TRANSPARENCY COMMITTEE

OPINION

16 February 2011

Review of the dossier for the proprietary medicinal products included for a period of 5 years by Order of 27 June 2005 (Journal Officiel of 12 July 2005)

**PULMOZYME 2500 U/2.5 ml, nebuliser solution**
B/6 x 2.5 ml (CIP code: 364 674-8)
B/30 x 2.5 ml (CIP code: 364 675-4)

**Applicant: ROCHE**

Deoxyribonuclease 1 (dornase alfa)
ATC code: R05CB13

List I
Medicine for initial six-monthly hospital prescription only.
Renewal not restricted.

Date of Marketing Authorisation: 10 March 1994
Amendment to the Marketing Authorisation: 8 October 2009 (amendment of the “Adverse effects” section)

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

1.1. Active ingredient
Deoxyribonuclease 1 (dornase alfa)

1.2. Indication
Treatment of bronchial congestion in cystic fibrosis patients with a forced vital capacity (FVC) of greater than 40% of predicted and over 5 years of age to improve pulmonary function.

1.3. Dosage
“2.5 mg (corresponding to 2500 U) deoxyribonuclease l by inhalation once daily. Inhale the contents of one ampoule (2.5 ml of solution) undiluted using a recommended jet nebuliser/compressor system (see SPC. Methods of handling).

Some patients over the age of 21 years may benefit from twice daily dosage.

Most patients gain optimal benefit from regular daily use of PULMOZYME. In studies in which PULMOZYME was given in an intermittent regimen, improvement in pulmonary function was lost on cessation of therapy. Patients should therefore be advised to take their medication every day without a break.

Patients should continue their regular medical care, including their standard regimen of chest physiotherapy.

Administration can be safely continued in patients who experience exacerbation of respiratory tract infection.

Safety and efficacy have not yet been demonstrated in patients under the age of 5 years, or in patients with forced vital capacity less than 40% of predicted.”

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

Transparency Committee Opinion of 8 June 1994

Application for inclusion on the list of medicines approved for hospital use:

Actual benefit:

The actual benefit of PULMOZYME (improvement in pulmonary function and reduction in infectious exacerbations) demonstrated in several short-term clinical studies needs to be confirmed in the long term. In addition, short-term tolerance needs to be verified in the long term, particularly as regards immunoallergic effects.

Marketing authorisation was granted on the basis of interim efficacy criteria demonstrating its activity in a serious disease without major treatment options. Additional studies have been requested, in children by age group and adults, with a follow-up:
- of pulmonary function including exploration of the bronchioli and the pulmonary interstices
- of the weight curve
- of the rate of anti-DNase antibodies and IgE
- of monthly bacteriology.

The Transparency Committee would also like to know the results of these.

At the end of these studies, it would be desirable to be able to evaluate the actual benefit provided by PULMOZYME, particularly in terms of the reduction in patients’ functional disability and therefore in terms of quality of life or indeed survival.

Despite these shortcomings, given the severity of the disease (median patient survival 20 to 25 years) and the lack of any active treatment for the symptoms of cystic fibrosis, the arrival of a new medicine which can improve pulmonary function is an important contribution.

**Transparency Committee Opinion of 24 November 2004**

Request for inclusion on the list of medicines refundable by National Health Insurance:

**Actual benefit:**

Cystic fibrosis is a serious disease which is life-threatening for patients. This proprietary medicinal product is intended as a symptomatic treatment.

The efficacy of PULMOZYME can be described as modest in terms of short-term improvement in pulmonary function, less marked longer-term decline in pulmonary function and the reduction in respiratory exacerbations. The safety profile of this product is generally good.

There are no similar medicines.

**Public health benefit:**

In terms of public health, while cystic fibrosis is nowadays a serious incurable disease, burden of this disease is moderate because of its low prevalence.

Since no drug treatment has proved efficacy in the bronchial congestion of cystic fibrosis patients, the therapeutic need is not totally covered.

According to the data supplied, PULMOZYME has not demonstrated any impact on mortality or on quality of life. The expected reduction in terms of morbidity, given the current therapeutic agents, is low.

Transferability is acceptable.

Consequently, in the light of the available data, the proprietary medicinal product PULMOZYME is expected to have an impact on public health.

The level of this public health impact is low.

The actual benefit of PULMOZYME is substantial.

**Improvement in actual benefit (IAB):**

PULMOZYME provides a moderate improvement in actual benefit (level III) in the management of cystic fibrosis patients over 5 years of age with a forced vital capacity (FVC) greater than or equal to 40% of predicted.
Transparency Committee Opinion of 16 February 2005

Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use for PULMOZYME 2500 U/2.5 ml, nebuliser solution, box of 30 ampoules:

The actual benefit is substantial.

This proprietary medicinal product does not provide an improvement in actual benefit (IAB V) compared to PULMOZYME 2500 U/2.5 ml, box of 6 ampoules.

3 SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2010)

R : Respiratory system
R05 : Cough and cold preparations
R05C : Expectorants, excl. combinations with cough suppressants
R05CB : Mucolytics
R05CB13 : Dornase alfa (deoxyribonuclease)

3.2. Medicines in the same pharmaco-therapeutic category

There is no medicine in the same therapeutic category with demonstrated efficacy in the treatment of bronchial congestion in cystic fibrosis patients.

3.3. Medicines with a similar therapeutic aim

None.

4 UPDATE ON THE DATA AVAILABLE SINCE THE PREVIOUS OPINION

The company has submitted new data to support its application:

- a Cochrane meta-analysis, to determine whether the use of dornase alfa in cystic fibrosis patients was associated with improved mortality and morbidity compared to placebo or other mucolytics and to identify any adverse events associated with its use. (Jones, 2010\(^1\));

- an analysis of data from the Epidemiologic Registry of Cystic Fibrosis (ERCF) that compared the long-term effectiveness (1 and 2 years) in routine clinical practice of dornase alfa in terms of pulmonary function and frequency of acute pulmonary exacerbations (Hodson, 2003\(^2\));

- a preliminary analysis of data from the North American Cystic Fibrosis Registry that characterized the rate of decline of forced expiratory volume in 1 second (FEV\(_1\)) in patients who received dornase alfa continuously for 2 years, compared to the 2 years


before the start of treatment and compared to patients who had never received dornase alfa (Konstan, 20073 and 20084);

- an efficacy study that evaluated the long-term effect of dornase alfa on inflammation markers in the bronchoalveolar lavage fluid (Paul, 20045); given the non-comparative methods of this study and the choice of a non-clinical endpoint, this study will not be described below;

- an analysis of safety data for the 6829 patients treated with dornase alfa from the Epidemiologic Registry of Cystic Fibrosis (ERCF) which included 15,979 patients (McKenzie, 20076).

4.1. Efficacy

Meta-analysis by Jones (2010)
The aim of this meta-analysis was to determine whether the use of dornase alfa in cystic fibrosis patients was associated with improved mortality and morbidity compared to placebo or other mucolytics and to identify any adverse events associated with its use. (Jones, 2010);

The analysis included all randomised comparative studies, published or unpublished, which compared dornase alfa to placebo or another mucolytic treatment in adult and children, of any age, with cystic fibrosis diagnosed clinically and by sweat or genetic testing.

The primary efficacy endpoints used were:
- Changes in lung function (FEV₁ and FVC) from baseline
- change from baseline in quality of life
- mean number of exacerbations
- number of deaths

These endpoints were evaluated at 1, 3, 6, 12 months and annually thereafter.

Results:
The searches identified 43 trials, of which 15 trials met the inclusion criteria, including a total of 2469 patients. Twelve studies compared dornase alfa with placebo or another treatment which in one study was hypertonic saline.

Data from 3 additional publications based on a study that evaluated the cost/efficacy ratio of dornase alfa were used.

| Table 1: Results in the primary endpoints for the comparison of dornase alfa (once a day) vs placebo |

---

4 Konstan MW. Dornase alfa progression of lung disease in cystic fibrosis. Pediatric Pulmonology 2008 :43 :S24-S28
## Comparison of dornase alfa versus placebo

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Duration</th>
<th>Number of studies</th>
<th>Number of patients</th>
<th>Difference or RR or odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>% variation in FEV₁ (relative)</td>
<td>1 month</td>
<td>4</td>
<td>248</td>
<td>Diff. = 9.92</td>
<td>[6.92; 12.93]*</td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td>1</td>
<td>320</td>
<td>Diff. = 7.30</td>
<td>[4.04; 10.56]</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>1</td>
<td>647</td>
<td>Diff. = 5.80</td>
<td>[3.99; 7.61]</td>
</tr>
<tr>
<td></td>
<td>1 month</td>
<td>1</td>
<td>80</td>
<td>Diff. = 1.00</td>
<td>[-13.93; 15.93]</td>
</tr>
<tr>
<td>Patients with exacerbations</td>
<td>2 years</td>
<td>1</td>
<td>410</td>
<td>Diff. = 3.24</td>
<td>[1.03; 5.45]</td>
</tr>
<tr>
<td>% variation in FVC (relative)</td>
<td>1 month</td>
<td>4</td>
<td>241</td>
<td>Diff. = 9.49</td>
<td>[6.34; 12.63]*</td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td>1</td>
<td>318</td>
<td>Diff. = 5.10</td>
<td>[1.23; 8.97]</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>1</td>
<td></td>
<td>Diff. = 3.80</td>
<td>[2.62; 4.98]</td>
</tr>
<tr>
<td>% variation in FVC (absolute)</td>
<td>2 years</td>
<td>1</td>
<td>410</td>
<td>Diff. = 0.70</td>
<td>[-1.24; 2.64]</td>
</tr>
<tr>
<td>Number of patients with exacerbations</td>
<td>6 months</td>
<td>1</td>
<td>647</td>
<td>RR = 0.81</td>
<td>[0.61; 1.06]</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>470</td>
<td>RR = 0.71</td>
<td>[0.49; 1.02]</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>1 month</td>
<td>4</td>
<td>253</td>
<td>OR = 5.30</td>
<td>[0.25; 114.47]*</td>
</tr>
<tr>
<td></td>
<td>3 months</td>
<td>1</td>
<td>320</td>
<td>OR = 1.57</td>
<td>[0.55; 4.52]</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>1</td>
<td>647</td>
<td>OR = 1.01</td>
<td>[0.06; 16.21]</td>
</tr>
<tr>
<td></td>
<td>2 years</td>
<td>1</td>
<td>470</td>
<td>OR = 0.0</td>
<td>[0.0; 0.0]</td>
</tr>
</tbody>
</table>

* : Statistically significant heterogeneity test

A statistically significant difference was shown in favour of dornase alfa (once a day) compared to placebo in the mean FEV₁ and FVC measured at 1 month, 3 months, 6 months and 2 years of treatment. In these same periods, no statistically significant difference was observed in the number of patients with exacerbations or in the number of deaths (see Table 1).

On the other hand, no statistically significant difference in terms of mean percentage change in FEV₁ and quality of life has been shown between dornase alfa (once a day) and hypertonic saline.

The impact of these results is limited given:

- the great heterogeneity of the results, probably due to the heterogeneity of the studies, particularly for the patient inclusion criteria (severity of disease, patients’ age);
- the poorly specified method (particularly the double-blind randomisation method), except for two studies;
- the lack of pooled data for most of the studied parameters and times.
European Registry of Cystic Fibrosis (Hodson, 2003)
The aim was to show whether dornase alfa could have an long-term effectiveness in routine clinical practice in terms of pulmonary function (FEV₁) and frequency of acute pulmonary exacerbations in cystic fibrosis. The patients analysed were those included in this registry between January 1994 and November 1998 who had data collected over 2 years.

Results for FEV₁ (n = 2,023):
The change in FEV₁ compared to baseline was 2.5% after 1 year and 0.3% after 2 years in patients treated with dornase alfa, and -1.1% after 1 year and -2.3% after 2 years in patients untreated with dornase alfa. The difference between treated and untreated patients was 3.6% (95% CI = [1.8; 5.3]) at 1 year and 2.5% (95% CI = [0.7; 4.4]) at 2 years.
An analysis by age group showed that patients between 6 and 13 years appeared to benefit most from the treatment: change of 3.6% at 1 year in the treated group vs -1.3% in the untreated group and change of +2.7% at 2 years in the treated group vs -1.7% in the untreated group.

Results for acute pulmonary exacerbations (n = 4,299):
The variation in the annual incidence of exacerbations was -0.19 in the dornase alfa group and +0.06 in the untreated group, a difference of -0.25 (95% CI = [-0.12; -0.39]). This difference represents one exacerbation avoided every 4 years.

North American Registry of Cystic Fibrosis (Konstan, 2007 and 2008)
The aim was to characterize the rate of decline of FEV₁ in patients between 8 and 38 years of age, whether or not treated with dornase alfa. Patients when initially treated with dornase alfa (index event) were selected if they had been enrolled in the registry for the prior 2 years with no documented use of dornase alfa (baseline period), and remained on dornase alfa for ≥ 80% of time for the following 2 years (follow-up period). Among the 6,697 patients included, 2,706 were in the dornase alfa group and 3991 in the group without dornase alfa.
At the index event, the FEV₁ was 80.5% of predicted in the dornase alfa group and 86.7% in the untreated group. After 2 years, an improvement in FEV₁ of 2.66% was observed in the dornase alfa group and not in the group without dornase alfa.
These preliminary results need to be confirmed.

4.2. Adverse effects

4.2.1. Summary of product characteristics (update of 8 October 2009)
“The adverse effects data reflect the clinical trial and post-marketing experience of using PULMOZYME at the recommended dose regimen.
Adverse effects attributed to PULMOZYME are rare (< 1/1000). In most cases, the adverse effects are moderate and transient in nature and do not require alterations in PULMOZYME dosage.

Eye disorders:
Conjunctivitis.

Respiratory, thoracic and mediastinal disorders:
Dysphonia, dyspnea, pharyngitis, laryngitis, rhinitis (all non-infectious).

Gastrointestinal disorders:
Dyspepsia.

Skin and subcutaneous tissue disorders:
Rash, urticaria.

General disorders and administration site conditions:
Chest pain (pleuritic/non-cardiac), pyrexia.
**Investigations:**
Reduction in pulmonary function as measured by the results of functional investigations.

Patients who experience adverse events common to cystic fibrosis can, in general, safely continue administration of PULMOZYME.

In clinical trials, few patients experienced adverse events resulting in permanent discontinuation from dornase alfa and the discontinuation rate was observed to be similar between placebo (2% of patients) and dornase alfa (3% of patients).

Upon initiation of dornase alfa therapy, as with any aerosol, pulmonary function may decline and expectoration of sputum may occur at the start of treatment with dornase alfa.

Less than 5% of patients treated with dornase alfa have developed antibodies to dornase alpha and none of these patients have developed IgE antibodies to dornase alfa. Improvement in pulmonary function tests has still occurred even after the development of antibodies to dornase alfa”.

**4.2.2. European epidemiological registry (McKenzie, 2007)**
This registry included, in 9 European countries including France, for a period from 1994 to 2000, 15,979 patients with cystic fibrosis, 6,829 of whom were treated with PULMOZYME.

Half the patients were less than 5 years old at the time of inclusion and it is thought that 96% of French patients were included during this period.

About half (48%) of the patients were treated with PULMOZYME at least once during the study. Of the 15,865 serious adverse events observed, 0.18% were regarded as possibly linked to PULMOZYME. Haemoptysis was the commonest adverse event, but of the 411 notified, only 19 (4.6%) were regarded as possibly linked to PULMOZYME. No death linked to PULMOZYME was reported.

**4.2.3. Pharmacovigilance**
During the period corresponding to the last PSURs (periods from 01/07/2004 to 30/04/2008 and from 01/05/2008 to 30/06/2009), it was estimated that 43,638 patients a year were treated with dornase alfa worldwide.

Of the 105 adverse effects linked to dornase alfa, the most commonly observed were: haemoptysis, cough and dysphonia (n = 31), chest pain, fever and malaise (n = 19), vomiting and diarrhoea (n = 14).

26 of these adverse effects were considered to be serious. The most commonly observed were: haemoptysis and pulmonary haemorrhage (n = 10), general disorders and abnormalities at the administration site, mainly malaise (n = 5), gastrointestinal disorders, mainly vomiting (n = 3).

Four cases of exposure during pregnancy were reported which did not cause any adverse effects and the outcome of the pregnancy was favourable in the 2 cases in which it was specified.

These data did not lead to any changes to the SPC.

**4.3. Conclusion**

A meta-analysis of 15 randomised, double-blind studies (2,469 patients) compared dornase alfa (once a day) to placebo or hypertonic saline (1 study) in adult and child patients with cystic fibrosis. A statistically significant difference has been shown in favour of dornase alfa compared to placebo in terms of mean FEV$_1$ and FVC measured at 1 month, 3 months, 6 months and 2 years of treatment. In these same periods, no statistically significant difference was observed in the number of patients with exacerbations or in the number of deaths. No statistically significant difference was seen between dornase alfa administered once a day and hypertonic saline in the percentage variation in FEV$_1$ and quality of life.
The impact of these results is limited because of the great heterogeneity of the results, probably linked to the heterogeneity of the studies, particularly in the patient inclusion criteria (severity of the disease, patients’ age), a poorly specified method (particularly the double-blind randomisation method) except for two studies and the absence of pooled data for most of the parameters and periods studied.

Analysis of the Epidemiologic Registry of Cystic Fibrosis showed an improvement in FEV$_1$ in patients treated for 2 years with dornase alfa whereas it declined in patients untreated with dornase alfa. The difference between the two groups in FEV$_1$ expressed as a % of predicted was 3.6% (95% CI = [1.8; 5.3]) at 1 year and 2.5% (95% CI = [0.7; 4.4]) at 2 years. A reduction in the number of exacerbations was shown in patients treated with dornase alfa (difference of -0.25 exacerbation per patient and per year compared to those untreated, i.e. one exacerbation avoided every 4 years; 95% CI = [-0.12; -0.39]). A similar result was produced by a preliminary analysis of data from the North American Registry of Cystic Fibrosis. After 2 years, the improvement in FEV$_1$ as a % of predicted was 2.66% in the dornase alfa group and absent in the group without dornase alfa.

All these results confirm the modest efficacy of dornase alfa in slowing down the long-term decline in lung function and in reducing the occurrence of exacerbations.

The tolerance data from the European Registry of Cystic Fibrosis and from pharmacovigilance are in accordance with the current SPC.

5 DRUG USAGE DATA

Cystic fibrosis is a rare disease; consequently, PULMOZYME is too little prescribed to feature on prescription panels.

6 TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Re-assessment of actual benefit

Cystic fibrosis is a serious disease which is life-threatening for patients.

This proprietary medicinal product is intended as a symptomatic treatment.

Public health benefit:
In terms of public health, while cystic fibrosis is a serious disease which is at present incurable, the burden of this disease is moderate because of its low prevalence. In the indication concerned it is low because of the small number of patients. Since, apart from this proprietary medicinal product, there is no drug treatment with proven efficacy in the bronchial congestion of cystic fibrosis patients, it can be considered that the therapeutic need is still not covered. According to the new data supplied, PULMOZYME has still not demonstrated any impact on mortality or on quality of life. In addition, the impact of PULMOZYME on morbidity does not seem to be confirmed in routine clinical practice. Consequently, in view of the new data available, the proprietary medicinal product PULMOZYME does not have any public health benefit.
On the basis of the available data, the efficacy of PULMOZYME can be described as modest in terms of short-term improvement in pulmonary function, less marked longer-term decline in pulmonary function and reduction in respiratory exacerbations. The adverse effects linked to treatment with dornase alfa are rare, moderate and transient. The efficacy/adverse effects ratio is moderate. There are no similar medicines. The actual benefit provided by PULMOZYME is moderate.

6.2. Therapeutic use

The management of patients with cystic fibrosis requires the intervention of a multidisciplinary team (treating doctor, specialised centres, paramedical team with a physiotherapist and a nurse). Treatment is symptomatic and necessary for life.

It is based on chest physiotherapy, suitable antibiotic therapy, an adequate calorie intake and external compensation of pancreatic failure.

Dietetic management consists of a high-calorie, lipid-normal diet, the use of lipid-soluble vitamins (A, D, E, K) and trace elements (iron, zinc, selenium), supplementation with sodium chloride and pancreatic extracts. Chest physiotherapy must be given daily. The antibiotic therapy is needed in the event of an exacerbation or a chronic infection.

Inhaled dornase alfa is one of the medicines for cystic fibrosis. It permits a modest improvement in pulmonary function and a minimal reduction in the number of exacerbations necessitating intravenous antibiotic therapy. It is recommended that the dornase alfa aerosol should be preceded by proximal bronchial drainage. Nebulisation must be followed by a chest physiotherapy session 30 minutes later.

The effect of dornase alfa disappears rapidly when treatment is stopped.

The clinical and functional action of PULMOZYME vary from one patient to another, and there is no means of predicting this response. According to experts, about 30% of patients are responders to treatment, particularly if it is started early in the development of the disease. The value of prescribing PULMOZYME will therefore have to be assessed for each patient and re-evaluated every 6 months. PULMOZYME must be stopped in the event of poor compliance.

The available clinical studies of treatments with inhaled corticosteroids or bronchodilators do not allow the recommendation of their systematic prescription. Beta-2-mimetic treatment can be offered in the event of exacerbations, or during a stable period in long-term treatment (with regular re-assessment of the clinical benefit) or for the nebulisation of short-acting beta-2-mimetics before starting the physiotherapy session, to improve bronchial drainage. The other treatments for respiratory disorders in cystic fibrosis are a short course of oral corticosteroids, after a 14-day course of antibiotics prescribed for an exacerbation, in cases where there is no clinical and/or functional improvement (expert opinion), or in cases of allergic pulmonary aspergillosis.

A lung or even liver transplant may be offered as a last resort in advanced forms.

---

6.3. Transparency Committee recommendations

The Transparency Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance.

Packaging: appropriate for the prescription conditions.

Reimbursement rate: 35%