

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

Colestyramine

CZ/W/002/pdWS/001

Rapporteur:	Czech Republic
Start of the procedure (day 0):	21.04.2009
Date of this report:	30.06.2009
Deadline for Rapporteur's preliminary paediatric assessment report (PPdAR) (day 70):	30.06.2009
Deadline for CMS's comments (day 85):	15.07.2009
Date re-start procedure (day 90):	20.07.2009
Deadline for CMS's comments (day 115):	14.08.2009
Finalisation procedure (day 120):	19.08.2009

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Questran, Questran Loc
INN (or common name) of the active substance(s):	Colestyraminum
MAH (s):	Bristol-Myers Squibb Company AKIS PANAYIOTOU & SON LTD
Pharmaco-therapeutic group (ATC Code):	Bile acid sequestrant
Pharmaceutical form(s) and strength(s):	Powder for oral suspension

I. EXECUTIVE SUMMARY

Colestyramine is mainly known as a cholesterol-lowering agent, it belongs to the class of bile acid sequestrants (BAS). Colestyramine resin is orally administered and absorbs and combines with the bile acids in the intestine to form an insoluble complex which is excreted in the faeces. This results in a continuous, though partial, removal of bile acids from the enterohepatic circulation by preventing their reabsorption. Colestyramine is used in the following indications:

- Reduction of serum cholesterol levels and prevention of coronary heart disease
- For the relief of pruritus associated with partial biliary obstruction
- As an adjunct to rehydration therapy, for relief of diarrhea due to bile acid malabsorption, associated with the following etiological groups:
 - Diarrhea resulting from disease and/or loss of the ileum;
 - Diarrhea resulting from functional disturbances (organic or surgical)-Crohns disease, vagotomy, diabetic vagal neuropathy or management of radiation induced diarrhoea.

Paediatric dosage: In accordance with Section 4.2 of the SmPC, the initial dose in children aged 6 to 12 years is determined by the following formula:

$$\frac{\text{Childs weight in kg} \times \text{Adult dose}}{70}$$

Subsequent dosage adjustment may be necessary where clinically indicated.

Children under 6 years: The dose has not been established in infants and children under 6 years.

II. RECOMMENDATION

Based on the study review, an indication for colestyramine in acute watery diarrhea of children cannot be supported, because the use of colestyramine does not provide any benefit in this indication as compared to the placebo.

No amendments to the sections of SmPC are proposed and no consequential regulatory action is required.

III. INTRODUCTION

MAH was requested by EMEA and submitted one completed paediatric study for colestyramine, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert statement has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Questran and no amendments to the sections of the product information are proposed.

Therefore no consequential regulatory action is required.

In addition, the following documentation has been included:
PSUR Colestyramine: 02 April 2007 to 01 April 2008

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study

Powder for oral administration

IV.2 Non-clinical aspects

Not applicable.

IV.3 Clinical aspects

Clinical study

Study number 3028, titled "A Double Blind-blind, Randomized, Placebo Controlled Clinical Trial on the use of Cholestyramine in Acute Diarrhea in Children"

The study was conducted from October 01, 1989 to November 23, 1990

Final study report is dated December 18, 1991

Investigator: Perla D. Santos-Ocampo, M.D.

Description: This clinical trial was conducted to determine the efficacy and safety of Colestyramine in acute watery diarrhea in children 3 to 36 months of age.

➤ **Methods**

- Objective(s)

The objectives of the study were as follows:

1. To determine if use of cholestyramine in acute watery diarrhea of infancy and childhood will effectively lead to a reduction in:
 - a. duration of diarrhea, in hours, after initiation of treatment with the drug
 - b. stool output in g/kg admission body weight, on the 24th, 48th and 72nd hour after randomization and total stool output from admission to cessation of diarrhea
 - c. number of stool motions, on 1st, 2nd and 3rd 24 hour interval after randomization and total stool motions from admission to cessation of diarrhea
 - d. Volume of ORS (oral rehydration salts) needed in ml/kg admission body weight for maintenance requirements.
2. To determine if cholestyramine can be safely administered as measured by:
 - e. weight gain (loss) as percentage increase (or loss) at the end of 24, 48th and 72nd hours and after diarrhea stops, compared with admission weight
 - f. occurrence of vomiting in terms of frequency and weight of vomitus
 - g. occurrence of hypo- or hypernatremia
 - h. occurrence of metabolic acidosis
 - i. occurrence of hypo or hyperchloremia

- Study design

The study was a randomized, double-blind placebo-controlled trial with patients assigned to receive either colestyramine or a placebo. Patients were randomly assigned to a formulation. Investigators were blinded to the code.

- Study population /Sample size

Sixty patients (3-36 months of age) were randomized, 51 completed the trial. Comparing the colestyramine group (25) and the placebo group (26). Males only were included, to facilitate urine collection.

- Treatments

Each sachet contained either 2g of colestyramine and 1.65 gm of saccharose or for placebo, 2g microcrystalline cellulose and 1.65 gm of saccharose. The two formulations were identical in appearance and packed in separate similar looking sachets numbered serially.

Patients were monitored and dehydration was corrected using ORS or IV therapy following recommendations of the WHO. A standard WHO-recommended ORS solution (ORESOL) distributed by the Department of Health was utilized for oral rehydration.

➤ **Results**

Mean duration of diarrhea, stool output, frequency of stool motions and ORS intake during the maintenance phase did not differ significantly between the two groups. Weight gain was observed in both groups at the end of the 24th, 48th and 72nd hour and on discharge. Differences in the mean percentage weight gain were not significant.

The use of colestyramine did not result in reported side effects of the drugs, namely persistent vomiting and intestinal obstruction. No patients developed clinically significant biochemical derangements such as hypernatremia, hyperchloremia and metabolic acidosis.

In the colestyramine group a 3 months old child with history of 20 hours diarrhea and dehydration developed an episode of convulsion and was withdrawn from the study.

However as the result, **the efficacy of colestyramine treatment with ORS in acute watery diarrhea in children aged 3 to 36 months does not differ to the placebo treatment with ORS.**

Therefore this clinical trial has reinforced the current recommendations of the World Health Organization concerning treatment of diarrhea.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

MAH submitted one pediatric trial only regarding the medicinal product colestyramine. Colestyramine as an active substance was studied in indication of watery diarrhea only. Submitted trial has not shown any benefit of colestyramine as compared to the placebo. Therefore based on this study, the indication for colestyramine in acute watery diarrhea of children cannot be supported, because the use of colestyramine does not provide any benefit in this indication as compared to the placebo (with ORS in the two groups). **It is concluded that oral rehydration therapy in conjunction with adequate nutritional support during and after diarrheal episodes should remain the main approach in the management of acute diarrhea in children.**

Colestyramine as an active substance was not studied in the main indication -reduction of plasma cholesterol in hypercholesterolaemia.
 Based on the submitted data no amendments of Summary of Product Characteristics are required.
 And no further regulatory action is required.

➤ **Overall conclusion**

Based on the one study only provided by MAH, the indication for watery diarrhea cannot be supported. Other indications of colestyramine as lipids lowering drug, as drug in the treatment of pruritus or detoxification have not been studied.

➤ **Recommendation**

No further regulatory action is required.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable

VII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

COLESTYRAMINE		
Marketing Authorization Holder	For country	Name of product
Bristol-Myers Squibb GesmbH, Columbusgasse 4 1101 Vienna, Austria	Austria	QUANTALAN sugar free
Bristol-Myers Squibb Belgium SA Chaussée de La Hulpe, 185 1170 BRUSSELS	Belgium	Questran, powder for oral suspension.
AKIS PANAYIOTOU & SON LTD P.O. BOX 22578 1522 Nicosia CYPRUS	Cyprus	Questran, powder for oral suspension
Bristol-Myers Squibb spol. s r.o., Prague, Czech Republic	Czech Republic	QUESTRAN, powder for oral suspension
Bristol-Myers Squibb AB Box 15200 161 15 Bromma Sweden	Denmark	Questran Loc, powder for oral suspension
Bristol-Myers Squibb AB Box 15200 167 15 Bromma Sweden	Finland	Questran, powder for oral suspension

COLESTYRAMINE		
Marketing Authorization Holder	For country	Name of product
Bristol-Myers Squibb 3, Rue Joseph Monier 92506 Rueil-Malmaison France	France	Questran
Bristol-Myers Squibb GmbH & Co. KGaA Arnulfstraße 29 80636 München	Germany	Quantalan [®] zuckerfrei, Powder for oral suspension
Bristol-Myers Squibb AB Box 15200 167 15 Bromma, Sweden	Iceland	Questran, powder for oral suspension
BRISTOL-MYERS SQUIBB S.r.l. Via del Murillo, km 2,800 Sermoneta (LT), Italy.	Italy	Questran 4 g powder for oral suspension
Bristol-Myers Squibb Holdings Limited, t/a Bristol-Myers Pharmaceuticals, Swords, County Dublin.	Ireland	QUESTRAN, Powder for Oral Suspension
Bristol-Myers Squib B.V. Vijzelmolenlaan 9 3447 GX Woerden	Netherlands	Questran [®] , powder for oral suspension 4 g Questran [®] -A, powder for oral suspension 4 g
Bristol-Myers Squibb AB Box 15200, S-167 15 Bromma, Sweden	Norway	Questran 4 g, powder for oral suspension
Bristol-Myers Squibb AB Box 15200, S-167 15 Bromma, Sweden	Norway	Questran Loc 4 g, powder for oral suspension
Bristol-Myers Squibb Farmacêutica Portuguesa, SA. Edifício Fernão de Magalhães, Quinta da Fonte 2780 Porto Salvo	Portugal	QUANTALAN, Powder for oral suspension.
Bristol-Myers Squibb spol. s r.o., Olivova 4, 110 00 Praha 1, Czech Republic	Slovakia	Questran Sugar free
Bristol-Myers Squibb AB Box 15200 167 15 Bromma, Sweden	Sweden	Questran 4 g powder for oral suspension
Bristol-Myers Squibb AB	Sweden	Questran Loc 4 g powder for

COLESTYRAMINE		
Marketing Authorization Holder	For country	Name of product
Box 15200 167 15 Bromma, Sweden		oral suspension
Bristol-Myers Squibb Holdings Limited t/a Bristol-Myers Pharmaceuticals Uxbridge Business Park Sanderson Road Uxbridge Middlesex UB8 1DH	UK	QUESTRAN, powder for oral suspension
Bristol-Myers Squibb Holdings Limited t/a Bristol-Myers Pharmaceuticals Uxbridge Business Park Sanderson Road Uxbridge Middlesex UB8 1DH	UK	QUESTRAN LIGHT, powder for oral suspension

MS COMMENTS:

No comments were received from member states.