ATTACHMENT 4b

Agenzia Italiana del Farmaco

AIFA

AMYOTROPHIC LATERAL SCLEROSIS: TREATMENT AND RESEARCH PERSPECTIVES

The purpose of this document is to propose a consideration on the treatment of Amyotrophic Lateral Sclerosis (ALS), with special reference to certain recent provisions that ordered the National Health Service to supply patients with the drug IGF-1/IGF-BP3. Starting with an analysis of the current situation some proposals for intervention will be discussed.

ALS is a progressive neurodegenerative disease (characterized by degeneration of the 1st and 2nd motoneuron), gradually worsening by involving the respiratory muscles and eventually causing the patient's death. The etiopathogenesis of the disease is unknown to date. In the United States a relevance of the disease is estimated at approximately 6 per 100.000 inhabitants and annual incidence of approximately 1.5 out of 100.000. In Italy the estimated annual incidence is approximately 2.5 out of 100,000 inhabitants, for a total of approximately 1500 new ALS patients/year.

At this time there is no drug that can cure the disease, or modify its progression for patients in a clinically significant manner. Riluzole (Rilutek®), the only drug with registered labeling authorization (in the European Union and in the United States) for ALS, is the only therapy that showed, in clinical trials, an extension compared to the placebo of approximately 3 months in the survival of patients suffering from the disease. Riluzole therefore is currently prescribed to extend life or delay mechanical ventilation in patients suffering from ALS.

Several other molecules are at this time the subject of trials. Recently the American Academy of Neurology published in the journal *Neurology* the results of as rigorous evaluation of available literature on neuroprotectors potentially useful in ALS, in order to identify which of these molecules merit to be studied first within the scope of stage III clinical trials (Traynor *et al*. 2006). Based on the information cited in this article and what is available on the web site, clinicaltrials.gov, that lists trials currently in progress, it is possible to identify approximately 20 substances currently in stage II and III of clinical testing on ALS. IGF-1 is also included among the molecules in this list, for which the need of further testing is justified by the absence of proof of effectiveness. Various tests trials with other products are also under way in Italy: two were approved and financed by AIFA within the scope of 2005 non-profit research competitions; other projects are being evaluated in AIFA 2006 competitions.

As far as IGF-1 (**I**nsuline-**like G**rowth **F**actor-1) is specifically concerned, it should be remembered that the drug is not approved for the treatment of ALS in any country worldwide. The drug was approved at the end of 2005 by the Food and Drug Administration (FDA) in the United States for a different product labeling: "*treatment of growth failure in children with severe and primary IGF-1 deficiency or with deletion of the GH (growth hormone) gene and who developed antibodies that neutralize the growth hormone*."

The reason why IGF-1 does not have labeling authorization for ALS (in Italy or in any other

country) is due to the fact that the two trials conducted thus far did not show a clinically relevant benefit for patients. The results of the two studies were contradictory: in fact, whereas the first trial, conducted in the United States, demonstrated that IGF-1 could improve certain patient functional parameters, the second (conducted in Europe) did not provide evidence of the superiority of IGF-1 over a placebo. Currently another study is in progress in the United States which involves approximately 300 patients, the results of which should be available in approximately one year. Therefore no study to date has demonstrated that IGF-1 can improve ALS patient survival. On the other hand, the American trial currently in progress highlights the scientific community's interest in this neurotrophic factor for ALS, confirming however its "experimental" and "in progress" nature.

The IGF-1/IGF-BP3 complex is a compound with properties similar to those of IGF-1 and potentially able to slow down the muscle atrophy process thus far demonstrated in pre-clinical studies (post-denervation rats). However, this drug has not yet been tested on patients suffering from ALS.

It must be pointed out how potentially effective drugs in the treatment of ALS can be brought out only within a research and clinical trial context. Administering drugs with a risk-reward profile that has not been adequately studied exposes patients to unnecessary risks and it does not lead to acquiring any valid information that can be extrapolated for all ALS patients.

For the reasons set forth above it is believed that e minimum requirements to provide the IGF-1 drug to patients suffering from ALS. Furthermore, the sizable resources necessary for this therapy (approximately EUR 140,000 per patient per year) must be understood as taken from treatments with proven scientific evidence for other pathologies. A similar conclusion obviously pertains also to IGF-1/IGF-BP3: this drug is also currently prescribed for long term treatment of growth failure in children with primary IGF-1 or GH deficiency (in the latter case, in subjects who developed anti-GH antibodies).

CONCLUSIONS

Based on the observations summarized above, after a lengthy discussion, the Technical and Scientific Committee believes that:

- **The requirements for the National Health Service to provide free of charge, (within the framework of Law 648/96), the IGF-1 and IGF-1/IGF-BP3 drugs for the treatment of patients suffering from ALS do not exist since it is not applicable;**
- **the use of IGF-1 and IGF-1/IGF-BP3 in ALS is not supported by regulatory tools (a drug without registered labeling authorization) or scientific grounds (the studies completed thus far do not offer evidence of IGF-1 being effective in ALS therapy, and IGF-1/IGF-BP3 to date has not even been studied on patients suffering from the disease);**
- **relevant outcomes for patients, such as survival, have never been investigated, therefore in this sense IGF-1 is not a "life saving" drug, as it is sometime referred to by the media;**
- **current scientific knowledge does not justify the use of the IGF-1 and IGF1/IGF-BP3 products for ALS outside a research environment (as it is still happening in the United States).**

Rome, November 21, 2006

Attachment: Technical document IGF-1 and ALS