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LipaCreon® Granules 300 mg Sachet & LipaCreon® Capsules 150 mg

Protocol for Special Investigation (All cases)

- Special Investigation (All cases) of LipaCreon in patients with pancreatic exocrine insufficiency due to Cystic Fibrosis -

Protocol No. : P12-893

LipaCreon® Granules 300 mg Sachet & LipaCreon® Capsules 150 mg
Protocol for Special Investigation (All cases)
- Special Investigation (All cases) of LipaCreon in patients with pancreatic exocrine insufficiency due to Cystic Fibrosis -

1. Objective of registry

The registry aims at collecting the information related to the safety and efficacy in the pancreatic exocrine insufficiency (PEI) patients due to cystic fibrosis (CF) receiving the treatment with LipaCreon in order to obtain the information for the effective and safe use of LipaCreon.

2. Planned number of cases for the registry and justification

Planned number of cases: All the cases

Justification:

The number of enrolled patients in the domestic clinical studies was few, and prompt collection of sufficient information is necessary. And the nationwide CF patient number who was reported during the whole year of 2004, was 13, and the total patients population of CF patient for 10 years from 1995 was 38*. The number of CF patients in Japan is extremely few. From this background, the target of the study is all the cases treated with LipaCreon.

*) The Research Result relating to the intractable pancreatic diseases conducted by MHLW Scientific Research Subsidiary Intractable Disease Research Enterprises during 2005 to 2007: 205-215, 2008

3. Target patients of registry

Patients with PEI attributable to primary disease of CF.

<Indications>

Replacement of pancreatic digestive enzymes in PEI

<Precautions for use related to indications>

Administer LipaCreon to patients with having symptoms of steatorrhea or other symptomatology due to PEI because of underlying diseases of chronic pancreatitis (CP) during non-compensatory period, pancreatectomy (PY) and pancreatic CF, etc.

<Contraindication>

(1) Patients with a history of hypersensitivity to the ingredient of LipaCreon.

(2) Patients with a history of hypersensitivity to porcine protein.

4. Dosage & administration method

Usually, 600 mg/meal of LipaCreon should be administered t.i.d. orally, immediately after meal.

In addition, the dose should be adjusted as needed based on patient's condition.

If dosage increase from usual daily dosage (1800mg) is to be done during the observation period or follow-up period, perform measurement of nutritious assessment items and monitor the symptoms relating to pancreatic exocrine insufficiency before the dosage increase. (Please refer 8. Items of registry (7) and (8))

[Precautions related to dosage and administration method]

In regarding to the adjustment of dosage and administration, age, weight, volume of meal, dietary and frequency of meal, etc. should be considered.

[Important Precaution]

In overseas, there were reports of stenosis of ileocecal area and colon (fibrosing colonopathy) in CF patients who have been administrated with high dosage of pancreatin products. So, careful observation should be provided and if any abnormality or change of abdominal symptom was found, appropriate action should be taken. Especially for patients with PEI due to CF, careful observation is necessary if patient is administered over 150 mg (equivalent to1/2 sachet or one capsule) per kg body weight per day of Pancrelipase.

5. Number of planned institutions for registry by department

The registry will take place in departments of pediatric, internal medicine, digestive organs, and gastroenterology, etc. The number of the planned institutions is unknown because the contract will be signed after confirming the CF patient's availability in that institution.

6. Method of registry

(1) Request/Contract of the Registry

The target medical institutions are where LipaCreon is to be adapted/delivered and any CF patient is under or planning to be provided treatment. Medical Representative in charge of each medical institution explains to the doctors and relating people in charge, the purpose, target subjects and method of this registry sufficiently. In case the acceptance for the participation to this registry was obtained, he/she takes actions for the contract. The contract is to be signed between the head of medical institution and the sponsor in writing.

(2) Selection of target patients and registration

1) Prospective registry method is employed. It is an all cases registry.
2) Doctor in charge of this registry registers the patient is under or planning to be provided treatment by LipaCreon, by sending facsimile the registration form to the registration center. The registration form should include following items :
   ① Patient ID No., ② Sex, ③ Date of birth or age,
   ④ Inpatient/outpatient classification,
   ⑤ Start date of administration,
3) In case any patient who had been administered with LipaCreon were enrolled, the information before the enrollment is to be collected as much as possible if it is required in the registry items.

(3) Observation Period

The observation period for a case is at least 52 weeks from the start of administration of LipaCreon. Even if the administration period exceeded 52 weeks, the assessment is to be done at the time of 52^{nd} weeks. After 52^{rd} week, administration status, concomitant use drug status, nutritious assessment items, symptoms relating to pancreatic excretion insufficiency and adverse events should be described in the Follow-up Case Report Form, and it should be submitted to the sponsor company.

(4) Description and submission of the Case Report Form

In this Registry, the Case Report Form is consisted of seven report brochures. After each whole follow-up period per case is completed, follow-up items should be fulfilled on all the registered cases (incl. discontinued cases). After all items were fulfilled, final confirmation date

should be written, signature should be done, and seal should be done before submission.

The Case Report Form (1): From the first administration date to 52nd week

The Case Report Form (2) – (7): After 52rd administration, one CRF per year

(5) Discontinued cases

In this Registry, the cases which the administration was discontinued during the observation period, or which follow-up became impossible due to patient's visit stopped, or other reasons, will be handled as "discontinued cases". For these discontinued cases, stopped date, reason of stopping, assessment done until the discontinuation should be written in the forms.

7. Planned registry period

Planned registry period:	From the release of Lipa Creon to 31st March 2018
Case registration period:	From the release of Lipa Creon to 31st March 2017
Observation period:	For 52 weeks from the start of administration of LipaCreon. Even if the administration period exceeded 52 weeks, the assessment is to be done at the time of 52nd weeks.
Follow-up period:	After the 52rd week, administration status, concomitant use drug status, nutritious assessment items, symptoms relating to pancreatic excretion insufficiency and adverse events should be described in the Follow-up Case Report Form annually, and it should be submitted to the company.

After administration of LipaCreon started, the information will be collected until the end of March 2018. First 52 weeks from the start will be observation period and 53 weeks and onwards will be follow-up period.

8. Survey items

(1) Items required for specifying the patient:

Patient ID No.

(2) Patient background:

Sex, presence or absence of pregnancy/breast feeding (female only), date of birth or age, inpatient/outpatient classification, start date of administration, concomitant diseases (hepatic, renal or respiratory disorders, other), history of disease, history of allergy, prior treatment drug (digestive enzyme product)

(3) Administration status of LipaCreon:

Daily dose, administration period, drug regimen compliance, the reason for a change in dose

(4) Administration status of concomitant drugs:

[Other digestive enzyme products]:

Presence or absence of treatment with other digestive enzyme product, drug name, daily dose, administration period

[Other concomitant drugs]:

When additional information is required at the onset of adverse event, etc., the following information is investigated:

Presence or absence of information for the concomitant drugs, drug name, administration route, reason for use, daily dose, administration period

(5) Adverse events

All the undesirable or unintended diseases, or their symptoms, signs or abnormal changes in laboratory test values, etc. that have occurred in the patients administered LipaCreon are handled as the adverse events regardless of the causal relation to LipaCreon. The adverse events whose causal relation to LipaCreon is not deniable are handled as adverse reactions.

Concerning the adverse events that occur from the start to the completion of administration of LipaCreon, the following items are investigated. In principle, the course of adverse event is observed until the event is judged by the physician in charge of registry to cause no clinical problem.

Diseases, symptoms, signs or abnormal changes in laboratory test values which were attributed to the cystic fibrosis, will not be regarded as adverse event, but as the events attributed to cystic fibrosis.(please refer to ([(6) Events attributed to cystic fibrosis])

1) Presence or absence of adverse event 2) Name of adverse event

3) Date of onset　4) Seriousness　5) Administration of LipaCreon　6) Measure taken about the adverse event　7) Date of outcome (or outcome confirmation date)　8) Outcome　9) Causal relation to LipaCreon　10) Factors other than LipaCreon　11) Symptoms and history of adverse event　12) Laboratory test results related to the adverse event　13) Comment on the adverse event

(6) Events attributed to cystic fibrosis

Information regarding below items should be collected on the diseases, symptoms, signs or abnormal changes in laboratory test values which were attributed to the cystic fibrosis occurred after administration of LipaCreon.

1) Presence or absence of event attributed to cystic fibrosis
2) Name of event
3) Date of onset　4) Measure taken about the event
5) Date of outcome (or outcome confirmation date)
6) Outcome

(7) Nutrition assessment items

The following nutrition assessment items are determined before the start and after 4, 8 and 24 weeks from the start of administration of LipaCreon, at the end of observation period or at the time of discontinuation during observation period, and per year or at the end of follow-up period or at the time of discontinuation during follow-up period.

If the dosage increase from usual dosage (1800mg/day) is to be done during the observation period or follow-up period, perform assessment before the dosage increase.

- BMI (Height, body weight)
- Serum total protein
- Albumin
- Total cholesterol
- Triglyceride
- Hemoglobin

(8) Symptoms relating to pancreatic exocrine insufficiency

Following symptoms should be monitored at the timing before the start of aministration, 4^{th}, 8^{th}, 24^{th} week after administration started, and completion/discontinuation of follow-up during the observation period,

and per year or at the end of follow-up period or at the time of discontinuation during follow-up period. If the dosage increase from usual dosage (1800mg/day) is to be done during the observation period or follow-up period, those symptoms should be monitored before the increase will take place.

- Steatorrhea
- Frequency of defecation
- Diarrhea
- Bad odor of feces
- Appetite loss
- Abdominal distention

(9) Overall improvement rating

The overall improvement is assessed in the following 4 grades after 24 weeks from the start of administration of LipaCreon, and at the end of observation period at 52nd week or at the time of discontinuation.

Effective, unchanged, aggravation, unassessable

(10) Discontinuation

When the administration is discontinued during the observation period, or when follow-up became impossible due to patient's visit stopped, or other reasons, the date of discontinuation and the reason for discontinuation is stated in the CRFs.

(11) Case of pregnancy

The information related to pregnancy is separately investigated in the pregnant case and the case whose pregnancy is found during the observation period at the point the pregnancy is known and after the birth of baby.

Survey schedule

Survey items	Time point						
	At the start of administration	During observation period				During Follow-up period	
		After 4 weeks	After 8 weeks	After 24 weeks	After52 weeks or at the discon-tinuation	Per year	At the end of Follow-up Period (Mar. ’18) or at the discon-tinuation
Registration	○						
Patient background	○						
Administration status of LipaCreon	○	○				○	○
Administration status of concomitant drug	○	○				○	○
Nutrition assessment items*	○	○	○	○	○	○	○
Symptoms relating to pancreatic exocrine insufficiency *	○	○	○	○	○	○	○
Overall improvement rating				○	○		
Reason for discontinuation					At the time of discon-tinuation ○		At the time of discon-tinuation ○
Adverse events	Investigation from the start of administration and throughout the observation period						
Events attributed to cystic fibrosis	Investigation from the start of administration and throughout the observation period						

* : If dosage increase from usual daily dosage (1800mg) is to be done during the observation period or follow-up period, perform measurement of nutritious assessment items and monitor the symptoms relating to pancreatic exocrine insufficiency before the dosage increase.

9. Timing, items and methods of analysis

(1) Timing of analysis

After 3 or 4 years from start of registry, the interim analysis is to be done. And at the end of registry, the final analysis is to be done.

(2) Matters related to case formation

- Number of registered cases and number of cases from which the CRF is collected
- Number of cases accepted for safety and efficacy analysis
- Number of cases excluded from analysis and the reason for exclusion

(3) Matters related to safety

- Adverse reaction onset status
- Factors considered to have influence on the safety (The incidence of ADRs by patient background)
- Adverse event and serious adverse event

(4) Matters related to effectiveness

- Changes in nutrition assessment items
- Overall improvement rating
- Factors considered to have influence on the efficacy (The list related to efficacy by patient background)

10. System organized for the conduct of registry

Abbott Japan Co., Ltd.

- Post-marketing Studies Manager : Yoshiaki Ino
  Post Marketing Study Group, Medical, Pharma Products Group

11. Name and address of the person who consigned this job, and the scope of consigned job

Person who consigned this job

(1) Address: 4-6-10, Koishikawa, Bunkyo-ku, Tokyo
Name: Hitoshi Suzuki, Post-marketing Studies Manager
Eisai Co., Ltd.
Scope of consigned job: Conduct of special investigation (request for the conduct, contract conclusion, collection of registration cards and re-survey, collection of CRFs and re-survey, collection of adverse event information, etc.)

(2) Address: 2-3-19, Kouraku, Bunkyo-ku, Tokyo
Name: EPS Co., Ltd.
Scope of consigned job: Case registration job, data management job, statistics analysis job)

12. Medical Professional

(1) Address: 1-1, Seiryocho, Sendai Aoba-ku, Miyagi
Affiliation: Department of Gastroenterology, Tohoku University School of Medicine
Name: Toru Shimosegawa (Professor)
Scope of work: Medical advice for this investigation.

(2) Address: 4-30-11, Chuo, Ota-ku, Tokyo
Affiliation: Department of Respiratory disease, Omori Red Cross Hospital
Name: Kunihiko Yosimura
(Department director of respiratory tract medicine)
Scope of work: Medical advice for this investigation.

13. Other necessary matters

(1) Amendment of registry plan

When a new finding is obtained during this registry period, the necessity or not of the protocol amendment is investigated, and the amendment is made as required. The necessity or not of the protocol amendment is also investigated when the approval on a partial change in the dosage & administration or indication & effect (excluding the case when a new re-evaluation period is designated), etc. is granted, and the amendment is made as required.

(2) Measure taken when any problem or doubt arises

The conduct of new special investigation or post-marketing clinical study is investigated in the following cases so as to detect or confirm these factors or to verify the assumption, etc. obtained as a result of investigation.

1) When critical safety concern such as the onset, etc. of unknown & serious adverse reaction is suggested.
2) When a definite increase in the incidence of adverse reaction is observed.
3) When any problem is found in the safety and efficacy in comparison with the results of study conducted up to the time of approval.

Attachment

(a) Agreement for PMS

(b) Outline for Special Investigation

(c) Registration form for Special Investigation

(d) Case report form for Special Investigation