</b> <i>The in-use shelf life of this product is 3 months from the date of opening</i>					
<b>Severity:</b> Severe					
<b>Condition:</b> Dry Eye Syndrome					
<b>Indication:</b> Severe Dry Eye Syndrome					
<b>Clinical criteria:</b> Patient must be sensitive to preservatives in multi-dose eye drops					

***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.