Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Pancreatic extract

Proprietary Product Name: Creon Micro

Sponsor: Abbott Products Pty Ltd

February 2011

TGA Health Safety Regulation

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- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Contents

I. Introduction to Product Submission **4**
Submission Details 4
Product Background 4
Regulatory Status 5
Product Information 6
II. Quality Findings **6**
Drug Substance (active ingredient) 6
Drug Product 6
Bioavailability 7
Quality Summary and Conclusions 7
III. Nonclinical Findings **7**
IV. Clinical Findings **8**
Introduction 8
Pharmacokinetics 8
Drug Interactions 9
Pharmacodynamics 9
Efficacy 11
Safety 23
List of Questions 29
Clinical Summary and Conclusions 29
V. Pharmacovigilance Findings **30**
VI. Overall Conclusion and Risk/Benefit Assessment **30**
Quality 30
Clinical 31
Risk-Benefit Analysis 32
Outcome 33
Attachment 1. Product Information **33**

I. Introduction to Product Submission

Submission Details

Type of Submission	New formulation
Decision:	Approved
Date of Decision:	28 September 2010
Active ingredient(s):	Pancreatic extract
Product Name(s):	Creon Micro
Sponsor's Name and Address:	Abbott Products Pty Ltd Locked Bag 1070, Pymble, NSW, 2073
Dose form(s):	Granules, enteric coated minimicrospheres
Strength(s):	60.12 mg corresponding to 5 000 lipase units per scoop
Container(s):	Glass bottle
Approved Therapeutic use:	Creon Micro is indicated as pancreatic enzyme replacement in paediatric and adult patients with pancreatic exocrine insufficiency (PEI). Pancreatic exocrine insufficiency is often associated with, but not limited to: - Cystic fibrosis, - Chronic pancreatitis, - Pancreatic surgery, - Gastrointestinal bypass surgery (for example, Billroth II gastroenterostomy), - Ductal obstruction of the pancreas or common bile duct (for example, from neoplasm).
Route(s) of administration:	Oral
Dosage:	The dose of Creon Micro required is adjusted according to the fat content of the meal and the severity of the disease. For details see the Product Information (PI) document.
ARTG Number (s)	166118

Product Background

Porcine pancreatic enzyme extract, containing various concentrations of lipase, amylase and protease for pancreatic enzyme replacement in conditions associated with pancreatic exocrine insufficiency, has been available in Australia for over 30 years. Solvay Pharmaceuticals Australia Pty Ltd (now Abbott Products Pty Ltd) has submitted a Category 1 application to register Pancreatic Extract (Creon Micro) enteric-coated minimicrospheres, thereby completing the conversion of the sponsor's Creon product range to dibutyl phthalate (DBP) – free formulations. DBP has been associated with safety concerns in the past. Creon Micro (Pancreatin, minimicrospheres, 5,000 lipase BP[1] units) has the same enzyme activity per gram minimicrospheres as Creon 25,000, but the minimicrospheres have a smaller size. The smaller particle size facilitates swallowing of the medicine by infants, young children and older patient, unable to swallow capsules. Concomitantly, the sponsor is updating the product

[1] ***units*** of enzyme activity. 1 ***BP unit*** equals 1 European Pharmacopoeia (***PhEur) unit.***

information documents. The sponsor intends to withdraw the DBP containing product Creon 5,000 pancreatic extract 75 mg capsule following approval of Creon Micro which is intended as a replacement.

The following DBP-free pancreatic extract (Creon) dosage forms and strengths are currently approved by the TGA:

- Creon 40,000 pancreatic extract 400 mg capsule
- Creon 25,000 pancreatic extract 300 mg capsule
- Creon 10,000 pancreatic extract 150 mg capsule

No changes are proposed to the currently approved formulations of Creon 10,000, Creon 25,000 and Creon 40,000. The sponsor contends that all Creon minimicrosphere (MMS) products are the same formulation but different dose strengths. Hence, clinical data from different dose strengths have been submitted in support of the present application.

The **current indication** section for each of the Creon capsule strengths reads:

"*Creon capsules are indicated as pancreatic enzyme replacements in conditions associated with pancreatic exocrine insufficiency (PEI) such as cystic fibrosis, chronic pancreatitis, post pancreatectomy, post-gastrointestinal bypass surgery (for example, Billroth II gastroenterostomy) and ductal obstruction.*"

The **proposed expansion** to the indications of each strength and dosage form of Creon products in the proposed updated product information reads:

"*Creon is indicated as pancreatic enzyme replacement in paediatric and adult patients with pancreatic exocrine insufficiency (PEI).*

Pancreatic exocrine insufficiency is often associated with, but not limited to:

- *cystic fibrosis*
- *chronic pancreatitis*
- *pancreatic surgery*
- *gastrointestinal bypass surgery (for example, Billroth II gastroenterostomy)*
- *ductal obstruction of the pancreas or common bile duct (for example, from neoplasm)*
- *gastrectomy*
- *pancreatic cancer*
- *Shwachman-Diamond Syndrome*
- *acute pancreatitis"*

Based upon Australasian Clinical Practice Guidelines for nutrition in Cystic Fibrosis 2006, the key goal of pancreatic enzyme replacement therapy is to improve the patient's nutritional status and growth as well as controlling symptoms of maldigestion (for example, steatorrhoea). This is achieved through optimal dietary intake using a diet without restriction of fat content (> 100 g fat per day if over five years of age), unless the patient is overweight. The dose of Creon required is adjusted according to the fat content of the meal and the severity of the disease.

Regulatory Status

Abbott's pancreatin is currently registered in over 85 countries worldwide under the trade names Creon, Kreon, Pankreon, Pankreozym, Pancrin and Papine. Creon Micro is registered in Argentina (15th September 2006), Ireland (23rd June 2006), the United Kingdom (3rd August 2004) and Germany (28th November 2005).

The registration status for Creon 5,000 (Pancreatin) as per the sponsor is (Table 1):

Table 1.

Country	Registration Name	Registration Number	Registration Date	Launch Date
Argentina	Creon 5,000 Pediátrico	53232	15-Sep-2006	Not available
Ireland	Creon for Children 5,000 Gastro-Resistant Granules	PA 108/025/004	23-Jun-2006	01-Jan-2007
United Kingdom	Creon Micro Pancreatin 60.12 mg	PL 00512/0179	03-Aug-2004	09-Jan-2004
Germany	Kreon für Kinder	6076233.00.00 (ENR: 0076233)	28-Nov-2005	15-Apr-1994

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

The drug substance manufacturing process for Creon Micro is identical to that currently registered for Creon 25,000 pancreatic extract 300mg capsule bottle (AUSTR 158452). The drug product for Creon Micro is derived from the same drug substance batch as for Creon 25,000 but having smaller sized minimicrospheres. The manufacturing process for Creon 25000 has been recently reviewed by the TGA and will not be reviewed here.

Drug Product

Pancreas powder gastro resistant pellets 5,000 are brownish pellets. 20 g pellets are filled in a colourless glass bottle (type I or type III) with a low-density polyethylene stopper. A dosing spoon which acts as a dosing device is also packed in the unit carton containers. The content of Pancreas Powder in one dosing unit of 100.00 mg pellets is 60.12 mg corresponding to 5000 lipase units. One dosage unit is measured with a dosing spoon as dosing device.

Manufacture

The product is manufactured as per other Creon products and is a direct product of the approved manufacturing process used for Creon Pancreas Powder gastro-resistant Pellets 25,000 (AUST R 158452). The pellets used for the 5,000 drug product are obtained by using pellets of a smaller size within set limits. Creon 5,000 does not undergo a sterilisation process due to the nature of the product however strict microbiological limits are in place throughout the manufacturing process.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product and appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product.

The proposed shelf life is 2 years when stored below 25°C. In-use stability data have also been submitted. The proposed shelf life and storage condition for the opened product is 12 weeks when stored below 25°C.

The label states "Store below 25°C in a dry place. Keep container tightly closed. Do not use if the seal is broken or missing. Use within 3 months after opening"

Bioavailability

No new data were submitted under this heading.

Quality Summary and Conclusions

The administrative, product usage, chemical, pharmaceutical and microbiological information submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

Issues of concern

Recommendation for registration was given following clarification from the sponsor regarding issues relating to container closure and label requirements.

III. Nonclinical Findings

- The nonclinical dossier for Creon Micro is identical to that submitted to support the registration of the DBP-containing form of Creon 40,000 (AUST R 143137) which contains substantially higher concentrations of lipase (40,000) amylase (25,000) and protease (1,600). The original data have not been re-evaluated for this application unless identified as necessary to substantiate proposed text in the PI documents.

- Similar to Creon 5,000 capsules, Creon Micro contains the lowest concentrations of lipase (5,000 BP units) amylase (3600 BP units) and protease (200 BP eq. units) of the Creon product range but it does not contain the excipient DBP which has been associated with safety concerns in the past.
- There are no nonclinical issues regarding the registration of Creon Micro because:
  - à The non clinical package to support the registration of Creon 40,000 (evaluated according to current standards in 2008) did not identify safety concerns regarding this higher-strength product and no objections to registration were raised on nonclinical grounds.
  - à Creon Micro is a direct, 1/5th, down-scaled version of Creon 25,000 mg capsule (AUST R 158452) which was registered on the basis of chemistry and quality control data only and for which non clinical data were deemed not to be required.
  - à The major formulation difference between Creon Micro and registered Creon forms is that the former is presented as free granules/microspheres rather than encapsuled granules/minimicrospheres. This is not considered to be an important difference from a toxicological view-point. Further, the dosage instructions for the existing encapsulated forms already recommend the capsules be opened and the contents added to soft food (with a low pH) for those with swallowing difficulties.

Conclusions and recommendations

There are no nonclinical objections to the registration of Creon Micro.

IV. Clinical Findings

Introduction

One study was submitted in support of pharmacokinetics, *Study S245.2.003*. Data from six clinical studies were submitted in support of pharmacodynamics (PD). The studies were: *Study KREO.629, Study S248.2.001, Study S245.3111, Study S245.4004, Study K224.5.011,* and *Study S245.3107*.

A total of 19 studies were submitted in support of efficacy. There were nine studies submitted in support of efficacy in subjects with pancreatic exocrine insufficiency (PEI) due to cystic fibrosis (CF): *Study S245.3.126, Study S223.3.101, Study S223.3.102, Study S245.3.105, Study K245.5002, Study K245.5004, Study S248.3002, Study S245.3118,* and *Study S245.3003*. There were three studies in subjects with PEI due to CP: *Study S223.2.01, Study K245.5005* and *Study S245.3.115*. There were two comparator controlled studies in subjects with CP or post-pancreatectomy: *Study K245.5003* and *Study S248.3.001*. There were two studies in subjects with acute pancreatitis: *Study S248.4.001* and *Study S248.4.002*. There was one study conducted in subjects post-gastrectomy: *Study S248.3.102*. There were two studies conducted in subjects with diabetes mellitus: *Studies S245.3.112* and *S245.3.113*.

The data presented in the submission were predominantly from previously marketed formulations. However, the safety of the active ingredient is demonstrated in this data, and in addition, the active ingredient has been marketed for several decades.

All the studies presented in the submission were stated to conform to Good Clinical Practice.

Pharmacokinetics

One study was submitted in support of pharmacokinetics, ***Study S245.2.003***. This was a double-blind crossover "bioequivalence" study in subjects with PEI due to chronic pancreatitis. The study compared duodenal lipase activity for the DBP free formulation of Creon compared with the DBP containing formulation. In order to measure duodenal lipase activity each subject had a double-lumen duodenal tube and a separated single-lumen naso-gastric tube inserted under fluoroscopic control. The study formulations were:

- The DBP free Creon formulation (in the study report called "the to be marketed product" (TbMP)) MMS[2] 12,000, 5 capsules, total dose 60,000 lipase units (as proposed for Creon Micro).
- The DBP containing Creon formulation (in the study report called "the currently marketed product" (CMP)) MMS 10,000, 5 capsules, total dose 60,000 lipase units. Each treatment was administered as a single dose.

Fourteen subjects were randomised and included in the safety population. Nine subjects were analysed in the efficacy population. All subjects were male and the age range was 37 to 66 years. The mean (standard deviation (SD)) pancreatic lipase (polyethylene glycol (PEG)-corrected) activity in the duodenum was 282528 (265442) U for TbMP and 282787 (288778) U for CMP. The point estimate was 1.13 for the relative lipase activity, (TbMP/CMP) which was within the equivalence range specified in the study protocol (0.70 - 1.43). However, the 95% CI for the point estimate were 0.76 to 1.69 and were outside of the range. When non-PEG corrected overall lipase activity was analyzed, mean values were 141885 (152894) U for TbMP and 114030 (112369) U for CMP with a point estimate of 1.12 (0.70 to 1.80) for the

[2] Minimicrospheres trade mark

relative lipase activity. Mean (SD), overall PEG-corrected PPL activity at the duodenum was 95025 (66308) U for TbMP and 94061 (93393) U for CMP. The point estimate for the relative lipase activity was 1.11 (0.68 to 1.81). There was no significant difference between treatments in pyloric or duodenal outputs of fatty acids.

Evaluator's overall conclusions on pharmacokinetics

Bioequivalence was not demonstrated by the normally accepted criteria. However, pancreatic lipase is not absorbed into the body and the sponsor has demonstrated similar lipase activity at the point of action which is the duodenum.

Drug Interactions

No new data submitted under this heading.

Pharmacodynamics

Study Kreon 629 *was an open-label study with a six-day placebo run-in period followed by a six day treatment period under Kreon in CF-patients. Healthy children served as controls. The radioactively labelled carbon dioxide ($^{13}CO_2$) breath test with ^{13}C-labelled hiolein (a mixture of ^{13}C-labelled long chain triglycerides) was used for the non-invasive determination of exocrine pancreatic function in healthy subjects and in patients with cystic fibrosis. The study treatments, in the CF patients, were:*

- *Placebo, for a 6 day run-in period*
- *Kreon, 1500 U/kg, 1000 U/g fat intake, for a 6 day treatment period*

Hence, the children with cystic fibrosis were treated with placebo for a 6 day run-in period followed by Kreon for 6 days, while the healthy controls did not receive any treatment. The pharmacodynamic outcome measures were: the hydrogen (H_2)-value (parts per million (ppm)) and delta-value (‰), determined by the rice breath test and also by the combined rice-hiolein breath test. The delta-value describes the ^{13}C concentration of the taken breath sample in reference to the known concentration of a standard gas according to the formula:

$$\text{Delta } ‰ = \frac{R_p - R_{ST}}{R_{ST}} \times 1000$$

, whereby R_p = isotope ratio of the sample and R_{ST} = isotope ratio of the standard

The values of each measured time point and of the area under the curve (AUC) up to each time point were analysed for both parameters; H_2 and delta-value.
The study included eleven children with CF aged 5 to 14 years: seven (63.6%) female, and four (36.4%) male. The controls were twelve children aged 6 to 15 years of which 50% were males. Delta values were lower in untreated than in treated CF patients. Delta-values were similar for untreated patients and healthy children and there was no significant difference between treatment with Kreon and placebo. H_2-values were higher for untreated patients compared with healthy children and CF children treated with Kreon. H_2-values were similar during treatment with Kreon and placebo. Stool fat content and overall weight were higher in untreated CF patients and stool chymotrypsin was lower (see Table 2).

Table 2. Summary of stool analysis volunteers versus patients. All subjects.

	Volunteers (N = 12)	Patients	
		Placebo (N = 7)	Kreon® (N = 11)
Stool fat (g/24h)			
Geometric mean	1.8	10.9	5.6
Median	2.8	10.9	6.6
Range	0.4 - 3.5	2.1 - 33.5	1.6 - 15.8
p-value[b]	-	0.004	0.011
Stool weight (g/24h)			
Geometric mean	44.2	140.3	67.7
Median	66.2	137.7	65.7
Range	8.3 - 116.7	70.0 - 353.7	24.7 - 188.3
p-value[b]	-	0.002	0.325
Chymotrypsin[a]			
Geometric mean	10.8	1.0	3.7
Median	11.9	0.6	5.1
Range	1.9 - 23.9	0.1 - 6.0	0.6 - 8.3
p-value[b]	-	0.002	0.002

[a] N = 11 for volunteers
[b] the p-values give the results of the two-sample Wilcoxon test comparing patients vs. volunteers

Study S248.2.001 *was an open label, single centre, single treatment study of the effects of Creon MMS on triglyceride digestion and gastric emptying time in children with CF compared with healthy controls. The measure of fat digestion was pulmonary excretion of ^{13}C-octanoate (gastric emptying) and ^{13}C-triglyceride (lipase activity). The study treatment was Creon MMS 25,000, given in two single dose treatments on Day 1 and Day 5 prior to test meals. The study included eleven otherwise healthy children with PEI due to CF, with an age range of 5 to 19 years; seven males and four females. As controls there were eleven healthy volunteers, with an age range of 5 to 20 years; four males and seven females. There was no significant difference between the treated CF patients and the controls in pancreatic lipase activity or in gastric emptying time.*

Study S245.3111 *was a single centre, randomised, open label, three way, crossover study of equivalence of effect using the ^{13}C-mixed triglyceride breath test. The initial study was followed by a non-randomised study comparing gastric emptying using the ^{13}C-octanoic breath test in subjects with CF and healthy volunteers. The study treatments were: Creon MMS, Pancrease and placebo. The treatments were administered as a single dose of 2500 lipase units per gram fat. The study included 21 subjects with PEI due to CF, with an age range 4 to 17 years, eleven (52.4%) female, ten (47.6%) males. Twelve of these subjects were entered into a follow up study in comparison with 13 healthy volunteers; age range 9 to 18 years, five (38.5%) females, eight (61.5%) males. There was no significant difference in effect between Creon and Pancrease for ^{13}C-mixed triglyceride breath test. There was no difference between subjects with CF and healthy volunteers in the ^{13}C-octanoic breath test.*

Study S245.4004 was a double-blind crossover study investigating the dose-dependent effect of Creon on fat assimilation in comparison with placebo. The study was conducted at two centres using the ^{13}C-triglyceride breath test. The four dose levels were:

- Placebo
- Creon MMS 5000 (one capsule with 5,000 FIP[3] units of lipase),
- Creon MMS 15,000 (three capsules each with 5,000 FIP units of lipase),
- Creon MMS 40,000 (four capsules each with 10,000 FIP units of lipase)

Dosing was based per 15 g fat meal. There were three single doses on three separate study days with a 3-7 day washout period. The study included twelve children with PEI due to CF; age range 4 to 31 years; seven (58.3%) females; five (41.7%) males. The outcome measure was cumulative % of exhaled $^{13}CO_2$ after 6 hours (shown as % of dose). There was a significant difference between placebo and all Creon doses and between the high dose and low doses Creon (but not between the high and medium doses of Creon) in fat assimilation.

Study K224.5.011 was a double-blind crossover study to compare the passage through the pylorus of enteric-coated pancreatic enzyme pellets in subjects with PEI caused by chronic pancreatitis. Subjects were treated with Creon 25,000 MMS or placebo and tested using the cholesteryl- ^{13}C-octanoic breath test. The study was terminated prematurely because of inadequate recruitment rates. Data were available for analysis for only four subjects with PEI. No conclusions could be drawn from the study.

Study S245.3107 was a double-blind, placebo-controlled, randomized cross-over study with a volunteer control group in an open design. The main objective was to investigate the effect of Creon 10,000 MMS on gastrointestinal function in patients with pancreatic exocrine insufficiency due to chronic pancreatitis. Insufficient subjects with PEI were recruited (four of a planned sample size of eight) and the study was terminated early. The pharmacodynamic data were not analysed.

Evaluator's overall conclusions on pharmacodynamics

Creon MMS increases fat absorption in subjects with pancreatic insufficiency. The clinical evaluator was not clear as to whether any studies were conducted with the formulation that is proposed for marketing in Australia. The sponsor later confirmed that throughout all clinical studies gastro-resistant granules (minimicrospheres) have been used and most of the studies were performed with the previously registered formulation containing DBP (dibutylphthalate).

Efficacy

Efficacy data in subjects with PEI due to CF

Study S245.3.126 was a multicentre, double-blind, randomised, placebo-controlled, cross-over study to assess the efficacy and safety of pancrelipase delayed release 24,000 Unit capsule in subjects with PEI due to CF. The study was conducted at ten centres in the US.

The study included subjects 12 years or older with:

- confirmed diagnosis of cystic fibrosis (CF) by two sweat tests or gene analysis.
- confirmed pancreatic exocrine insufficiency by historical CFA < 70% without supplementation or current or historical faecal elastase < 50 μg/g stool (tested within the last 12 months).
- currently receiving treatment with a commercially available pancreatic enzyme product on a stable dose for more than 3 months.
- clinically stable condition without evidence of acute respiratory disease or any other acute condition.

[3] 1 ***FIP unit=*** 1 European Pharmacopeia unit= 1 British Pharmacopeia unit = 4.15 US Pharmacopeia units

· stable body weight defined as no more than a 5% decline within the previous 3 months.

The study treatments were:

· Pancrelipase delayed release 24000 unit capsules were to be administered to achieve a dose of 4000 lipase units/g fat based on the prescribed fat intake per meal/snack
· Placebo

The treatment duration was 2 weeks, with 5 to 6 days of treatment with pancrelipase. Subjects were randomized to treatment sequence using an Interactive Voice Response System (IVRS).

The primary efficacy outcome measure was the comparison of CFA in the pancrelipase delayed release and placebo treatment periods. The CFA was calculated from fat intake and fat excretion according to the following formula: CFA (%) = 100 [fat intake – fat excretion] / fat intake. Secondary efficacy outcome measures were: the comparisons of coefficient of nitrogen absorption (CNA), stool fat, stool weight, and clinical symptomatology in the pancrelipase delayed release and placebo treatment periods. The safety outcome measures were: adverse events (AEs), vital signs, physical examination, and safety laboratory values. Hypothesis tests were performed using analysis of variance (ANOVA). The sample size calculations assumed a difference of 14% in CFA, a standard deviation of 20% and an effect size of 0.7. It used a two sided level of significance of 0.05 and a power of 90% and resulted in a sample size of 24.

A total of 32 subjects were randomised and 31 out of these completed the study. The age range was 12 to 43 years; 21 (65.6%) were male, and 11 (34.4%) were female. Thirty one subjects were Caucasian and one was Hispanic. There was a significant increase in fat absorption with pancrelipase: least squares mean (95% CI) difference in CFA (pancrelipase - placebo) was 39.02 (range 32.26 to 45.79) p<0.001. There was a significant increase in nitrogen absorption with pancrelipase: least squares mean (95% CI) difference in CNA (pancrelipase - placebo) was 35.20 (range 29.63 to 40.78) p<0.001. There was a significant decrease in stool weight, fat content and nitrogen content in subjects treated with pancrelipase compared with placebo (Table 3).

Table 3. Summary of Stool Fat, Stool Weight, and Stool Nitrogen by Treatment Group Modified Full Analysis Sample.

Parameter	Statistic	Pancrelipase (N=30)	Placebo (N=29)	Pancrelipase - Placebo (N=29)	P-Value [1]
Stool Fat (g)	n	29	29	29	
	Mean (SD)	51.7 (40.9)	237.9 (110.7)	-186.2 (100.3)	
	Median	40.0	221.0	-193.0	
	Min/Max	9/202	45/493	-424/23	
	LS Mean (SE) [1]	51.8 (12.9)	239.0 (12.9)	-187.2 (18.2)	<0.001 **
	LS Mean 95% CI [1]	(25.4, 78.2)	(212.6, 265.4)	(-224.5, -149.8)	
Stool Weight (g)	n	29	29	29	
	Mean (SD)	589.0 (271.3)	1569.3 (683.7)	-980.4 (533.5)	
	Median	567.0	1493.0	-902.0	
	Min/Max	102/1374	560/3149	-2244/-62	
	LS Mean (SE) [1]	590.0 (69.6)	1574.3 (69.6)	-984.4 (98.5)	<0.001 **
	LS Mean 95% CI [1]	(447.1, 732.8)	(1431, 1717)	(-1186.4, -782.3)	
Stool Nitrogen (g)	n	29	29	29	
	Mean (SD)	8.41 (5.39)	29.00 (13.21)	-20.59 (9.42)	
	Median	7.50	28.50	-21.00	
	Min/Max	1.4/31.0	9.0/69.8	-39.8/-5.6	
	LS Mean (SE) [1]	8.40 (1.20)	29.09 (1.20)	-20.69 (1.69)	<0.001 **
	LS Mean 95% CI [1]	(5.95, 10.86)	(26.64, 31.54)	(-24.16, -17.22)	

Study S223.3.101 was a multicentre, randomised, double-blind parallel group with an open label run-in phase. The study included subjects with cystic fibrosis and with clinical pancreatic exocrine insufficiency who were 7-18 years of age. The study was conducted at six centres in the US.

The study treatments were:

1. Creon MMS 20,000. The dose ranged from 1081.77 to 15782.93 lipase units/kg/day.
2. Placebo

The open label phase lasted until subjects were stabilised on Creon and the dose was individualized for each patient while on a high fat diet using clinical symptoms as a guide. The double-blind dose was to be same as that established during open-label treatment and this phase lasted from 2-3 weeks.

Using prior data from Protocol RK.223.00.02, the sample size estimation was for 40 evaluable subjects (20 per treatment), with a Type I error rate of 0.05, standard deviation of 21.54, giving an 80% power to detect a difference of 20 points in change from baseline CFA between Creon and placebo.

A 72 hour stool collection was performed during the run-in phase and also during the treatment phase. The primary efficacy outcome measure was the change from baseline to final assessment in CFA. Secondary efficacy outcome measures were: stool frequency, stool consistency, and clinical global improvement. Hypothesis tests were performed using analysis of covariance.

A total of 47 subjects were entered into the run-in phase, of these 38 were randomised: 20 to placebo and 18 to Creon. A total of 36 subjects completed the study (18 in each group). Of the randomised subjects, 20 (52.6%) were female, 18 (47.4%) were male, 36 (94.7%) were Caucasian, one was Black and one was stated to be of "other race". The age range was 7.0 to 17.9 years. There was no difference in daily fat intake between the treatment groups.

There was a significant difference in CFA between Creon and placebo: the mean (standard error (SE)) was 84.11 (2.22) for the Creon group and 52.15 (5.01) for the placebo group, p=0.000. There was a significantly greater stool fat excretion in the placebo group: the mean (SE) was 20.74 (2.98) for the Creon group and 62.19 (9.53) g/24h for the placebo group, p=0.001. Stool frequency was greater and stool consistency was softer in the placebo group. Global improvement scores were significantly better in the Creon group than in the placebo group (Table 4).

Table 4. Clinical Global Improvement (Intent-to-Treat (ITT) Patient Sample).

Status at Study End Compared to the Beginning of Double-Blind	Placebo		CREON®20		p-value
	19		18		
	N	%	N	%	
VERY MUCH IMPROVED	.	.	.	.	0.000
MUCH IMPROVED	.	.	1	5.6	.
MINIMALLY IMPROVED	1	5.3	3	16.7	.
NO CHANGE	5	26.3	12	66.7	.
MINIMALLY WORSE	7	36.8	2	11.1	.
MUCH WORSE	6	31.6	.	.	.
VERY MUCH WORSE	.	.	.	.	.

p-value based on Cochran-Mantel-Haenszel row mean scores test, controlling for center.
p-value of 0.000 indicates p<0.001.

Study S223.3.102 was a multicentre, randomised, double-blind parallel group study with an open label run-in phase conducted to compare the effectiveness of Creon MMS 20,000 to placebo. The study was sponsored and coordinated by Solvay Pharmaceuticals and conducted at six centres in the US. The study included males and females 18 to 40 years of age; with a diagnosis of cystic fibrosis (documented by sweat chloride results >70 mmol/L); clinical symptoms of exocrine pancreatic insufficiency with a history of steatorrhoea; stabilized on diet; and with a dose of pancreatic enzyme supplementation which provides satisfactory symptom control (that is acceptable stool frequency, stool consistency, flatulence, nausea and abdominal pain) for one month or more as documented by medical history and information collected from the patient during the screening period.

The study treatments were:

1. Creon MMS 20,000. The dose ranged from 979.8 to 12270.1 lipase units/kg/day.
2. Placebo

The open-label Creon dose was individualized for each patient while on a high fat diet using clinical symptoms as a guide. During the double-blind phase the subjects took the same number of Creon capsules as at the end of the open label treatment phase. Treatment duration was 2-3 weeks.

Two 72 hour faecal collections were performed, the first during the open label phase and the second during the double-blind phase. The primary efficacy outcome measure was the change from open-label (baseline) to double-blind (final) assessment in CFA. The secondary efficacy outcome measures were: frequency of bowel movement, stool consistency, and clinical global improvement.

Hypothesis testing was performed using analysis of covariance. Using prior data from Protocol RK.223.00.02, the sample size estimation was for 40 evaluable subjects (20 per treatment) (details outlined above in Study S223.3.101).

A total of 50 subjects entered the open-label phase, of these 36 were randomised to treatment (18 in each group). A total of 34 subjects completed the study: 17 in each group. There were 22 (61.1%) males, 14 (38.9%) females; the age range was 18 to 53.6 years; and all subjects were Caucasian. There was no difference between the groups in daily fat intake.

There was a significant difference in CFA between Creon and placebo: the means (SE) were 87.2 (1.7) and 50.9 (7.3), respectively, p=0.000. There was a significantly greater stool fat excretion in the placebo group: the means (SE) were 19.1 (3.2) and 80.8 (13.6) g/24h for the Creon and placebo groups, respectively, p=0.000. Stool frequency was greater and stool consistency was softer in the placebo group. Global improvement scores were significantly better in the Creon group than in the placebo group (Table 5).

Table 5. Clinical Global Improvement (ITT Patient Sample).

Status at Study End Compared to the Beginning of Double-Blind	Placebo		CREON®		p-value*
	18		18		
	N	%	N	%	
NOT ASSESSED**	.	.	2	11.1	0.000
VERY MUCH IMPROVED	.	.	.	.	.
MUCH IMPROVED	.	.	1	5.6	.
MINIMALLY IMPROVED	.	.	3	16.7	.
NO CHANGE	5	27.8	11	61.1	.
MINIMALLY WORSE	5	27.8	.	.	.
MUCH WORSE	7	38.9	1	5.6	.
VERY MUCH WORSE	1	5.6	.	.	.

* p-value based on Cochran-Mantel-Haenszel row mean scores test, controlling for center, using center pooling. p-value of 0.000 indicates p < 0.001.

** "Not Assessed" category is not included in the test for difference between treatments.

Study S245.3.105 was a multicentre, open-label, crossover study to investigate patients preference for Creon MMS compared with Creon MS. The study was sponsored and coordinated by Solvay Pharmaceuticals and conducted at three centres in the United Kingdom. The study included male or female children with PEI due to CF requiring pancreatic enzyme replacement therapy. A total of 60 subjects were screened, of whom 59 were entered into the study: 57 subjects were included in the safety analysis and 54 were included in the efficacy analysis. The age range was 3 to 17 years; 33 (55.9%) were male, and 26 (44.1%) were female. The study duration was for 10 weeks including a run-in period of 2 weeks, and two treatment phases of 4 weeks each. The study treatments were Creon MMS 10,000 and Creon MS 8,000. The dose was calculated according to lipase units during the run-in period and it was kept constant during the treatment phase. The efficacy outcome measures were: patient preference (determined at the end of each treatment period), stool collection data, clinical symptomatology, clinical global impression of disease symptoms, and patient diary. Hypothesis tests were performed using Chi square, Fisher exact test. The safety outcome measures were AEs and vital signs. Creon MMS was preferred by 47 (87%) of 54 subjects and Creon MS by four (7%) whereas three subjects were undecided (p<0.0001). There was no clinically or statistically significant difference between the treatments for the other efficacy parameters

Study K245.5002 was a multicentre, open-label, crossover study to investigate patient's preference for Creon MMS compared with Creon MS. The study was sponsored and coordinated by Solvay Pharmaceuticals and conducted at 12 centres in France. The study included subjects that were; aged≥4 years, with cystic fibrosis documented by two sweat

tests, or by gene analysis; and had PEI proven by pancreatic function test within the previous 12 months; and were taking pancreatic enzyme therapy for at least 6 months. A total of 70 subjects were enrolled, 69 subjects were randomised, and 55 were included in the efficacy analysis. The age range was 3 to 25 years; 41 (59.4%) subjects were male and 28 (40.6%) were female. The study treatments were Creon MMS 10,000 and Creon MS 12,000. Treatment duration was 4 weeks and included two treatment periods of 2 weeks duration each. The efficacy outcome measures were: subject's preference for treatment; clinical symptomatology (stool frequency, stool consistency and abdominal symptoms); and global evaluations of therapeutic response. Hypothesis tests were performed using the Chi square, Fisher exact test. The safety outcome measures were AEs and vital signs. There was a preference for Creon MMS: 39 (57%) subjects preferred Creon MMS, 16 (23%) preferred Creon MS and 14 (20%) were undecided (p=0.003). There were no clinically or statistically significant differences between the treatments for the other efficacy endpoints.

Study K245.5004 was a multicentre, double-blind, crossover study to demonstrated equivalent effect on CFA for Creon MMS and Creon MS. The study was sponsored and organised by Solvay Pharmaceuticals and conducted at six centres. The study included children aged ≥4 years, with proven CF and PEI who took pancreatic enzyme replacement therapy for at least 6 months prior to entry. The study treatments were Creon MMS 10,000 and Creon MS 8,000. Treatment duration was 7 weeks. The primary efficacy outcome measure was CFA. The secondary efficacy outcome measures were: stool fat, steatocrit, stool weight, clinical symptomatology, clinical global impression of disease symptoms, treatment preference, stool frequency, stool consistency, flatulence, abdominal pain, and a breath test. Hypothesis tests were performed and included ANOVA and a Wilcoxon sign rank test. A total of 34 subjects were enrolled, of which 33 were included in the efficacy analysis. There were 17 (50%) male subjects, 17 female and the age range was 3 to 30 years. For the intention-to-treat (ITT) population analysis, equivalence was not demonstrated as the 95% CI for ratio of CFA Creon MMS / Creon MS was 0.0902 to 1.105, and therefore outside the pre-specified range of 0.905 to 1.105. However, for the per protocol analysis the 95% CI was within the pre-specified range: 0.908 to 1.031. There was no significant difference between treatments in stool parameters. There was no significant difference between the treatments in breath test. There was no significant difference in symptomatology or global measures.

Study S248.3002 was a two centre, randomised, double-blind crossover study to demonstrate that CFA is equivalent for Creon MMS 25,000 and Creon MS 25,000. The study was sponsored and coordinated by Solvay Pharmaceuticals. The study included children aged ≥4 years with PEI caused by CF, and requiring pancreatic enzyme replacement therapy. The study treatments were: Creon MMS 25,000 and Creon 25 000 MS with the dosage determined individually during the run-in period using Creon 8,000 based on lipase units. The sponsor commented that two crossover periods of two weeks duration were performed during which the two Creon 25 000 treatments were administered at one third of the capsules of the run-in period.

The primary efficacy outcome measure was CFA. Secondary efficacy outcome measures were: fat excretion, stool weight, clinical symptomatology, global evaluation of disease symptoms, treatment preference, stool frequency, stool consistency, abdominal pain and flatulence. Hypothesis tests were performed using ANOVA. A total of 34 subjects were screened, 33 were enrolled and 29 were included in the analysis. Twenty eight subjects were evaluated for CFA. Twenty (60.6%) subjects were male, 13 (39.4%) were female, and the age range was 3 to 23 years. Equivalence was demonstrated for CFA since the 90% CI for ratio of CFA Creon MMS / Creon MS was within the pre-specified range of 0.905 to 1.105.

In the ITT analysis: 90% CI for ratio of CFA Creon MMS / Creon MS was 0.990 to 1.085. This was confirmed by the PP analysis. There was no significant difference between treatments in stool parameters. There was no significant difference between treatments in symptomatology. There was no significant difference between treatments in global scores.

Study S245.3118 was a multicentre, randomised, open label reference controlled, crossover study to investigate parents preference for Creon MMS for Children (Creon Micro) over Creon MMS 10,000 (in France approved as Creon 12 000) . The study was sponsored and co-ordinated by Solvay Pharmaceuticals and conducted at 13 centres in France. The study included infants of either gender with PEI due to CF, aged 6 to 36 months, with proven diagnosis of CF (by either two sweat tests or gene analysis) and PEI. The study treatments were:

1. Creon MMS for Children, oral granules
2. Creon MMS 10,000, oral capsules

Dose was determined according to the subject's usual dose of lipase. The study duration was 30 days, including two treatment periods of 2 weeks each. Subjects were block randomised by study site.

The primary efficacy outcome measure was the parent's preference for treatment. Secondary efficacy outcome measures were: CFA, fat intake and excretion, energy intake and excretion, stool weight and clinical symptomatology.

Hypothesis testing used the Prescott's test and the Wilcoxon test. The sample size calculations assumed that 20% of the parents have no preference, 60% of the parents have a preference for Creon for Children and that 20% of the parents have a preference for Creon 10, 000. Applying Prescott's test with a level of significance of 0.05 (two sided, exact) and using a t-test approximation, a statistical power of 80%, 18 subjects per sequence would be required to complete both periods. Assuming a 10% dropout rate, 40 subjects (20 per sequence) would be required.

A total of 40 subjects were randomised and all were included in the safety analysis whereas 39 were included in the ITT analysis: 22 (56.4%) subjects were female, 17 (43.6%) were male. The two treatment blocks were similar in demographic characteristics and in pre-study pancreatic enzyme replacement dosing. There was no significant difference between treatments in parents' preference: 20 (51%) parents preferred Creon for Children, 9 (23%) preferred Creon MMS 10,000 whereas 10 (26%) had no preference (p=0.0662). CFA, mean (SD) was 77.7% (13.1%) for Creon for Children and 78.7% (14.0%) for Creon 10, 000 (p = 0.3513) (Table 6). There was no difference in stool fat content or weight (Table 6). There was no difference between treatments in clinical symptomatology as reported by the investigator or as reported by parents.

Table 6. Efficacy Parameters Related to Stool Collection.

Parameter	Statistic	Creon for children (N=39)	Creon 12000 U (N=39)	CfC - C12K (N=39)
Mean Number of units taken:		9.15 spoons	4.54 capsules	
CFA (%)				
	n	39	39	39
	Mean (SD)	77.7 (13.1)	78.7 (14.0)	-1.0 (11.5)
	Median	79.1	79.4	-1.7
	Min / Max	35.5/96.4	33.9/98.3	-23.7/27.8
				p = 0.3513
Fat intake (g/day)				
	n	39	39	39
	Mean (SD)	42.8 (15.1)	41.9 (13.7)	0.9 (13.6)
	Median	39.3	40.0	-1.2
	Min / Max	14.3/88.6	15.8/73.7	-24.1/43.2
				p = 0.7267
Fat excretion (g/day)				
	n	39	39	39
	Mean (SD)	9.2 (5.4)	8.3 (5.0)	0.9 (4.1)
	Median	9.0	7.6	0.9
	Min / Max	1.4/23.3	0.7/18.5	-11.6/11.7
				p = 0.1197
Energy intake (kcal/day)				
	n	39	39	39
	Mean (SD)	1105 (258)	1118 (304)	-13 (192)
	Median	1100	1100	-21
	Min / Max	608/1632	590/1793	-380/583
				p = 0.3513
Fecal energy content (kcal/day)				
	n	39	39	39
	Mean (SD)	137.7 (73.9)	134.7 (75.4)	3.0 (50.1)
	Median	134.0	115.0	10.0
	Min / Max	33.0/337.0	8.0/302.0	-165.0/81.0
				p = 0.4189
Mean stool weight (g/day)				
	n	39	39	39
	Mean (SD)	88.2 (45.3)	87.3 (49.5)	0.9 (34.0)
	Median	84.0	81.0	2.0
	Min / Max	23.0/180.0	4.5/229.0	-113.0/71.0
				p = 0.4853

p=p-value of two-sided Wilcoxon test which was applied to the within-subject differences period II - period I to compare treatment sequences

Study S245.3003 was a two centre, open label, single arm study to evaluate the effect on stool and coefficient of fat excretion of Creon for Children (Creon Micro) in infants with PEI due to CF. The study was sponsored and coordinated by Solvay Pharmaceuticals and conducted at two centres in Italy. The study included infants with PEI due to CF, aged 1 to 24 months; with CF diagnosed by two sweat tests or gene analysis; PEI proven by steatorrhoea or by chymotrypsin in the stool; and baseline a CFA >70%. The study treatment was Creon MMS for Children (Creon Micro). The mean daily dose was 73677.4 lipase units,

corresponding to 8215.7 lipase units/kg body weight, and 2205.2 lipase units/g fat intake. The subjects were treated with a dose of 2000 lipase units per g of fat intake according to dosing guidelines for cystic fibrosis patients. Treatment duration was 8 weeks. The treatment phase was preceded by a 10 day baseline period. Two, 72 hour fat balance studies were performed; one at baseline and one at Week 2. The primary efficacy outcome measure was the CFA. Secondary efficacy outcome measures were steatorrhoea, faecal energy loss, stool characteristics, gastrointestinal symptoms, response (CFA >90%), hematology and biochemistry parameters, nutritional parameters, and patient's acceptance.

All 12 enrolled subjects completed the study and were included in the ITT analysis. There were seven (58.3%) female subjects, five (41.7%) male, and the age range was 0.9 to 22.9 months. All subjects were Caucasian.

For the ITT sample, the primary efficacy parameter CFA significantly increased from a baseline (mean) of 58.0% to 84.7% after two weeks: the mean (95% CI) increase was 26.7% (12.9% to 40.4%) p=0.0013. After two weeks of treatment, four subjects (33%) were responders (CFA>90%). At baseline, all subjects had steatorrhoea, and after two weeks of treatment seven subjects (58%) had steatorrhoea. There was a statistically and clinically significant decrease in stool fat from 13.26 to 5.28 g/day, p=0.0013. Mean stool weight decreased from 109.6 to 79.3 g/day, and mean dietary fat intake increased from 32.02 to 34.27 g/day. Overall the treatment was well accepted and there were few gastrointestinal symptoms reported from the study subjects. Patient diaries indicated an improvement in gastrointestinal symptoms and in stool consistency during the study (Table 7).

Table 7. Subject's Diaries.

	Creon (N = 12)								
Parameter	Treatment Period 1			Treatment Period 2			Treatment Period 3		
Category	n	Mean	(SD)	n	Mean	(SD)	n	Mean	(SD)
Stool Frequency									
Stools per day	12	2.9	(1.3)	12	2.3	(0.8)	12	2.2	(0.8)
Gastrointestinal Symptoms, Percentage of Days With									
None	12	76.3	(32.1)	12	85.8	(29.2)	12	88.9	(17.7)
Mild	12	11.2	(11.1)	12	7.1	(11.3)	12	3.8	(5.1)
Moderate	12	7.7	(14.8)	12	4.7	(11.3)	12	5.0	(9.1)
Severe	12	4.8	(11.1)	12	2.4	(8.2)	12	2.3	(5.3)
Stool Consistency, Percentage of Days With									
Hard	12	30.5	(27.7)	12	27.2	(31.9)	12	27.5	(30.9)
Normal	12	57.6	(35.7)	12	71.2	(26.3)	12	68.7	(30.4)
Watery	12	17.9	(24.3)	12	7.2	(10.7)	12	8.0	(12.6)
Oily	12	8.4	(16.6)	12	5.5	(11.8)	12	5.5	(9.4)

Studies investigating efficacy in cp

Study S223.2.01 was a multicentre, randomised, double-blind, placebo controlled, parallel group study to investigate the effect of Creon MMS 10,000 on steatorrhoea in adults with PEI due to CP. The study was sponsored and coordinated by Solvay Pharmaceuticals and

conducted at 31 centres in the US. The study treatments were Creon MMS 10,000 and placebo. Treatment duration was 4 weeks, and included a 2 week open-label run-in phase followed by a 2 week treatment phase. The efficacy outcome measures were: change in CFA (primary outcome measure), stool parameters and global scores. There were 64 subjects enrolled in the run-in phase, and 27 were randomised: 13 to Creon and 14 to placebo. Eighteen (66.7%) subjects were male, nine (33.3%) were female and the age range was 31 to 74 years. There was a significant improvement in CFA in the Creon group compared with placebo: mean (95% CI) 36.7 (range -32.5 to 105.8) for Creon and 12.1 (range -29.8 to 54.1) for placebo, p=0.0185. There was a significant improvement in fat excretion, stool consistency and stool frequency in the Creon group compared with placebo (Table 8). There was no significant difference between the treatments in global scores.

Table 8. Summary of secondary efficacy parameters.

Parameter	Placebo			CREON® 10			
	Single-Blind Placebo Phase	Double-Blind Phase	Change[2]	Single-Blind Placebo Phase	Double-Blind Phase	Change[2]	p-Value[3]
Fat Excretion (g/day)	63.1 (7.2)	51.8 (9.4)	-11.4 (7.1)	n=12 75.1 (18.4)	n=12 18.6 (4.0)	n=12 -56.5 (17.4)	0.0181
Stool Consistency Hard Normal Soft Watery	 0 (0.0%) 2 (14.3%) 10 (71.4%) 2 (14.3%)	 0 (0.0%) 0 (0.0%) 13 (92.9%) 1 (7.1%)	—	 1 (7.7%) 3 (23.1%) 6 (46.2%) 3 (23.1%)	 1 (7.7%) 4 (30.8%) 8 (61.5%) 0 (0.0%)	—	0.0102[4]
Stool Frequency (stools/72hr)	14.0 (3.6)	14.6 (4.1)	0.6 (1.0)	10.8 (2.1)	5.2 (0.8)	-5.6 (1.5)	0.0015
Investigator CGIDS	1.6 (0.3)	2.0 (0.2)	0.4 (0.2)	1.8 (0.2)	1.5 (0.3)	-0.3 (0.3)	0.0435
Patient CGIDS	1.7 (0.3)	2.1 (0.2)	0.4 (0.2)	1.8 (0.2)	1.5 (0.3)	-0.3 (0.3)	0.0634

[1] Numbers in parentheses represent the standard error of the means. Except as noted, table includes **14** placebo patients and **13** CREON® patients.
[2] Change in mean value from the single-blind placebo phase to the double-blind phase.
[3] ANOVA for H_0: Treatment means are equal with respect to change from the single-blind placebo phase to the double-blind phase.
[4] Fisher Exact test.

Study K245.5005 was a multicentre, randomised, double-blind, parallel group, placebo controlled study with the aim to demonstrate superior efficacy of Creon MMS 10,000 over placebo in adults with PEI due to CP. The study was sponsored and coordinated by Solvay Pharmaceuticals and conducted at three centres in South Africa. The total daily dose was 16 capsules: four capsules at each main meal (three meals) and two capsules at each fat-containing snack (two snacks). The study duration was 4 weeks which included a 2 week run-in period (Week 1 with placebo and Week 2 with Creon) followed by a 2 week double-blind phase. Two 72 hour faecal collections were conducted, the first at the end of the placebo phase and the second at the end of the double-blind phase. The primary efficacy outcome measure was CFA. Secondary efficacy outcome measures were stool fat, fat intake, stool weight and clinical symptomatology. A total of 40 subjects were enrolled but since seven subjects dropped out during the run-in phase, 33 subjects were randomised to treatment: 17 to Creon, 16 to placebo. One subject in each group was withdrawn because of stool fat <10g/day in the placebo run-in phase. Hence, there were 31 subjects in the ITT sample. The age range was 40 to 66 years, 31 (93.9%) subjects were male and two (6.1%) were female. There was a significant improvement in CFA in the Creon group compared

with placebo: mean (95% CI) treatment difference, placebo-Creon -21.3 (range -35.1 to -7.4). Stool fat was significantly less in the Creon group compared with placebo (Table 9). There were no significant differences between the treatment groups for change in stool weight, body weight, global scores, stool frequency, stool consistency abdominal pain or flatulence.

Table 9. Summary of stool fat analysis (g/day)

							Difference placebo - Creon 95 % CI			
		N	Median	Range	Mean	STD	Mean	lower	upper	p-value*
unadjusted	Placebo	15	35.0	9.4-86.0	43.3	23.9	23.7	8.4	39.0	0.004
	Creon	16	16.5	7.0-72.0	19.6	16.5				
baseline adjusted	Placebo	15	6.6	-73 - 55	1.7	33.3	27.6	4.4	50.9	0.021
	Creon	16	-16.7	-92 - 10.2	-25.9	29.5				

* two-sided two-sample t-test

Study S245.3.115 was a multicentre, randomised, double-blind parallel group study to demonstrate superior efficacy of Creon MMS over placebo. The primary efficacy outcome measure was CFA (%). The study was sponsored and coordinated by Solvay Pharmaceuticals and conducted at 32 centres in Japan. The study included adults, aged≥20 years, with PEI due to CP or post-pancreatectomy with CP in the non-compensatory phase or who had a pancreatectomy, with at least 7.5 g/day of stool fat excretion at screening. The study treatments were Creon MMS 10,000 packaged in sachets of 40,000 units, dosed as either 40,000 or 80,000 units three times daily and placebo. There was a run-in phase of 5 days followed by treatment phase of 7 days. Secondary efficacy measures were: stool fat excretion, stool weight, and stool frequency.

A total of 153 subjects were screened, of these 53 were withdrawn because their fat excretion was <7.5 g/day. In addition, 4 subjects withdrew consent and 1 developed pancreatic carcinoma. A total of 95 subjects were randomised of which 94 completed the study (one subject withdrew consent during the run-in phase). Thirty one subjects were excluded from the per protocol data set (PPS) analysis because of protocol deviations. In the PPS dataset there were 53 (84%) males, 10 (16%) females, 55% of the population were aged >65 years; and 35 (37%) had CP and 59 (63%) had pancreatectomy. There was no significant improvement in CFA for the 80,000 dose when the PP dataset was analysed, but there was a significant improvement when the full analysis set was analysed: mean (SD) improvement 15.5 (21.8)%, p=0.0148. There was no significant improvement following the 40,000 unit dose. The 80,000 unit dose caused a significant decrease in stool fat content: mean (SD) difference -10.1 (15.6) g/day, p=0.0231. There was no significant difference for the 40,000 unit dose. There was no significant difference with Creon treatment in stool weight or stool frequency.

Comparator controlled studies in subjects with PEI due to CP or pancreatectomy

Study K245.5003 was a multicentre, randomised, double-blind crossover study to demonstrate equivalent efficacy for Creon MMS, 10,000 and Creon MS 10,000. The study was sponsored and coordinated by Solvay Pharmaceuticals and conducted at eight centres in Germany. The study included adults with PEI due to CP and requiring enzyme replacement therapy. The study treatments were Creon MMS 10,000 and Creon MS 10,000. The dose was 16 capsules per day divided between meals and snacks. Treatment duration was 7 weeks. The primary efficacy outcome measure was CFA. Secondary efficacy outcome measures were fat excretion, stool weight, stool frequency, stool consistency, abdominal pain, global evaluation of the therapeutic response and patients' preference. A total of 38 subjects

were enrolled out of which 37 were analysed for safety. The age range was 28 to 71 years and 30 (81.1%) were male and seven (18.9%) were female. All were Caucasian. Twenty three subjects were analysed for efficacy. Equivalence was not demonstrated because the mean (90% CI) for the ratio of CFA Creon MMS / Creon MS was 1.014 (0.921 to 1.117) and the 90% CI did not lie in the pre-specified range of 0.905 to 1.105. There was no significant difference in fat excretion, stool weight, elastase, stool consistency, stool frequency, flatulence, abdominal pain, global scores or treatment preference.

Study S248.3.001 was a single centre, randomised, double-blind crossover to demonstrate that CFA is equivalent for the MMS and MS formulations of Creon. The study was sponsored by Solvay Pharmaceuticals. The study included adults with PEI caused by partial or total pancreatectomy requiring pancreatic enzyme replacement therapy. The study treatments were Creon MMS 25,000 and Creon MS 8000. The dosing ratio was 1:3, MMS: MS. The dose was determined during the run-in period and according to pre-study lipase requirements. The study duration was 6 weeks, comprising a 2 week run-in followed by two 2 week treatment phases. The primary efficacy outcome measure was CFA. Secondary efficacy outcome measures were: dietary fat intake, stool weight, fat excretion, stool frequency, stool consistency, flatulence, abdominal pain and global scores. A total of 27 subjects were enrolled of which 23 were randomised, 22 were analysed for safety and 20 were included in the ITT analysis. Of the enrolled subjects, 22 (81.5%) were male, five (18.5%) were female, and the age range was 22 to 73 years. The mean (90% CI) for the ratio of CFA MMS/MS was 0.977 (0.819 to 1.185), and the 90% CI was outside of the range 0.905 to 1.025. Hence, the sample size was too small to demonstrate equivalence. Dietary fat intake and stool weight were greater with MMS, $p<0.05$. There was no significant difference between the groups for fat excretion, stool consistency, stool frequency, flatulence, abdominal pain or global scores.

Studies in subjects with acute pancreatitis

Study S248.4.001 was a multicentre, randomised, double-blind, placebo controlled, parallel group study of Creon MMS in subjects in a re-feeding status after acute pancreatitis (AP). The study was sponsored and coordinated by Solvay Pharmaceuticals at three centres in Germany.

The study included:

- Men and women, at least 18 years of age.
- Subject had suffered from moderate to severe AP defined as follows:
    1. CRP > 120 mg/L
    2. Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score ≥4
    3. SPA and SPL > threefold above normal
- Subject fulfilled the following conditions for re-feeding:
    1. C-reactive protein (CRP) < 50 mg/L
    2. SPA and SPL < twofold above normal
    3. Need of analgesics not higher than at the start of the acute phase
    4. Need of H2-receptor antagonists or antacids not higher than at the start of the acute phase (subjects with chronic pancreatitis).

The study treatments were:

1. Creon MMS 25,000
2. Placebo

The dose of study treatment was two capsules with each of the three main meals, and one capsule per snack. Treatment duration was for 26 to 30 days.

The primary efficacy outcome measure was the time to >200 μg faecal elastase /g stool. Secondary efficacy outcome measures were: body weight, oral glucose tolerance test, absolute values of human faecal elastase in stool, CRP, serum pancreatic amylase, serum pancreatic lipase, APACHE-II score, abdominal pain and quality of life score (Functional Assessment of Cancer Therapy – Pancreatic Cancer (FACT-Pa)). Hypothesis testing used log-rank test and Analysis of Covariance (ANCOVA).

From a total of 57 subjects who consented to participate, 56 were randomised (27 to Creon and 29 to placebo). Twenty were included in the ITT population: 11 in the Creon group and 9 in the placebo. The age range was 23 to 81 years, 35 (62.5%) subjects were male, and 21 (37.5%) were female. There was no significant difference between the treatment groups for the primary efficacy outcome measure. Five subjects in each treatment group had recovered from PEI by Day 28 (that is, they had reached an elastase value of≥200 mcg/g stool); log rank p=0.64. There was no significant difference between the treatment groups for the secondary efficacy outcome variables.

Study S248.4.002 was a single centre, randomised, double-blind parallel group pilot study to evaluate the efficacy of Creon MM 25,000 in patients recovering from acute pancreatitis with mild PEI. The study only enrolled 21 subjects and was not sufficiently powered to detect any significant differences between the treatment groups.

Studies in subjects post-gastrectomy

Study S248.3.102 was a two centre, randomised, double-blind parallel group study to prove superior efficacy of Creon MMS 20,000 compared with placebo with respect to baseline adjusted CFA in adults with PEI due to gastrectomy. The number of subjects available for analysis (n=7) was insufficient for statistical analysis.

Studies in subjects with diabetes mellitus

Studies S245.3.112 and ***S245.3.113*** were multicentre, randomised, double-blind, parallel group studies to investigate the efficacy of Creon MMS 10,000 over placebo in subjects with PEI and diabetes mellitus (Type 1 in Study S245.3.112 and Type 2 in Study S245.3.113). Both studies were stopped prematurely because of poor recruitment. The data from the two studies, including a total of 30 subjects, were pooled for analysis, but limited conclusions could be drawn from the results due to the small sample.

Evaluator's overall conclusions on clinical efficacy

Creon MMS was demonstrated to be superior to placebo in the management of subjects with PEI due to CF. The treatment effect was clinically significant and demonstrated by improvements in fat absorption, stool consistency, stool frequency, stool fat content and in symptomatology. Creon MMS was demonstrated to be equivalent to Creon MS. Creon for Children was demonstrated to be equivalent to Creon MMS 25,000.

In subjects with PEI due to CP or post-pancreatectomy there was a significant improvement in fat absorption, fat excretion, stool consistency, stool consistency with Creon MMS compared with placebo. This improvement was clinically significant.

Efficacy was not demonstrated in subjects with acute pancreatitis, post-gastrectomy or with diabetes mellitus.

Safety

The data presented in the current Australian submission were predominantly from previously marketed formulations. However, the safety of the active ingredient was demonstrated in this data. In addition, the active ingredient has been marketed for several decades.

Patient exposure

In the development program, 32 subjects were exposed to Creon 24,000 in placebo controlled studies, 271 to Creon in placebo-controlled studies and 761 subjects were exposed to all Creon products in multiple dose studies. A total of 356 subjects with CF were exposed to Creon but only eight subjects received Creon for more than 1 year. A total of 132 subjects with CP were exposed to Creon, but only six subjects received Creon for more than 1 year. A total of 137 subjects were exposed to Creon following pancreatic surgery, but only 12 received Creon for more than 1 year. The subjects with CF were aged 0.1 to 53.5 years, those with chronic pancreatitis were aged 28.8 to 75 years and those treated following pancreatic surgery were aged 19.5 to 80 years.

Adverse events

Treatment-emergent adverse events (TEAEs) were reported in 207 (58.1%) subjects with CF in the multiple dose studies. In placebo controlled studies there was lower rate of AEs observed following Creon treatment compared to placebo. The most commonly reported TEAEs in the Creon group were: cough n=43 (12.1%), headache n=42 (11.8%), abdominal pain n=31 (8.7%), vomiting n=23 (6.5%) and pyrexia n=23 (6.5%).

In subjects with CP in placebo controlled studies, TEAEs were reported more frequently in the Creon group than in the placebo group (in 24 (43.6%) and 14 (31.1%) subjects, respectively). In multiple dose studies, 70 (53.0%) subjects with CP reported TEAEs, and these were predominantly gastrointestinal (Table 10).

Table 10. Summary of Treatment Emergent Adverse Events in Chronic Pancreatitis Patients (N (%)), occurring in >5% subjects.

	Studies with Creon		
	Placebo-Controlled		**All Multiple-Dose Studies**
MedDRA Primary SOC	**Creon**	**Placebo**	**All Creon**
No. of Patients at Risk	55 (100.0)	45 (100.0)	132 (100.0)
Any TEAE	24 (43.6)	14 (31.1)	70 (53.0)
Gastrointestinal Disorder	13 (23.6)	7 (15.6)	42 (31.8)
Abdominal Distension	3 (5.5)	0 (0.0)	9 (6.8)
Abdominal Pain	1 (1.8)	2 (4.4)	9 (6.8)
Constipation	5 (9.1)	1 (2.2)	9 (6.8)
Nausea	2 (3.6)	0 (0.0)	9 (6.8)
Diarrhea	1 (1.8)	1 (2.2)	7 (5.3)
General Disorders and Administration Site Conditions	4 (7.3)	5 (11.1)	23 (17.4)
Malaise	1 (1.8)	2 (4.4)	9 (6.8)
Hepatobiliary Disorders	2 (3.6)	0 (0.0)	9 (6.8)

Hepatic Function Abnormal	2 (3.6)	0 (0.0)	7 (5.3)
Infections and Infestations	0 (0.0)	1 (2.2)	9 (6.8)
Nasopharyngitis	0 (0.0)	0 (0.0)	8 (6.1)
Metabolism and Nutrition Disorders	2 (3.6)	5 (11.1)	19 (14.4)
Anorexia	0 (0.0)	0 (0.0)	7 (5.3)
Musculoskeletal and Connective-Tissue Disorders	4 (7.3)	1 (2.2)	13 (9.8)
Back Pain	1 (1.8)	1 (2.2)	8 (6.1)

In subjects treated with Creon following pancreatectomy, 91 (66.4%) reported TEAEs in the multiple dose studies. In the placebo controlled studies, the rate of TEAEs was slightly higher in the Creon group compared with the placebo group (n=29 (65.9%) and n=13 (59.1%), respectively). The most commonly reported TEAEs were: abdominal pain 20 (14.6%) and diarrhoea (13.9%) (Table 11).

Table 11. Summary of Treatment Emergent Adverse Events in Pancreatic Surgery Patients N (%).

	Studies with Creon		
	Placebo-Controlled		All Multiple-Dose Studies
MedDRA Primary SOC/preferred term	**Creon**	**Placebo**	**All Creon**
No. of Patients at Risk	44	22	137 (100)
Any TEAE	29 (65.9)	13 (59.1)	91 (66.4)
Gastrointestinal Disorder	19 (43.2)	8 (36.4)	60 (43.8)
Abdominal Pain	5 (11.4)	2 (9.1)	20 (14.6)
Diarrhea	7 (15.9)	3 (13.6)	19 (13.9)
Abdominal Distension	2 (4.5)	3 (13 6)	14 (10.2)
Vomiting	3 (6.8)	0 (0.0)	14 (10.2)
Nausea	1 (2.3)	0 (0.0)	11 (8.0)
Flatulence	0 (0.0)	1 (4.5)	10 (7.3)
Constipation	2 (4.5)	1 (4.5)	8 (5.8)
Abdominal Tenderness	0 (0.0)	0 (0.0)	7 (5.1)
General Disorders and Administration Site Conditions	5 (11.4)	3 (13.6)	32 (23.4)
Malaise	2 (4.5)	1 (4.5)	14 (10.2)
Pyrexia	1 (2.3)	0 (0.0)	12 (8.8)
Hepatobillary Disorders	1 (2.3)	0 (0.0)	10 (7.3)
Hepatic Function Abnormal	0 (0.0)	0 (0.0)	8 (5.8)
Infections and Infestations	2 (4.5)	0 (0.0)	15 (10.9)
Nasopharyngitis	1 (2.3)	0 (0.0)	10 (7.3)
Metabolism and Nutrition Disorders	7 (15.9)	4 (18.2)	26 (19.0)
Hyperglycemia	5 (11.4)	0 (0.0)	13 (9.5)
Anorexia	0 (0.0)	0 (0.0)	7 (5.1)
Musculoskeletal and Connective Tissue Disorders	4 (9.1)	1 (4.5)	17 (12.4)
Back Pain	3 (6.8)	0 (0.0)	13 (9.5)
Nervous System Disorders	4 (9.1)	1 (4.5)	12 (8.8)
Headache	4 (9.1)	0 (0.0)	12 (8.8)

Serious adverse events (saes) and deaths

Nine deaths were reported in total: five in studies of Creon and four in the compassionate program in Japan. The deaths appear to have been related to the underlying disease process rather than Creon treatment.

SAEs were reported in 17 (4.8%) subjects with CF treated with Creon in the multiple dose studies. Infections and infestations comprised the largest group of treatment emergent SAEs in this group. SAEs were reported in four (3.0%) of subjects with CP treated with Creon in the multiple dose studies, with no SAE being reported in more than one subject. Sixteen (11.7%) subjects treated with Creon after pancreatic surgery reported SAEs, predominantly related to the underlying conditions of these patients.

Laboratory findings

There were no clinically significant abnormalities in laboratory values reported during the clinical trials.

Safety in special populations

Studies comparing the DBP- free with the DBP- containing Creon formulation

In Study S245.2.003, three subjects (23.1%) experienced a TEAE during treatment with the DBP- free Creon formulation; vomiting (n=3), cough, and increased bronchial secretion (n=1/group). Four subjects (33.3%) had a TEAE during treatment with DBP- containing Creon formulation; flatulence, tracheitis, hypoglycemia, and hypertension (n=1/group). One subject withdrew due to an AE. There were no SAEs. There were no deaths reported during the study.

Studies investigating Creon for Children

In ***Study S245.3118***, 17 (42.5%) subjects reported at least one TEAE during treatment with Creon for Children (Creon Micro). Similarly, 17 (43.6%) subjects given Creon 12,000 reported at least one TEAE. There were no deaths reported during the study. One subject in the Creon for Children group withdrew because of a TEAE: abdominal pain/diarrhoea/vomiting. SAEs were reported in one subject in each group. In the Creon for Children group, one patient had bronchial obstruction/ otitis media. One patient given Creon 12,000 had pseudomonas lung infection.

In ***Study S245.3003***, TEAEs were reported in 9 (75%) subjects. The most commonly reported TEAEs were pyrexia (n=4) and cough (n=3). There were no deaths. There were no SAEs. There were no withdrawals due to AEs. There were no clinically significant abnormalities in haematology or biochemistry parameters.

Immunological events

No data relating to immunological events were presented in the submission.

Safety related to drug-drug interactions and other interactions

There were no data from drug interaction studies included in the submission.

Discontinuation due to adverse events

Eight (2.2%) subjects with CF, one (0.8%) with chronic pancreatitis and five (3.6%) of those treated following pancreatic surgery withdrew because of AEs. The most common AE leading to discontinuation in subjects with CF was gastrointestinal disorders (Table 12). The two subjects with CP who withdrew reported abdominal AEs including abdominal pain (n=1), diarrhoea (n=1), dyspepsia (n=1) and injury (n=1). The subjects treated with Creon following pancreatic surgery reported gastrointestinal AEs which included abdominal distension (n=1), abdominal pain (n=1), flatulence (n=1) and anorexia (n=3).

Table 12. Summary of Treatment Emergent Adverse Events Leading to Withdrawal in Cystic Fibrosis Patients (N (%)).

	Studies with Creon 24,000		Studies with Creon		
	Placebo-Controlled		Placebo-Controlled		All Multiple-Dose Studies
MedDRA Primary SOC	Creon 24,000	Placebo	Creon	Placebo	All Creon
No. of Patients at Risk	32 (100.0)[a]	31 (100.0)[a]	36 (100.0)	38 (100.0)	356 (100.0)
Any TEAE Leading to Withdrawal	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	7 (2.0)
Gastrointestinal Disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.7)
Diarrhea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.1)
Abdominal Pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)
Flatulence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)

[a] Patients were exposed to both Creon 24,000 and placebo (crossover study)

Post marketing experience

From January 1 1984 to August 31 2008 there were 852 spontaneous reports of suspected adverse drug reports (ADRs). The most frequently reported symptoms concerning the gastrointestinal tract were abdominal pain (21%), diarrhoea (14%), nausea (7%), flatulence (6%), and constipation (5%), while the most frequent skin reaction were rash (6%), pruritus (5%), and urticaria (3%).

A periodic safety update report (PSUR) for pancreatin covering the time period 14th April 2007 to 13th April 2008 was provided. Exposure during the period covered by the report was estimated at 198,000 patient years. During that time, 41 serious and unlisted non-serious ADRs were received from healthcare professionals, and 44 medically unconfirmed reports from consumers or other non-healthcare professionals were received. There were no reports of fibrosing colonopathy received during the time period. During the whole life-span of pancreatin, 183 serious ADRs had been received.

Studies supportive of safety (not mentioned elsewhere)

In Study S245.3.126 there were clearly fewer subjects in the pancrelipase group reporting TEAEs: at least one TEAE was reported by 12 (43.8%) and 20 (64.5%) subjects given pancrelipase and placebo, respectively. One subject reported an SAE: duodenitis/gastritis 2 weeks after the last dose of pancrelipase. One subject discontinued because of an AE (due to a decrease in body weight). There were no deaths.

Studies evaluable for safety

Study S245.3.117 was a long-term cohort study in three children with CF in Japan.

Study S245.2.002 was an open label, single arm study to confirm the efficacy and safety of Creon MMS in five subjects with PEI due to CF in Japan.

Study K245.5.703 was an open label, parallel group study to assess the digestive efficacy, safety and tolerance of Creon MMS conducted in Japan.

Study S245.3.103 was an open label, single treatment study to confirm the efficacy and safety of long term treatment with Creon MMS 10,000 in Japanese adults with PEI caused by CP, pancreatectomy, gastrectomy or other reasons.

Study S245.3.104 was an open label, single treatment study to confirm the efficacy and safety of Creon MMS 10,000 in Japanese subjects with PEI caused by chronic pancreatitis, pancreatectomy, gastrectomy or other reason.

Safety studies conducted for other indications

Study S245.3.110 was a double-blind, parallel group study to evaluate the superior efficacy of Creon MMS 10,000 over placebo on glycaemic control in Canadian subjects with insulin dependent diabetes.

Study S245.3.116 was a double-blind, parallel group study to investigate the superior efficacy of Creon MMS 10,000 over placebo in subjects with Human Immunodeficiency Virus (HIV) and diarrhoea caused by protease inhibitors.

Study S245.3.119 was a double-blind crossover study to evaluate the CFA in HIV-infected subjects after treatment with Creon MMS 25,000 compared with placebo.

Other studies with safety data

Study S245.4011 was an observation post-marketing study conducted to confirm the safety profile of Creon MMS 40,000 under marketed conditions. The study was of limited value because only serious suspected AEs were reported, and no such events were observed during the study.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a "list of questions" to the sponsor is generated. The clinical evaluator posed the following questions to the sponsor:

1. EFFICACY

The following conditions are included in the requested indication[4] but no clinical data performed with Creon were included in support: *Ductal obstruction of the pancreas or common bile duct (for example, from neoplasm), Pancreatic cancer, Shwachman-Diamond Syndrome* and the following condition is included as an indication but the data submitted do not support efficacy: *Acute pancreatitis.* The clinical evaluator requested, if available, clinical data performed with Creon demonstrating efficacy for these indications.

No new clinical data performed with Creon were submitted in support of these indications.

Clinical Summary and Conclusions

Creon MMS was demonstrated to be superior to placebo in the management of subjects with PEI due to CF. The treatment effect was clinically significant and demonstrated by improvements in fat absorption, stool consistency, stool frequency, stool fat content and in symptomatology. Creon MMS was demonstrated to be equivalent to Creon MS. Creon for Children was demonstrated to be equivalent to Creon MMS 25,000. In subjects with PEI due to CP or post-pancreatectomy there was a significant improvement in fat absorption, fat excretion, stool consistency, and stool frequency with Creon MMS compared with placebo. This improvement was clinically significant. However, efficacy was not demonstrated in subjects with acute pancreatitis, post-gastrectomy or with diabetes mellitus.

[4] The sponsor commented that this request was based on literature data supporting the occurrence of PEI associated with these conditions

Creon Micro has a favourable adverse event profile and the new formulation has theoretical benefits over the currently marketed formulation. There was no indication that the new formulation has any additional risk associated with it. There was no additional evidence that the colonic strictures arising from treatment with Creon were anything other than rare adverse events. The sponsor commented that colonic strictures have been reported in patients with cystic fibrosis taking high doses of pancreatin preparations and that case control studies did not reveal evidence for the association between Creon and the appearance of fibrosing colonopathy Studies in the paediatric population did not identify any specific risks in this age group.

Benefit risk assessment

Benefits

Creon MMS results in improved fat absorption and in improved stool consistency, decreased stool fat content, and decreased stool frequency in subjects with PEI. In subjects with PEI due to CF there was also an improvement in gastrointestinal symptomatology. These benefits were all clinically significant.

Risks

The AEs that occurred during treatment with Creon MMS were similar to those attributable to the underlying conditions for which the patients were being treated. In subjects with PEI due to CF there was a lower frequency of AEs following Creon MMS treatment compared with placebo. There were few SAEs and deaths during the clinical development program. Colonic stricture appears to be a rare and serious AE attributable to treatment with oral pancreatic enzyme formulations.

Safety Specification

There were no absent data from the Safety Specification.

Balance

The benefits of Creon MMS outweigh the risks of treatment in subjects with PEI.

Conclusions

Creon MMS has a favourable benefit-risk profile in subjects with PEI. The clinical evaluator recommends that Creon Micro (pancreatic extract 20 g enteric coated microspheres, 5,000 BP units per 100 mg measure) should be approved for marketing in Australia.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The pharmaceutical chemistry evaluator stated that:

The in-use shelf life of the Creon micro strength is documented as 3 months after opening in contrast to the other strengths (which are documented as 6 months).

The **issues of concern** were GMP clearance for the manufacturing site and that labels were not in compliance with TGO69 requirements[5]. These issues were resolved before registration. The **conditions of registration** regarding drug product batches from different drug substance batches require the provision to the Office of Laboratories and Scientific Services of two bottles from the first batch of Creon Micro imported into Australia for testing and evidence of satisfactory shipping conditions to Australia for every batch imported. An Annual Batch Release Report on the above products listing full batch details and quantities released during the previous year (including export products) should also be submitted.

Nonclinical

The toxicology evaluator stated that there were no nonclinical issues regarding the registration of Creon Micro.

Clinical

The clinical evaluator (CE) commented that bioequivalence was not demonstrated by the normally accepted criteria. However, pancreatic lipase is not absorbed into the body, and the sponsor has demonstrated similar lipase activity at the point of action, which is the duodenum.

The CE's overall conclusion on pharmacodynamics is that Creon MMS increases fat absorption in subjects with pancreatic insufficiency.

On the **overall efficacy outcome,** the clinical evaluator summarised that:

- Creon MMS was demonstrated to be superior to placebo in the management of subjects with PEI due to CF. The treatment effect was clinically significant and demonstrated by improvements in fat absorption, stool consistency, stool frequency, stool fat content and in symptomatology. Creon MMS was demonstrated to be equivalent to Creon MS. Creon for Children was demonstrated to be equivalent to Creon MMS 25,000.
- In subjects with PEI due to CP or post-pancreatectomy there was a significant improvements in fat absorption, fat excretion, stool consistency with Creon MMS compared with placebo. This improvement was clinically significant.
- Efficacy was not demonstrated in subjects with acute pancreatitis, post-gastrectomy or with diabetes mellitus.

Having reviewed all the available data including the post marketing experience on safety, the clinical evaluator concluded that:

- Creon MMS has a favourable adverse event profile and that the new formulation has theoretical benefits over the currently marked formulation. There was no indication that the new formulation has any additional risk associated with it. There was no additional evidence that colonic strictures arising from treatment with Creon was other than a rare adverse event. Studies in the paediatric population did not identify any specific risks in this age group.

Concluding, the clinical evaluator**:**

- Mentioned that ductal obstruction of the pancreas or common bile duct (for example, from neoplasm), pancreatic cancer and Shwachman-Diamond syndrome are included in the list of medical conditions with the PEI indication, but that **no evidence based studies** on them were included in the data submitted for evaluation.
- Stated that Creon MMS has demonstrated significant efficacy over placebo in the management of subjects with PEI due to CF, CP, post-pancreatectomy but not for

[5] Therapeutic Goods Order No. 69: General requirements for labels for medicines.

subjects with acute pancreatitis, post gastrectomy or diabetes mellitus. It is also stated that Creon MMS has a favourable adverse event profile and that the new formulation has theoretical benefits over the currently marketed formulation.

Risk-Benefit Analysis

Delegates' Comments

The Delegate agreed with the clinical evaluator that pancreatic extract 60.12 mg/100 mg enteric coated minimicrospheres (Creon Micro, Pancreatin minimicrospheres, 5,000 lipase BP units per 100 mg measure) is registrable based on the favourable efficacy and safety evaluated data outcome. The indication section needs to be trimmed to include only those PEI associated medical conditions for which **evidence based studies with Creon** were provided. In that regard, the inclusion of gastrectomy, acute pancreatitis, pancreatic cancer and Shwachman-Diamond syndrome in the list of PEI associated medical conditions under the indication section for each Creon strength is not supported by clinical studies performed with Creon and were requested to be deleted.

Proposed Action

The quality evaluator raised **issues of concern** relating to GMP clearance and label compliance and **listed some conditions of registration**.

The nonclinical evaluator has no objection to approval and has made comments and suggested modifications to the PI.

The Delegate proposed to recommend registration (with the conditions stated by the quality evaluator) of the new DBP-free pancreatic extract 60.12 mg/100 mg enteric coated minimicrospheres (Creon Micro / Creon – Pancreatin, minimicrospheres, 5,000 lipase BP units per 100 mg measure) provided the sponsor satisfactorily addressed the issues raised by the clinical and quality evaluators. There is no evidence based rationale to support the proposed expansion of the indications. Such expansion cannot simply be based on untested or unproven theoretical concepts, for the purpose of inclusion in the product information document. These recommendations are subject to the finalisation of all issues mentioned, including those relating to ACPM's deliberations to the satisfaction of the TGA.

The application was submitted to the ACPM for advice.

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded the Australian Drug Evaluation Committee), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ACPM recommends approval of the submission from Abbott Products Pty Ltd to register the new dosage form of Pancreatic Extract (Creon Micro / Creon) enteric coated minimicrospheres 60.12 mg / g for the indication:

> For use as a pancreatic enzyme replacement in paediatric and adult patients with pancreatic exocrine insufficiency (PEI), such as cystic fibrosis, chronic pancreatitis, post pancreatectomy, post-gastrointestinal bypass surgery(for example, Billroth II gastroenterostomy) and ductal obstruction.

In making this recommendation, the ACPM considered that there were no safety issues of concern for this item; however, after consideration of the data provided , the claims of efficacy in the wide range of indications proposed was not supported.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of *Creon Micro (pancreatic extract) 20g enteric coated minimicrospheres granules bottle*, indicated:

As pancreatic enzyme replacement in paediatric and adult patients with pancreatic exocrine insufficiency (PEI). Pancreatic exocrine insufficiency is often associated with, but not limited to:

- Cystic fibrosis,
- Chronic pancreatitis,
- Pancreatic surgery,
- Gastrointestinal bypass surgery (for example, Billroth II gastroenterostomy),
- Ductal obstruction of the pancreas or common bile duct (for example, from neoplasm).

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

CREON® MICRO

Pancreatic Extract Enteric-Coated Granules

Product Information

NAME OF THE DRUG

Pancreatic Extract

DESCRIPTION

Creon® Micro are porcine pancreatic enzyme preparations containing Pancreatic Extract encapsulated in enteric-coated granules with a pH-sensitive coating.

Each dosing unit of 100 mg of Creon® Micro contains Pancreatic Extract 60,12 mg equivalent to not less than 5,000 BP units lipase, 3,600 BP units amylase and 200 Ph. Eur. units protease. Inactive ingredients include macrogol 4000, hypromellose phthalate, dimethicone 1000 triethyl citrate, cetyl alcohol. One dosage unit is measured with a measuring scoop as dosing device.

PHARMACOLOGY

Administered orally, pancreatic extract assists in the digestion of proteins, carbohydrates and fats.

Creon® Micro has been specially formulated to combine the features of rapid homogeneous distribution with the chyme in the stomach, with resistance to inactivation by gastric acid and rapid dissolution in the alkaline pH of the duodenum. When the granules reach the small intestine the coating rapidly disintegrates (at pH > 5.5) to release enzymes with lipolytic, amylolytic and proteolytic activity to ensure the digestion of fats, starches and proteins. The products of pancreatic digestion are then either absorbed directly, or following further hydrolysis by intestinal enzymes. The granules are similar in size to food particles (0.7-1 mm in diameter), and mix homogeneously with the chyme while being protected from inactivation by gastric acid (pH 1) for up to 2 hours. They pass into the alkaline pH of the duodenum at least as quickly as the food they are intended to digest; here the enteric-coating rapidly dissolves releasing enzymes at the appropriate site.

Pharmacokinetic properties

Animal studies showed no evidence for absorption of intact enzymes and therefore classical pharmacokinetic studies have not been performed. Pancreatic enzyme supplements do not require absorption to exert their effects. On the contrary, their full therapeutic activity is exerted from within the lumen of the gastrointestinal tract. Furthermore, they are proteins, and as such undergo proteolytic digestion while passing along the gastrointestinal tract before being absorbed as peptides and amino acids.

CLINICAL TRIALS

Efficacy studies

In total, 23 studies investigating the efficacy of Creon in patients with pancreatic exocrine insufficiency have been conducted, among which 7 were either placebo or baseline controlled studies performed in patients with cystic fibrosis, chronic pancreatitis or post surgical conditions.

In all randomized, placebo-controlled, efficacy studies, the pre-defined primary objective was to show superiority of Creon over placebo on the primary efficacy parameter, the coefficient of fat absorption (CFA).

In cystic fibrosis (CF) the efficacy of Creon over placebo was demonstrated in three placebo-controlled studies, performed in paediatric and young adult CF patients and in one baseline-controlled study in infants of 1 – 24 months. In all, 118 patients were investigated in these trials.

Two double-blind placebo-controlled studies in 74 CF patients on individualized doses of Creon showed statistically significant ($p < 0.001$) and clinically relevant results after Creon treatment of 5-7 days. The mean CFAs in the placebo groups were 52.2% and 50.9% respectively as compared to those in Creon treated patients which were 84.1% and 87.2% respectively.

The third placebo-controlled study, a cross-over study, was performed in 32 paediatric and young adult CF patients. Patients on Creon achieved a mean CFA of 88.6% compared with 49.8% for patients on placebo ($p<0.0001$). The treatment duration was 5 days on a pre-planned dose of 4000 lipase units/g fat intake.

The-baseline-controlled study in 12 CF infants showed a mean CFA increase from 58.0% at baseline to 84.7 % after 8 weeks treatment with Creon on a dose of 2000 lipase units/g fat intake.

In chronic pancreatitis and pancreatic surgery three placebo-controlled studies in 161 adult patients were conducted and were each designed with a placebo run-in period followed by a double-blind parallel-group placebo or Creon treatment phase of 7 to 14 days. On average, patients in the Creon group achieved CFA values between 81.5 % and 86.6 % compared with CFA values between 56.3 % to 68% for patients on placebo (statistically significant differences).

Irrespective of the underlying disease, marked improvement was also noted with symptomatology associated with pancreatic enzyme insufficiency (e.g., stool frequency, stool consistency, flatulence and abdominal pain).

Studies in other diseases

Two double-blind, placebo controlled studies were performed in patients after acute pancreatitis (AP). One study in patients in a refeeding status after AP was stopped prematurely due to low recruitment. No treatment difference between Creon and placebo was found on the primary endpoint (time to normalization of faecal elastase > 200 μg/g stool) in 56 patients. However only a subgroup of 20 patients had low faecal elastase values at baseline. The other study in 21 subjects after AP was not sufficiently powered to detect any

relevant treatment differences in terms of QoL and gastrointestinal symptoms between Creon and placebo.

One double-blind, multi-center, placebo-controlled, randomized, parallel group aimed at proving superior efficacy of Creon in patients with PEI caused by total or partial gastrectomy. The study was stopped prematurely due to a too low recruitment rate with only seven patients evaluable for efficacy. No conclusion on the efficacy of Creon in gastrectomized patients could be drawn.

Two double-blind, placebo-controlled studies were performed to investigate the efficacy of Creon in 29 type 1 or 2 diabetes mellitus patients with mild PEI. Both studies were stopped prematurely because of poor recruitment. The pooled analysis of the limited data revealed no significant difference between the groups for the primary endpoint CFA. The change to baseline for stool fat reached statistical significance in favor of Creon ($p = 0.010$, -1.0 g fat/day in placebo and -6.5 g fat/day for Creon).

All studies confirmed the safe administration of Creon in the respective patient populations.

INDICATIONS

Creon® Micro is indicated as pancreatic enzyme replacement in paediatric and adult patients with pancreatic exocrine insufficiency (PEI).

Pancreatic exocrine insufficiency is often associated with, but not limited to:

- cystic fibrosis
- chronic pancreatitis
- pancreatic surgery
- gastrointestinal bypass surgery (eg. Bilroth II gastroenterostomy)
- ductal obstruction of the pancreas or common bile duct (e.g. from neoplasm)

CONTRAINDICATIONS

Creon® Micro is contraindicated in those patients who are known to be hypersensitive to porcine protein or any of the ingredients.

PRECAUTIONS

Fibrosing Colonopathy

Fibrosing colonopathy has been reported in cystic fibrosis patients treated with some high potency enzyme supplements. The mechanism of injury is unknown. Doses in excess of 10,000 BP units lipase/kg/day should be used with caution. Patients who use doses in excess of 10,000 BP units lipase/kg/day and who develop new symptoms or have a medical history of gastrointestinal complications should be reviewed regularly (e.g. by ultrasound).

Other

The presence of porcine parvovirus cannot be totally excluded in medicines containing extracts of pancreatic powder of porcine origin. However, there is no evidence of transmission of this virus to humans or of causing illness in humans. The presence of other porcine viruses also cannot be definitively excluded. However, no cases of transmission of an infectious illness associated with the use of porcine pancreatic powder extracts have been reported.

Use In Pregnancy

For pancreatic enzymes no clinical data on exposed pregnancies are available.
Animal studies show no evidence for any absorption of porcine pancreatic enzymes.
Although no reproductive or developmental toxicity would be expected, caution should be exercised when prescribing to pregnant women. If required during pregnancy, Creon should be used in doses sufficient to provide adequate nutritional status.

Use During Lactation

Animal studies suggest no systemic exposure of the breastfeeding women to porcine pancreatic enzymes, and no effects on the suckling child are anticipated. If required during lactation, Creon should be used in doses sufficient to provide adequate nutritional status.

Effects on ability to drive and use machines

Creon® Micro has no influence on the ability to drive and use machinery.

Interactions with Other Drugs

Antacids should not be taken concomitantly with Creon® Micro as the alkaline pH may break down the enteric-coating. Should antacid administration be considered necessary, it is recommended that at least one hour elapse between the intake of antacids and any Creon® Micro.
No interaction studies have been performed.

ADVERSE REACTIONS

In clinical trials involving over 600 patients with pancreatic exocrine insufficiency due to cystic fibrosis, chronic pancreatitis, and pancreatic surgery were exposed to Creon. The most commonly reported adverse reactions were gastrointestinal disorders and were primarily mild or moderate in severity.

The following adverse reactions have been observed during clinical trials with the below indicated frequencies.

Gastrointestinal disorders
Common (≥1/100, <1/10): nausea, vomiting, constipation, diarrhoea and abdominal distention.

Gastrointestinal disorders are mainly associated with the underlying disease. Similar or lower incidences compared to placebo were reported for diarrhoea (common ≥1/100, <1/10) and abdominal pain (very common, ≥1/10).

Skin and subcutaneous tissue disorders
Uncommon (≥/1,000, ≤1/100): rash
Pruritus and urticaria have been additionally identified as adverse reactions during postapproval use. Because these reactions were reported spontaneously from a population of uncertain size, it is not possible to reliably estimate their frequency.

Multiple clinical trials were conducted in other patient populations: HIV, acute pancreatitis, diabetes mellitus. No additional adverse drug reactions were identified compared to the above 3 patient groups.

Paediatric population
No specific adverse reactions were identified in the paediatric population. Frequency, type and severity of adverse reactions were similar in children with cystic fibrosis as compared to adults.

DOSAGE AND ADMINISTRATION

The granules can be added to small amounts of acidic soft food [pH < 5.5] that do not require chewing, such as apple sauce, mashed bananas or be taken with liquid [pH < 5.5]. The small measuring scoop that is provided with the bottle is designed to contain a dose of 100 mg of granules. This amount provides 5,000 units of lipase.
The mixture of Creon® Micro and soft food should be swallowed immediately without crushing or chewing, and followed with water or juice to ensure complete ingestion. Care should be taken to ensure that no drug is retained in the mouth.
Any mixture of the granules with food or liquids should be used immediately and should not be stored.

Based upon Australasian Clinical Practice Guidelines for nutrition in Cystic Fibrosis 2006, the key goal of pancreatic enzyme replacement therapy is to improve the patient's nutritional status and growth as well as controlling the symptoms of maldigestion (eg. steatorrhoea). This is achieved through optimal dietary intake using a diet without restriction of fat content (>100 g fat per day if over five years of age), unless the patient is overweight. The dose of Creon required is adjusted according to the fat content of the meal and the severity of the disease.

Dosing in paediatric and adult patients with cystic fibrosis:
Based upon a recommendation of the Cystic Fibrosis (CF) Consensus Conference, the US CF Foundation case-control study, and the UK case-control study, the following general dosage recommendation for pancreatic enzyme replacement therapy can be proposed:

- Weight-based enzyme dosing should begin with 1,000 lipase units/kg/meal for children less than four years of age and with 500 lipase units/kg/meal for those over age four.
- Dosage should be titrated according to the severity of the disease, control of steatorrhoea and maintenance of good nutritional status.
- Most patients should remain below or should not exceed 10,000 lipase units/kg body weight per day or 4,000 lipase units/gram fat intake

Dosing in adult patients with pancreatic exocrine insufficiency associated with other conditions:

- Initiate dose at 25,000 to 40,000 BP units of lipase per meal and half of that dose for snacks.
- Assess patient for clinical response and compliance to therapy
- If required, adjust dose up to 80,000 BP units of lipase per meal and half of that dose for snacks.

Agents which increase gastric pH, such as H_2-antagonists and proton pump inhibitors, have been reported to increase the activity of administered pancreatic lipase and may be helpful in patients who do not achieve adequate response to pancreatic enzyme therapy.
This is not an approved indication for these agents. Prescribers should decide, on the basis of published evidence, whether or not to use them in this way.

It is important to ensure adequate hydration at all times, especially during periods of increased loss of fluids. Inadequate hydration may aggravate constipation.

OVERDOSAGE

Extremely high doses of pancreatin have been reported to be associated with hyperuricosuria and hyperuricaemia.
In case of overdose, contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION

Creon® Micro: Round, light brown enteric-coated granules in glass bottles with LDPE closure (AUST R166118). Measuring scoop supplied.

STORAGE CONDITIONS

Store below 25°C. In warmer climates it may be necessary to store the product in the refrigerator. Keep the container tightly closed in order to protect from moisture**.** After opening use within 3 months. Keep out of reach of children.

SPONSOR

Abbott Products Pty Ltd
Level 1, Building 2 Pymble Corporate Centre
20 Bridge Street
PYMBLE NSW 2073
Tel: 1300 300 532

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Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au