CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Creon granulaat, gastro-resistant granules
Abbott B.V., the Netherlands

pancreatin

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 107907

18 March 2013

Pharmacotherapeutic group:	digestives incl. enzymes; enzyme preparations
ATC code:	A09AA02
Route of administration:	oral
Therapeutic indication:	exocrine pancreatic insufficiency in children and adults
Prescription status:	prescription only
Date of authorisation in NL:	15 November 2011
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Creon granulaat, gastro-resistant granules from Abbott B.V. The date of authorisation was on 15 November 2011 in the Netherlands.

The product is indicated for exocrine pancreatic insufficiency in children and adults.

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

This national procedure concerns a line extension to the registered products Creon 150 mg and 300 mg, modified-release capsules (NL License RVG 10656, 16055) and Creon Xtra forte 400 mg, gastro-resistant capsules (NL RVG 33166). The first marketing authorization was granted on 27 June 1988 for Creon 150 mg. This line extension concerns a different strength and pharmaceutical form.

The pellets of Creon granulaat have the same composition and the same normalized label claim as the pellets of Creon (forte) 300 mg that has been registered for over 20 years, but the particles have a lower average diameter.

The rationale for the development of this product is the gain in accuracy that is reached by the use of a small dose (5000 lipase units) allowing flexible dosing and offering the possibility to adapt the dose to the body weight and the meals of neonate and young children in a more adequate way.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the previous Creon authorisations. This information is not fully available in the public domain. Authorisations for line extensions are therefore linked to the ‘original’ authorised medicinal product. Reference is made to the non-clinical and clinical studies performed with Creon capsules. The MAH provided the results of 2 clinical studies, both regarding the same primary parameter of the coefficient of fat absorption (CFA). Assessment is discussed in section II.3 ‘Clinical aspects’.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a line extension.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is pancreatin (= “pancreas powder”), an established substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is partially soluble in water. It is a porcine pancreatic extract and comprises a mixture of enzymes with lipolytic, proteolytic and amylolytic activities (lipase, protease, amylase). Full dossier data of the drug substance have been provided.

Manufacturing process
The manufacturer is laid down. The manufacturing process is described in the dossier, including the reagents and solvents used, and the in-process controls. No class 1 organic solvents are used. Adequate criteria are included for the solvents and reagents, and also regarding the critical steps.
The manufacturing process is the same as that used for the registered pancreatin containing products (Creon/Creon forte/Creon Xtra forte gastro-resistant capsules) of the same MAH.

Quality control of drug substance
The drug substance specification is in line with the Ph. Eur. and contains criteria for additional quality aspects. Regarding viral quality the concerns first raised have been adequately solved.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for six production batches.

Stability of drug substance
The same stability studies have been submitted as for the registered products; justifying the claim for a retest period of 12 months when stored below 30 °C.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Creon granulaat are round, light brown granules. The product is presented per 20 grams packaged in a glass bottle, with a separate spoon as dosing device. The dosing unit is 100.00 mg pellets. The content of drug substance (pancreatin, pancreas powder) in 100 mg pellets is 60.12 mg, containing an activity of 5000 Ph. Eur. units lipase, 3600 Ph.Eur. units amylase and 200 Ph.Eur. units protease.

The excipients are:
Pellet core - macrogol 4,000;
Coating - hypromellose phthalate, cetyl alcohol, triethyl citrate, dimethicone 1,000.

The qualitative and quantitative composition of the different pellet strengths versus the registered capsules is identical, *i.e.* the quantities stated per gram of gastro-resistant pellets for pancreatin and the excipients apply to all strengths. The Creon granulaat pellets represent a smaller pellet size range vs. the pellets contained in the registered capsules. For the present product, the only difference with the pellets in the capsules is the smaller pellet size of 0.7-1.0 mm.

Pharmaceutical development

The development of the product has been described, the choice of the excipients is justified and their functions explained. Pancreas powder enzymes are the extracted mixture of enzymes of the pancreas. The stability of the enzymes is dependent on the pH of the gastrointestinal tract. It has been found that lipase and amylase are rapidly and irreversibly inactivated at pH values below 6. This key chemical characteristic is the reason for developing an enteric coated product, which protects the amylase and lipase activity until they reach the duodenum.
A product concept was created whereby the smallest possible, regularly shaped pancreas powder particles, so-called minimicrospheres or pellets can be produced and coated with gastro-resistant film, whereas the Creon granulaat pellets represent a smaller pellet size range vs. the pellets contained in the registered capsules. This was also the case with the batches in the pivotal clinical studies. The pellets products developed on the basis of this concept show significant differences from traditional products:

- Complete protection of the acid-sensitive pancreatic enzymes throughout passage through the acidic gastric region and rapid release of the enzymes on entry into the only weakly acidic to neutral duodenal region, where the enzymes exhibit local action.

The choices of the packaging and manufacturing process are justified.

Manufacturing process
The manufacturing process is the same as for the pellets in the registered capsules: premixing & wet mixing, formation of the (uncoated) pellets, spheronisation, drying and sieving, enteric coating and sieving. The manufacturing process has been adequately validated according to relevant European guidelines. Adequate process validation data on the product has been presented on several production batches of the pellets used in the capsules, regarding all critical parameters.

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

Quality control of drug product
The product specification includes tests for appearance, identity, enzymes activities, water content, residual solvents, microbiological purity and dissolution. Release and shelf-life limits are the same except for enzymes activities and water content, and are acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three production batches, demonstrating compliance with the release specification.

Dose uniformity
The packaging and the dosing device are acceptable. The results for uniformity of dosage units (Ph. Eur. 2.9.40) have been submitted regarding mass variation. Dose uniformity and accurate dosing of the spoon have sufficiently been demonstrated. Considering the design of the spoon it also seems possible for the user to adequately dose the pellets.

Stability of drug product
Stability data have been submitted on three production batches, stored in the proposed bottle for 37 months at 25°C/60% RH and 30°C/65% RH, and 6 months at 40°C/75% RH. The results justify the shelf-life of three years, with no special storage conditions, in the colourless glass bottle with LDPE stopper.
In-use stability studies have been submitted, justifying the in use shelf-life of three months, when stored below 25°C.

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. Virus safety has been demonstrated sufficiently.

II.2 Non-clinical aspects

Pancreatin has been available the European market for over 20 years. A non-clinical overview of the studies performed with regard to the pharmacology, pharmacokinetics and toxicology has been provided,

which is based on non-clinical studies and supported by 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 Board agreed that no further non-clinical assessment is required.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of pancreatin released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Benefit/risk assessment
The efficacy and safety of Creon 150 mg and 300 mg, modified-release capsules and Creon Xtra forte 400 mg, gastro-resistant capsules ant capsules are well established. They are registered and in use in the Netherlands since 1988, 1994 and 2006, respectively.
Creon granulaat pellets represent a smaller pellet size range vs. the pellets contained in the registered capsules. Otherwise these pellets are identical to the pellets of all Creon capsules (Creon 150 mg, 300 mg and 400 mg).The quality aspects of these products are comparable. The composition of Creon granules is more homogeneous and the separate pellets are the smaller fraction. The composition of the pellets and the other physical properties are not changed. It may therefore be assumed that the same efficacy and safety data apply for Creon granules.

Creon granules is a locally applied product (the active components are not absorbed as such), and this is why clinical pharmacokinetic research is missing.

Since 1960 the lipase activity as the main enzyme is the international accepted parameter for the activity of the whole product.

In accordance with the guidelines on locally applied products clinical studies have to be presented for the assessment of efficacy and safety.

From a large experience over more than 20 years documented in many clinical studies with Creon capsules and also from both studies with Creon granules, there are no doubts about a good safety profile of both products.

The most commonly reported adverse reactions were gastrointestinal disorders and were primarily mild or moderate in severity. Gastrointestinal disorders are mainly associated with the underlying disease. Similar or lower incidences compared to placebo were reported for abdominal pain and diarrhea.

Studies in patients with liver disease or renal insufficiency are also lacking. Because pancreatin is not absorbed from the digestive tract, this is acceptable.

The dosing prescriptions are sufficiently founded on the basis of international guidelines (especially for children) and against the background of a clinical experience of 20 years with Creon capsules.
The activity proportions between lipase, amylase and protease activities in the Creon pellets are the same as for Creon forte 300 mg and different regarding the other capsule strengths. The inaccuracy that is inherent in the use of a calibrated spoon is surpassed by the gain in accuracy that is reached by the use of a small dose (5000 lipase units) in the calibrated spoon allowing flexible dosing and offering the possibility to adapt the dose to the body weight and the meals of neonate and young children in a more adequate way.

Sufficient understanding regarding the pharmacodynamics (PD) has been delivered by several preclinical studies with Creon capsules and Creon granules to offer a firm ground for the efficacy of both products regarding the fat-absorption. The activity of the exogenous lipase is comparable to the activity of the

endogenous lipase in children as well as in adults with a coefficient of fat absorption of around 80% in the case of exogenous lipase. There is also sufficient proof of a statistically significant equivalent efficacy of Creon capsules and Creon granulate in 2 clinical studies (one pivotal and one supportive) both regarding the same primary parameter of the coefficient of fat absorption (CFA) and this effect is clinically relevant.

Pivotal study S245.3.118
This was an open-label, cross-over, randomized, reference-controlled, multi-center trial in 40 infants (between 6 and 36 months of age) with pancreatic exocrine insufficiency (PEI) due to cystic fibrosis (CF) that aimed to investigate the parent preference for Creon for children (Creon granulate) over Creon 12.000 (pancreatin capsules containing 12.000 U lipase) on a lipase per lipase basis, and to further evaluate the effect of pancreatic enzyme replacement therapy (PERT) on the Coefficient of Fat Absorption (CFA), stool weight, fecal energy, and clinical symptomatology (stool frequency, abdominal pain, and flatulence).

The results indicated that in the ITT subject sample, 20 parents (51%) preferred Creon granulate, nine (23%) preferred Creon 12.000, and 10 (26%) had no preference. This was close to statistical significance ($p = 0.0662$), using Prescott's test. In the probability-proportional-to-size (PPS) subject sample 19 parents (50%) preferred Creon micro, nine (24%) preferred Creon 12 000, and 10 (26%) had no preference ($p = 0.0911$). Furthermore, CFA was similar for both treatments, mean (standard deviation (SD)) CFA was 77.7% (13.1%) for Creon granulate and 78.7% (14.0%) for Creon 12.000 (not significant: $p = 0.3513$, Wilcoxon test). Of note, the mean unit lipase intake per kg body weight and day was slightly lower for Creon granulate than for Creon 12.000: means (SD) were 3969 (2333) for Creon granulate and 4310 (2763) for Creon 12.000, and both were lower than at baseline (4488 [3039]). No major differences between treatments were seen for the other efficacy parameters.
The study concluded that Creon micro was preferred by the majority of subjects (parents) over Creon 12.000 with the same efficacy on the basis of comparable lipase dose administration.

Supportive study S248.3.003
This open-label, baseline controlled, multi-center study was designed mainly to evaluate the efficacy of Creon granulate in 12 infants, aged 1-23 months with proven diagnosis of CF and PEI and a CFA < 70%. The primary efficacy parameter was CFA, secondary efficacy parameters were steatorrhea, fecal energy loss, stool characteristics, gastrointestinal symptoms, response (CFA > 90%), hematological and biochemical parameters, nutritional parameters, and patient acceptance. The analysis of the results showed that the primary efficacy parameter, CFA, significantly increased from a baseline mean of 58.0% to a mean of 84.7% after two weeks (mean increase 26.7%, $p = 0.0013$, paired t-test). At baseline, all subjects had steatorrhea, and after treatment seven subjects (58%) had steatorrhea. Mean stool fat decreased by 7.98 g/day, and mean fecal energy decreased by 100.6 kJ/day. Both decreases were statistically significant ($p = 0.0013$ and $p = 0.0177$). No major changes were seen for hematological and biochemical parameters with the exception of increases of vitamins A and E. Height and weight increased, but the weight for height percentile remained nearly constant and close to 100%. Subject acceptance of therapy was very good for the majority of the subjects.

In summary, Creon micro was efficacious regarding the improvement of the CFA, stool fat excretion, and fecal energy loss in infants with PEI due to CF. The subject acceptance was mostly very good

The presented studies offer sufficient evidence of efficacy and safety of Creon granulate in small children. These studies do not deliver a definite proof of superiority above treatment with other Creon products.

In conclusion, the benefit-risk balance is positive. The efficacy and safety of Creon granulate are at least comparable to Creon. Creon granulate offers extra possibilities for adequate dosing, especially in the youngest age groups.

Risk management plan
The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. A risk management plan has been provided.

Safety concern	Proposed action	Description	MEB assessment
Potential risks			
Fibrosing colonopathy	Routine pharmacovigilance	-	approved
	PSURs	-	approved
	SPC	A warning has been included in section 4.4 of the SPC.	Fibrosing colonopathy have been reported in cystic fibrosis patients taking high doses of pancreatin preparations.
	PIL	A warning has been included.	Approved
	United States observational study (United States patient registry)	Estimate the incidence and risk factors for FC in US patients with CF taking Creon.	Interim report and final report of the study should be submitted when completed.
Viral exposure from the product source	Routine pharmacovigilance	-	
	Enhanced Pharmacovigilance	-	
	SPC	A warning has been included in section 4.4.	Approved
	PIL	none	
	United States epidemiological study (point prevalence design)	To evaluate the risk of transmission of selected porcine viruses.	Interim report and final report of the study should be submitted when completed.

Product information

SPC
The content of the SPC approved during the national procedure is in accordance with those accepted for Creon capsules.

Readability test
The package leaflet has not been evaluated via a user consultation study. Reference is made to the successfully user tested PIL for Creon capsules. There are no significant differences between the content of the parent and daughter leaflet because they contain the same active substance for different formulations. The most critical information for safe and effective use is the same for both leaflets. The overall layout, design and writing style of the leaflet being bridged is similar to the tested leaflet. No separate user testing is required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Creon granulaat, gastro-resistant granules has a proven chemical-pharmaceutical quality and is a legitimate line extension of Creon 150 mg, 300 mg and 400 mg capsules. Creon capsules is a well-known medicinal product with an established favourable efficacy and safety profile.

The efficacy of Creon granulate was demonstrated to be comparable to Creon. From a large experience over more than 20 years documented in many clinical studies with Creon capsules and also from both studies with Creon granules, there are no doubts about a good safety profile of both products.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of Creon capsules. The SPC, package leaflet and labelling are in the agreed templates.

In the Board meeting of 24 March 2011, the quality and clinical aspects of the new pharmaceutical form were discussed. The Board decided that the benefit-risk ratio is positive.

The MEB, on the basis of the data submitted, has granted a marketing authorisation. Creon granulaat, gastro-resistant granules was authorised in the Netherlands on 15 November 2011.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CF	Cystic Fibrosis
CFA	Coefficient of Fat Absorption
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PEI	Pancreatic Exocrine Insufficiency
PERT	Pancreatic Enzyme Replacement Therapy
PIL	Package Leaflet
PPS	Probability-proportional-to-size
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Transfer of the marketing authorisation.	--	MA transfer	5-10-2011	2-1-2012	Approval	N
Response to questions regarding viral safety information.	--	--	15-12-2011	27-1-2012	Approval	N
Change in the name and/or address of a manufacturer (including where relevant quality control sites) or supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the product dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier. Change in the name and/or address of a manufacturer of the finished product, including quality control sites.	--	IA/G	25-9-2012	11-10-2012	Approval	N