Examination of the file of the proprietary medicinal product registered for a period of 5 years from 06/11/2006 (Official Gazette of 31/01/2008).

LOMUDAL 20 mg/2 ml, solution for nebulisation
B/48 vials (CIP code: 324 119-3)

Applicant: SANOFI-AVENTIS FRANCE

sodium cromoglycate
ATC code: R03BC01

List II

Date of Marketing Authorisation (national procedure): 12/12/1980

Reason for request: Renewal of inclusion on the list of proprietary medicinal products refundable by National Health Insurance.
1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Sodium cromoglycate

1.2. Indications
“- Continuous anti-inflammatory treatment of mild persistent asthma.
Mild persistent asthma is defined by the existence of diurnal symptoms more than once a week and less than once a day and/or nocturnal symptoms more than twice a month, a PEF or an FEV\textsubscript{1} higher than 80% of the predicted values and a variability in the PEF of between 20 and 30%.
The variability in the PEF is evaluated over the day:
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\frac{\text{evening PEF} - \text{morning PEF}}{\frac{1}{2} (\text{evening PEF} + \text{morning PEF})}
\]
- Prevention of exercise-induced asthma.”

1.3. Dosage
The usual dosage is 4 vials daily divided into 4 aerosol therapy sessions.
In the event of destabilisation of the asthma or insufficient control of the symptoms, treatment with an inhaled corticoid should be quickly considered.
A unit dose that has been started should be used within 12 hours.

Method of administration
This solution of cromoglycate should be inhaled using a nebulisation device (nebuliser).”

2 REMINDER OF THE COMMITTEE’S OPINIONS AND THE CONDITIONS OF INCLUSION

Committee’s opinion of 23 March 2000 (re-assessment of the AB)
The actual benefit is moderate in children and low in adults.

Committee’s opinion of 4 October 2006 (re-inclusion)
“The data provided by the applicant are unlikely to modify the conclusions of the Transparency Committee’s previous opinion.
The data obtained from a knowledge of the pathologies concerned and the way in which they were managed have been taken into account. They are unlikely to modify the actual benefit compared with that mentioned in the Transparency Committee’s previous opinion.
The actual benefit provided by this proprietary medicinal product remains moderate in children and low in adults in the Marketing Authorisation’s indications.”
3.1. **ATC Classification (2011)**

- **R** Respiratory system
- **R03** Drugs for obstructive airway diseases
- **R03B** Other drugs for obstructive airway diseases, inhalants
- **R03BC** Anti-allergic agents, excluding corticoids
- **R03BC01** Cromoglicic acid

3.2. **Medicines in the same therapeutic category**

3.2.1. **Strictly comparator medicines**

LOMUDAL 20 mg/2 ml is the only sodium cromoglycate proprietary medicinal product presented in the form of a solution for nebulisation indicated in mild persistent asthma and in exercise-induced asthma.

3.2.2. **Not strictly comparator medicines**

These are other LOMUDAL proprietary medicinal products:
- LOMUDAL 5 mg/dose, suspension for inhalation in a pressurised container
- LOMUDAL 20 mg, powder for inhalation

Although included on the list of proprietary medicinal products reimbursed by National Insurance, a request was made to delist these medicinal products, concerning which the Transparency Committee issued a favourable opinion (Committee opinion dated 4 July 2007).

3.3. **Medicines with a similar therapeutic aim**

The other medicines indicated in asthma: short-acting and long-acting beta-2 agonist bronchodilators, anticholinergic bronchodilators, theophylline and its derivatives, inhaled corticoids.
4.1. Efficacy
The applicant has provided six studies published in the literature.

4.1.1. Asthma in children

Cochrane meta-analysis (2010): cromoglycate versus placebo\(^1\)

This is an update of the review published in 2003, previously referenced in the re-inclusion file of 2006.
Twenty-three controlled, randomised, double-blind studies that had evaluated the efficacy of cromoglycate versus placebo in the basic treatment of asthma in children (0-18 years) and published up to October 2009 were selected. The percentage of symptom-free days, the main judgement criterion, was evaluated in four studies. No significant difference between cromoglycate and placebo was revealed (p = 0.06). Furthermore, the scope of the results of this meta-analysis are limited in that the majority of the studies were carried out with small patient numbers and a publication bias is suspected.

Turpenein (2008): cromoglycate versus inhaled corticoids\(^2\)

This randomised study on children recently diagnosed as having asthma compared the efficacy and the effect on growth of three treatment regimens:
- continuous budesonide: continuous administration of budesonide, 400 µg twice daily for 1 month, followed by 200 µg twice daily from the 2\(^{nd}\) to the 6\(^{th}\) month, then 100 µg twice daily from the 7\(^{th}\) to the 18\(^{th}\) month.
- intermittent budesonide: 400 µg twice daily during months 1 to 6, then only in the event of exacerbation during months 7 to 18.
- cromoglycate: 10 mg three times daily for 18 months.

The budesonide groups received the treatment as double-blind; the treatment with cromoglycate was open-label.
The main assessment criterion was peak expiratory flow (PEF) measured in the morning.

Results:
After 6 months, no significant difference was observed in the morning PEF between the three groups.

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\(^1\) Van Der Wouden JC, Uijen JHJM, Bernsen RMD, Tasche MJA, De Jongste JC, Ducharme F. Inhaled sodium cromoglycate for asthma in children. *Cochrane Database Syst. Rev.* 2010

Zielen (2006): cromoglycate versus inhaled corticoids

This randomised, double-blind study evaluated the efficacy of inhaled budesonide and cromoglycate in asthmatic children aged less than 36 months. The 3-month treatment period was extended with a 6-month follow-up period (without the treatments in the study). The primary efficacy endpoint was the exacerbation rate at 3 months.

Results: 82 children of 18 months average age (11.6-31.2) were included. The exacerbation rates at 3 months were lower in the budesonide group (5.4%) than in the cromoglycate group (31.7%, p = 0.003). After the follow-up period without treatment for 6 months, these rates were 30% and 49% respectively without any statistically significant difference (p = 0.062).

4.1.2. Cochrane meta-analysis in adult and childhood asthma

Cromoglycate versus inhaled corticoids

This meta-analysis included the controlled randomised studies that had compared the efficacy of the inhaled corticoids with that of cromoglycate in the basic treatment of persistent adult or childhood asthma. The main judgement criterion was the occurrence of exacerbations, defined as the number or proportion of patients with asthmatic episodes, asthma attacks or attacks requiring the use of systemic corticoids.

Results: 17 studies that had included 1,279 children and 8 studies that had included 321 adults were used for the analysis. In the paediatric population, the average number of exacerbations per patient per year was analysed in one study only. The occurrence of exacerbations when using inhaled corticoids was less than when using cromoglycate with a difference of -1.18 (95% CI = [-2.15 ; -0.21], p = 0.017). A difference which was also significant was revealed in favour of the inhaled corticoids in the symptom scores and use of bronchodilators. There was no difference in the number of symptom-free days, school absenteeism, nocturnal symptoms or quality of life. Out of 15 studies that had studied ventilatory functional parameters, the improvement in the average FEV1 was greater with the inhaled corticoids than with cromoglycate, as was the improvement in the PEF.

In the adult population, one study evaluated exacerbations, the main judgement criterion of the meta-analysis. There was no difference between the inhaled corticoids and cromoglycate groups in this criterion: -3.30 exacerbations/patient/6 months (95% CI = [-5.62; -0.98], p = 0.0053).

4.1.3. Exercise-induced asthma

Cowan (2010): cromoglycate versus formoterol versus montelukast

This randomised, double-blind, cross-over study compared the efficacy of cromoglycate with that of formoterol and that of montelukast in patients with exercise-induced asthma with a rate of inhaled nitrogen monoxide lower than 35 ppb. This study is part of a broader study, whose rationale was based on adaptation of the treatment to the phenotype of the patient, classified as a strong exhaler or weak exhaler of nitrogen monoxide, a marker of inflammation of the airways. The patients whose exhaled nitrogen monoxide was higher than 35 ppb were treated with inhaled fluticasone; the patients

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whose rate of exhaled nitrogen monoxide was lower than 35 ppb received one of the three treatments in a cross-over trial.

The efficacy endpoints were the percentage of patients who had a reduction by half in the percentage decrease in the FEV$_1$ (definition of the responder patients) and a reduction in the bronchial reactivity to mannitol (expressed by a doubling or more of the dose of mannitol causing a decrease in the FEV$_1$ of 15%). The patients were treated for two weeks, with a week of wash-out separating each period of treatment. The parameters were evaluated at the end of each period.

Results: Out of 39 patients who had bronchial hyper-reactivity to mannitol, 19 had a rate of exhaled nitrogen monoxide lower than 35 ppb. These 19 patients, aged between 14 and 38, were randomised and received either cromoglycate or formoterol or montelukast for two weeks. A wash-out period of one week separated each treatment period.

In terms of responders, no significant difference was observed between the groups: 50% with cromoglycate, 53% with formoterol and 47% with montelukast.

Likewise, no significant difference was observed in terms of reduction of bronchial hyper-reactivity: 63% with cromoglycate, 61% with formoterol and 47% with montelukast. The scope of the results of this study is limited because of the small number of patients.

4.2. Tolerance
The pharmacovigilance data (PSUR covering the periods from 2 February 2006 to 1 February 2007, from 2 February 2007 to 1 February 2008 and from 2 February 2008 to 1 February 2009) did not disclose any sign of adverse effects. No modification in the sections “Undesirable effects”, “Special warnings and precautions for use” and “Contraindications” has occurred since the previous examination by the Transparency Committee.

According to the SPC, the undesirable effects that might occur with LOMUDAL are:
- Possibility of allergic reactions of the skin rash or pruritus type.
- Cases of isolated dysuria have been reported on rare occasions.
- In the long-term, cases of pulmonary infiltrates together with hypereosinophilia have been reported which can also be attributed to the asthmatic disease itself.

4.3. Conclusion
The five studies provided (two of which were meta-analyses), which evaluated the efficacy of sodium cromoglycate in asthma in children and adults, do not disclose any advantage of sodium cromoglycate over the use of inhaled corticoids which are the treatments currently recommended in the basic treatment of persistent asthma.

The study on exercise-induced asthma included too few patients to conclude on the comparison between sodium cromoglycate, formoterol and montelukast.

5 DRUG USAGE DATA

According to the IMS data (cumulative rolling prescription August 2011), the prescriptions of LOMUDAL 20 mg/2ml are too low for inclusion in the panel.
6.1. Re-assessment of the actual benefit

Continuous treatment of mild persistent asthma:

Persistent asthma is characterised by progression to a disability and/or degradation in quality of life. In exceptional cases, it may affect the patient’s vital prognosis. This proprietary medicinal product is intended as a symptomatic treatment. The efficacy/adverse effects ratio of this proprietary medicinal product in this indication is modest. The basic treatment of mild persistent asthma is based on low-dose inhaled corticoids in monotherapy or in combination with montelukast. LOMUDAL 20 mg/2 ml no longer has a place in the treatment strategy.

There are more effective therapeutic drug alternatives. Consequently, the actual benefit from LOMUDAL 20 mg/2 ml in this indication, taking into account the available alternatives, is insufficient to be covered by National Insurance.

Prevention of exercise-induced asthma:

Exercise-induced asthma is characterised by progression to a disability and/or degradation in the quality of life. In exceptional cases, it may affect the patient’s vital prognosis. This proprietary medicinal product is intended as a preventive treatment. The efficacy/adverse effects ratio of this proprietary medicinal product in this indication is modest.

The preventive treatment of exercise-induced asthma is based on the short-acting and long-acting beta-2 agonists and montelukast. LOMUDAL 20 mg/2 ml no longer has a place in the treatment strategy.

There are more effective therapeutic drug alternatives. Consequently, the actual benefit from LOMUDAL 20 mg/2 ml in this indication, taking into account the available alternatives, is insufficient to be covered by National Insurance.

6.2. Transparency Committee recommendations

The transparency Committee does not recommend inclusion on the list of medicines refundable by National Health Insurance.