



HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

31 January 2007

BUCCOBET 0.1 mg, oromucosal tablet
B/50 (CIP: 3741470)

Applicant: DB PHARMA

Betamethasone valerate

List I

Date of validated Marketing Authorisation: 28 June 1996 (Licence of Right 10/07/1968)
Variation of 21 February 2006: change of name and holder of distribution rights.

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals.

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Betamethasone valerate

1.2. Indication

Local treatment of inflammation of the oral mucosa and oropharynx.

1.3. Dosage

Slowly suck the tablets without chewing or swallowing them, until they have completely disintegrated.

5 to 10 tablets per day, in divided doses.

NB:

BUCCOBET 0.1 mg, oromucosal tablet, is the new name of BETNEVAL BUCCAL 0.1 mg, oromucosal tablet

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

A ALIMENTARY TRACT AND METABOLISM

A01 STOMATOLOGICAL PREPARATIONS

A01A STOMATOLOGICAL PREPARATIONS

A01AC CORTICOSTEROIDS FOR LOCAL ORAL TREATMENT

2.2. Medicines in the same therapeutic category

None

2.3. Medicines with a similar therapeutic aim

These are all medicinal products used in the treatment of inflammation of the oral mucosa in particular oral lichen planus, oral ulcers and bullous diseases: systemic or topical analgesics, disinfectants, immunosuppressive treatments, corticoid therapies etc.

3 ANALYSIS OF AVAILABLE DATA

The company submitted 3 studies and a meta-analysis.

3.1. Efficacy

- CAWSON study 1968¹,

Randomised, double-blind trial comparing betamethasone valerate 0.1mg oromucosal tablets (n=30) with hydrocortisone 2.5 mg oromucosal tablets (n=18) in the treatment of oral lichen planus.

The results of treatment were evaluated qualitatively from the appearance and size of the lesions.

Results:

¹ Cawson RA. Treatment of oral lichen planus with betamethasone. Br Med J.1968 Jan13;1(584):86-9.

- Betamethasone group: 20 clear improvements (13 cases of complete disappearance of lesions, 7 cases with slight residual lines), 7 partial improvements, 2 failures and 1 withdrawal.
- Hydrocortisone group: 3 cases with slight residual lines, 12 failures and 3 worsenings.

This study is not very relevant because of the small sample size, the absence of a placebo group, the poor choice of assessment criteria, and comparator (hydrocortisone 2.5 mg oromucosal tablet which is not marketed in France). However, topical betamethasone valerate was observed to have an effect on the reduction of lesions in oral lichen planus .

- GREENSPAN study 1978²

Randomised, double-blind trial comparing betamethasone valerate oromucosal tablets with betamethasone valerate administered in aerosol form (400 µg/jour) in the treatment of oral lichen planus in 19 patients.

Treatment was evaluated qualitatively from the size of the lesions and the pain and discomfort (good or moderate result or failure).

This study cannot be reviewed by the Transparency Committee because of the very small sample size and because the comparator is not marketed in France.

- YEOMAN study 1978³

Randomised, double-blind, crossover trial comparing betamethasone valerate aerosol (500-600 µg/jour) with placebo in the treatment of recurrent oral ulcerations in 18 patients.

This study was not reviewed by the French Transparency Committee as it was carried out on betamethasone valerate aerosol which is not the subject of the present evaluation.

- The purpose of the meta-analysis conducted by the Cochrane group⁴ was to evaluate the efficacy and safety of palliative treatments of oral lichen planus compared to placebo: topical ciclosporin, topical and systemic retinoids, topical corticosteroids and UV phototherapy.

This meta-analysis could not confirm the efficacy of betamethasone valerate oromucosal tablets, as the pharmaceutical form of betamethasone valerate tested was an aerosol.

3.2. Adverse effects

No safety data was presented in the studies. According to the SPC, there may be a risk of oropharyngeal candidiasis.

3.3. Conclusion

The studies provided in the dossier are not very relevant. Only the CAWSON study suggests that betamethasone valerate oromucosal tablets have a positive effect on the lesions of oral lichen planus with a good safety.

² Greenspan JS, Yeoman CM, Harding SM. Oral lichen planus. A double-blind comparison of treatment with betamethasone valerate aerosol and pellets. *Br Dent J.* 1978 Feb 7;144(3):83-4.

³ Yeoman CM, Greenspan JS, Harding SM. Recurrent oral ulceration. A double-blind comparison of treatment with betamethasone valerate aerosol and placebo. *Br Dent J.* 1978 Feb 7;144:114-116

⁴ Chan ES-Y, Thornhill M, Zakrewska J. Interventions for treating oral lichen planus. *Cochrane Database Of Systemic Reviews* 1999,issue 2.Art.No.:CD001168.DOI:10.1002/14651858.CD001168.

4.1. Actual Benefit

The condition concerned by this proprietary product is not life-threatening for the patient, nor does it cause serious complications, any disability, or a marked deterioration in quality of life.

This proprietary product is intended to provide curative treatment.

This efficacy/safety ratio of this proprietary product is moderate.

This proprietary product is a medicinal product for to be used as a first or second line treatment depending on the disorders concerned by the indication of the MA.

There are alternative pharmacological and non-pharmacological therapies.

Public health benefit:

Taking into account the absence of precise data on the incidence of inflammation of the oral mucosa and oropharynx, the public health burden cannot be quantified.

The improvement of the management of these disorders does not constitute an identified public health priority (as other therapies are currently available).

A review of the clinical trial data and existing treatments shows that this medicinal product is not expected to have a benefit in terms of morbidity.

Consequently, this proprietary product is not expected to benefit public health.

The actual benefit of this medicinal product is moderate.

4.2. Improvement in actual benefit

BUCCOBET does not provide an improvement in actual benefit (IAB V) in the management of the conditions concerned by the MA indication.

4.3. Therapeutic use

The range of conditions concerned by the indication of the MA is broad, so that it is impossible to precisely define the therapeutic use of BUCCOBET. However certain inflammations of the oral mucosa, such as oral lichen planus, oral lesions in bullous dermatosis and oral ulcers may require local corticoid therapy:

Lichen planus is a benign inflammatory dermatosis with a chronic course that is usually papular and pruriginous. The most frequent site of lichen planus is the oral mucosa. Oral lichen planus leads to the appearance of fine interlocking whitish lines which may be accompanied by erythematous, erosive or bullous lesions.

It is recommended not to treat asymptomatic oral lichen planus whereas topical corticosteroids may be proposed for first-line treatment of erosive forms. Depending on the seriousness and/or response to local corticosteroids, tacrolimus, ciclosporin and systemic corticosteroids may be proposed. Accompanying measures such as avoidance of irritants (tobacco, alcohol etc.) and dental care should be recommended. Systemic or topical (xylocaine gel) analgesic treatment must generally be combined.

Photopheresis may be used in severe cases resistant to other therapies⁵.

Cicatricial pemphigoid is a rare bullous dermatological disorder. It is characterized by the appearance of mucocutaneous blisters which cause scarring when they heal. Its seriousness is related to possible conjunctival involvement and blindness, or a rare and sometimes life-threatening involvement of the nasal and laryngeal mucosa.

⁵ O.Chosidow, B.Cribier, L.Le Cleach. Lichen Plan. In Thérapeutique dermatologique, Médecine-Sciences Flammarion 2001.

The disease may begin by oral lesions, usually comprising chronic erosive gingivitis and may have an exclusively oral progression with no other sites⁶.

The management of cicatricial pemphigoid is based on a certain number of topical treatments, which may be sufficient in limited forms of the disease or which are intended to improve patient comfort and prevent the inflammatory progression of the disease, in particular to the eye. However, in most cases, systemic treatment is required (immunosuppressive agents in particular)⁷.

Pemphigus is a bullous auto-immune disease of the skin and mucosa caused by the production of auto-antibodies directed against interkeratinocyte adherens junctions.

Corticosteroids constitute the primary therapy for pemphigus. The usual regimen involves the use of a high dose from the outset (1 to 1.5 mg/kg/day of prednisone equivalents). If the disease is not rapidly controlled by these doses, it is usually recommended to use an immunosuppressive treatment or even plasma exchanges⁸.

Local corticoid therapy may be useful in localized forms of pemphigus including at the level of the oral mucosa.

Oral ulcers⁹.

The treatment of oral ulcers must be appropriate to the very different clinical forms. In every case, it is advised to remove or treat any foci of orodental infection and to avoid food known by the patient to cause the onset of mouth ulcers. Oral ulcers run a self-limited course. There is no specific curative treatment for oral ulcers. The purpose of the proposed, topical or systemic treatments, is to relieve pain and accelerate healing. The medicinal products used for disease-modifying therapy to limit the incidence of recurrences have only a delaying effect and are not constantly effective.

No local treatment has been found to be effective against oral ulcers. The use of topical corticosteroids is controversial. When they are applied from the prodrome, before the onset of ulceration, they reduce pain and the duration of bouts of mouth ulcers. They are not very effective against giant mouth ulcers. The use of local corticosteroids on the oral mucosa does not seem to cause any systemic or local adverse reaction apart from mycoses after prolonged use.

⁶ Agbo-Godeau S , de Lima Soares P , Szpirglas H . Pemphigoïde cicatricielle:prise en charge en stomatologie. Rev Stomatol.Chir.Maxillofac.,2004;105,4,206-210

⁷ Bédane C . Pemphigoïde cicatricielle. *IN: Thérapeutique dermatologique, Médecine-Sciences Flammarion* 2001.

⁸ P.Joly et JC Roujeau. Pemphigus. *IN: PIERRE GODEAU: TRAITE DE MEDECINE. 4th ed. Paris: Flammarion, Médecine-Sciences, 2004: 761-763*

⁹ Agbo-Godeau S, Szpirglas H. Aftoses buccales. *IN: Thérapeutique dermatologique, Médecine-Sciences Flammarion* 2001.

4.4. Target population

It is impossible to estimate the target population because of the wide range of indications. However, according to the experts, the theoretical target population of BUCCOBET 0.1mg for erosive oral lichen planus may be estimated to be 120,000 patients (1% of the population with oral lichen planus)^{10,11} including 20% who require topical corticosteroids.

4.5. Recommendations of the Transparency Committee

The Transparency Committee recommended inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indications and at the posology in the Marketing Authorisation.

4.5.1. Packaging: Appropriate to the conditions of prescription.

4.5.2. Reimbursement rate 35%.

¹⁰ Edwards PC, Kelsch R. Oral lichen planus: clinical presentation and management. J Can Dent Assoc.2002 Sep;68(8):494-9.

¹¹ Buser D , Meier E, Magnin P , Rees T.D. Lichen plan oral. 2nd part: possibilités de traitement et concept thérapeutique actuel. Rev Mens Suisse Odontostomatol .vol 111:2/2001