Summary

On 28 October 2005, orphan designation (EU/3/05/324) was granted by the European Commission to ACE Pharmaceuticals BV, The Netherlands, for levamisole hydrochloride for the treatment of nephrotic syndrome.

Levamisole is recommended for use in high-dose steroid-dependent nephrotic syndrome in children, as adjuvant therapy following relapse on corticosteroids such as prednisone; or as an alternative to the use of an alkylating agent or cyclosporin. In these patients, Levamisole has been shown to induce a significant number of complete remissions, reduce the steroid requirements necessary to induce such a remission, and decrease the incidence of relapse of the disease.

Levamisole

Levamisole is the active levo-isomer of tetramisole hydrochloride. Levamisole hydrochloride is an immunomodulator which has originally been used as an anthelmintic but which also has been used in malignant diseases and rheumatoid arthritis. Interest has been gained in the use of Levamisole Hydrochloride as adjunctive treatment for Steroid Sensitive Nephrotic Syndrome (SSNS).

Background

Nephrotic syndrome is a relatively rare disease that occurs in 2 to 7 per 100,000 children. Nephrotic syndrome might occur without apparent causes (especially in children) or as a result of a number of illnesses that can damage the glomeruli, the filtering units of the kidneys. Nephrotic syndrome is a chronically debilitating and life-threatening condition. It is marked by very high levels of protein in the urine (proteinuria), due to leakage of proteins through those damaged glomeruli from the blood into the urine. This severe loss of protein, typically leads to accumulation of fluid (edema) and low levels of protein the blood (hypoproteinaemia). Normally Idiopathic Nephrotic Syndrome (INS) in children is treated with corticosteroids. While the majority of children with nephrotic syndrome respond to corticosteroids, 70% experience relapses. In most of these children corticosteroids therapy has to be repeated frequently, putting them at risk of the adverse effects of corticosteroids. To reduce steroid toxicity in these patients several alternative non-corticosteroid immunosuppressive agents have been proposed of which cyclophosphamide and cyclosporine are used most commonly. Drawbacks of both drugs are their potential serious adverse effects such as carcinogenesis, infertility, nephrotoxicity, hypertension and hirsutism. Levamisole

also reduces steroid toxicity, but exhibits less serious side effects. Furthermore, Levamisole may be effective in patients in whom cyclophosphamide and cyclosporine are not.

Objective of the Phase III-trial

ACE Pharmaceuticals BV, in cooperation with the Academic Medical Centre Amsterdam, the Netherlands, intends to assess the effectiveness of one year of alternate days Levamisole treatment in a dose of 2.5 mg/kg in the prevention of relapses and prolonging time to relapse after cessation of corticosteroids treatment in children with steroid sensitive Nephrotic Syndrome.

This trial will also be performed to evaluate whether the effect of Levamisole varies with disease status and/ or with prior treatment with Cyclophosphamide. Furthermore, steroid sparing effect, effectiveness, pharmacokinetics and safety of treatment with Levamisole will be assessed.

Study design

This study is of an international, multi-centre, double blind, placebo controlled, randomized Clinical Trial (RCT) followed by a cohort study, using the infrastructure of the RCT. Furthermore pharmacokinetic values will be obtained.

Study population

The study population concerns patients of less than 18 years of age presenting with Idiopathic Nephrotic Syndrome and frequent relapses (with or without steroid dependence) and which were not treated with Levamisole for this indication before. Because of the low prevalence of this condition, all of the patients which meet these criteria and of which written informed consent has been received may be included in the study.

Intervention

A dosage of 2.5 mg/ kg will be administered on alternating days with a maximum of 150 mg versus placebo.

Endpoints

The primary endpoint is defined as the time to relapse which is the time between start of the Levamisole treatment and end of the study.

Secondary outcomes are:

- § Average amount of steroids administered per month during the study
- § Evaluation whether treatment effect differs with underlying disease process (steroid dependency yes/no) and prior use of disease modifying agents (yes/no)
- § Prednisone dosage when relapse occurs.

Projectleaders

Principal Investigator:

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Coordinator:

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Subsidy

- § De Nierstichting
- § Stichting Zeldzame Ziekten Fonds

Why should a clinical trial on Levamisol be performed in the treatment of nephrotic syndrome in childhood?

1. **Levamisole is not registered for this indication**

2. **Levamisole is effective**

   Since 1980, 20 studies have been performed to the efficacy of Levamisole in the prevention of relapses of idiopathic nephrotic syndrome (INS). All of them conclude that it is an effective drug in this indication. Some studies have also shown that Levamisole can also be effective after failure of cyclophosphamide and cyclosporine.

3. **Levamisole toxicity is low**

   Levamisole is well tolerated. It has been use for more than 25 years in the indication of idiopathic nephrotic syndrome (INS). Since the first report (Tanpaichitr et al, 1980), 758 Levamisole-treated patients with INS are reported up to date (July 2006). Side effects of Levamisole have been uncommon and always reversible. It includes neutropenia, thrombocytopenia and cutaneous side-effects. Among all the reports, only one mentions two patients presenting with neurological side-effects occurring during treatment (Palcoux et al, 1994), that resolved after discontinuation of Levamisole.

   In a recent e-mail investigation in ESPN (European Society for Pediatric Nephrology) members, all Levamisole users having responded (30 centers) consider that side-effects are acceptable.

4. **Levamisole is used in 75% of pediatric nephrology centers in Europe**

   A recent e-mail investigation among ESPN members has shown that 75% (30/41) of pediatric nephrology centers in Europe use Levamisole mostly as second step drug in NS of children and attest of a lack of significant side-effects.

5. **Several questions about the use of Levamisol remain to be answered**

   a. The steroid-sparing effect of Levamisole has not been quantified so far.
   b. The effects and side-effects of a treatment longer than 1 year has not been determined.

c. A comparison of action and side effects of Levamisole vs. cyclophosphamide (the other second line drug in the treatment of nephrotic syndrome) has not been done so far.
d. To prove efficacy, a comparison of placebo vs. verum is necessary.

6. **The mode of action of Levamisole remains unknown**
   The study of its mechanism can enlight the pathogenic mechanism of INS

7. **Parents of patients become aware of the treatment and ask for it**

8. **A study on Levamisole in nephrotic syndrome will be supported by the ESPN**
   The secretary general of the ESPN guaranties his strong support for a study on Levamisole on a European level.

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