COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Colestyramine sugar-free 4 g Focus, powder for oral suspension

(colestyramine)

NL Licence RVG 124229

Date: 20 July 2020

This module reflects the scientific discussion for the approval of Colestyramine sugar-free 4 g Focus, powder for oral suspension. The marketing authorisation was granted on 6 January 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
GCA	Glycocholic Acid Sodium Salt Hydrate
GCDA	Sodium glycochenodeoxycholate
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TDCA	Sodium taurodeoxycholate hydrate
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Colestyramine sugar-free 4 g Focus, powder for oral suspension from Focus Care Pharmaceuticals B.V.

The product is indicated for:

1. Reduction of increased concentrations of total cholesterol and LDL-cholesterol in patients with primary and secondary hypercholesterolemia as addition to diet and other measures, when the response to these is insufficient.
2. Relief of pruritus associated with partial biliary obstruction.
3. Treatment of diarrhoea:
   a. resulting from illness and/or ileal resection, choleraic diarrhoea
   b. resulting from vagotomy, radiation-induced diarrhoea and partial gastrectomy

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a hybrid application. Colestyramine sugar-free 4 g Focus, powder for oral suspension was developed with the aim of achieving and establishing pharmaceutical equivalence and *in vitro* bioequivalence with the innovator product, Questran Light 4 g powder for oral suspension as marketed in the EU by Bristol Myers Squibb since 1971. In the Netherlands the innovator product Questran-A, 4 g powder for oral suspension (NL Licence RVG 14276) was registered by CHEPLAPHARM Arzneimittel GmbH on 4 February 1991.

Colestyramine is considered a locally applied, locally acting product. It is an insoluble substance with high molecular weight, given in relatively big particles which do not dissolve or disintegrate. For this reason, after oral administration, colestyramine, like other ion exchange resins of similar characteristics, is 100% excreted unchanged from the intestinal tract by the faecal route.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, as bioequivalence cannot be demonstrated through bioavailability studies.
To support this hybrid application, the MAH has submitted as report four *in vitro* equivalence studies.

II. QUALITY ASPECTS

II.1 Introduction

Colestyramine sugar-free 4 g Focus is a white or almost white fine powder with slight orange odour, packed in single-dose sachets. Each sachet contains 4 grams of the active substance

colestyramine. Before administration the powder is mixed with water, or fruit juice or other liquid. The packaging is a multilayer complex composed of paper/polyethylene/aluminium/ polyethylene.

The excipients are: natural orange flavour (maltodextrin, acacia (E414), flavouring preparation, flavouring substances, natural flavouring substances, butylhydroxyanisole (E320)), propylene glycol, xanthan gum (E415), citric acid (E330), aspartame (E951), silica colloidal anhydrous.

II.2 Drug Substance

The active substance is colestyramine, an established active substance described in the European Pharmacopoeia (Ph. Eur.). The active substance is a white or almost white powder and is insoluble in water. Polymorphism and stereochemistry are not applicable for this active substance. The substance is manufactured by two suppliers.

The CEP procedure is used for one manufacturer of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph. Eur.

For the other manufacturer of the active substance the Active Substance Master File (ASMF) procedure is used. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process for the active substance from the first manufacturer is covered by the CEP; therefore no details on the manufacturing process have been included.
The manufacturing process in the ASMF is adequately described. The starting materials are acceptable. No class 1 solvents nor any heavy metal catalysts are used during synthesis. Water is the solvent used in the last step of synthesis.

Quality control of drug substance

The drug substance specification of the MAH is in line with the Ph. Eur. and contains additional tests for microbiological quality, particle size and an impurity. The specification is acceptable in view of the route of synthesis and the various European guidelines.

Batch analytical data demonstrating compliance with the drug substance specification have been provided for five full-scaled batches of drug substance from the ASMF-holder and four full-scaled batches from the CEP-holder.

Stability of drug substance

The active substance from the CEP-holder is stable for 2 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Stability data on the active substance have been provided for eleven full-scale batches stored at 25°C/60% RH (60 months) and two full-scale batches stored at 40°C/75% RH (6 months). No significant changes are observed. The proposed retest period of 60 months and storage condition 'Preserve in the airtight original packaging' without temperature restrictions are acceptable.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. A physical comparison of the test and reference product as well as *in vitro* bioequivalence studies have been provided. The qualitative compositions of the test product for commercial-scale batches and the reference product are the same. In addition, the test and reference product have the same quantitative composition with regards to the drug substance.

The initial composition, as used for the primary stability batches and for the batch used in the bioequivalence in vitro studies, is identical to that proposed for commercialisation with the exception that the initial composition included an additional 0.03 g/sachet of colouring agent sunset yellow FCF (E 110; complies with EC 231/2012). The removal of this colouring agent is justified. No differences in performance, quality or stability of the drug product are expected based on the presence of this excipient. Furthermore, the qualitative compositions of the test and reference product are the same, when sunset yellow FCF is not included in the composition as is the case for the batch formula for marketing. The exchange capacities (assay) of the test and reference product differ less than 5% and the reference product, sourced from Sweden, is representative for the Dutch market.

The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process exists of sieving, mixing and packaging. The product is manufactured using conventional manufacturing techniques. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot-scale batches. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with Ph. Eur. requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, exchange capacity, degradation products, elemental impurities, uniformity of dosage units (mass variation), loss on drying and microbiological quality. The release and shelf-life requirements/limits are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches with the composition proposed for commercialisation and six pilot-scale batches (with active substance from both suppliers) with the composition including sunset yellow FCF. All batches demonstrate compliance with the release specification.

Stability of drug product
Stability data on the product have been provided for six pilot-scaled batches (three batches with active substance from each supplier) stored at 25°C/60% RH (up to 60 months), 30°C/65% RH (1 year) and 40°C/75% RH (6 months) The conditions used in the stability studies are according to the ICH stability guideline and the batches were stored in the proposed commercial packaging. No significant changes were observed in accelerated or intermediate conditions, but a significant decrease in exchange capacity was observed in long-term conditions. A shelf life of 48 months without special storage conditions has been granted, as it is covered by real time stability data. The product is stable when exposed to light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Colestyramine sugar-free 4 g Focus, powder for oral suspension has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Colestyramine sugar-free 4 g Focus is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Questran-A, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Colestyramine is a well-known active substance with established efficacy and tolerability. It has been on the market for a long time, i.e. more than four decades in Europe and it has been widely used. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the MEB agreed that no further clinical studies are required.

Colestyramine is an insoluble substance with high molecular weight, given in relatively big particles which do not dissolve or disintegrate. For this reason, after oral administration, colestyramine, like other ion exchange resins of similar characteristics, is 100% excreted unchanged from the intestinal tract by the faecal route (Thomson WG, 1971[1]). Therefore, studies on bioavailability and bioequivalence of the product are not applicable.

To support this hybrid application, the MAH has submitted as report four *in vitro* equivalence studies:

- two equilibrium binding studies (with and without acid pre-treatment)
- two kinetic binding studies in 0.3 mM aqueous bile acid salts solution (with and without acid pre-treatment).

[1] Thompson WG: Cholestyramine. Can Med Assoc J 104:305–309, 1971

The reference product used in the quality and in vitro comparison is Questran Loc 4 g powder for oral suspension from the Swedish market.

The studies were conducted in line with recommendations from US Draft Guidance on Cholestyramine, FDA (June 2015). The studies are based on monitoring and recording the amount of bile acid salts absorbed by colestyramine when it is in contact with a solution in excess of bile acid salts.

IV.2 Pharmacokinetics

IV.2.1 Equilibrium binding studies

Methods

The equilibrium binding studies have has been conducted under conditions of constant time and varying concentrations of bile acid salts (0.1,0.3, 1.0, 3.0, 7.0, 10.0, 20.0, and 30.0 mM).

For test and reference products, the amount of bile acid salts (expressed in µmoles and as percentage) bound to colestyramine (10 mg) has been calculated, taking into account the concentration of bile acid salts obtained in the solution at equilibrium and the initial concentration introduced into the system.

A mix of different bile acid salts were used: Glycocholic Acid Sodium Salt Hydrate (GCA), Sodium taurodeoxycholate hydrate (TDCA), and sodium glycochenodeoxycholate (GCDA).
One equilibrium study has been conducted in intestinal fluid without acid pre-treatment and one with acid pre-treatment. For the acid treatment, the product has been soaked in 0.1 N hydrochloric acid (1:1 w/v) at 37°C for 1 hour. It has been centrifuged and the supernatant has been aspirated. The product has been washed with SIF until pH 6.8 is attained. Finally, it has been dried before use.

The Langmuir binding constants k1 and k2 should be determined based on total bile salt binding (GCA+GCDA+TDCA). The T/R ratio have been calculated for k1 and k2 and the 90% confidence interval (CI) has been calculated for k2 using the Minitab 16 statistical software.
The binding of bile acid salts, at constant temperature, could be described by the following Langmuir-type equation:

$$\frac{C_{eq}}{x/m} = \frac{1}{k_1 x\, k_2} + \frac{C_{eq}}{k_2}$$

Ceq = Concentration of the bile acid salt remaining in the solution at the end of incubation time (µmol/mL)
x/m = µmol of bile acid salt bound per mg of resin
k1 = Affinity constant, it is related to the magnitude of the forces involved in the binding process
k2 = Langmuir-capacity constant, it indicates the apparent maximum amount of a bile acid salt that can be adsorbed per unit weight of colestyramine

Results

Next graphics correspond to Langmuir equation representation:sorption isotherms obtained for the equilibrium bile acid salts from simulated intestinal fluid at 37°C by test and reference product.

Figure 1. Equilibrium study in intestinal fluid without acid pretreatment

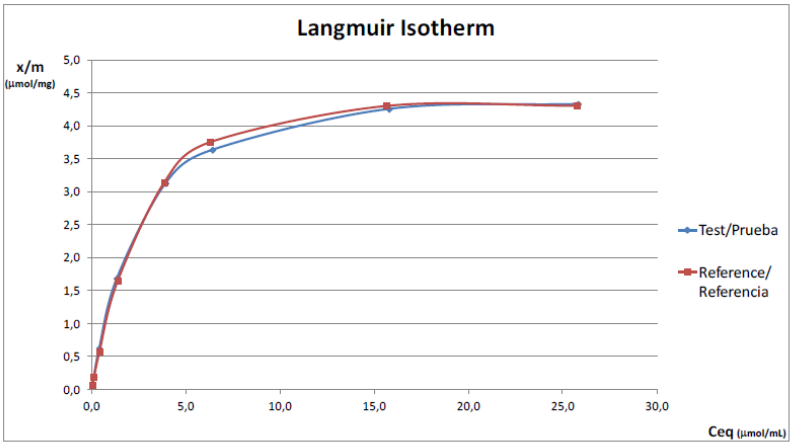
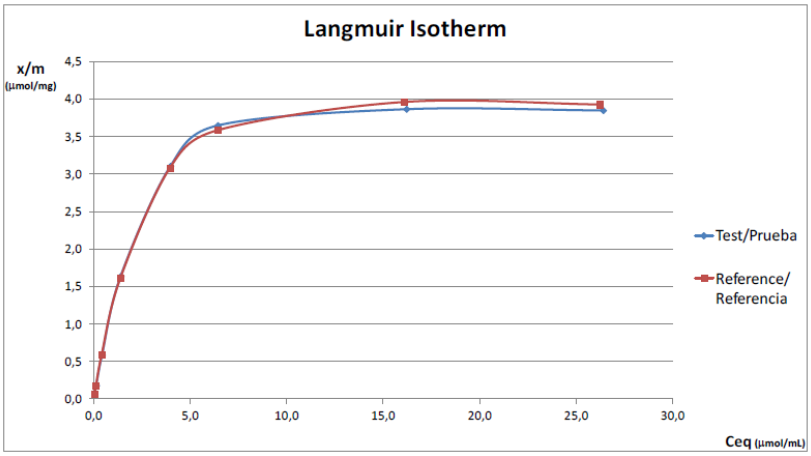


Figure 1

Figure 2. Equilibrium study in intestinal fluid with acid pretreatment



Micromoles and percent binding of bile acid salts to 10 mg of resin at each concentration is presented in tables below.

Table 1. Binding of bile acids to 10 mg of resin in intestinal fluid with acid pretreatment

	Test		**Reference**	
mM	**µmol**	**%**	**µmol**	**%**
0,1	0,6646	66,07	0,6292	62,54
0,3	1,9376	64,21	1,8435	61,09
1,0	6,2166	61,80	5,8204	57,87
3,0	16,8470	55,83	16,4360	54,47
7,0	31,2981	44,45	31,4632	44,68

10,0	36,3676	36,15	37,5609	37,34
20,0	42,5677	21,16	43,0587	21,40
30,0	43,3083	14,35	43,0784	14,28

Table 2. Binding of bile acids to 10 mg of resin in intestinal fluid with acid pretreatment

	Test		**Reference**	
mM	**µmol**	**%**	**µmol**	**%**
0,1	0,6558	65,04	0,6150	60,99
0,3	1,7778	58,78	1,7879	59,11
1,0	5,8583	58,11	5,8855	58,38
3,0	16,3824	54,17	16,1406	53,37
7,0	31,0963	44,06	30,8437	43,71
10,0	36,5227	36,23	35,8769	35,59
20,0	38,6959	19,19	39,6422	19,66
30,0	**38,5307**	12,74	**39,3044**	13,00

The equivalence results are presented in the tables below.

Table 3. Equivalence results equilibrium binding study without acid pre-treatment

k_1 Affinity constant		**Test**	**Reference**	**Ratio**
	Mean	0.4210	0.3917	1.1
	SD	0.03	0.03	

k_2 Capacity constant		**Test**	**Reference**	**Ratio**	**BE criteria**
	Mean	4.7909	4.8357	1.0	
	SD	0.17	0.11		
	90% CI	97% - 101%			90% – 110%

Table 4. Equivalence results equilibrium binding study without acid pre-treatment

k_1 Affinity constant		**Test**	**Reference**	**Ratio**
	Mean	0.4778	0.4585	1.0
	SD	0.07	0.09	

k_2 Capacity constant		**Test**	**Reference**	**Ratio**	**BE criteria**
	Mean	4.2615	4.3681	1.0	
	SD	0.22	0.34		
	90% CI	95% - 101%			90% – 110%

IV.2.2 Kinetic binding study

Methods

The kinetic binding studies have been conducted by incubating test and reference product for eight different lengths of time, and with two constant concentrations (0.3mM and 3mM) of bile acid salts in the presence of sodium chloride.

Results

Micromoles and percent binding of bile acid salts to 10 mg of resin at each time point is presented in the tables below.

Table 1. Binding of 0.3mM bile acids to 10 mg of resin

Time(hr)	Test		Reference		Ratio
	mM	%	mM	%	
0.25	1.6928	56.15	1.4529	48.19	1.2
0.50	1.6876	55.98	1.4780	49.02	1.1
1.0	1.7928	59.46	1.5652	51.91	1.1
2.0	1.8370	60.93	1.6139	53.53	1.1
4.0	1.9558	64.87	1.9972	66.24	1.0
8.0	2.0269	67.23	2.0589	68.29	1.0
16.0	2.1274	70.56	2.0123	66.74	1.1
24.0	2.0849	69.15	2.0376	67.58	1.0

Table 6. Binding of 3mM bile acids 3mM to 10 mg of resin

Time(hr)	Test		Reference		Ratio
	mM	%	mM	%	
0.25	12.6096	41.82	11.6583	38.66	1.1
0.50	13.3013	44.11	12.9002	42.78	1.0
1.0	13.9861	46.38	14.4527	47.93	1.0
2.0	14.1851	47.04	14.7493	48.91	1.0
4.0	14.9997	49.74	15.7655	52.28	1.0
8.0	15.6045	51.75	17.3148	57.42	0.9
16.0	16.3987	54.38	16.6857	55.33	1.0
24.0	**17.8003**	**59.03**	**18.0636**	**59.90**	**1.0**

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Colestyramine sugar-free 4 g Focus, powder for oral suspension.

Table 7. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The MEB agrees that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Questran-A. No new clinical studies were conducted. The clinical pharmacology, efficacy and safety of colestyramine is well known and has been adequately described in the submitted clinical overview. The indications applied for are identical to the approved indications of the originator Questran-A.

The EMA published the draft Guideline on equivalence studies for the demonstration of therapeutic equivalence for products that are locally applied, locally acting in the gastrointestinal tract as addendum to the guideline on the clinical requirements for locally applied, locally acting products containing known constituents (23 March 2017 CPMP/EWP/239/95 Rev. 1). According to this draft guideline, for those locally applied, locally acting products with a mechanism of action based on binding to components of the GI milieu through the whole intestine (e.g. cholestyramine, colestipol, calcium acetate, sevelamer) *in vitro* studies based on their binding capacity (e.g. *in-vitro* equilibrium and dynamic binding studies) are considered acceptable surrogates for the assessment of efficacy, as long as excipients are not critical and disintegration and dissolution profiles in the physiological pH range are similar.

The equilibrium binding studies have been appropriately conducted. Equivalent sorption has been shown for test and reference product. In the kinetic binding studies both products had similar adsorption profiles over time. Adsorption is fast, at the first timepoint the adsorption is close to maximum for both concentrations of bile acid. Based on the submitted *in vitro* equivalence studies Colestyramine sugar-free 4 g Focus powder for oral suspension is considered equivalent with Questran-A 4 g powder for oral suspension.

Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with 4 participants, followed by two rounds with 10 participants each. The developed questionnaire contained 15 questions specific to Colestyramine sugar-free 4 g Focus and 3 specific to the format of the package leaflet. The questions addressed all the key safety issues and concerns. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Colestyramine sugar-free 4 g Focus, powder for oral suspension has a proven chemical-pharmaceutical quality and is a hybrid form of Questran-A 4 g powder for oral suspension. Questran is a well-known medicinal product with an established favourable efficacy and safety profile.

Based on *in vitro* equivalence studies Colestyramine sugar-free 4 g powder for oral suspension is considered equivalent with Questran-A4 g powder for oral suspension.

The Board followed the advice of the assessors.
The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Colestyramine sugar-free 4 g Focus was authorised in the Netherlands on 6 January 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse