

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

**Ranitidine
(ranitidine hydrochloride)**

SE/W/007/pdWS/001

Rapporteur:	Sweden
Start of the procedure (day 0):	2009-08-28
Finalisation procedure (day 90):	2009-11-26
Date of this report:	2010-02-09
Deadline for comments from Marketing Authorisation Holders	

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VII
INN (or common name) of the active substance(s):	Ranitidine
MAH (s):	See section VII
Pharmaco-therapeutic group (ATC Code):	A02BA02
Pharmaceutical form(s) and strength(s):	Coated tablets 150 and 300 mg
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I. EXECUTIVE SUMMARY

Ranitidine hydrochloride is a histamine H₂-receptor antagonist that inhibits gastric acid secretion. The active ingredient is well known. Ranitidine was first approved in Italy in 1981 and is now available in 130 countries. Ranitidine is approved in all EU countries either through MR procedures or by national procedures. Ranitidine is available in tablets (150 mg and 300 mg), syrup 150 mg/10 ml and solution for injection 25 mg/ml.

In 2007, there was an EU Worksharing procedure for the assessment of paediatric data for Zantac (active ingredient ranitidine hydrochloride). The procedure was ended on the 13th of March 2008. The outcome as a result of that procedure is not yet published. Submitted material in this procedure overlaps a little with the Zantac paediatric WS. References 11 and 14 were included in the former procedure as well as in the present one. However, the additional data submitted in this procedure do not alter the conclusions made in the Zantac procedure.

II. RECOMMENDATION

The SPCs for ranitidine tablets, syrup and injection are to be updated as a result of the EU paediatric worksharing procedure for the assessment of paediatric data for Zantac in 2007. The submitted data within the present procedure do not give rise to any additional recommendations.

III. INTRODUCTION

Four MAHs have submitted 14 literature references and one abstract (case report) for ranitidine (12 paediatric studies and 2 studies in pregnant women), in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

The MAH (Sanofi-Aventis) has further submitted a short critical expert overview based on 4 published articles (2 performed in children and 2 in pregnant women).

The MAH (Aurobindo) also submitted 46 abstracts. Inclusion of children was obvious from only 2 of the abstracts and these studies are included in the present report, references 4 and 7.

The MAHs stated that the submitted paediatric studies do not influence the benefit risk for ranitidine and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Clinical aspects

Introduction

The MAHs submitted one Critical Expert Overview and 16 literature references that have been assessed.

Clinical literature references submitted

1. Ameen VZ, Pobiner BF, Giguere GC, Carter EG. Ranitidine (Zantac) syrup versus Ranitidine effervescent tablets (Zantac) EFFERdose) in children: a single-center taste preference study. *Paediatr Drugs* 2006;8(4):265-70.
2. Tam YH, Yeung CK, Lee KH. Seven-day is more effective than 4-day ranitidine bismuth citrate-based triple therapy in eradication of *Helicobacter pylori* in children: a prospective randomized study. *Aliment Pharmacol Ther* 2006;24(1):81-6.
3. Elzinga-Huttenga J, Hekster Y, Bijl A, Rotteveel J. Movement disorders induced by gastrointestinal drugs: two paediatric cases. *Neuropediatrics* 2006;37(2):102-106 [abstract only].
4. Canani RB, Cirillo P, Roggero P, Romano C, Malamisura B, Terrin G, et al. Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *Pediatrics* 2006;117(5):e817-e820.
5. Garbis H, Elefant E, Diav-Citrin O, Mastroiacovo P, Schaefer C, Vial T, et al. Pregnancy outcome after exposure to ranitidine and other H2-blockers: a collaborative study of the European Network of Teratology Information Services. *Reprod Toxicol* 2005;19:452-8.
6. Orenstein SR, Blumer JL, Faessel HM, McGuire JA, Fung K, Li BU, et al. Ranitidine, 75 mg, over-the-counter dose: pharmacokinetic and pharmacodynamic effects in children with symptoms of gastro-oesophageal reflux. *Aliment Pharmacol Ther* 2002;16(5):899-907.
7. Lugo RA, Harrison AM, Cash J, Sweely J, Vernon DD. Pharmacokinetics and pharmacodynamics of ranitidine in critically ill children. Abstract. *Crit Care Med.* 2001;29(4):759-64.
8. James LP, Stowe CD, Farrar HC, Menendez AA, Argao EA. The pharmacokinetics of oral ranitidine in children and adolescents with cystic fibrosis. *J Clin Pharmacol* 1999;39(12):1242-7.
9. Ruigómez A, Rodriguez LAG, Cattaruzzi C, Troncon MG, Agostinis L, Wallander M-A, Johansson S. Use of cimetidine, omeprazole and ranitidine in the pregnant women and pregnancy outcomes. *Am J Epidemiol* 1999;150(4):476-81.
10. Wells TG, Heulitt MJ, Taylor BJ, Fasules JW, Kearns GL. Pharmacokinetics and pharmacodynamics of ranitidine in neonates treated with extracorporeal membrane oxygenation. *J Clin Pharmacol* 1998;38(5):402-7.

11. Kuusela AL. Long-term gastric pH monitoring for determining optimal dose of ranitidine for critically ill preterm and term neonates. *Arch Dis Child Fetal Neonatal Ed* 1998;78(2):F151-3.
12. Maekawa N, Nishina K, Mikawa K, Shiga M, Obara H. Comparison of pirenzepine, ranitidine, and pirenzepine-ranitidine combination for reducing preoperative gastric fluid acidity and volume in children. *Br J Anaesth* 1998;80:53-7.
13. Cothran DS, Borowitz SM, Sutphen JL, Dudley SM, Donowitz LG. Alteration of normal gastric flora in neonates receiving ranitidine. *J Perinatol.* 1997;17(5):383-8.
14. Kuusela AL, Ruuska T, Karikoski R, Laippala P, Ikonen RS, Janas M, Mäki M. A randomized, controlled study of prophylactic ranitidine in preventing stress-induced gastric mucosal lesions in neonatal intensive care unit patients. *Crit Care Med* 1997;25(2):346-51.
15. Kaufman SS, Loseke CA, Young RJ, Perry DA. Ranitidine therapy for esophagitis in children with developmental disabilities. *Clin Pediatr (Phila)* 1996;35(9):451-6.
16. Rosenthal M, Miller PW. Ranitidine in the newborn. *Arch Dis Childhood* 1988;63:88.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

There is no new information concerning pharmacokinetics, efficacy or safety in the submitted literature references that will lead to additional modifications of the recommendations from the Zantac paediatric worksharing procedure in 2007.

➤ Recommendation

The SPCs for ranitidine tablets, syrup and injection are to be updated as a result of the EU paediatric worksharing procedure for the assessment of paediatric data for Zantac in 2007. The submitted data within the present procedure do not give rise to any additional recommendations.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable

VII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Marketing Authorisation Holder	Name of the medicinal products
Faribérica - Produtos Farmacêuticos, S.A.	Gastrulcer 150 and 300 mg coated tablets
SANOFI-AVENTIS PRODUTOS FARMACE	PEPTAB 150 and 300 mg tablet
Winthrop Farmacêutica Portugal, Lda.	Ranitidina Winthrop Comprimidos 150 mg and 300 mg coated tablets
Aurobindo Pharma Italia	Ranitidina TAD 150 and 300 mg coated tablets