20 November 2014
EMA/CHMP/473530/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sevelamer carbonate Zentiva

International non-proprietary name: Sevelamer carbonate

Procedure No. EMEA/H/C/003971

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Sevelamer carbonate Zentiva
Applicant:	Genzyme Europe BV Gooimeer 10 1411 DD Naarden The Netherlands
Active substance:	sevelamer carbonate
International Nonproprietary Name:	Sevelamer carbonate
Pharmaco-therapeutic group (ATC Code):	Sevelamer (V03AE02)
Therapeutic indication(s):	Sevelamer carbonate Zentiva is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis. Sevelamer carbonate Zentiva is also indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus $\geq$ 1.78 mmol/L. Sevelamer carbonate Zentiva should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy Vitamin D_3 or one of its analogues to control the development of renal bone disease.
Pharmaceutical forms:	Film-coated tablet; Powder for oral suspension
Strengths:	2.4 g and 800 mg
Route of administration:	Oral use

Packaging:	bottle (HDPE) and sachet (LDPE)
Package sizes:	180 tablets, 60 sachets and 90 sachets

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List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan

1. Background information on the procedure

1.1. Submission of the dossier

The applicant sanofi-aventis recherche et développement submitted on 5 June 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Sevelamer carbonate Zentiva, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 February 2014.

The applicant applied for the following indication:

> Sevelamer carbonate Zentiva is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis.
>
> Sevelamer carbonate Zentiva is also indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus > 1.78 mmol/L.
>
> Sevelamer carbonate Zentiva should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy Vitamin D3 or one of its analogues to control the development of renal bone disease.

The legal basis for this application refers to:

Article 10(c) of Directive 2001/83/EC – relating to informed consent from a marketing authorisation holder for an authorised medicinal product.

The application submitted is composed of administrative information together with a letter from Genzyme Europe BV allowing use to be made of relevant quality, non-clinical and/or clinical data of the original marketing authorisation for Renvela.

This application was submitted, in accordance with Article 82.1 of Regulation (EC) No 726/2004**,** as a multiple of Renvela authorised on 10 June 2009.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Not applicable

Market exclusivity

Not applicable

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application. The original medicinal product Renvela was approved in the EU on 10 June 2009.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

Genzyme Ireland Limited
IDA Industrial Park
Old Kilmeaden Road
Waterford
IRELAND

Genzyme Limited
37 Hollands Road
Suffolk
Haverhill
CB9 8PU
UNITED KINGDOM

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bart Van der Schueren Co-Rapporteur: Johann Lodewijk Hillege

- The application was received by the EMA on 5 June 2014.
- The procedure started on 27 July 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 01 September 2014.
- During the meeting on 25 September 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 September 2014.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 October 2014.
- During the meeting on 23 October 2014, the CHMP adopted updated List of Questions.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 03 November 2014.
- During the meeting on 20 November 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Sevelamer carbonate Zentiva.

2. Scientific discussion

2.1. Introduction

This application has been submitted in accordance with Council Regulation 726/2004, by the applicant sanofi-aventis recherche et développement on behalf of Genzyme Europe B.V. , a Sanofi Company, for an Informed Consent Marketing Authorization Application for Sevelamer carbonate Zentiva (sevelamer carbonate), as per Article 10c of Directive 2001/83/EC.

In February 20th, 2014, the EMA confirmed that this application was eligible for submission for a Community Marketing Authorisation under "automatic access" for duplicate applications.

During the February CHMP meeting, the Rapporteur Dr Bart Van der Schueren was appointed.

The reference product, Renvela (EMEA/H/C/000993), which was first authorised in the Community through the Centralised Procedure on 10 June 2009, is indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis and for the control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus > 1.78 mmol/L.

This marketing authorization application contains a Module 1 only. For the quality, pre-clinical and clinical data, reference is made to the documentation approved for the reference product, Renvela.

A letter of Informed Consent was annexed to the application form (annex 5.2). In this annex the Marketing Authorisation Holder, Genzyme Europe B.V., provides the applicant, sanofi-aventis recherche et développement, full consent to access all data contained in the Renvela Marketing Authorisation for the purpose of this Informed Consent Application.

2.2. Quality aspects

As Sevelamer carbonate Zentiva is submitted under an informed consent application, article 10(c) of directive 2001/83/EC, only module 1 is provided and module 3 of the duplicate dossier cross-refers to the up-to-date module 3 of the original dossier (Renvela), which have been assessed and approved, including all post-marketing procedures.

2.3. Non-clinical aspects

2.3.1. Introduction

Since this application is an informed consent of the Renvela application, the non-clinical data in support of the Sevelamer carbonate zentiva application are identical to the up-to-date quality data of the Renvela dossier, which have been assessed and approved, including all post-marketing procedures.

2.3.2. Environmental risk assessment

In accordance with the scope described in the CHMP guideline, given that this application is for products that are already authorized, the absence of a phased approach ERA as specified in the guideline, is considered justified in that the total quantity of the drug substance sevelamer carbonate is not expected

to increase upon approval of this marketing authorization. Consequently, marketing approval would not add to the environmental impact.

2.3.3. Conclusion on the non-clinical aspects

In this informed consent application, there are no issues related to the non-clinical data, which have been assessed for Renvela application and adequately reflected in the Product Information.

2.4. Clinical aspects

As Sevelamer carbonate Zentiva is submitted under an informed consent application, article 10(c) of directive 2001/83/EC, only module 1 is provided and module 2 of the duplicate dossier cross-refers to the up-to-date module 2 of the original dossier (Renvela), which has been assessed and approved. No new clinical data is provided.

2.5. Clinical safety

RMP version 6 was provided with this submission.

This RMP version 6 being strictly identical to the RMP approved for the reference product Renvela at the end of the Renewal Procedure (EMA/H/C000993/R/0027), no further assessment of the present RMP is deemed necessary.

The MAH was requested to replace “Renvela” by the correct Product Name “Sevelamer carbonate Zentiva” throughout the RMP.

Below is a short overview of the content of the Risk Management Plan which is identical to Renvela:

Summary of the safety concerns

The following table summarizes the ongoing safety concerns with sevelamer carbonate.

Summary of the safety concerns

Important identified risks	Intestinal obstruction/ileus – intestinal perforation
Important potential risks	Peritonitis in peritoneal disease patients
	Arteriovenous fistula site complications in hemodialysis patients
	Difficulty swallowing Renvela tablets
	Off-label use in children
	Drug interactions with ciprofloxacin, ciclosporin, mycophenolate mofetil, levothyroxine and tacrolimus
	Vitamin deficiency
Important missing information	Data on use in hyperphosphataemic chronic kidney disease patients on peritoneal dialysis
	Data on use in hyperphosphataemic chronic kidney disease patients not on dialysis with serum phosphorus ≥ 1.78 mmol/l
	Use in pregnancy and lactation
	Use in hepatic impairment and immunocompromised patients

Pharmacovigilance Plan

III.5.1. Table of ongoing and planned additional pharmacovigilance studies/activities in the pharmacovigilance plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Epidemiological report of the risk of peritonitis in relation to sevelamer hydrochloride (Renagel ®) and sevelamer carbonate (Renvela ®) use in peritoneal dialysis patients based on data collection and analysis patients based on data collection and analysis conducted by the French Peritoneal Dialysis Registry (RDPLF) Phase I & II (cat 3)	To determine the risk of peritonitis in relation to Renvela in PD patients	Peritonitis in PD patients	4th annual report and 5 year bridging report submitted in PBRER on 09 July 2013	Annual submission with a DLP of 31 December for 5-10 years.

The 4th annual report of the risk of peritonitis in relation to sevelamer conducted by the Registre de Dialyse Péritonéale de Langue Française (RDPLF) being completed to date, the MAH was requested to move this study from the "Table of ongoing and planned additional pharmacovigilance studies/activities in the pharmacovilance plan" (III.5.1) to the "Table of completed studies from the post-authorization pharmacovigilance plan" (III.5.2) below.

III.5.2. Table of completed studies from the post-authorization pharmacovigilance development plan

Table 3 - Completed studies from the post-authorization pharmacovigilance development plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of final study report
Drug utilization studies - Utilisation of Renvela (cat 3)	To monitor frequency of Renvela use in hyperphosphataemic CKD patients not on dialysis with serum phosphorous ≥ 1.78 mmol/L	Use in hyperphosphataemic CKD patients not on dialysis with serum phosphorous ≥ 1.78 mmol/L	Completed	30-Jun-2011 (PSUR 4)
	To monitor frequency of Renvela use in hyperphosphataemic CKD patients on peritoneal dialysis	Use in hyperphosphataemic CKD patients on peritoneal dialysis		
	To monitor frequency of Renvela use in patients less than 18 years	Off-label use in children		
Post-authorisation safety study (PASS) – SVCARB06009 Renvela® post-marketing observational study to monitor the clinical use in adult hyperphosphataemic chronic kidney disease patients not on dialysis with serum phosphorus > 1.78 mmol/L (FUM 007) (cat 3)	To monitor the clinical use in hyperphosphataemic CKD patients not on dialysis with serum phosphorous ≥ 1.78 mmol/L	To monitor the clinical use in hyperphosphataemic CKD patients not on dialysis with serum phosphorous ≥ 1.78 mmol/L	Completed	09-Jul-2013 (PBRER 5)

Risk Minimization Measures

The below table summarizes the proposed risk minimization activities that will be performed in order to ensure the safe use of sevelamer carbonate in hyperphosphataemic CKD patients.

Table 12 – Summary of risk minimization measures

Safety concern	Routine risk minimization activities	Additional risk minimization activities
Important identified risks		
Intestinal obstruction/ileus - Intestinal perforation	SmPC	None
Important potential risks		
Peritonitis in PD patients	SmPC	Educational materials for patients and healthcare professional
AVF site complications in HD patients	None	Educational materials for patients and healthcare professionals
Difficulty swallowing sevelamer carbonate tablets	SmPC	None
Off-label use in children	SmPC	None
Drug interactions with ciprofloxacin, ciclosporin, mycophenolate mofetil, levothyroxine and tacrolimus	SmPC	None
Vitamin deficiency	SmPC	Educational materials for patients and healthcare professional
Important missing information		
Data on use in hyperphosphataemic CKD patients on PD	SmPC	None
Data on use in hyperphosphatemic CKD patients not on dialysis with serum phosphorus ≥1.78 mmol/L	SmPC	None
Data on the use of sevelamer carbonate in pregnant or lactating women	SmPC	None
Data on the use of sevelamer carbonate in patients with hepatic impairment, immunocompromised patients	None	None

2.6. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The CHMP considered that the risk management plan version 6 is acceptable.

3. Benefit-Risk Balance

This Marketing Authorisation application for Sevelamer Carbonate Zentiva has been submitted by Genzyme Europe BV as an informed consent application in accordance with Article 10c of Directive 2011/83/EC, as amended.

As a consequence, quality, safety and efficacy of the Sevelamer Carbonate Zentiva medicinal product are identical to the up-to-date quality, non-clinical and clinical profile of Renvela. The application for Sevelamer Carbonate Zentiva concerns the identical strengths to those approved for Renvela and consists of only Module 1. Information on the scientific discussion can be found on the Renvela CHMP assessment reports and in the European Public Assessment Report (EPAR) published on the EMA website.

Consequentially, and in line with the assessment of data undertaken in the framework of the Renvela initial marketing authorisation application as well as within all post-autorisation procedures, the CHMP considers that the benefit/risk balance for Sevelamer Carbonate Zentiva is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Sevelamer Carbonate Zentiva in the treatment for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis. Sevelamer carbonate Zentiva is also indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus $\geq$ 1.78 mmol/L. Sevelamer carbonate Zentiva should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy Vitamin D_3 or one of its analogues to control the development of renal bone disease.

Is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

  The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management system (RMP)**

  The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent

updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.