

**Rapporteur's  
Public Assessment Report  
for paediatric studies submitted in accordance  
with Article 45 of Regulation (EC) No1901/2006, as  
amended**

**Naltrexone**

**NO/H/001/pdWS/001**

**Marketing Authorisation Holders:  
AOP Orphan Pharmaceuticals AG and  
Bristol-Myers Squibb**

<b>Rapporteur:</b>	NO – Inger Heggebø
<b>Start of the procedure (day 0):</b>	27 February 2009
<b>Date of this report:</b>	29 May 2009
<b>Deadline for Rapporteur's preliminary paediatric assessment report (PPdPAR) (day 70):</b>	08 May 2009
<b>Deadline for CMSs' comments (day 85):</b>	23 May 2009
<b>Finalisation (day 90):</b>	28 May 2009

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Identified: Ethylex, Nalorex, Naltrexone, Nemexin
INN (or common name) of the active substance(s):	Naltrexone
MAH (s):	AOP Orphan Pharmaceuticals AG and Bristol-Myers Squibb
Pharmaco-therapeutic group (ATC Code):	N07BB04
Pharmaceutical form(s) and strength(s):	Tablets
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## **I. INTRODUCTION**

AOP Orphan Pharmaceuticals AG and Bristol-Myers Squibb have submitted one completed paediatric study each for naltrexone, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short expert overview has also been provided by Bristol-Myers Squibb. According to Bristol-Myers Squibb, marketing authorisations for Naltrexone are held in the following EEA countries: Belgium, Finland, France, Germany, Greece, Ireland, Luxembourg, the Netherlands, Portugal, Spain and United Kingdom.

None of the MAHs claim that the submitted paediatric studies influence the benefit/risk for naltrexone and hence, there is no consequential regulatory action.

This conclusion is endorsed by the Rapporteur, and this is endorsed by the other member states.

The paediatric population refers to all ages below 18 years.

## **II. SCIENTIFIC DISCUSSION**

### **II.1 Information on the pharmaceutical formulation used in the clinical studies**

From the brief documentation provided by the MAHs, the pharmaceutical formulations used are not explicitly stated, but have presumably been tablets 25/50 mg in the study submitted by AOP Orphan Pharmaceuticals AG.

In the study provided by Bristol-Myers Squibb, naltrexone 25 mg tablets were used and these were administered in combination with a highly palatable pudding and/or juice.

### **II.2 Non-clinical aspects**

No non-clinical documentation was provided.

### **II.3 Clinical aspects**

#### **1. Introduction**

Two studies were identified to meet the criteria spelled out by Article 45 EU regulation EC 1901/2006.

These studies have not been included in the preceding naltrexone related regulatory procedures and hence, have not been distinctly evaluated as to its potential impact to the respective label information. Thus, the evaluation is based on the following 2 previously not reviewed documents.

There is no clinical pharmacokinetic information included in the documentation provided by the MAHs.

## 2. Clinical studies

### **MAH: AOP Orphan Pharmaceuticals AG**

As the information provided by AOP Orphan Pharmaceuticals AG regarding the study performed in adolescent alcoholics is from a published article, the following has been based on the abstract from this article:

#### **Naltrexone treatment of adolescent alcoholics: an open-label pilot study, Deas D *et al.*, J Child Adolesc Psychopharmacol. 2005 15(5):723-8.**

This 6-week open-label trial of naltrexone was conducted in a preliminary fashion to determine whether naltrexone would be safe, well tolerated, and lead to a reduction in alcohol consumption in adolescents with alcohol dependence.

Five outpatient treatment-seeking adolescents who met Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition (DSM-IV) criteria for alcohol dependence were recruited. The Child Schedule for Schizophrenia and Affective Disorders (K-SADS), Structured Clinical Interview for DSM (SCID), and the Family History Questionnaire were administered at baseline. The Time-Line Follow-Back (TLFB) and two craving scales (Adolescent Obsessive Compulsive Drinking Scale [A-OCDS] and a craving analog scale) were administered at baseline and weekly thereafter. Each subject received a 10-day supply of naltrexone (50 mg) and a 100-mg riboflavin capsule. Subjects were instructed to take naltrexone and riboflavin simultaneously.

The results showed that overall, the average drinks per drinking day (DDD) decreased significantly from baseline to the end of week 6 with an average reduction of 7.61 standard drinks. There was a significant reduction in the average A-OCDS total score, A-OCDS Irresistibility subscale score and craving analog score. Nausea was the only side-effect reported, and there were no elevations of liver enzymes. Naltrexone was well tolerated by the alcohol-dependent adolescent. The data presented in the article suggested that naltrexone was safe and well tolerated in adolescent alcoholics. It was concluded that naltrexone might lead to a significant reduction in alcohol consumption and craving in adolescent alcoholics, but that larger, randomised, controlled trials are needed.

#### Assessors' comment:

As known from the literature, the effect of naltrexone in treating alcohol dependence in adults has been extensively evaluated. Several controlled studies have been performed in this population. Most of the studies show a significant effect of naltrexone, however there are also studies not showing this. The reason behind this might be that the effect is moderate and only significant when naltrexone is combined with adequate psychosocial therapy. Hence, only prescribing naltrexone is not helpful, it has to be combined with systematic counselling.

The above described study in alcoholic adolescents is a published 6-page article of an open label uncontrolled study in only 5 adolescents with a mean age of 16.8 years. The adolescents were administered naltrexone orally, with flexible dosing (25 or 50 mg daily). It seems that clinical treatment with psychosocial interventions only was offered after completion of the 6-week trial. The report claims good results and few side effects. Because 2 subjects had missing data at different points between week 4 and 6, data for all 5 subjects were analysed up to week 3 only. This implies that there are results from the whole data set only up to week 3.

There are several limitations to this study (e.g. open, non-blinded assessments, brief length and small sample size, no concomitant psychosocial therapy offered) and no firm scientific conclusions can therefore be drawn.

In the article it is stated that a 12-week, placebo-controlled, randomised trial in adolescent alcoholics with naltrexone was conducted using similar methodology as in the study described above. However, the results from this 12-week study have not been submitted by the MAH.

**Conclusion:** The document has limited scientific value. No firm conclusions can be drawn.

**MAH: Bristol-Myers Squibb (BMS)**

BMS has submitted a clinical study report (dated September 13 1993) for Study DUP 393-015, titled: "Effect of naltrexone on the autistic syndrome, double blind, placebo controlled crossover design study".

In addition, BMS has appended a statement by Dr. Noel Mpono, MD, Mature Products Physician, Global Pharmacovigilance & Epidemiology, Research & Development at BMS and a 3 year Periodic Safety Update Report (PSUR), covering the period 20 November 2003 to 19 November 2006.

The information regarding study DUP 393-015 is mainly taken from the study synopsis.

**Study DUP 393-015** was a double-blind, placebo-controlled, crossover study designed to:

- 1) define the temporal factor for a therapeutic effect of naltrexone on the autistic syndrome
- 2) integrate social interaction as a major facet of naltrexone therapy and,
- 3) determine any effect of opioid blockade on the plasma serotonin, epinephrine, norepinephrine, substance P, vasopressin, enkephalin, and beta-endorphin concentration in the autistic child.

Twenty (17 males and 3 females) autistic children ranging in age from 5 to 13 years (mean:  $8.4 \pm 2.3$  years) entered and completed the study (10 patients from France, 3 patients from Austria and 7 patients from Hungary). All 20 patients who entered completed the study.

Each patient went through a 12-week study period consisting of a two-week baseline, a three-week period of either naltrexone or placebo treatment, a two-week mid baseline period, a second three-week period of either naltrexone or placebo treatment, and finally a two-week post baseline period. Naltrexone, 0.5 mg/kg, was administered orally three times per week. The order of naltrexone and placebo treatment was randomly determined. Dosing was to be administered by the patients' parents or care givers three times a week over two separate three-week periods. Assessments of compliance were not planned.

Patients were rated on a weekly basis according to the following assessments:

- o Behavioural Summarized Evaluation for Autism (BSE-A)
- o Childhood Autism Rating Scale (CARS)
- o Clinical Global Impression (CGI) consisting of severity, improvement and efficacy index
- o Childhood Psychiatric Rating Scale (CPRS)
- o Early Social Communication Scale (ESCS)
- o Conners Parent Teacher Questionnaire (PTQ)

BSE-A was considered to be the primary outcome measure.

The examiner filled out the four behavioural rating scales based on the child's behaviour of the last one and a half hours during each visit. The ESCS evaluation was done based on a videotaped session of the child in the presence of a psychologist during the clinic visit. The PTQ was based on the parents' evaluation of the behaviour during the week previous to the clinic visit.

Blood samples for the determination of dopamine, norepinephrine, serotonin, beta-endorphin, substance P, arginine-vasopressin, adrenocorticotrophic hormone (ACTH), and transaminases (AST [SGOT] and ALT [SGPT]) were obtained at the end of the baseline period and at the end of the first and second periods of randomised treatment. Safety assessments included the measurement of transaminases.

minases at the end of the baseline period and at the end of the first and second periods of randomised treatment. Adverse clinical events were monitored throughout the study.

The results showed that there were no statistically significant differences between naltrexone and placebo in seven of the eight assessments. For the total BSE, there was evidence of an unequal residual effect; therefore only data from the first treatment period was used.

A statistically significant ( $p < 0.05$ ) difference occurred between naltrexone versus placebo only with the CPRS scale. This result is in disfavour of naltrexone as it implies that the patients were rated as being more severely autistic during naltrexone treatment.

In the study report it is stated that there were a total of 7 scheduled efficacy evaluations which were not recorded or not obtained. These did not cause any exclusion from the analysis, since the analysed value from each treatment period was the median of all evaluations during the period. If one evaluation was missing, the median was calculated from the remaining observations in the given period.

For the CGI improvement scale and/or efficacy index there were 14 patients missing 1 or more baseline values. For 4 of these patients all baseline values were missing. These 4 patients were therefore partially excluded from the correlation and principal component analyses, since change from baseline could not be computed for improvement and efficacy index.

There was no statistically significant difference between naltrexone and placebo treatment for any of the laboratory parameters.

Fifteen of the 20 patients reported an adverse clinical event. Nine patients reported adverse clinical events during treatment with placebo and 9 patients during treatment with naltrexone. Vomiting was the most frequently reported adverse clinical event; 4 patients in the naltrexone group and 3 patients in the placebo group.

**PSUR (period covered 20 November 2003 to 19 November 2006):**

It is stated in the PSUR that during the reporting period, among files for which the age of the patient was reported, there were 3 initial spontaneous non-serious reports of AEs occurring in patients 16 years of age and younger. The company states that the safe use of naltrexone in paediatric patients younger than 18 years has not been established. It is claimed that non-serious AEs reported in the paediatric patients were events listed in the Company Representative Label, and/or may have been AEs related to the patient's disease process. It was concluded that the events reported in the age-specific population have not adversely influenced the overall safety profile of this product.

Assessors' comment:

Study DUP 393-015 is performed in only a small number of children between 5 and 13 years. The children were administered oral naltrexone of approximately 0.5 mg/kg daily for 12 weeks.

The study showed no statistically significant evidence that naltrexone improved the overall autistic behaviour in the 20 children evaluated in this study. Among the 8 overall scales analysed, 7 of them indicated no significant difference between naltrexone and placebo at the 0.05 level, this included also the primary outcome measure BSE-A. With CPRS the patients were in fact rated as being more severely autistic during naltrexone treatment than during placebo treatment ( $p < 0.05$ ).

Conclusion: The document has limited scientific value and no firm conclusions can be drawn from the study.

### **3. Discussion on clinical aspects**

Both the MAHs conclude that the review and evaluation provides no evidence in support of label change for naltrexone regarding paediatric indications or dosing.

The Rapporteur agrees with the conclusion of the MAHs. None of the two studies reviewed fulfils the basic scientific standard required for a change in the SPC labelling. Thus, there is no evidence for a change in the SPC labelling.

## **III. Rapporteur's Overall Conclusion AND RECOMMENDATION**

### **III.1 Overall conclusion**

Two studies have been identified by the MAHs to meet the criteria for clinical trial documentation in the context of clinical trials performed in children with naltrexone spelled out by Article 45 EU regulation EC 1901/2006.

This conclusion is based on a review of these 2 studies performed in very small patient populations of children and adolescents.

No firm scientific conclusions can be drawn about the efficacy or side effects of naltrexone in children and adolescents from these studies, and it is concluded that the documents have limited scientific value.

It is therefore concluded, in agreement with the proposal from the MAHs, that there is no evidence for a change in the SPC labelling.

### **III.2 Recommendation**

No further action required.