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Committee for Medicinal Products for Human Use (CHMP)

Xyrem

(Sodium Oxybate)

Procedure No. EMEA/H/C/000593/P45 012

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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I. ASSESSMENT

Introduction
This report covers the following post-authorisation commitments undertaken by the MAH: Submission of the available data under the framework of article 45 of the paediatric regulation EC/1901/2006

Assessment
The data provided are only 7 publications not related to internally available reports and that have nothing in common but the fact at least one paediatric patient has been exposed to sodium oxybate.

Narcolepsy
ADPE05F0107
A retrospective study (review) was performed for the treatment of narcolepsy-cataplexy with sodium oxybate. In total 17 patients have been treated with sodium oxybate. One patient did not initiate drug owing to expense considerations. The mean age of patients was 36.9 years (range 9.5 - 78) and the mean duration of treatment was 5.1 months (range 1 - 12). No information is available on the number of patients under the age of 18 years in this trial. Nine of 16 (56.5%) reported improvement in cataplexy, and 8/16 (50%) reported improved daytime alertness. A refreshed feeling upon awaking in the morning was indicated by 8/16 (50%) subjects. Tolerable side effects were seen in 9/16 subjects (56.5%) and have consisted of difficulty staying asleep between doses or early in the morning in 5/9, and constipation in 4/9 subjects. It is concluded that sodium oxybate was modestly effective in treating narcolepsy-cataplexy. Constipation and insomnia were the most common side effects.

ADPE06J2109
A retrospective / chart view was studied to evaluate the efficacy and side-effect profile of off-label sodium oxybate (gamma hydroxybutyrate) therapy in severe childhood narcolepsycataplexy.

A group of eight children aged between 8-15 years, with severe cataplexynacrolepsy was selected. Three of them had failed treatment for cataplexy with other medications. The frequency of cataplexy was routinely documented and severity was graded post-hoc on an arbitrary scale. All data were gathered retrospectively from chart review and analyzed. Differences between the base line and final ESS score and the estimated cataplexy frequency and severity were evaluated using the Wilcoxon signed rank test. The duration of therapy has ranged from 3 to 28 months. The dose has ranged from 3 to 7 gm per day. Before sodium oxybate therapy, all subjects had sub-optimally controlled sleepiness and cataplexy.

Following treatment with sodium oxybate, 7/8 subjects (88%) improved. Cataplexy frequency decreased from a median of 38.5 to 4.5/week (p=0.0078). Cataplexy severity decreased from 2.75 to 1.75 (p=0.06). The Epworth Sleepiness Scores improved from a median of 19 to 12.5 (p=0.02). Suicidal ideation, dissociative episodes, tremor and constipation occurred in one subject each and terminal insomnia in two. Three of the eight (38%) discontinued therapy. Two stopped the drug owing to side effects and one due to problems with postal delivery of the medication.

Anestesiology

ADPE07L0530

A prospective randomized trial was undertaken to compare two (gamma-hydroxybutyrate GHB max 150 mg/kg or chlorprothixene/Phenobarbital CP max 1 mg/kg) sedation protocols in 28 pediatric patients. The mean age was of 32 months (range 8 - 75) with known or suspected malignancies undergoing MRI studies. The main outcome parameter was the difference in recovery time (defined as time interval between end of MRI procedure until awake with age-appropriate behaviour). The study was performed according to principles established in the declaration of Helsinki. The target was deep sedation (level 5 on the Ramsay scale). Systolic and diastolic blood pressure have been continuously recorded before, during, and after MRI examination. Statistical analysis was performed using SPSS.

All patients completed the study, and all procedures were successfully carried out with no failure to complete planned MRI examinations. The time to induce sedation was less with CP ($p<0.48$) as compare to (GHB $p<0.057$). Recovery was significantly quicker with GHB ($p<0.01$) than CP ($p<0.05$).Despite premedication the most common side effect in GHB group was vomiting, but no child aspirated. There were no seizers in any group. CP sedation significantly increased mean maximal heart rate $<p<0.01$), tachycardia was the most frequent and prominent side effect in this group. Mean diastolic blood pressure fell in both groups ($p<0.05$), somewhat more markedly in the CP group. However, in none of the patients were reductions in either heart rate or diastolic blood pressure below age specific reference values.

Only one patient, in the GHB group, experienced a brief and transient drop in oxygen saturation (<90%) during the procedure, which did not require any therapeutic intervention. It is concluded that GHB sedation provides a reasonable alternative sedative drug for children undergoing non-invasive diagnostic procedures.

ADPE07J1212

A letter to editor; Meyer et al (ADPE07L0530) wrote comments on an article by Mencia et al. on analgesia. They add their experience on the use of gamma-hydroxybutyrate for sedation in children and recommended GHB sedation as a reasonable alternative for children undergoing noninvasive diagnostic procedures. The author (Mencia et al.) replies to the comments with no experience with this sedative drug in children and careful scrutiny needs for effectiveness and safety of this practice.

2.5.4.3 Other

ADPE06J1109

A case report of an eight-year-old child with bithalamic lesions resulting from an episode of ADEM displaying insomnia, severely disrupted sleep and sever attention and behavioral regulation difficulties. He was treated with sodium oxybate after he failed to respond to traditional treatment interventions with stimulant medications in the daytime or chloral hydrate, melatonin, dyphenhydramine, and temazepam for sleep problems at night. After 6-months treatment with sodium oxybate, this child’s sleep profile was normalized with complete resolution of sleep fragmentation. There was also significant improvement in executive function skills and attention processing abilities, as well as improvement in frustration tolerance and impulse control.

II. RAPPORTEUR'S OVERALL CONCLUSION AND FURTHER ACTION IF REQUIRED

Of the 7 publications only 2 pertain to the indication for which Xyrem is approved. Although the data available for these publications suggest that the efficacy seen in patients over 18 years old might also be present in children the data available are not sufficient to allow firm conclusions. From the adverse reactions reported in the publications the MAH make some comments about terms that are listed and not listed but these are not particularly relevant since authors in publications do not follow very systematic methods of reporting ADR and the numbers are quite low. A proper development in children should be the basis for any recommendation.

The other publications pertain to an indication that is not approved and the doses that were used are much higher than approved (anaesthesia) thus the data are not informative for the Narcolepsy situation.

Overall Conclusion:

☒ PAC fulfilled (all commitments fulfilled) - No further action required

This PAC is considered fulfilled and the SPC does not require any amendment at this stage in the light of the new data provided.