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(57) Abstract

The invention relates to the use of physiologically acceptable enzyme mixtures with lipolytic, proteolytic and amylolytic activity, of microbial or animal origin, but especially to the use of digestive enzyme mixtures such as pancreatin or digestive enzyme mixtures containing pancreatin, for treating diabetes. The invention also relates to the production of medicaments suitable for this treatment. One variant of the invention relates to the use of this enzyme mixture with lipolytic, proteolytic and amylolytic activity, especially digestive enzyme mixtures such as pancreatin or digestive enzyme mixtures containing pancreatin, for the adjuvant treatment of Type I and Type II Diabetes mellitus.

(57) Zusammenfassung

Beschrieben wird die Verwendung von physiologisch akzeptablen Enzymgemischen mit lipolytischer, proteolytischer und amylolytischer Aktivität mikrobiellen oder tierischen Ursprungs, insbesondere aber von Verdauungsenzymgemischen wie z.B. Pankreatin oder pankreatinhaltigen Verdauungsenzymgemischen, zur Behandlung von Diabetes, und zur Herstellung von für diese Behandlung geeigneten Arzneimitteln. In einer Variante betrifft die Erfindung die Verwendung dieser Enzymgemische mit lipolytischer, proteolytischer und amylolytischer Aktivität, insbesondere aber von Pankreatin oder pankreatin–haltigen Verdauungsenzymgemischen zur adjuvanten Behandlung von Diabetes mellitus sowohl vom Typ I als auch vom Typ II.

Medicinal product for the treatment of diabetes

Description

The present invention relates to the use of physiologically acceptable enzyme mixtures with lipolytic, proteolytic and amylolytic activity, but especially of mixtures of digestive enzymes such as pancreatin, for the treatment of diabetes and for the manufacture of medicinal products suitable for this treatment. The invention relates especially to the use of these enzyme mixtures with lipolytic, proteolytic and amylolytic activity, but especially of pancreatin or mixtures of digestive enzymes containing pancreatin, for the adjuvant therapy of both type I and type II primary diabetes.

The term diabetes is usually understood to mean diabetes mellitus. In addition to other, e. g. secondary, forms of diabetes that may occur as sequelae of other primary diseases, essentially two main groups of disorders of carbohydrate metabolism are distinguished, i. e. type I diabetes due to insulin deficiency and type II diabetes due to reduced action of insulin, the course of the disease depending on the type concerned, among other factors. Diabetes is furthermore a chronic disease with a variety of pathological manifestations and is accompanied, for example, by disorders of lipid metabolism, circulation and glucose metabolism. The typical symptoms of this disease include elevated blood sugar (hyperglycaemia), excretion of sugar in the urine (glycosuria), tendency to infections and pruritus. Diabetes tends to be a progressive disorder and in many cases is also accompanied by various complications. Known complications include, for example, neurological and vascular diseases. It is therefore necessary to adjust the therapy to each individual case in each phase of the disease and to select the suitable medicinal product for each individual

case. It may also be desirable for this therapy to supplement the selected primary medications with other medicinal products in the form of an adjuvant treatment which can exert a supporting effect on the therapy and beneficially influence the further course of the disease.

Therefore, it is the objective of the invention to provide novel pharmaceutical preparations for the treatment of diabetes mellitus. In particular, it is the objective of the invention to provide novel pharmaceutical preparations for adjuvant therapy in the treatment of diabetes which exert an additional supportive effect on the treatment and beneficially influence the further course of the diabetic illness, for example by reducing the incidence of late complications.

According to the invention, physiologically acceptable enzyme mixtures with lipolytic, proteolytic and amylolytic activity, such as suitable enzyme mixtures of microbial origin and/or especially mixtures of digestive enzymes of animal origin such as preferably pancreatin or pancreatin-like mixtures of digestive enzymes, are used for the manufacture of pharmaceutical preparations for the treatment of diabetes mellitus in larger mammals and humans.

For the present invention, physiologically acceptable enzyme mixtures with lipolytic, proteolytic and amylolytic activity can be used that are of any animal or microbiological origin. The enzyme mixtures with lipolytic, proteolytic and amylolytic activity used for the invention can therefore be both of purely microbial origin, purely animal origin or may also be a mixture of enzymes of animal and microbial origin.

In one variant of the invention, therefore, the enzyme mixture used is of purely microbial origin. Especially enzymes produced by bacteria, i. e. by the Bacillus or

Pseudomonas strains, or by fungal cultures such as moulds, for example of the Rhizopus or Aspergillus strains, are especially suitable as microbial enzymes. Examples of such physiologically acceptable bacterial and/or mould fungi enzymes are already described in the state of the art, e. g. in connection with their synthesis and use for the treatment of maldigestion. Lipases may be derived from, for example, Bacillus or Pseudomonas strains, amylases and also lipases from mould fungi, for example of the Rhizopus strain, and proteases, for example, also from Aspergillus.

In particular, one preferred variant of the invention, however, will involve the use of those mixtures of digestive enzymes with lipolytic, proteolytic and amylolytic activity that in their properties closely resemble pancreatin. For the present invention, therefore, mixtures of digestive enzymes containing pancreatin and especially pancreatin itself are preferably used, and one or more microbial enzymes, i. e. enzymes synthesised by microorganisms, of the group of lipases, proteases and amylases may however if desired be added to the pancreatin or the mixtures of digestive enzymes containing pancreatin.

Pancreatin is a known enzyme mixture with lipolytic, proteolytic and amylolytic activity which is commercially available for example, under the trade name Creon®, in the form of granules, pellets or capsules containing enteric-coated microspheres and is used medically for enzyme replacement, for example in pancreatic insufficiency, digestive insufficiency after stomach operations, liver and biliary diseases, cystic fibrosis and chronic pancreatitis. Pancreatin is generally obtained as a mixture of natural enzymes by extraction from porcine pancreas, for example according to the processes described in German patent applications DE 25 12 746 and DE 42 03 315, and is then converted into the desired galenical form in a manner known

to the art. The pancreatic enzymes are usually administered orally in the form of solid preparations.

In one variant of the invention, the pharmaceutical preparations manufactured in accordance with the invention contain preferably pancreatin or mixtures of digestive enzymes containing pancreatin. These pharmaceutical preparations manufactured according to the invention may contain pancreatin or mixtures of digestive enzymes containing pancreatin and if desired in addition to pancreatin one or more physiologically acceptable enzymes from the group of lipases, proteases and amylases, of the kind that can be obtained from microorganisms. Microbial enzymes suitable for use as this supplement include especially the bacterially synthesised enzymes already mentioned above, for example by the Bacillus or Pseudomonas strains, or by fungal cultures such as mould fungi, for example of the Rhizopus or Aspergillus strains. The lipases added to the pancreatin or the mixtures of enzymes containing pancreatin may originate, for example, from Bacillus or Pseudomonas strains, added amylases and lipases from mould fungi, for example of the Rhizopus strain, and added proteases, for example, also from Aspergillus.

It has now been found that the physiologically acceptable enzyme mixtures with lipolytic, proteolytic and amylolytic activity which can be obtained from microbial and/or animal sources and described with reference to this invention, can be used not only for the treatment of digestive-enzyme deficiency states - of the kind associated for example with pathological changes of the pancreas due to chronic pancreatitis, digestive insufficiency after stomach operations, liver or biliary diseases - but surprisingly are also suitable for the treatment of primary diabetes mellitus in larger mammals and humans. In particular, however, the aforementioned physiologically acceptable enzyme mixtures with lipolytic, proteolytic and amylolytic activity,

preferably however, for example, pancreatin itself or mixtures of digestive enzymes containing pancreatin which also contain microbial enzyme supplements, such as one or more microbial lipases, proteases and/or amylases, are suitable for adjuvant therapy in the management of diabetes, exert an additional effect supporting the diabetes therapy and beneficially influence the further course of the diabetic disease, i. e. especially by helping reduce late complications of the diabetic disease.

The use of the physiologically acceptable enzyme mixtures used according to the invention, preferably, for example, pancreatin or mixtures of digestive enzymes containing pancreatin where appropriate with further microbial enzyme supplements also exhibits advantages in those patients who in addition to the primary diabetes mellitus have complications relating to coexisting exocrine pancreatic insufficiency.

The pharmaceutical preparations according to the invention may contain in addition to the described microbial enzyme mixtures and/or mixtures of digestive enzymes of animal origin, such as especially pancreatin or mixtures of digestive enzymes containing pancreatin, pharmaceutical auxiliaries and/or additives and, if appropriate, stabilisers.

For example, the enzyme mixtures may be contained in an effective quantity (in each case determined on the basis of the active units of the lipolytic, proteolytic and amylolytic components) together with conventional pharmaceutical auxiliaries and/or vehicles in solid or liquid pharmaceutical preparations. The lipolytic activity per dose unit may be generally within a range of 5000 to 45000 Ph. Eur. lipase units, the proteolytic activity generally within a range of 200 to 3000 Ph. Eur. protease units and the amylolytic activity generally within a range of 3500 to 45000 Ph. Eur.

amylase units (Ph. Eur. = European Pharmacopoeia). Examples of typical dose units are, for example, enzyme mixtures with the following activities: a) approx. 10000 Ph. Eur. lipase/approx. 8000 Ph. Eur. amylase/approx. 600 Ph. Eur. protease; b) approx. 25000 Ph. Eur. lipase/approx. 18000 Ph. Eur. amylase/approx. 1000 Ph. Eur. protease; and c) approx. 40000 Ph. Eur. lipase/approx. 40000 Ph. Eur. amylase/approx. 2600 Ph. Eur. protease units. Examples of solid formulations are preparations for oral administration such as tablets, coated tablets, capsules, powders, granules or pellets. These solid preparations may contain conventional inorganic and/or organic pharmaceutical vehicles such as lactose, talc or starch as well as conventional pharmaceutical auxiliaries such as lubricants or tablet disintegrants. Liquid preparations such as solutions, suspensions or emulsions of the active ingredients may contain the usual diluents such as water, oils and/or suspending agents such as polyethylene glycols and the like. Further auxiliaries such as preservatives, flavouring agents, stabilisers (e. g. complex lipids) and the like may also be added.

The enzyme mixtures can be mixed and formulated with the pharmaceutical auxiliaries and/or vehicles in a manner known to the art. To manufacture solid dosage forms, the enzyme mixtures may, for example, be mixed with the auxiliaries and/or vehicles in the usual manner and wet or dry granulated or pelleted. Granules, pellets or powder can be filled directly into capsules or sachets or compressed into tablet cores in the usual manner. If desired, these cores can be coated in the manner known to the art. Liquid preparations can be obtained by dissolving or dispersing the components and, if required, further auxiliaries, in a suitable liquid vehicle, in the form of solutions or suspensions.

The antidiabetic effects and the beneficial influence on the course of the diabetic disease, especially in adjuvant therapy as part of an antidiabetic regimen, can be

demonstrated for the physiologically acceptable enzyme mixtures with lipolytic, proteolytic and amylolytic activity used in accordance with the invention, such as, for example, the microbial enzyme mixtures and especially pancreatin or mixtures of digestive enzymes containing pancreatin described above, by determining the effect on pharmacological parameters of the kind generally used to evaluate diabetic diseases. Such parameters may, for example, be an improvement, i. e. decrease, in glycosylated haemoglobin (HbA_{1C}), a decrease in blood glucose level, a reduced number of hypoglycaemic attacks and a decrease in hyperglycaemia.

A double-blind, multicentre, placebo-controlled parallel groups study with pancreatin in the form of Creon® 10000 Minimicrospheres® (minimicrospheres in capsules) was conducted on insulin-dependent diabetic patients (IDDM = type I) with additional exocrine pancreatic insufficiency to demonstrate the positive effects of the described enzyme mixtures on glycaemic control. The patient group (male/female) was randomly assigned with a number of about 74 patients per group. Treatment was given over a period of four months at an oral dosage of 16 to 18 Creon capsules daily. Four capsules were administered with each of the main meals (3 daily) and two capsules with snacks (2 to 3 daily). One capsule of Creon® 10000 Minimicrospheres® contained 150 mg of pancreatin with the stated enzyme contents of 10000 Ph. Eur. lipase units, 8000 Ph. Eur. amylase units and 600 Ph. Eur. protease units. The placebo group received corresponding placebo minimicrosphere capsules without enzyme activity.

The efficacy of the enzyme mixture used in terms of glycaemic control was determined by measuring the glycosylated haemoglobin level (HbA_{1C}). In this context positive influencing of the HbA_{1C} level as a clinically relevant improvement in the diabetes mellitus status is desired. Further diabetic parameters used were blood glucose level (insulin/glucagon), evaluation of hypoglycaemic

attacks, status of lipid-soluble vitamins (A, D and E), daily insulin dose, body mass index and hyperglycaemic episodes.

Following a preliminary assessment for selection of the patient sample, the patients completed a run-in phase of 8 weeks (without administration of enzyme mixture/placebo) to establish the patients on individual insulin dosages. Before commencing the actual double-blind parallel groups study period of 4 months, a baseline assessment was carried out. The insulin dose had to remain as stable as possible during the study (± 10%), with the exception of the first month of treatment, in which an adjustment of the insulin dosage was permitted. Insulin adjustment required after randomisation resulted in exclusion of the patient from the study, but short-term adjustments due, for example, to acute illness were allowed. The patients underwent several interim assessments during the study, and a further assessment was carried out at the end. Gastroenterological parameters such as faecal fat, stool characteristics, coefficient of fat absorption (CFA) and clinical symptoms were also evaluated separately from the diabetic parameters.

The study outlined above showed that diabetic parameters are beneficially influenced by the administration of pancreatin, both in terms of positive influencing of glycosylated haemoglobin (HbA_{1C}) as well as improved glycaemic control manifested, for example, by stabilisation of blood glucose curves (smoothing) and, for example, reduction of hypoglycaemic attacks and of hyperglycaemia. The results of the study therefore demonstrate that the administration of physiologically acceptable enzyme mixtures with lipolytic, proteolytic and amylolytic activity according to the invention can bring about an improvement in diabetes mellitus status. It was demonstrated independently of these findings that in the sample of diabetic patients with coexisting exocrine pancreatic insufficiency the gastroenterological parameters such as faecal fat, stool

characteristics, CFA and clinical symptoms are also beneficially influenced and that the overall nutritional status of these patients is improved. Physiologically acceptable enzyme mixtures with lipolytic, proteolytic and amylolytic activity - especially pancreatin or mixtures of enzymes containing pancreatin, also with the microbial enzyme supplements described - are therefore suitable for the manufacture of pharmaceutical preparations for the treatment of diabetes mellitus, especially for the adjuvant therapy of diabetes mellitus; in these cases the diabetes mellitus may also be accompanied by exocrine pancreatic insufficiency.

The pharmacological beneficial effects of the enzyme mixture used on the diabetic parameters and on the improvement of the diabetes mellitus status will be further elucidated by the clinical study described in the following and by the results achieved therewith.

Clinical Study

For the evaluation of the efficiency of Creon® 10000 Minimicrospheres® in comparison with placebo on the glycaemic control of insulin-dependent diabetic patients (IDDM = insulin dependent diabetes mellitus) with exocrine pancreas insufficiency a double-blind multicentre placebo-controlled parallel group study was conducted.

I. Study Design

The following clinical investigational report is an interim evaluation of a study on the efficacy of Creon® 10000 Minimicrospheres® in the treatment of insulin-dependent patients (IDDM) by glycaemic control. Thus, the report gives an overview on the study and on the interim results achieved after recruitment of about half of the required patients.

Study Objective

The main aim of this study was the evaluation of the effect of Creon® 10000 Minimicrospheres® on the glycaemic control in insulin-dependent diabetic patients with exocrine pancreatic insufficiency.

Several variables are available for evaluating the glycaemic control. The most important parameter is HbA_{1c}, which should be lower in the treatment group compared to the placebo group. This parameter was chosen as main parameter. Additional parameters which were investigated are the number of hyperglycaemic attacks and hyperglycaemic episodes, fasting and postprandial blood glucose levels, daily insulin dose, body weight and the plasma levels of lipid-soluble vitamins (A/D and E). Furthermore parameters of the exocrine dysfunction of the pancreas were assessed, including stool frequency and consistency, abdominal pain, meteorism, flatulence and the clinical global impression of the disease rated by the patient and the investigator.

Tolerability and safety were assessed by means of standard tests.

Patient Population

In this study patients with an insulin-dependent diabetes mellitus were recruited. This patient population was chosen as a model sample for diabetes mellitus patients, as this group is most clearly defined. It was planned to include 74 patients per treatment group leading to an overall sample size of 148 patients.

Patients should have an onset of the disease before the age of 30 and should have started insulin therapy within the first year after diagnosis. Patients with proven non-insulin-dependent diabetes mellitus were excluded.

To ensure that the patients being randomised had a certain degree of exocrine pancreatic insufficiency, the faecal elastase-1 values were evaluated. This parameter is a measure to determine the presence of an exocrine pancreatic dysfunction. To enter the study the value of elastase-1 had to be below or equal to 100 µg/g stool. Patients having values above this were excluded from the study. Patients with an exocrine pancreatic insufficiency due to any other reasons than insulin-dependent diabetes mellitus (e.g. chronic pancreatitis, cystic fibrosis) were excluded from the study.

Other inclusion criteria were: male and female gender and age of at least 18 years.

Further exclusion criteria were any other severe illness which would have limited participation in or completion of the study (with the exception of findings related to the disease of the study), known allergy to pancreatin and/or porcine insulin, any type of malignancy involving the digestive tract within the last five years, any type of gastrointestinal surgery and short bowel syndrome, haemachromatosis, any history of drug abuse including alcohol, positive urine pregnancy test or existing pregnancy or lactation (in females), severe allergy or any history of severe abnormal drug reactions, suspected non-compliance or non-cooperation, intake of any experimental active ingredient within 4 weeks prior to the entry of the study and any other reason which, in the investigator's opinion, would prohibit the participation of the patient in the study.

Design:
All patients, having signed the informed consent form, underwent the pre-screening for elastase-1 in stools. If the elastase-1 values were lower than or equal to 100 µg/g stool and the patients fulfilled the inclusion criteria and were not barred by the exclusion criteria, they were entered into the run-in period of at least 8 weeks.

During the run-in period the patient had to achieve a stable insulin dosage, including no change in the number of insulin injections and the type of insulin, no switch from standard treatment to intensive treatment or from injections to use of pumps. The HbA_{1c} levels had to be in a range of 0.07 to 0.10 (in metric units). Body weight had to be stable with not more than 5 kg difference between the assessments.

At the end of the run-in period suitable patients were randomised to either Creon® 10000 Minimicrospheres® or placebo. The treatment period was scheduled for 16 weeks with several interim assessments after 1, 2, 4 and 10 weeks and a final assessment at 16 weeks. During the first 4 weeks insulin adjustments were allowed. After 4, 10 and 16 weeks a wide range of investigations for glycaemic control were performed (see Study Objective).

Treatment and Dosages:
Patients [were] randomly allocated either Creon® 10000 Minimicrospheres® or placebo.

The patients were scheduled to receive 16 to 18 capsules/day. The number of capsules per meal was fixed. For the three main meals 4 capsules and for the (2 to 3) additional snacks 2 capsules were taken by the patients.

This equals 40000 Ph. Eur. lipase units per main meal and 20000 Ph. Eur. lipase units per snack. A total daily dose of 160000 to 180000 Ph. Eur. lipase units was administered. This reflects the dose which was used in clinical trials in chronic pancreatitis patients and should therefore be adequate for the treatment of patients with exocrine pancreatic insufficiency.

Statistics:
The analysis of the primary parameters was an analysis of covariance using a linear model with covariate as the baseline, the fixed main effects of treatment and centre, the respected measures over time, and the interaction of treatment by centre. The alpha level for the testing was 5%. The analysis was performed on the intent-to-treat sample which consisted of all randomised patients having at least one HbA_{1c} measurement under stable insulin dose after 4 weeks of treatment. As subsequently only the resulting interim analysis will be reported, a peer-protocol group was not defined.

The sample size was calculated to be 74 patients per group using an alpha level of 5%, a standard deviation for HbA_{1c} of sigma = 0.015 and a power of 80% to detect a difference of 0.007.

An interim analysis was planned once half of the patients had completed the study (37 patients per group).

II. Results of the Study

Patient Group:
Due to low recruitment the interim analysis was performed with 71 patients being randomised to either Creon® 10000 Minimicrospheres® or placebo. The 71 patients are included in the safety sample and have at least received one dose of study drug.

Based on the criteria for the test group intended for the treatment (intent-to treat sample, = ITT) 65 patients were used for the analysis of HbA_{1c} (Table 1).

Table 1: Patient Test Group

	Placebo N	**Creon N**	**Total N**
Safety sample	36	35	71
ITT sample	36	29	65

ITT = intent-to treat

Demographic Data:

The following Table 2 gives an overview on the most important demographic data.

Table 2: Demographic Data

Parameter	Placebo	Creon	Total
Sex [N(%)]			
Male	21 (58.3)	23 (65.7)	44 (62.0)
Female	15 (41.7)	12 (34.3)	37 (38.0)
Ethnic origin [N(%)]			
Caucasian	36 (100.0)	34 (97.1)	70 (98.6)
Black	-	1 (2.9)	1 (1.4)
Age [years]			
Mean ± SD	42.7 ± 10.0	46.6 ± 8.9	44.6 ± 9.6
Range	24 - 64	30 - 63	24 - 64
male (mean ± SD)	44.7 ± 10.4	45.7 ± 9.7	45.2 ± 10.0
female (mean ± SD)	40.0 ± 9.0	48.3 ± 7.3	43.7 ± 9.2
Weight [kg]			
Mean ± SD	74.5 ± 11.8	79.2 ± 12.9	76.8 ± 12.5
Range	47 - 93	54 - 103	47 - 103
Male (mean ± SD)	79.8 ± 9.0	84.7 ± 9.3	82.4 ± 9.4
Female (mean ± SD)	67.0 ± 11.5	68.6 ± 12.5	67.7 ± 11.8
Height [cm]			
Mean ± SD	171.1 ± 10.1	173.2 ± 10.0	172.1 ± 10.0
Range	152 - 190	156 - 191	152 - 191
Male (mean ± SD)	176.3 ± 7.4	179.1 ± 6.4	177.8 ± 7.0
Female (mean ± SD)	163.8 ± 8.7	161.8 ± 3.6	162.9 ± 6.9
BMI [kg/m^2]			
Mean ± SD	25.4 ± 3.0	26.4 ± 3.6	25.9 ± 3.3
Range	18 - 31	19 - 34	18 - 34
Male (mean ± SD)	25.7 ± 2.6	26.5 ± 3.2	26.1 ± 3.0
Female (mean ± SD)	24.9 ± 3.6	26.1 ± 4.3	25.5 ± 3.9

SD = Standard Deviation
BMI = Body Mass Index

As can be seen from the table, both treatment groups are comparable concerning demographic data, although more males were randomised in the Creon group, which subsequently led to slightly higher values for height, weight and body mass index in the Creon group. However, these differences can be

regarded as not being important for the interpretation of the results of efficacy.

The same is true for the age of onset of diabetes, duration of the disease or duration of insulin treatment. In all cases there were only small differences in the mean or median values between the two treatment groups. Therefore, the severity of the disease can be regarded as similar in both treatment arms.

The elastase-1 values at pre-screening were also not significantly different between the two groups (57.3 ± 26.5 for Creon versus 62.0 ± 29.8 for placebo).

Efficacy Parameter:
The results of the most important parameters of the HbA_{1c} are summarised in Table 3. The table contains the data from the ITT sample.

Table 3: HbA_{1c} - ITT sample

	Placebo		**Creon**	
	N	**mean**	**N**	**mean**
Week 4	36	0.07967	29	0.07779
Difference between treatments	Mean: 0.00187 SEM: 0.00086 P=0.0330			
Week 10	36	0.08131	29	0.07876
Difference between treatments	Mean: 0.00254 SEM: 0.00112 P=0.0268			
Week 16	36	0.08273	29	0.08034
Difference between treatments	Mean: 0.00238 SEM: 0.00138 P=0.0902			

SEM = Standard Error of the Mean

Table 3 shows that Creon leads to statistically significant lower levels of HbA_{1c} after 4 and 10 weeks and a clear trend

even after 16 weeks. This indicates that Creon has the potential to improve glycaemic control in patients with insulin-dependent diabetes mellitus.

This is underlined by Table 4 showing the number of patients improved, unchanged or worsened compared to the baseline HbA_{1c} values.

Table 4: Number of patients improved, unchanged or worsened compared to the baseline HbA_{1c} values.

	Placebo			Creon		
	improved	unchanged	worsened	improved	unchanged	worsened
Week 4	13	5	18	15	5	9
Week 10	12	2	22	12	5	12
Week 16	4	4	26	11	3	15

Far more patients under placebo treatment had a worsening of their HbA_{1c} levels over time compared to Creon. The tendency of worsening is relatively small under Creon, whereas under placebo the majority of patients became worse. Again a clear indication that Creon is effectively able to improve glycaemic control of insulin-dependent diabetes mellitus. The reason why many patients worsened lies in the study design, which required virtually optimal treatment before randomisation, which leads under normal conditions to a rapid deterioration of the glycaemic control, as seen in the placebo group. Creon is able to reduce this deterioration.

Similar findings were observed for the number of occurrences of mild to moderate hyperglycaemic attacks (Table 5).

Table 5: Change in the number of hyperglycaemic attacks

	Placebo			Creon		
	<0	=0	>0	<0	=0	>0
Week 4	11	9	16	8	7	14
Week 10	13	13	10	13	3	11
Week 16	14	10	12	14	8	8

<0 fewer attacks compared to baseline
=0 same number of attacks compared to baseline
>0 greater number of attacks compared to baseline

Table 5 shows that nearly 50% of the patients receiving Creon had fewer mild to moderate hyperglycaemic attacks compared to the placebo group, where only 39% of patients had this finding.

For the number of increased glucose levels per week - an indicator of hyperglycaemic periods - a similar but less strong effect was found.

Fasting and non-fasting blood glucose levels were not significantly different, as was the dosage of insulin needed by the patients.

The numbers of adverse events were not different in the two treatment arms. Some adverse events were observed in the digestive system under Creon treatment and more adverse events in the metabolic/nutritional disorder and respiratory system group of adverse events under placebo treatment. The number of patients dropping out for adverse events was the same in both groups.

III. Conclusion

Overall, there is strong evidence that Creon is beneficial in the treatment of insulin-dependent diabetic patients having exocrine pancreatic insufficiency and leads to better

glycaemic control. This means that Creon should be added to the treatment of those patients in order to improve the most important factor in their treatment.

As insulin-dependent diabetic patients were used as model it can be estimated that the same beneficial effects should also be seen in non-insulin-dependent diabetic patients, in particular as long as they also have an exocrine pancreatic insufficiency.

The example below is intended to explain the manufacture of a pharmaceutical preparation containing pancreatin which is suitable for the treatment of diabetes, and especially for adjuvant therapy of diabetes, without, however, restricting the scope of the invention.

Example

120 kg pancreatin was mixed in a commercially available mixer with 30 kg of polyethylene glycol 4000 and thoroughly moistened with about 20 kg of propan-2-ol.

The mixture was pressed through an extruder fitted with a perforated plate with holes of 0.8 mm internal diameter and a downstream cutting device. This arrangement produced strand sections with a strand length of up to 20 mm.

The strand sections were crushed in portions of about 15 kg in a rounding machine (type Caleva) and rounded into spherically shaped pellets, whereby 300 g of liquid paraffin and, depending on the time the material spent in the rounding machine (3 to 6 min), about 300 to 700 g of propan-2-ol was added to each portion.

After drying in a commercially available tray drier, a yield of about 90% of pancreatin microsphere cores with a diameter

of 0.7 to 1.4 mm, screened through a 0.7 mm sieve (separation of undersized particles < 0.7 mm) and a 1.4 mm sieve (separation of oversized particles > 1.4 mm), with a pancreatin content of about 78% was obtained. The bulk density was 0.7 g/ml.

The microsphere cores were then provided with an enteric coating in the manner known to the art in a conventional film coating apparatus, using a solution of hydroxypropylmethyl cellulose phthalate (type HP55), dibutyl phthalate, liquid paraffin and silicon oil (Dimethicone 1000) in acetone. The resulting yield was about 90% enteric-coated pancreatin microspheres with a diameter ranging between 0.7 to 1.6 mm, screened with a 0.7 mm sieve (separation of undersized particles < 0.7 mm) and a 1.6 mm sieve (separation of oversized particles > 1.6 mm) with a content of about 60% pancreatin, with reference to the film-coated microspheres, and a bulk density of 0.8 g/ml.

The microspheres were then filled into commercially available hard gelatin capsules or sachets.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Use of physiologically acceptable enzyme mixtures with lipolytic, proteolytic and amylolytic activity for the manufacture of pharmaceutical preparations for the treatment of type I primary diabetes mellitus in larger mammals or humans.

2. Use in accordance with Claim 1, wherein a mixture of microbially synthesized lipases, proteases and amylases is used as enzyme mixture.

3. Use in accordance with Claim 1, wherein pancreatin or a pancreatin-like mixture of digestive enzymes is used as enzyme mixture.

4. Use in accordance with Claim 1, wherein pancreatin and a pancreatin-like mixture of digestive enzymes is used as enzyme mixture.

5. Use in accordance with Claim 3 or 4, wherein a mixture of digestive enzymes containing pancreatin is used as a pancreatin-like mixture of digestive enzymes.

6. Use in accordance with any one of Claims 3 to 5, wherein pancreatin or a mixture of digestive enzymes containing pancreatin is used, one or more microbial enzymes from the group of lipases, proteases and amylases being additionally added to the pancreatin or the mixture of digestive enzymes containing pancreatin.

7. Use in accordance with any one of Claims 1 to 6, wherein pharmaceutical preparations for the adjuvant treatment of primary diabetes mellitus are manufactured.

8. Use in accordance with any one of Claims 1 to 7, wherein pharmaceutical preparations for the treatment of diabetes mellitus accompanied by exocrine pancreatic insufficiency are manufactured.

9. Process for the manufacture of pharmaceutical preparations for the treatment of type I primary diabetes mellitus, wherein a quantity of a physiologically acceptable enzyme mixture with lipolytic, proteolytic and amylolytic activity that is effective in improving the clinical parameters of diabetes and/or effective in reducing the late complications of diabetes, together with conventional pharmaceutical auxiliaries, is converted into a suitable dosage form.

10. The process in accordance with Claim 9, wherein pancreatin or a pancreatin-like mixture of digestive enzymes is used as enzyme mixture.

11. The process in accordance with Claim 9, wherein pancreatin and a pancreatin-like mixture of digestive enzymes is used as enzyme mixture.

12. A method of treating type I primary diabetes mellitus in larger mammals or humans, the method including the administration of a therapeutically effective amount of a physiologically acceptable enzyme mixture with lipolytic, proteolytic and amylolytic activity.

13. The method in accordance with Claim 12, wherein a mixture of microbially synthesized lipases, proteases and amylases is used as enzyme mixture.

14. The method in accordance with Claim 12, wherein pancreatin or a pancreatin-like mixture of digestive enzymes is used as enzyme mixture.

15. The method in accordance with Claim 12, wherein pancreatin and a pancreatin-like mixture of digestive enzymes is used as enzyme mixture.

16. The method in accordance with Claim 14 or 15, wherein a mixture of digestive enzymes containing pancreatin is used as a pancreatin-like mixture of digestive enzymes.

17. The method in accordance with any one of Claims 14 to 16, wherein one or more microbial enzymes from the group of lipases, proteases and amylases is

added to the pancreatin or the mixture of digestive enzymes containing pancreatin.

18. The method in accordance with any one of Claims 12 to 17 for the adjuvant treatment of primary diabetes mellitus.

19. The method in accordance with any one of Claims 12 to 18 for the treatment of diabetes mellitus accompanied by exocrine pancreatic insufficiency.

20. Use of physiologically acceptable enzyme mixtures for the manufacture of pharmaceutical preparations substantially as hereinbefore described with reference to the formulation example.

21. A method of treating type I primary diabetes mellitus substantially as hereinbefore described with reference to the clinical examples.

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