HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

4 January 2012

Examination of the dossier for a medicinal product included for a 5-year period starting on 7 January 2006 (Official Gazette of 25 October 25 2007)

RHINOFLUIMUCIL, nasal spray solution
10 ml bottle (CIP code: 326 371-1)

Applicant : ZAMBON FRANCE

N-Acetylcysteine
Tuaminoheptane (sulphate)
Benzalkonium (chloride)

List II

Date of Marketing Authorisation: 22 April 1983
Revision: 25 April 2005 (harmonisation of SPCs for decongestant vasoconstrictors following the pharmacovigilance survey)

Reason for request: Renewal of inclusion on the list of medicines refundable by National Health Insurance.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

N-Acetylcysteine
Tuaminoheptane (sulphate)
Benzalkonium (chloride)

1.2. Indications

“Local symptomatic treatment of nasopharyngeal conditions with excessive mucosal secretion”

1.3. Posology and method of administration

"Adults: 2 sprays 3 to 4 times a day
Children (over 30 months): 1 spray 1 to 2 times a day.”

It should be noted that the marketing authorisation committee on 25 February 2010 re-evaluated the risk/benefit ratio of RHINOFLUIMUCIL as unfavourable in children under 15 years. Consequently, like other nasal decongestant vasoconstrictors, RHINOFLUIMUCIL is now contraindicated in children and adolescents under 15 years. The amendment to the SPC has not yet been received.

2 REVIEW OF THE COMMITTEE'S OPINIONS AND CONDITIONS OF INCLUSION

Committee Opinion of 30 November and 14 December 1983

"New combination in the form of nasal drops, the advantage of which, compared with the class of sulphur-containing aqueous solutions containing an antiseptic combined with a vasoconstrictor, would be the absence of rebound and habituation vasoconstrictor effect." This presumed advantage needs to be verified after use.

The Transparency Committee proposes inclusion at a reimbursement rate of 40% on the list of medicines refundable by National Insurance and on the list of medicines approved for use by hospitals and various public services."

Opinion of the Committee of 29 February 1984

"Following the ARSAC hearing, the Committee confirms that currently no rebound effect is observed during short-term treatment for an acute pathology."

Committee Opinion of 3 April 1991 and 18 June 1997

"The Transparency Committee recommends continued inclusion in all the indications and at the dosages in the Marketing Authorisation."

Opinion of the Committee of 27 September 2000

"The actual benefit of RHINOFLUIMUCIL is low.
The Transparency Committee recommends continued inclusion in all the indications and at the dosages in the Marketing Authorisation."

Opinion of the Committee of 6 September 2006

"The AB of this medicinal product remains low in the indication of the marketing authorisation.
The Transparency Committee recommends continued inclusion on the list of medicines refundable by National Insurance in the indications and at the dosages in the Marketing Authorisation.

Opinion of the Committee of 3 January 2007

"The condition covered by this medicinal product is not serious.
This medicinal product is a symptomatic treatment.
The efficacy/safety ratio of this medicinal product is modest.
This medicinal product is an adjunctive medication.
There are numerous alternatives. However, RHINOFLUIMUCIL is the only vasoconstrictor indicated in children as young as 30 months.
The actual benefit of RHINOFLUIMUCIL is low.

The Transparency Committee recommends provisional continued inclusion on the list of medicines refundable by National Insurance pending re-assessment of the risk/benefit ratio of the product by the marketing authorisation committee."

3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2011)

R:	Respiratory system
R01:	Nasal preparations
R01A:	Decongestants and other nasal preparations for topical use
R01AB:	Sympathomimetics, combinations excl. corticosteroids
R01AB08:	Tuaminoheptane

3.2. Medicines in the same therapeutic category

These are nasal and oral decongestant preparations containing an alpha sympathomimetic vasoconstrictor (see the table on the next page).

3.3. Medicines and treatments with a similar therapeutic aim

Other medicines indicated in symptomatic treatment of rhinitis:

- RHINOTROPHYL (ethanolamine tenoate), indicated in local adjuvant treatment of conditions of the nasopharyngeal mucosa (insufficient AB),
- solutions for nasal irrigation.

Nasal and oral decongestant preparations containing an alpha sympathomimetic vasoconstrictor:

Route of administration	Medicinal product	Active ingredient(s)	Prescription conditions	AB	Indication
Non-combined vasoconstrictors					
Nasal use	ATURGYL	oxymetazoline	List II	low	Local short-term symptomatic treatment of congestive and inflammatory states during acute rhinitis in adults and adolescents over 15 years
	PERNAZENE	oxymetazoline	List II	low	
Oral use	SUDAFED	pseudoephedrine	Not listed	low	Treatment during colds in adults and adolescents over 15 years: - of blocked nose - of clear nasal discharge
Combined vasoconstrictors					
Nasal use	DERINOX	naphazoline prednisolone	List II	Low*	Local short-term symptomatic treatment of congestive and inflammatory states during acute rhinitis in adults and adolescents over 15 years
	DETURGYLONE	oxymetazoline prednisolone	List I	Low*	
	RHINAMIDE	ephedrine benzoic acid	List II	Insufficient, pending re-assessment of the class*	
	RHINOFLUIMUCIL	N-acetylcysteine tuaminoheptane benzalkonium	List II	Low, pending re-assessment of the risk/benefit ratio in children by the marketing authorisation committee*	Local symptomatic treatment of nasopharyngeal conditions with excessive mucosal secretion (adults and children > 30 months)
Oral use	RHINADVIL	pseudoephedrine ibuprofen	Not listed	Low*	In adolescents (15-17 years) and adults, in the symptomatic treatment of nasal congestion associated with acute presumably viral rhinosinusitis with headache and/or fever
	RHINUREFLEX	pseudoephedrine ibuprofen	Not listed	Low*	

*: AB as of 21 September 2011 (initial examination). The actual benefit of these proprietary medicinal products was re-evaluated at the same time as that of RHINOFLUIMUCIL. The Transparency Committee took the view that their actual benefit was insufficient.

4 UPDATE ON THE DATA AVAILABLE SINCE THE PREVIOUS OPINION

4.1. Efficacy

The company has provided one randomised, double-blind study conducted in children comparing the efficacy of RHINOFLUIMUCIL to placebo in nasal obstruction.

Inclusion criteria: children aged 30 months to 6 years with infectious rhinitis presumed to be of viral origin with nasal obstruction defined as the presence of mouth breathing AND absence of condensation (or a faint spot) on a Glatzel mirror after nasal irrigation with physiological saline by the investigator.

Treatments:
- RHINOFLUIMUCIL: 1 spray in each nostril, morning and evening before bedtime for 5 days.
- Placebo: same

Primary efficacy endpoints:
- percentage of patients with nasal obstruction demonstrated by a score ≤ 2 in the Glatzel mirror (sum of the scores for each nostril) and mouth breathing 10 min after the first instillation of the study product;
- assessment by the parents of the presence of breathing noise during night sleep 1 hour after falling asleep (resolution of breathing noises modelled by a Kaplan-Meier curve).

Results:
A total of 209 patients were included; the ITT population was 206 patients (104 in the RHINOFLUIMUCIL group and 102 in the placebo group), defined as patients for whom an overall Glatzel score was obtained 10 min after the first instillation of the study product.
The mean age of the patients was 4 ± 1. Before the start of treatment, 48% of patients had a Glatzel score of 2, 40% had a score of 1 and 10% had total nasal obstruction.

No significant difference was observed between RHINOFLUIMUCIL and placebo in terms of percentage of patients with nasal obstruction: 12% of patients had no nasal obstruction with RHINOFLUIMUCIL versus 11.8% with placebo (p = 0.87)

Night breathing noises decreased gradually with no statistically significant difference between the two groups.

4.2. Adverse effects/Tolerance

A first national pharmacovigilance survey looking at adverse effects occurring with nasal and oral decongestants was carried out in 2001. As a result of this survey, the SPCs of all decongestants were harmonised to take account of the exceptional occurrence of haemorrhagic stroke, stating the contributing factors, the lack of additional efficacy and risks associated with the concomitant use of two vasoconstrictors, and contraindicating them in children under 15 years.

Following the report of new cases of serious adverse effects occurring since this survey, in particular myocardial infarction in young subjects with no risk factors, a new national pharmacovigilance survey was conducted in 2007-2008 on the cardiovascular and CNS adverse effects of vasoconstrictors used as oral and nasal decongestants in ENT medicine.

Examination of the results of this latest survey showed that these products caused serious cardiovascular effects such as myocardial infarction, arrhythmia, transient ischaemic attack, ischaemic stroke and cerebral haemorrhage. These effects occur for the most part in situations of misuse (combination of two vasoconstrictors, not adhering to the treatment duration and dosage) and/or in patients with risk factors. However, the incidence of these adverse effects remains low in relation to the number of patients exposed.

Given the pharmacological properties of vasoconstrictors (indirect or alpha sympathomimetics) and the serious adverse effects identified during pharmacovigilance surveys, the SPCs of all vasoconstrictors used as oral or nasal decongestants in ENT medicine were again harmonised by introducing the following changes (see appended details of changes):

- emphasising that it is a treatment reserved for adults and adolescents over 15 years;
- adding information alerting prescribers, pharmacists and patients to the danger and contraindication of combining two vasoconstrictors regardless of their route of administration;
- adding a warning that the treatment duration must be adhered to;
- adding a warning of the need to stop treatment if cardiovascular adverse effects occur;
- updating the contraindicated and non-recommended drug interactions;
- updating the cardiovascular adverse effects

RHINOFLUIMUCIL did, however, retain an indication in children over 30 months due to its seemingly better tolerance based on pharmacovigilance data and pending specific efficacy and tolerance data in this age bracket. On the basis of new data obtained, the marketing authorisation committee on 25 February 2010 took the view that the risk/benefit ratio of RHINOFLUIMUCIL had become unfavourable in children and adolescents under 15 years. The amendment to the SPC has not yet been received.

4.3. Conclusion

A randomised, double-blind study evaluated the efficacy of RHINOFLUIMUCIL versus placebo in 206 children aged from 30 months to 6 years with infectious rhinitis presumed to be of viral origin. No statistically significant difference between the two treatments was observed for either of the two primary efficacy endpoints, nasal obstruction and resolution of night breathing noises.

As was the case for other vasoconstrictors used as nasal decongestants, the risk/benefit ratio of RHINOFLUIMUCIL was deemed unfavourable in children and adolescents under 15 years by the marketing authorisation committee on 25 February 2010. The amendment to the SPC has not yet been received.

5 DATA ON USE OF THIS PRODUCT

According to IMS-EPPM data, RHINOFLUIMUCIL was the subject of 6 million prescriptions in one year (moving annual total to May 2011). The mean prescribed duration of treatment was 6.7 days and the mean daily dose was 8.3 sprays.

6 TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Re-assessment of actual benefit

Acute nasopharyngitis most often affects children. It is mainly of viral origin, benign and self-limiting. It is often accompanied by involvement of the sinus mucosa in addition to the nasal and pharyngeal mucosa, leading to a congestive state of the upper airways.

This medicinal product is a symptomatic treatment.

Due to the risk, although rare, of serious cardiovascular adverse effects associated with the presence of tuaminoheptane, the efficacy/safety ratio of this proprietary medicinal product is low.

This product combines a vasoconstrictor, tuaminoheptane, with a mucolytic, N-acetylcysteine, and an antiseptic, benzalkonium chloride, and yet, according to the AFSSAPS recommendations[1] (2005), whereas tuaminoheptane can be used in the symptomatic treatment of acute uncomplicated nasopharyngitis alongside nasal irrigation and nasal suctioning or blowing and treatment with an antipyretic, mucolytics and antiseptics are not recommended in this clinical situation. The efficacy of this fixed combination has not been shown to be greater than that of tuaminoheptane alone.
Furthermore, although RHINOFLUIMUCIL is still indicated in children aged 30 months or older, unlike other vasoconstrictors indicated only in adolescents over 15 years, there are no clinical efficacy or tolerance data supporting the use of RHINOFLUIMUCIL in children aged 30 months or older.
Consequently, this proprietary medicinal product is of no therapeutic benefit.

There are therapeutic alternatives containing a non-combined vasoconstrictor.

The actual benefit of RHINOFLUIMUCIL, nasal spray solution, is henceforth insufficient for reimbursement by National Insurance.

6.2. Transparency Committee recommendations

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

The transparency Committee recommends deletion from the list of medicines refundable by National Health Insurance and the list of medicines approved for use by hospitals and various public services.
The Committee requests that, for all medicinal products containing a nasal decongestant vasoconstrictor, the prescription and dispensing conditions be redefined by AFSSAPS and harmonised.

[1] General antibiotic therapy in current practice in upper respiratory tract infections in adults and children, AFSSAPS, October 2005.