HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

04 January 2006

Alfalastin 33.33 mg/mL, powder and solvent for an injectable solution
Vial of powder and 30 mL vial of solvent with transfer needle with filter (CIP code: 566 112-9)

Applicant: Laboratoire Français du Fractionnement et des Biotechnologies

Human alpha-1 antitrypsin

List I

Medicine for hospital prescription only.

Date of Marketing Authorisation: 8 July 2005 (French Marketing Authorisation)

Reason for application: Inclusion on the list of drugs approved for hospital use

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Human alpha-1 antitrypsin (AAT)

1.2. Background

Alfalastin is the only replacement therapy for serious forms of primary AAT deficiency in subjects with the PiZZ or PiSZ phenotype with pulmonary emphysema (rare disease). Alfalastin has benefited from the status of Temporary Authorisation for Use since 1995.

Human AAT has been marketed in North America and Germany for more than 15 years.

1.3. Indications

Alfalastin is the only replacement therapy for serious forms of primary AAT deficiency in subjects with the PiZZ or PiSZ phenotype with pulmonary emphysema.

1.4. Administration (dosage, method and route)

Treatment should be started as soon as possible after the onset of the first signs of emphysema. Treatment should be given:

- either continuously, especially in the case of very aggressive emphysema,
- or in separate courses during episodes of bronchopulmonary infection.

The only known factor for developing emphysema is continuous or recurrent exposure to airborne contaminants likely to increase intrapulmonary protease load. The patient must therefore stop smoking, and protection from any work-related airborne contaminants is strongly recommended.

A dose of 60 mg/kg of Alfalastin given by intravenous injection once a week will result in an AAT plasma concentration similar to that of subjects without a deficiency.

AAT concentration should be determined in treated patients once a month for the first six months of treatment, then every 3–4 months. The dose to be injected should then be corrected if necessary to maintain a minimum plasma concentration of between 11 µM (0.50 g/L) and 15 µM (0.70 g/L).

Method and route of administration

Alfalastin is a powder to be reconstituted immediately before use with water for injection, using the method described in the section "Instructions for use and handling".

Alfalastin should only be injected intravenously, in a single injection immediately after reconstitution, at a flow rate not exceeding 4 mL/min.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

B : BLOOD AND BLOOD-FORMING ORGANS
B02 : ANTIHAEMORRAGICS
B02A : ANTIFIBRINOLYTICS
B02AB : PROTEINASE INHIBITORS
B02AB02 : Alpha-1 antitrypsin

2.1 Medicines in the same therapeutic category

2.2.1 Comparator medicines

Not applicable

2.2.2 Comparisons that have been carried out

Not applicable

2.2 Medicines with a similar therapeutic aim

The other drugs indicated for the treatment of pulmonary emphysema are symptomatic drugs such as bronchodilators, combinations of bronchodilators and inhaled corticosteroids, and oral corticosteroids.

3 ANALYSIS OF AVAILABLE DATA

Five clinical trials were submitted in support of the application:

- one placebo-controlled trial (Dirksen A., 1999)
- two prospective comparative cohort studies (treated/untreated patients) (Seersholm N., 1997; AAT Deficiency Registry Study Group, 1998)
- one retrospective comparative cohort study (before/after treatment) (Wencker et al, 2001)
- one prospective non-comparative study assessing long-term safety (Wencker M., 1998)

3.1. Efficacy

Clinical trial by Dirksen A. (1999)

Aim : to compare decline in FEV1 in patients with the PiZZ phenotype receiving AAT or placebo.
Method: multicentre, double-blind, randomised, placebo-controlled trial.
Patients: 56 patients (mean age 47 years), former smokers, 66% of them male, with the PiZZ phenotype, with emphysema and moderate to severe bronchial obstruction (FEV1: 30-80%)
Baseline AAT concentration ≤ 11 µM.
Treatment:
AAT: infusion of 250 mg/kg every 28 days.
Placebo: albumin 4%
Follow-up 3–5 years.
Primary outcome: FEV1 measured every day at home and every 3 months during the consultation.

Results: There was no significant difference in FEV1 decline (post-bronchodilator) over time between the placebo (25.2 mL/year) and AAT (26.5 mL/year) groups.
From the 23rd or 24th day after infusion, most serum AAT concentration values were below the 11 µM threshold regarded as protective. However, it should be noted that the dose used in this trial was not consistent with the dose validated by the Marketing Authorisation (250 mg/kg 1x/month rather than 60 mg/kg 1x/week in the Marketing Authorisation).

Cohort studies:

● Two prospective cohort studies compared FEV1 decline over time in patients with a severe AAT deficiency, and deterioration in pulmonary function, whether treated with AAT not:

- Seersholm N. study (1997) carried out in 198 treated German patients and 97 untreated Danish patients.
  Mean follow-up was 3.2 years in the treated group and 5.8 years in the untreated group.
  Annual decline in FEV1 was significantly lower in patients treated with AAT (53 mL/year) than in untreated patients (74.5 mL/year), with a difference of 21.5 mL/year.

- "AAT Deficiency Registry Study Group" study (1998) in 1129 patients
  There was no difference between the treated and untreated groups in annual decline in FEV1. When baseline FEV1 was included in the statistical analysis, the difference observed between the groups was significant in favour of treatment with AAT in the subgroup of patients whose baseline FEV1 was between 35% and 49% of the theoretical value (difference of 26.8 mL/year [CI 95% 2.8 ; 50.9]).

  NB: the results of these studies should be interpreted with caution as they were non-randomised, uncontrolled studies with substantial recruitment bias.

● A retrospective cohort study (Wencker M., 2001) measured progression of pulmonary emphysema in 96 patients with a severe AAT deficiency, before and after a period during which they received AAT. Follow-up was approximately 4 years. The decline in FEV1 was significantly lower during the treatment period (annual decline in FEV1 = 34.3 mL/year compared with 49.2 mL/year, i.e. a difference of 14.9 ± 61.4 mL/year) when the entire population of included patients was taken into account.

  NB: the result of this study should be interpreted with caution as it was a retrospective study in a small population.

3.2. Undesirable effects

One study specifically measured long-term safety of treatment with AAT.

Wencker M. (February 1998)
Aim: to assess the safety of treatment with AAT and monitor change in pulmonary function.
Method: non-comparative prospective cohort study.
Patients: 443 patients with CT signs of pulmonary emphysema, serum AAT concentration <35% of normal value (or <11 µM), FEV1<65% theoretical value or annual decline in FEV1>120 mL. Patients had to stop smoking during the study.
Treatment: AAT at a dose of 60 mg/kg 1x/week.
Results: Mean follow-up was 37.8 months.
Phenotypes for the 443 patients included were: 394 = PiZZ, 31 = PiSZ, 6 = PiZ and 3 = PiFZ; 9 patients = another phenotype or unknown.

Overall, 124 adverse events were reported in 65 patients. In most of these patients, they occurred at the time of infusion (fever, rash, nausea and vomiting, fatigue).
Admission to hospital or medical intervention was required for 5 serious adverse events: anaphylactic reaction in 4 patients and aggravation of congestive heart failure combined with respiratory failure in 1 patient. No deaths nor any cases of virus transmission were reported.

3.3. Conclusion

Four studies assessing the efficacy of replacement therapy with AAT were submitted in support of the application. Only one was a placebo-controlled clinical trial. The other three were cohort studies comparing clinical outcomes between treated and untreated patients (2 studies) or between periods before and after treatment (1 study).

Patients included in these studies had a severe AAT deficiency (serum concentrations below the protective threshold of 11 µmol/L) combined with pulmonary emphysema. However, deterioration in pulmonary function was very variable and results were analysed in relation to baseline FEV1 on inclusion. Most patients had the PiSZ and/or PiZZ phenotype, or else phenotype was not determined.

It is difficult to interpret the results of these studies because of their design (mostly non-randomised, non-placebo controlled studies), recruitment bias (small population or non-homogenous groups), and in the Dirksen study, the use of doses other than those validated by the Marketing Authorisation.

Taken together, these studies suggest that replacement therapy with AAT has an effect on decline in FEV1. The slowing of the FEV1decline would appear to be minor and varies between the studies. In the placebo-controlled clinical trial, there were no significant differences between the groups in terms of annual decline in FEV1 after 3–5 years' follow-up (decline of 25.2 mL/year on placebo compared with 26.5 mL/year on AAT).

There are no long-term data (longer than 5 years).

Treatment was generally well tolerated and the most common side effects were observed at the time of infusion (fever, nausea, vomiting and fatigue).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Primary AAT deficiency rarely manifests clinically. It is mainly seen in smokers or patients exposed to airborne contaminants in the work environment. The deficiency is severe in patients with a PiSZ or PiZZ phenotype, in whom it causes serum AAT levels below the protective threshold of 11 µmol/L. When an AAT deficiency is expressed clinically, it is usually associated with development of emphysema which gradually leads to incapacity through respiratory failure, leading to marked degradation in quality of life. It islife-threatening in the long-term.

The drug is given as replacement therapy.

Public Health Benefit

- Although serious forms of primary AAT deficiency in patients with the PiZZ or PiSZ phenotype and with pulmonary emphysema are life-threatening in the long-term, the public health burden is low because these forms are rare.
- The different forms of treatment currently used in these patients do not cover the treatment need . Nevertheless, there is insufficient evidence to suggest that Alfalastin satisfies this need.

- In view of the small number of patients concerned, the design of the studies submitted, and the very variable results between the studies, Alfalastin is not expected to have any impact on morbidity or mortality in the overall French population.

Consequently, in the current state of knowledge, Alfalastin is not expected to have any public health benefit.

The efficacy of AAT replacement therapy has mainly been assessed from cohort studies of a low level of evidence. Results from these studies suggest that it has an effect on annual decline in FEV1, but this effect is small and inconsistent. In a placebo-controlled clinical trial, no significant differences were demonstrated between groups in terms of annual decline in FEV1 after 3–5 years' follow-up (decline of 25.2 mL/year on placebo compared with 26.5 mL/year on AAT).
The most common side-effects were observed at the time of infusion.
The efficacy/side effects ratio is low.

This drug is a first-line therapy in patients with AAT deficiency and a PiSZ or PiZZ phenotype, who experience deterioration in pulmonary function.

The actual benefit of Alfalastin is low.

4.2. Improvement in actual benefit

Alfalastin does not contribute any improvement in actual benefit (level V) in the normal management of patients with a serious form of primary AAT deficiency (PiZZ or PiSZ phenotype) combined with pulmonary emphysema.

4.3. Therapeutic use

Management of patients with severe AAT deficiency and a PiSZ or PiZZ phenotype combined with emphysema consists of non-specific therapies for chronic obstructive bronchial disease (giving up smoking, for smokers; elimination of airborne contaminants in the workplace; pulmonary rehabilitation; bronchodilators; corticosteroids; oxygen therapy) and replacement therapy by AAT infusion..

The dose is 60 mg/kg once a week either continuously, especially in very aggressive forms, or in courses during episodes of infection. This dose will result in an AAT plasma concentration similar to that of subjects without a deficiency. Treatment should be initiated as soon as the first symptoms of pulmonary emphysema occur (see Marketing Authorisation).

According to the validated indication, Alfalastin is reserved for patients with a PiSZ or PiZZ phenotype.

4.4. Target population

The target population for Alfalastin is defined as patients with severe forms of primary AAT deficiency with the PiZZ or PiSZ phenotype, combined with pulmonary emphysema.

According to published data, by far the majority of cases of pulmonary emphysema occurring in patients with primary AAT deficiency are associated with the PiZZ phenotype. The target population may therefore be estimated from the population with the PiZZ phenotype.

According to the available epidemiological data (de Serres 2003), there are estimated to be 7700 people in France with the PiZZ phenotype.

There are no epidemiological data that could be used to establish the proportion of the population with the PiZZ phenotype who will develop pulmonary emphysema.

At present, approximately 80 patients in France are being treated with Alfalastin (Temporary Authorisation for Use), i.e. 1% of patients with the PiZZ phenotype (company data).

The international scientific community, particularly the World Health organisation (WHO), recognises that AAT deficiency is underdiagnosed even though it is one of the most common genetic diseases. Constantly, the target population for Alfalastin is probably greater than 80 people.

In North America and Germany, where AAT has been marketed for about 15 years, approximately 5–6% of PiZZ subjects are treated. If improved diagnostic measures were introduced in the future, the population could also reach 5–6% of patients with the PiZZ phenotype, i.e. 400–480 patients.

NB: this extrapolation does not take account of differences that may exist between countries in terms of organisation of patient care that may affect whether or not patients are treated (in the American cohort, some of the patients not treated were not treated for financial reasons).

4.5. Transparency Committee recommendations

Approval of inclusion on the list of medicinal products approved for use in hospitals and various public services in the indications and at the doses given in the Marketing Authorisation.

Packaging: suitable for conditions of prescription and supply.