

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

**Anexate Solution for Inj/Inf 500 micrograms/5ml
(FLUMAZENIL)**

IE/W/0006/pdWS/001

Rapporteur:	Ireland
Start of the procedure (day 0):	29/10/2010
Date of this report:	18/01/2011
Deadline for Rapporteur's preliminary paediatric assessment report (PPdAR) (day 70):	01/02/2011
Deadline for CMS's comments (day 85):	01/02/2011
Date re-start procedure (day 90):	
Deadline for CMS's comments (day 115):	
Finalisation procedure (day 120):	17/02/2011

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Anexate Solution for Inj/Inf 500 micrograms/5ml –
INN (or common name) of the active substance(s):	FLUMAZENIL
MAH (s):	Roche Products Ltd
Pharmaco-therapeutic group (ATC Code):	V03AB25
Pharmaceutical form(s) and strength(s):	Solution for injection or infusion
Rapporteur's contact person:	Name Cathy Wright Tel: Tel: +353 1 6764971 Email: cathy.wright@imb.ie
Name of the assessor(s)	Name: Brian Aylward Tel: Tel: +353 1 6764971 Email: brian.aylward@imb.ie

I. EXECUTIVE SUMMARY

Based on the submitted literature, and following comments from the Concerned Member States, SmPC changes are proposed in sections 4.1, 4.2 and 5.2, with associated changes to the PL.

II. INTRODUCTION

Several MAHs submitted paediatric studies and case reports for flumazenil, 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 Flumazenil and that there is no consequential regulatory action. However, an opportunity exists to update paediatric dosing information across the various SmPCs, as paediatric dosing information has been presented as part of this procedure which has been previously accepted by some Competent Authorities.

III. SCIENTIFIC DISCUSSION

III.1 Information on the pharmaceutical formulation used in the clinical studies

This medicinal product has only one pharmaceutical formulation, a solution for injection or infusion.

III.2 Non-clinical aspects

No additional non-clinical information was presented during this procedure.

III.3 Clinical aspects

III.3.1 Introduction

The MAH submitted reports and abstracts for several studies and literature reports related to flumazenil use in the paediatric population. Of these, only one (Hoffmann et al.) is deemed to contain relevant clinical information which might lead to changes to the product information.

III.3.2 Clinical study

RESEARCH REPORT No N-138'351

An open-label study of the safety of flumazenil (Ro 15-1788) when used in children to reverse the residual CNS depressant effects of benzodiazepine-induced conscious sedation.

J Hoffmann et al

➤ Description

One hundred seven patients aged 1 to 17 years (mean age, 7 years) received flumazenil up to a maximum of 1.0 mg, given at a rate not to exceed 0.2 mg/min, to reverse the central nervous system effects of midazolam used to produce conscious sedation. Flumazenil was well-tolerated and effective in this paediatric population. No patient experienced a serious adverse event attributable to flumazenil. The five most frequently occurring adverse events, each with a frequency between 5% and 7% of patients, were abnormal crying, dizziness, nausea, fever and headache. Ninety-two percent of patients (97 of 106) were responders according to the primary efficacy parameter (Clinical Global Impression - much or very much improved at 10 minutes after the start of flumazenil administration). Of 60 patients who had a composite sedation scale (OAA/S) score of 5 (fully alert) at the 10 minute assessment, only 7 experienced re-sedation (at least a one point decrease in sedation scale score). Re-sedation in these patients occurred between 19 and 50 minutes after the start of flumazenil administration (mean, 25 minutes). All seven patients were in the 1-5 year age group. A qualitative comparison made between pharmacokinetic parameters (AUC, elimination half-life, plasma clearance, apparent volume of distribution) obtained in a subset of 31 (29 evaluable) children (stratified according to age: 1-5 years, 6 to 12 years and 13 to 17 years) and in a historical population of adults (n-16) indicated that there were no age-related differences in the pharmacokinetic parameters across the age range of children who participated in this study. In addition there were no gross differences in the pharmacokinetics of flumazenil between children when compared to adults from previous studies, although greater variability was seen in the children. The dose titration scheme, based on body weight, which was utilized in this study, appears well-tolerated and effective.

➤ Comparison of Pharmacokinetics in Children and Adults

The pharmacokinetics of flumazenil observed in the paediatric patient population in this study were compared to those seen in an earlier study conducted in adults. Although greater variability was seen in the paediatric group the mean clearance and volume of distribution were similar to the parameters seen in 16 healthy adult subjects participating in a dose-proportionality study of 0.4, 1, 2 and 3 mg doses given intravenously over five minutes. The harmonic mean elimination half-life in both children and adults was less than one hour. An ANOVA was also conducted on clearance and volume of distribution between the children and adults. The results showed no significant differences between the two populations.

III.3.3 Discussion on clinical aspects

The presented data suggests that flumazenil is safe and effective in reversing midazolam-induced conscious sedation when used at the doses defined in the protocol. No inferences regarding the safety or efficacy of flumazenil with regard to the treatment of re-sedation, as only limited data were generated during this study.

With regards to the pharmacokinetic profile of flumazenil in the paediatric population, the data presented in this study suggest that the profile is similar to that in adults, although there is increased variability in children.

IV. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

Paediatric data from the open-label study by Hoffmann et al have been presented to various Competent Authorities in the past which have lead to the introduction of dosing information in section 4.2 of their respective SmPCs. This information has also been included in section 4.2 of the Core Safety profile which resulted from a recent PSUR work-sharing procedure for flumazenil.

Following comments from the CMSs, information has also been added to section 4.1

In addition, pharmacokinetic data were generated during this study which suggest that there is no difference between the pharmacokinetic profiles in children and adults. These data have been reflected in Section 5.2 of the SmPC.

The other literature references included in this application are not considered sufficient to warrant regulatory action at this time.

➤ Recommendation

A Type II variation is requested from the MAH to update sections 4.1, 4.2 and 5.2. The text suggested for section 4.2 is consistent with that already circulated following the conclusion of a recent PSUR work-sharing procedure for flumazenil.

Section 4.1

For the reversal of conscious sedation induced with benzodiazepines in children > 1 year of age,

Section 4.2

Children above 1 year of age

For the reversal of conscious sedation induced with benzodiazepines in children > 1 year of age, the recommended initial dose is 10 micrograms/Kg (up to 200 micrograms) administered intravenously over 15 seconds. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, further injection of 10 micrograms/kg may be administered (up to 200 micrograms) and repeated at 60 second intervals where necessary (a maximum of 4 times) to a maximum total dose of 50 micrograms/Kg or 1 mg, whichever is lower. The dose should be individualised based on the patient's response. No data are available on the safety and efficacy of repeated administration of flumazenil to children for re-sedation.

Section 5.2

Paediatric population

In children above one year old, the half life elimination is shorter and the variability is higher than in adults, approximately of 40 min with a range of 20 to 75 min. Clearance and volume of distribution, by kg of body weight are the same than in adults.

Warnings regarding the use of flumazenil in children below 1 year of age have already been included in section 4.4 following the previous work-sharing procedure.