

5.16 CATIONIC OPHTHALMIC EMULSION, PRESERVATIVE FREE,

Eye drops containing heavy mineral oil 0.5% and light mineral oil 0.5%, 10 mL,

Cationorm[®],

Seqirus (Australia) Pty Ltd

1 Purpose of Application

- 1.1 The minor submission requested a General Schedule, Authority Required (STREAMLINED) listing of cationic ophthalmic emulsion, preservative free (Cationorm[®], hereafter referred to as Cationorm) for the treatment of severe dry eye syndrome in patients who are sensitive to preservatives in multi-dose eye drops.
- 1.2 The requested listing was based on a cost-minimisation approach compared with the lowest cost PBS-listed preservative-free, multi-dose eye drops.

2 Background

Registration status

- 2.1 Cationorm was TGA registered in July 2019 as a Medical Device Class IIb, hydrating and lubricating emulsion, which protects the ocular surface and relieves the discomfort and irritation due to dry eye caused by prolonged use of contact lenses or environmental condition.

Previous PBAC consideration

- 2.2 Cationorm has not been previously considered by the PBAC for the treatment of severe dry eye syndrome in patients who are sensitive to preservatives in multi-dose eye drops.
- 2.3 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 Public Summary Document (PSD) on ocular lubricants). The most recent recommendation of preservative-free, multi-dose eye drops was in July 2019 for Evolve[®] carmellose 0.5% (hereafter referred to as Evolve carmellose) and Evolve[®] hypromellose 0.3% (hereafter referred to as Evolve hypromellose), where PBAC considered that compared to some eye drops that contain preservatives, Evolve carmellose and Evolve hypromellose are likely to have superior safety. The PBAC recommended the products 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 (paragraph 6.1, Evolve carmellose and Evolve hypromellose PSD, July 2019).

3 Requested listing

3.1 The proposed restrictions are provided below with Secretariat suggested additions in italics and deletions in strikethrough.

Name, Restriction, Manner of administration and form	PBS item code	Max. qty	No. of Rpts	DPMQ	Proprietary Name and Manufacturer	
CATIONIC OPHTHALMIC EMULSION <i>liquid paraffin + glycerol + tyloxapol + poloxamer-188 + trometamol hydrochloride + trometamol + cetalkonium chloride eye drops, 10 mL</i>	[NEW]	1	5	\$ [REDACTED]	Cationorm®	Seqirus (Australia) Pty Ltd

Restriction Summary [new] / Treatment of Concept: [new]

Concept ID	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 type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input checked="" type="checkbox"/> Authority Required - Streamlined
	Episodicity: Chronic
	Severity: Severe
	Condition: Dry eye syndrome
[7869]	Indication: The treatment of Severe dry eye syndrome
[7875]	Clinical criteria:
[7874]	Patient must be sensitive to preservatives in multi-dose eye drops
[26237]	Administrative Advice: <i>The in-use shelf life of Cationorm is 3 months from the date of opening.</i>

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

4 Comparator

4.1 The minor submission nominated preservative-free, multi-dose ocular lubricants currently listed on the PBS as the comparators to Cationorm.

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 as it was a minor submission.

Consumer comments

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

Clinical trials

- 5.3 The minor submission was based on two clinical trials comparing Cationorm with preservative-free ocular lubricants (Refresh® and Vismed®) to demonstrate that Cationorm is at least non-inferior in terms of efficacy and safety compared with other preservative-free ocular lubricants in patients with dry eye disease (DED). However, the submission noted that no clinical evidence was presented to support the claim of non-inferiority for efficacy and safety in the recent considerations of preservative-free, multi-dose ocular lubricants (NovaTears PSD March 2018; Evolve carmellose and Evolve hypromellose PSD July 2019).
- 5.4 A literature search was conducted to identify relevant randomised controlled trials (RCTs) evaluating the efficacy, tolerance, and safety of Cationorm in patients with DED. Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the re-submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation	Inclusion for clinical evaluation
NVG07F105 / Amrane (2014)	Evaluation of ocular tolerance and exploration of the efficacy of Cationorm 1% unpreserved eye drops, versus Refresh in patients with bilateral mild to moderate dry eye syndrome.	Clinical Study Report, 12 June 2008	Included
NVG07F105 / Amrane (2014)	Amrane, M., et al. Ocular tolerability and efficacy of a cationic emulsion in patients with mild to moderate dry eye disease – A randomised comparative study.	<i>Journal Francais d'Ophthalmologie</i> , 2014;37(8):589-598	Included
NVG11F120 / Robert (2016)	Robert, Pierre-Yves, et al. 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</i> , 2016;26(6): 546-555	Included
Supplementary trial(s)			
Study 07-50	Not available	Clinical Study Report	Excluded; single-dose installation;
Aragona (2011)	Aragona, P., et al. Assessment of the efficacy of Cationorm in patients with moderate dry eye compared with Optive® and Emustil® eye drops.	<i>Acta Ophthalmologica</i> , 2011;89.	Excluded (abstract provided in Appendix A)

Source: Table A2, p30 of the submission

- 5.5 The pivotal studies (Amrane 2014 and Robert 2016) for Cationorm used Cationorm preservative free, single-dose eye drops while the requested listing was for Cationorm preservative-free, multi-dose eye drops. The submission considered that the difference in pharmaceutical form used in the trials versus Australian clinical practice is expected to have no impact on the results of clinical evaluation given the same content in the both forms.
- 5.6 The comparator in Amrane 2014, Refresh, is not PBS listed. However, the active ingredient in Refresh, polyvinyl alcohol, is the same active ingredient in PBS-listed item Liquifilm® Tears™ (preserved). Similarly, Vismed® as comparator in Robert 2016 is not PBS listed but contains the same active ingredient of hyaluronate sodium (HS) as PBS-listed item Hylo®-Fresh (noting the concentrations between these products are

different). As such, the submission considered the comparators in the pivotal trials to be reasonable proxies of preservative-free ocular lubricants listed on the PBS.

5.7 The Amrane 2014 study included patients with mild to moderate DED whereas the Robert 2016 study was based on the patient population who had moderate to severe DED with keratitis or keratoconjunctivitis, which would be more applicable to the requested PBS population (severe DED).

5.8 The key features of the studies are summarised in the table below.

Table 2: Key features of the included evidence

Trial ID/First Author	Design	Duration	Intervention	Comparator	Patient population
NVG07F105 / Amrane (2014)	Randomised, open-label, multicentre, Phase II	28 ± 3 days	Cationorm 1 drop per eye, 4 times daily (n = 44)	Refresh preservative-free, single-dose eye drops (PVA-P) 1 drop per eye, 4 times daily (n = 35)	Patients with mild to moderate DED (n = 79); Cationorm vs PVA-P mean age (±SD): 61.3 yrs (±15.4) vs 61.9 yrs (±12.5); patients were well balanced at baseline with respect to objective signs (including TBUT, CFS, Lissamin green staining, Schirmer's score) and subjective ocular symptoms
NVG11F120 / Robert (2016)	Randomised, multicentre, reference-controlled, parallel-group, investigator-masked, Phase III	84 ± 3 days	Cationorm 1 drop per eye, 4 times daily (FAS: n = 44)	Vismed preservative-free (Hypotonic HS; 0.18%) (FAS: n = 41)	Patients with moderate to severe DED with keratitis or keratoconjunctivitis (n = 85); Cationorm vs HS mean age (±SD): 60.0 yrs (14.6) vs 65.3 yrs (11.1); patients were similar at baseline with respect to objective clinical signs and subjective ocular symptoms

Abbreviation: CFS = corneal fluorescein staining; FAS = full analysis set; HS = hyaluronate sodium; PVA-P = polyvinyl alcohol/povidone; SD = standard deviation; TBUT = tear film break-up time; DED = dry eye disease
Source: Table 6, p16 of the submission

Clinical claim

5.9 The submission claimed non-inferior comparative effectiveness and safety of Cationorm compared with other preservative-free ocular lubricants, containing the active ingredients of polyvinyl alcohol (Refresh or Liquifilm Tears) or HS (Vismed or Hylo-Fresh).

5.10 The PBAC considered that the claims of non-inferior comparative effectiveness and safety were reasonable.

Economic analysis

5.11 A cost-minimisation approach was adopted to determine the proposed price of Cationorm against the lowest cost PBS-listed preservative-free, multi-dose eye drops, assuming that Cationorm is at least non-inferior to the current PBS-listed preservative-free ocular lubricants.

5.12 The submission noted the PBAC's advice that "carmellose 0.5% and hypromellose 0.3% were recommended on the basis that the price proposed by the sponsor resulted

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in a lower cost per treatment compared to other currently listed preservative-free eye drops.” (paragraph 6.1, Evolve carmellose and Evolve hypromellose PSD, July 2019). As such, the cost-minimisation analysis was performed on a per treatment basis, which was previously accepted by the PBAC at its July 2019 meeting. The submission presented costs per treatment for the currently listed preservative-free, multi-dose eye drops (see table below).

Table 3: Comparison of costs per treatment of preservative-free, multi-dose ocular lubricants currently available on the PBS to Cationorm

Brand name	Treatment and formulation	AEMP ^a	Number of treatment ^b for both eyes	AEMP per treatment ^c for both eyes	Cost-minimising AEMP for Cationorm ^d
Tears Again®	Soy lecithin 1% + tocopherol 0.002% + vitamin A palmitate 0.025% (spray)	\$22.78 (\$11.39 per unit)	100	\$0.228	\$43.97
Hylo-Forte®	Hyaluronate sodium 0.1%	\$20.90	150	\$0.139	\$26.89
Hylo-Fresh®	Hyaluronate sodium 0.2%	\$20.90	150	\$0.139	\$26.89
NovaTears®	Perfluorohexyloctane	\$20.00	140	\$0.143	\$27.57
Evolve® Carmellose 0.5%	Carmellose sodium 0.5%	\$17.00	125	\$0.136	\$26.25
Evolve® Hypromellose 0.3%	Hypromellose 0.3%	\$17.00	125	\$0.136	\$26.25

^a prices from March 2020 Pharmaceutical Benefits Schedule

^b the number of treatments per bottle are represented by the number of drops or actuations contained in one bottle.

^c cost per treatment for both eyes calculated using AEMP divided by total number of treatments per pack rounded to third decimal.

^d based on total of 193 treatments for Cationorm for both eyes. The minor submission presented a laboratory test performed by the manufacturer which reported that the bottle with a dropper, configured to deliver 62.5% flow control (with liner cap and filter protection valve), delivered a mean dose weight of 26.4 mg (equivalent to approx. 26.4 µL per drop). A bottle of Cationorm provides 386 drops in total (10.2 mL ÷ 0.0264 mL) given that each bottle has a content volume of 10.2 mL.

Abbreviations: AEMP = approved ex-manufacturer price

Source: Table 10, p20 of the submission

5.13 The submission proposed an AEMP of \$23.80 for Cationorm, which is lower than the AEMP arrived at by cost-minimisation to the lowest cost comparators (\$26.25).

Estimated PBS usage & financial implications

5.14 The minor submission used a market share approach to estimate the extent of use and financial impact of listing Cationorm on the PBS/RPBS.

5.15 The minor submission assumed that Cationorm would only substitute for preservative-free, multi-dose eye drops available on the PBS. Therefore, the minor submission did not include the proportion of substitution for the existing PBS-listed preservative-free, single-dose eye drops as this would overestimate the cost savings to the PBS. The submission also did not include Evolve carmellose and Evolve hypromellose in the estimates because these items were listed in December 2019 and had limited usage statistics available. The PBAC considered that these approaches were appropriate and would likely have minimal impact on the estimates.

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5.16 The minor submission noted that the risk of wastage is very low given that patients typically require multiple drops over the course of a day. The PBAC considered this was reasonable.

5.17 The minor submission estimated the net saving to the PBS/RPBS of \$ [REDACTED] in Year 1 of listing, with a total net saving to the PBS/RPBS of \$ [REDACTED] over the first 6 years of listing. The submission assumed 30% uptake of Cationorm by Year 6. This is summarised in the table below.

Table 4: Estimated use and financial implications

	2021	2022	2023	2024	2025	2026
Estimated financial implications of Cationorm						
Number of scripts dispensed	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cost to PBS/RPBS less copayments ^a	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Estimated financial implications for displaced preservative-free, multi-dose eye drops						
Number of scripts dispensed ^b	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cost to PBS/RPBS less copayments	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Net financial implications						
Net cost to PBS/RPBS	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]

^a The calculation was based on the proposed DPMQ of \$ [REDACTED] (Dispensed price for maximum quantity) for Cationorm.

^b Displaced drugs include (PBS item code) Soy lecithin 1% (5545W, optometric), Soy lecithin 1% (9448G), Hyaluronate sodium 0.2% (2171G, optometric), Hyaluronate sodium 0.2% (2253N), Hyaluronate sodium 0.1% (2184Y, optometric), Hyaluronate sodium 0.1% (2181T), Perfluorohexyloctane 100% (11439C, optometric), Perfluorohexyloctane 100% (1146K)

Source: Section 4 workbook - Cationorm April 2020.

The redacted table shows that at Year 6, the estimated number of patients was 200,000 to < 300,000 and there would be a net cost saving to PBS/RPBS.

5.18 The submission noted that there are a total of 54 ocular lubricants listed on the PBS, of those, 24 ocular lubricants (12 among these 24 eye drops are multi-dose products) are preservative-free formulations available as authority required listings for patients who are sensitive to preservatives.

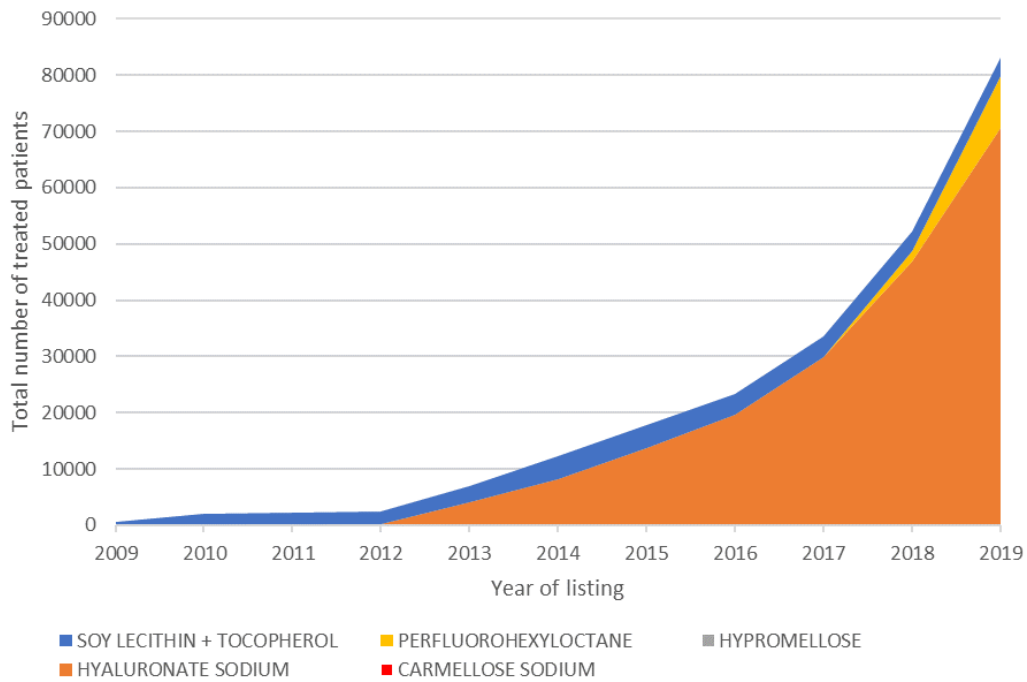
5.19 Given the large number of ocular lubricants on the PBS and the rapid market growth in this treatment space, the PBAC requested additional information from the Drug Utilisation Sub Committee (DUSC) Secretariat on the utilisation of preservative-free ocular lubricants; in particular, the number of patients supplied more than one product and whether this is a significant driver to market growth. The following points were noted from the data:

- The growth in the overall PBS market for preservative-free ocular lubricants appears to be mainly driven by the increasing utilisation of HS rather than the inclusion of additional listings into the market (Figure 1).

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- The majority of patients were dispensed a single ocular lubricant (Table 5). A low proportion of patients were identified as using two or more drugs. As such, the availability of alternative listings did not appear to be a significant factor in the growth of the overall market. It was noted that the submission assumed the overall market size would grow at similar, but diminishing rates; and that the listing of Cationorm is not expected to increase the overall use of ocular lubricants. However, the number of cases of concomitant use appeared to have increased from 2018 to 2020 (year to date as at April 2020).

Figure 1 Number of patients treated with preservative-free ocular lubricants by PBS listing



Note: The data was extracted based on the date of supply and includes the following PBS item code: 9448G, 5545W, '02181T', 2184Y, 2253N, 2171G, 11446K, 11439C, 11852T, 11853W, 11842G and 11849P.

Source: compiled by the DUSC Secretariat based on the PBS service data

Table 5: Number of cases of concomitant use identified by year

		Number of concomitant drugs			Total
		Single drug	Two drugs dispensed	Three drugs dispensed	
Total - Since first ever listing to 30 April 2020	Percent	94.0	5.9	0.1	100
Use of single versus multiple drug regimens by year:					
2013	Frequency	1099	21	0	1120
	Percent	98.1	1.9	0	100
2014	Frequency	2396	62	0	2458
	Percent	97.5	2.5	0	100
2015	Frequency	3380	90	0	3470
	Percent	97.4	2.6	0	100
2016	Frequency	4183	112	0	4295
	Percent	97.4	2.6	0	100
2017	Frequency	6020	166	0	6186
	Percent	97.3	2.7	0	100
2018	Frequency	9990	272	0	10262
	Percent	97.4	2.7	0	100
2019	Frequency	23575	1342	11	24928
	Percent	94.6	5.4	0.04	100
2020 (YTD April)	Frequency	46999	4151	42	51192
	Percent	91.8	8.1	0.08	100

Note: Drugs supplied within 30 days of each other (that is, within the median time between supplies of ocular lubricant listings) were assumed to be used concomitantly.

Source: compiled by the DUSC Secretariat based on PBS data from the Services Australia Pharmacy Claims database.

5.20 As a minor submission, the clinical evidence, economic analysis and financial estimates were not independently evaluated.

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

6 PBAC Outcome

6.1 The PBAC recommended the Authority Required (STREAMLINED) listing of cationic ophthalmic emulsion, preservative free (Cationorm) for the treatment of severe dry eye syndrome in patients who are sensitive to preservatives in multi-dose eye drops. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of Cationorm would be acceptable on a cost-minimisation basis at the lowest cost per treatment compared with other PBS-listed preservative-free, multi-dose ocular lubricants (Evolve® carmellose 0.5% and Evolve® hypromellose 0.3%).

6.2 The PBAC recalled that it previously considered all preservative-free eye drops were appropriate comparators in its July 2019 consideration for Evolve carmellose and

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Evolve hypromellose. Therefore, all preservative-free, multi-dose ocular lubricants currently listed on the PBS were appropriate comparators for Cationorm.

- 6.3 The PBAC noted the clinical evidence presented in the submission supported the claim that Cationorm is non-inferior in terms of efficacy and safety compared with other preservative-free ocular lubricants in patients with dry eye disease (DED), and considered the effectiveness and safety of Cationorm is likely to be comparable to other preservative-free, multi-dose eye drops available on the PBS.
- 6.4 The PBAC considered the listing of Cationorm would have minimal impact on growth of the market size for preservative-free ocular lubricants. Further, the PBAC noted the proposed price of Cationorm was lower than its cost-minimised price based on cost per treatment against the lowest cost comparators. Therefore, the PBAC considered that the listing of Cationorm would most likely be cost saving to Government.
- 6.5 The PBAC considered the requested restriction for Cationorm was appropriate. The PBAC advised the inclusion of the following administrative advice to the restriction “The in-use shelf life of Cationorm is 3 months from the date of opening” to align with other preservative-free, multi-dose ocular lubricants with a recommended shelf life.
- 6.6 The PBAC noted that the growth in the overall PBS market for preservative-free ocular lubricants appears to be mainly driven by the substantially increased utilisation of hyaluronate sodium (HS) and recommended the DUSC conduct a review on the utilisation of ocular lubricants.
- 6.7 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because Cationorm is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity over all other preservative-free, multi-dose 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 advised that under Section 101(3BA) of the *National Health Act 1953* Cationorm should be treated as interchangeable with other PBS-listed preservative-free, multi-dose ocular lubricants on an individual patient basis.
- 6.9 The PBAC advised that Cationorm is suitable for prescribing by nurse practitioners and optometrists, which aligns with other PBS-listed preservative-free, multi-dose ocular lubricants.
- 6.10 The PBAC advised that Cationorm should be exempt from the Early Supply Rule as it currently does not apply to other PBS-listed preservative-free, multi-dose ocular lubricants.
- 6.11 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 medicinal product:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty	No. of Rpts	Proprietary Name and Manufacturer	
CATIONIC OPHTHALMIC EMULSION liquid paraffin + glycerol + tyloxapol + poloxamer-188 + trometamol hydrochloride + trometamol + cetalkonium chloride eye drops, 10 mL	[NEW]	1	5	Cationorm®	Seqirus (Australia) Pty Ltd

Restriction Summary [new] / Treatment of Concept: [new]

Concept ID (for internal Dept. use)	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 type / Method: <input checked="" type="checkbox"/> Authority Required – Streamlined
[7869]	Indication: Severe dry eye syndrome
[7875]	Clinical criteria:
[7874]	Patient must be sensitive to preservatives in multi-dose eye drops
[26237]	Administrative Advice: The in-use shelf life of Cationorm is 3 months from the date of opening.

This restriction 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.