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Our reference
2019064038

Date 24 February 2020
Subject Brimonidine Stulln 2mg/ml eye drop solution, single-use packaging

Dear Mr Bruins,

In your letter of 11 November 2019 (CIBG-19-09084), you requested the National Health Care Institute to assess whether the product Brimonidine Stulln 2mg/ml eye drop solution, single-use packaging (described below as "Brimonidine Stulln"). is interchangeable with another product that is included in the Medicine Reimbursement System (GVS).

The marketing authorisation holder (MAH) of Brimonidine Stulln has submitted an application for the inclusion of this medication on List 1B of the Health insurance Regulations. The National Health Care Institute will answer your question on the basis of a limited review.

Brimonidine Stulln contains 2.0 mg brimonidine tartrate per ml solution, equivalent to 1.3 mg brimonidine. Brimonidine is an alpha sympathetic mimetic. Brimonidine Stulln contains no preservative.[1]

The registered indication is[1]:
Decrease of increased intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

- As monotherapy for patients for whom treatment with topical beta-blockers is contraindicated.
- As additional treatment with other eye pressure-reducing medication, when the desired IOP is not achieved with monotherapy.

The recommended dosage is one drop of Brimonidine Stulln in the affected eye(s), twice a day, with an interval of approximately 12 hours. No dose adjustment is required for elderly people. Brimonidine Stulln is not recommended for use in children younger than 12 years and is contraindicated for newborns and young children (younger than 2 years).[1]

Conclusions of interchangeability
It has already been established that the medication groups used in eye drops for the treatment of ocular hypertension and/or open-angle glaucoma (beta-blockers, prostaglandin agonists, carbonic anhydrase inhibitors, alpha sympathetic mimetics, and the parasympathetic mimetic pilocarpine) are not interchangeable.

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It has also been previously established that brimonidine eye drops are not interchangeable with eye drops with the other alpha sympathetic mimetics apraclonidine and phenylephrine. Both apraclonidine and phenylephrine have a separate place in the GVS due to a clinically relevant difference in indication area.

Brimonidine Stulln is the first preservative-free variant of the brimonidine eye drops containing a conservative (Alpagan® and various generics) that are already listed on List 1A in cluster 0S01EADG.
Brimonidine combination preparations included in the GVS are brinzolamide/brimonidine (Simbrinza®, YS01ECAG) and brimonidine/timolol (Combigan®, List 1B).[2] These are all eye drops containing preservatives.

In principle, the policy is to cluster the products by substance name, unless there is an exception. Since 2002, eye drops containing preservatives and preservatives-free eye drops have not been grouped into one cluster, as the preservative-free eye drops have a demonstrable therapeutic added value in the following subpopulations of patients:

- Those with a proven allergy to the preservative in question;
- Those for whom preservatives are contraindicated, such as in case of damage to the corneal epithelium or perforated corneal transplants;
- Those who are chronic frequent users of eye drops, particularly in case of dry eye syndrome and glaucoma;
- Patients in which the preservative gives rise to side-effects.[3]

It is therefore not recommended to cluster Brimonidine Stulln with the brimonidine eye drops containing preservatives. Therefore, Brimonidine Stulln is not interchangeable with another medicine that is included in the GVS and cannot be placed on List 1A. It has been reviewed whether Brimonidine Stulln is eligible for inclusion on List 1B.

Conclusion regarding placement on List 1B
The additives (except for the preservative) of Brimonidine Stulln and the other variants of brimonidine eye drops (including Alphagan®) are identical and contain the same type of solution (aqueous) and concentration of the same active substance (brimonidine tartrate). The pH is set in the same range (pH 5.5-6.5) and the osmolality is in the same range (275-315 mOsm/kg) for both products.[1,4]
The National Health Care Institute concludes, on the basis of the above, that the efficacy of Brimonidine Stulln and Alpagan® and its generics is at least equivalent, and that there are previously mentioned advantages of preservative-free eye drops for specific subpopulations of patients. Brimonidine Stulln therefore has added value compared to brimonidine eye drops containing a preservative in these specific subpopulations of patients and can be placed on List 1B.

Budget analysis conclusion
GIP data has been used to assess the number of patients who may be eligible for treatment with Brimonidine Stulln.[5] This assessment looked at the number of users of preservative-free eye drops in 2018. The GIP data shows that on average 29% of all patients use preservative-free eye drops (ranging from 9% to 40% for different medication classes).[5]

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For the calculation of the expected number of patients eligible for Brimonidine Stulln, the total number of users (n=9.176) of brimonidine containing preservatives (Alphagan® and various generics) has been taken into account, as well as the current market share of preservative-free eye drops.[5] For budget analysis, 29% of patients are not eligible for the use of brimonidine containing preservatives. This amounts to (9,176*29%) 2,661 patients.

It is not likely that Brimonidine Stulln will be used as part of a combination therapy, given that preservative-free combination preparations are preferred.[6]

The annual cost for Brimonidine Stulln is €427 per patient. The inclusion of Brimonidine Stulln eye drops in the GVS is accompanied by additional costs of €1.1 million, charged to the pharmaceutical budget. This is a maximum estimate given that some of the patients who cannot use preservative-containing brimonidine may currently be using different preservative-free eye drops. This makes it possible for Brimonidine Stulln to replace the use of other preservative-free eye drops (substitution). However, it is unclear to what extent this will happen, which means that no substitution has been calculated.

Advice
In conclusion, we advise you to include Brimonidine Stulln 2mg/ml eye drops, single-use solution on List 1B of the Medicine Reimbursement System (GVS). The inclusion means additional costs estimated at €1.1 million.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board

References
[1] EMA SmPC Brimonidine tartrate Stulln 2 mg/ml eye drop solution, single-use packaging. 2019
[2] CVZ CFH Report 06/15: timolol/brimonidine (Combigan®). 2006
[3] CVZ. CFH Report 02/09: Preservative-free eye drops. Amstelveen, 2002.
[4] EMA SmPC Brimonidine tartrate Mylan 2mg/ml eye drops. 2015
[5] Zorginstituut Nederland. GIP database. 2018
[6] European Glaucoma society. Terminology and guidelines for glaucoma. 4th ed., 2014.