

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

**Adumbran
Oxazepam**

SE/W/001/pdWS/001

**Marketing Authorisation Holder:
Boehringer Ingelheim**

Rapporteur:	SE
Start of the procedure (day 0):	11 December 2008
Date for Rapporteur's preliminary paediatric assessment report (PPdPAR) (day 70):	19 February 2009
Deadline for CMSs' comments (day 85):	06 March 2009
Date of final joint PdAR	29 May 2009
Date re-start procedure (day 90):	02 June 2009
Deadline for CMSs' comments (day 115):	27 June 2009
Finalisation procedure (day 120):	02 July 2009

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Adumbran
INN (or common name) of the active substance(s):	Oxazepam
MAH (s):	Boehringer Ingelheim
Pharmaco-therapeutic group (ATC Code):	N05BA04
Pharmaceutical form(s) and strength(s):	Tablets 10 mg

I. INTRODUCTION

Boehringer Ingelheim has submitted 4 completed paediatric studies for oxazepam, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Adumbran (oxazepam) and that there is no consequential regulatory action.

This conclusion is endorsed by the RMS.

MS comment:

Regarding the SPC of oxazepam containing products, we would like to mention that the following warning is included in the SPCs for oxazepam nationally: "*Benzodiazepines should not be given to children without careful assessment of the need to do so; the duration of treatment must be kept to a minimum.*" (in accordance with the Guideline "Summary of Product Characteristics for Benzodiazepines as Anxiolytics or Hypnotics"). We are of the opinion that this warning should be included in all SPCs for oxazepam in the EU, if not already included.

MAH agrees to include specific information concerning paediatric use in the SPC in chapter 4.4 *Special warnings and precautions for use* under the subheading "Specific patient groups".

The proposal is supported by the RMS and the proposed sentence will be included in Section 4.4 of the SPC.

The same sentence should be included in the PIL.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the clinical study(ies)

From the very brief documentation provided by the MAH, the pharmaceutical formulation used has been either suppositories (unknown strengths) or an oral liquid formulation (100 mg/100 ml).

Assessor's comment:

These formulations do not appear to be available at present.

II.2 Non-clinical aspects

No non-clinical documentation was provided.

II.3 Clinical aspects

1. Introduction

The Corporate Archive for Submission Documents was screened by the Boehringer Ingelheim and searched for clinical trial documentation in the context of clinical trials performed in children with oxazepam. Four studies, U70-0340, U70-0342, U76-0287 and U64-0066, 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 oxazepam related regulatory procedures and PSURs 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 4 unpublished and previously not reviewed documents.

The reports for these studies are available in local language (German and Italian) only, and the MAH has therefore in adjunction to the reports submitted short synopses for:

- U70-0340 Mayer TN. Investigations into the effect of Adumbran suppositories in children, 1970.
- U70-0342 Wurst F. Report on the experience with the use of Adumbran, 1970.
- U76-0287 Canova G. Clinical study of "Adumbran" syrup of Boehringer Ingelheim (generic name "oxazepam"), 1976.
- U64-0066 Jablonka E. Final report on the study of the product Z 10-TR at the university eye hospital in Mainz, 1972

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

2. Clinical studies

As the information provided by the MAH for each study was extremely brief, the MAHs synopses has been used in the following.

U70-0340 Mayer TN. Investigations into the effect of Adumbran suppositories in children, 1970

Study U70-0340 is an open label uncontrolled observational study performed in December 1969 and January 1970 in 21 children aged between 8 months and 10 years. Patients hospitalised for either

infections, gastrointestinal disorders or pluriorificial ectodermosis received a daily dose of 2 to 5 oxazepam suppositories (strength unknown) over 3 to 5 days. No reliable diagnostic criteria or validated efficacy or safety assessment instruments are presented. Onset of effect was reported after 30 minutes up to 1 hour. For 12 children a very good therapeutic response was observed, for the remaining 9 children the overall therapeutic response reported was rated as good, as excitation and irritability of children was reduced. For none of the children studied somnolence was reported as an adverse event. Due to the small number of children involved in this study relevant conclusions regarding the use of oxazepam in children cannot be drawn.

Assessor's comment:

This is an unpublished 2-page document (in German) of an open label un-controlled study in a small number of children between 8 months and 10 years with a variety of diagnoses. The diagnostic criteria or validated efficacy or safety assessment instruments are not presented. The children were administered oxazepam suppositories, the strength of the suppositories is not indicated in the document. The report claims good results and few side effects.

No firm scientific conclusions can be drawn from the study.

Conclusion: The document has no scientific value.

U70-0342 Wurst F. Report on the experience with the use of Adumbran, 1970.

Study U70-0342 is an open label uncontrolled observational study performed between July 1969 and May 1970 in 32 children aged between 3 and 16 years. Patients hospitalised for either anxiety, sleep disorders, psychological abnormalities or psychopathological conditions received oxazepam in either oral daily doses between 20 and 90 mg or as suppositories in doses between 7.5 and 15 mg. Treatment duration ranged between 3 and 8 weeks. No treatment discontinuation occurred due to adverse events.

Treatment of small infants was initiated with 5 mg three times daily, while infants received an initial dose of 10 mg three times daily. Adolescent initial dose ranged between 10 mg 4-5 times a day and 30 mg three times daily.

Onset of efficacy in terms of sedation was observed within week 1 to week 1.5. As adverse event in one case only tiredness was reported, which improved after dose reduction. In three small infants vomiting and/or diarrhoea was reported which was reported to be resolved after dose reduction. The small number of children involved in this study prevails to derive from the study findings relevant conclusions regarding the use of oxazepam in children.

Assessor's comment:

This is an unpublished 2-page document (in German) of an open label un-controlled study in a small number of children between 3 and 16 years with a variety of diagnoses. The diagnostic criteria or validated efficacy or safety assessment instruments are not presented. The children were administered oral oxazepam 20 – 90 mg daily for 3-8 weeks. The report claims good results and few side effects.

No firm scientific conclusions can be drawn from the study.

Conclusion: The document has no scientific value.

U76-0287 Canova G. Clinical study of "Adumbran" syrup of Boehringer Ingelheim (generic name "oxazepam"), 1976.

Study U76-0287 is an open label uncontrolled study in 33 children using an oxazepam oral liquid formulation (100 mg/100 ml). Children were aged between 5 months to 12 years, with 9 children aged below 2 years and 8 children older than 6 years. Mean duration of administration was 9 days ranging from 5 to 27 days. Doses administered were 1 mg/kg, in case of insufficient clinical response the dose was increased to 1.5 mg/kg. This regimen showed very good clinical global impression of efficacy in 29 patients, while for 3 patients a good response was reported. In one case the assessment of efficacy was not reported. No adverse events were reported, neither was vomiting and any intolerance reported for any of the small infants aged below 2 years. The small number of children involved in this study prevails to derive from the study findings relevant conclusions regarding the use of oxazepam in children.

Assessor's comment:

This is an unpublished 8-page document (in Italian) of an open label un-controlled study in a small number of children between 5 months and 12 years with a variety of diagnoses. The diagnostic criteria or validated efficacy or safety assessment instruments are not presented. The children were administered oral liquid formulation (100 mg/100 ml) oxazepam 5-27 days. The report claims good results and few side effects.

No firm scientific conclusions can be drawn from the study.

Conclusion: The document has no scientific value.

U64-0066 Jablonka E. Final report on the study of the product Z 10-TR at the university eye hospital in Mainz, 1972

Study U64-0066 is an open label uncontrolled observational study performed in 11 patients aged between 14 and 60 years. One patient was 14 years old and the other was 15 years old, while the remaining patients were aged between 22 and 60 years. Patients received 30 mg single oral administration of oxazepam. Intraocular pressure was measured 1 and 3 hours post dosing and compared to baseline. In none of the patients an increase in ocular pressure was observed. No adverse events were reported in any of the two children.

The small number of children involved in this study prevails to derive from the study findings relevant conclusions regarding the use of oxazepam in children.

Assessor's comment:

This is an unpublished 2-page document (in German) of an open label un-controlled study in 11 patients with glaucoma; only 2 patients were 15 years and below. No psychiatric diagnoses or validated efficacy or safety assessment instruments are presented. The children were administered oral 30 mg oxazepam as single dose. Intraocular pressures before and after oxazepam were measured. No increase in intraocular pressure or any adverse events were reported.

No firm scientific conclusions can be drawn about the efficacy or side effects of oxazepam in children from this study.

Conclusion: The document has no scientific value.

3. Discussion on clinical aspects

The MAH concludes that the review and evaluation provides no evidence in support of label change for oxazepam regarding paediatric indications or dosing.

The Rapporteur agrees with the conclusion of the Company. None of the four documents reviewed fulfils any 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

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

This conclusion is based on a review of these 4 unpublished, open label, un-controlled reports on small patient populations in children with various, mostly unspecified diagnoses. No reliable diagnostic criteria or validated efficacy or safety assessment instruments are presented in any of the studies.

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

The following sentence should be included in the SPC chapter 4.4 *Special warnings and precautions for use* under the subheading "Specific patient groups" and in the Package Leaflet under the heading "Take special care with X":

"Benzodiazepines should not be given to children without careful assessment of the need to do so; the duration of treatment must be kept to a minimum."

IV. RAPPORTEUR'S RECOMMENDATION

The sentence *"Benzodiazepines should not be given to children without careful assessment of the need to do so; the duration of treatment must be kept to a minimum"* should be included in the SPC chapter 4.4 *Special warnings and precautions for use* under the subheading "Specific patient groups" and in the Package Leaflet under the heading "Take special care with X".