

# **ENCRUSE<sup>®</sup> ELLIPTA<sup>®</sup> Drug Use Investigation**

## **Protocol/Implementation Guidance**

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## 1. Objectives

This investigation will be conducted to collect and assess information regarding the safety and effectiveness of ENCRUSE<sup>®</sup> ELLIPTA<sup>®</sup> (hereinafter referred to as “Encruse Ellipta”) in routine clinical practice.

## 2. Safety Specifications

In the investigation, safety specifications are defined as follows;

- Cardiovascular events

Since Encruse Ellipta contains a long-acting muscarinic receptor antagonist, the priority investigation matters are defined to monitor occurrence of them, etc. as follows;

- Cardiovascular events, urinary retention, eye related problems, gallbladder disorder, intestinal obstruction, anticholinergic effects, lower respiratory tract infection and pneumonia.

## 3. Study Population

This investigation will be conducted in patients who are first prescribed Encruse Ellipta for the approved indication of the product, “Relief of symptoms of obstructive airway disorder due to chronic obstructive pulmonary disease (COPD) (chronic bronchitis and emphysema)”.

## 4. Planned Sample Size and Its Rationale

- 1) Target number of patients: 1,000 (as number of subjects to be registered)
- 2) Rationale:

In the clinical study for Japanese COPD patients (131 pts), the incidence of adverse drug reactions (ADRs) related to “cardiovascular events”, an important identified risk of Encruse Ellipta, was 4% (5/131 pts). Among 5 patients, supraventricular tachycardia in 2 patients (2%), angina pectoris, palpitations, and sinus tachycardia in 1 patient each (0.76%) were reported as ADRs.

On assumption that the incidence used as a threshold for cardiovascular events is assumed to be 4%, 305 patients in the safety analysis set are required to check the incidence in the post-marketing surveillance with estimation accuracy which detects the 4% of threshold with a statistical power of  $\geq 80\%$  when the risk exists 2 times or more of the threshold. Accordingly, it is thought to be possible to examine the incidence of cardiovascular events in the drug use investigation with 1,000 patients.

## 5. Planned Number of Medical Institutions by Department

Approximately 200 medical institutions, primarily the department of respiratory medicine

## 6. Study Period

Study period: November 2015 to January 2019

Observation period: The observation period (duration of treatment with Encruse Ellipta) in each patient will be 1 year after the start date of administration of the product.

Planned registration period: November 2015 to October 2017

When the number of registered patients reaches the planned sample size, however, the registration may be discontinued before completion of the above-mentioned registration period.

## 7. Study Methods

In the investigation, the electronic data capture (EDC) system will be used for case registration and data collection.

### 1) Request for the investigation and contract

- (1) The medical representative (hereinafter referred to as “MR”) will explain the study objectives, study population, study items, study methods, etc. to the potential investigators, etc. of the medical institutions where Encruse Ellipta has been adopted and where the product is delivered, and request them to cooperate with the investigation.
- (2) Once agreement on cooperation with the investigation is obtained, a written contract should be concluded with the head (e.g., director) of the medical institution prior to initiation of the investigation.

### 2) Registration of study population

This investigation will be conducted by the central registration system.

- (1) The investigator will enter the information of patients for whom administration of Encruse Ellipta is initiated after conclusion of the contract and who are listed in “3. Study Population” in the EDC system within 14 days after the start date of administration of Encruse Ellipta (the start date of administration should be regarded as Day 1) to complete the registration of the patients.
- (2) When the number of registered patients reaches the contracted sample size, registration of patients at the study site will be completed.

### 3) Collection of data and entry in the EDC system.

- (1) The investigator will confirm the study items such as the characteristics of the registered patients.
- (2) The investigator will request the registered patients to fill out the “COPD Assessment Test (CAT)” at the initiation of treatment with Encruse Ellipta, and at 1 month and 1 year after the initiation of treatment (or at the discontinuation/completion of treatment if treatment with Encruse Ellipta is discontinued/completed).
- (3) The investigator will collect the CAT of the registered patients, review the content, and enter the information in the EDC system.

- (4) During the observation period, the investigator will monitor the information regarding safety and effectiveness, etc. If a patient does not visit the study site during the observation period, the investigator will obtain information regarding AEs, etc. by telephone, etc. as far as possible.
- (5) At the end of the observation period (or at the time of withdrawal/completion, if a patient has withdrawn from/completed administration of the drug), the investigator will record the obtained information in the EDC system and submit.

## 8. Study Items

The investigator will collect information regarding the following items, etc. as far as possible and enter it in the EDC system.

- 1) Information regarding the medical institutions  
Name of the institution, department, and investigator
- 2) Patient characteristics (at the start of administration of Encruse Ellipta)  
Identification number, sex, year of birth, start date of administration of Encruse Ellipta, hospitalization status, height, body weight, reason for use of Encruse Ellipta, type of COPD, stage classification, duration of COPD, history of cigarette smoking, Brinkman index, and presence or absence of complications (bronchial asthma, cardiovascular disorder, renal impairment, hepatic impairment other than the primary disease, etc.) and their names  
To protect the confidentiality regarding identification of an individual patient, the identification number should be a unique number assigned to each patient by the investigator, etc. In this investigation, any other diseases or symptoms than COPD that have existed prior to the initiation of treatment with Encruse Ellipta will be handled as “complications”.
- 3) Prior medication for COPD (4 weeks before the initiation of treatment)  
Presence or absence of prior medication for COPD 4 weeks before the initiation of treatment, and the category and product name of the medication
- 4) Status of treatment with Encruse Ellipta  
Single dose and daily dose frequency of Encruse Ellipta, start date of administration, end date of administration, and reason for revising Dosage and Administration during the observation period
- 5) Concomitant medications  
Presence or absence of concomitant medications, name of the medications, route of administration, reason for administration, during the observation period.
- 6) Concomitant therapies for COPD (other than medications)  
Presence or absence of concomitant therapies for COPD, name of the therapies, during the observation period.
- 7) COPD exacerbations

Number of COPD exacerbations during the 1-year period before and after the initiation of treatment with Encruse Ellipta

8) Respiratory function test (spirometry)

Presence or absence of use of short-acting beta<sub>2</sub>-agonists, forced expiratory volume in one second (FEV<sub>1</sub>), and forced vital capacity (FVC) at the initiation of treatment with Encruse Ellipta, at 1 month and 1 year after the initiation of treatment, on the day of assessment at the time of discontinuation/completion, and within 4 hours before measurement.

9) COPD assessment test (CAT)

Information of the “COPD Assessment Test (CAT)” filled out by patients at the initiation of treatment with Encruse Ellipta, at 1 month and 1 year after the initiation of treatment, and at the time of discontinuation/completion.

10) Global assessment of effectiveness

One year after the initiation of treatment with Encruse Ellipta or at the discontinuation/completion of treatment, the effectiveness of the product will be assessed comprehensively on a scale of two categories, “effective” or “not effective”, based on the progress of subjective symptoms and clinical findings, changes in respiratory function test results, COPD exacerbations, changes in CAT scores, etc., from the initiation of treatment to the completion of the observation period. If effectiveness cannot be determined for some reasons, it should be assessed as “indeterminable”, and the reason should be entered in the EDC system.

11) Status of continuation of treatment with Encruse Ellipta at the end of the observation period

Status of the continuation of treatment at the end of the treatment with Encruse Ellipta and reason for the discontinuation/completion

12) Pregnancy

Whether Encruse Ellipta has been administered to a pregnant woman or not, presence or absence of pregnancy during the observation period, and expected delivery date (if the patient is a female)

If Encruse Ellipta is administered to a pregnant woman or a patient is found to be pregnant during the observation period, follow-up should be performed on a mother and her fetus as far as possible regarding the course of delivery, miscarriage, abortion, etc. and AEs, etc.

13) AEs

Presence or absence of AEs after the initiation of treatment with Encruse Ellipta, name of diagnosis or symptoms, date of onset, outcome of AEs, date of outcome, seriousness, reason for assessing as serious, relationship with Encruse Ellipta, and other factors suspected of being related to AEs except Encruse Ellipta

(1) In the investigation, priority investigation matters are defined as follows;

- Cardiovascular events, urinary retention, eye related problems, gallbladder disorder, intestinal obstruction, anticholinergic effects, lower respiratory tract infection and pneumonia.
- (2) To capture the priority study item and adverse drug reactions (ADRs), the investigator will enter information regarding all AEs (e.g., diseases, symptoms, abnormal laboratory values) occurring after the initiation of treatment with Encruse Ellipta in the EDC system, regardless of the presence or absence of a relationship with the product. The relationship with Encruse Ellipta will be assessed on a scale of two categories, “related” or “not related”, and it will be entered in the EDC system.
  - (3) AEs assessed as “related” to Encruse Ellipta will be handled as suspected “ADRs” that are caused by the product.

## 9. Analysis Items and Methods

### 1) Analysis items

#### (1) Items related to patient disposition

- [1] Number of patients registered, number of patients whose case report form (CRF) was retrieved
- [2] Number of patients included in the safety and effectiveness analysis sets, number of patients excluded from the analysis sets and the reason for exclusion
- [3] Number of patients included in the analysis set for Effectiveness 1 (spirometry), number of patients excluded from the analysis set and the reason for exclusion
- [4] Number of patients included in the analysis set for Effectiveness 2 (global effectiveness assessment and CAT score), number of patients excluded from the analysis set and the reason for exclusion

#### (2) Patient demographic and baseline characteristics

##### Distribution of patient demographic and baseline characteristics

- Stage classification, duration of COPD, past treatment history, type of concomitant medications/therapies, history of cigarette smoking, age, body weight, complications, presence or absence of bronchial asthma, etc.
- CAT scores, number of COPD exacerbations
- Spirometry

#### (3) Items related to safety

- [1] Incidence of ADRs by MedDRA SOC and PT
- [2] Priority study item: MedDRA codes should be identified.
  - Cardiovascular events, urinary retention, eye related problems, gallbladder disorder, intestinal obstruction, anticholinergic effects, lower respiratory tract infection and pneumonia.
- [3] Explorative assessment of factors (patient demographic and baseline characteristics) that may affect the presence or absence of ADRs and the presence or absence of ADRs set as the priority study item
- [4] Subgroup analyses (elderly, etc.) by the presence or absence of ADRs

and the presence or absence of ADRs set as the priority study item

(4) Items related to effectiveness

[1] Effectiveness 1

- Distribution of FEV1
- Explorative assessment of the effects of factors (patient demographic and baseline characteristics) that may affect FEV1
- Subgroup analyses (elderly etc.) by FEV1

[2] Effectiveness 2

- Distribution of global effectiveness assessment and CAT score
- Explorative assessment of the effects of factors (patient demographic and baseline characteristics) that may affect the effectiveness and CAT score

2) Analysis methods

For factors that may affect the items related to the safety and effectiveness, etc., the odds ratios and their 95% confidence intervals will be calculated. The results will be graphically presented using a forest plot, etc., as appropriate. For comparison of the scores, etc., the mean values and quartile points, etc. of the values at the time of measurement and the changes from baseline will be calculated and graphically presented using a boxplot, as appropriate.

## 10. Organization

Same as the Risk Management Plan

## 11. Name and Address of the Outsourcees, and the Scope of Outsourced Operations

1) Registration operations

Outsourcee: Undecided

Scope: patient registration and other related operations

2) Data management operations

Outsourcee: Undecided

Scope: Data management and other related operations

3) Data tabulation operations

Contractor: Undecided

Scope: data tabulation and other related operations

4) EDC system operations

Outsourcee: Undecided

Scope: development and operation of EDC system and other related operations

## 12. Progress of the Investigation and Evaluation of the Results Obtained or the Timing of Milestones for Reporting to the Pharmaceuticals and Medical Devices Agency (PMDA) and Their Rationales

- At the time of a periodic safety reports: To conduct a comprehensive review of the safety information



- At the time of submission of the re-examination application: To prepare a final report based on the tabulation/analysis results obtained from fixed data in all retrieved CRFs.

### **13. Additional Measures That May Be Implemented Based on the Study Results and the Decision Criteria for the Initiation of These Measures**

At the milestone time points, the Risk Management Plan, including the following contents, will be reviewed.

- If the investigation discloses the incidence, date of onset of the primary study items such as cardiovascular events, urinary retention, eye related problems, gallbladder disorder, intestinal obstruction, anticholinergic effects, lower respiratory tract infection and pneumonia, reported as ADR's to Encruse Ellipta, necessity of revision of the prescribing information and other materials will be considered.
- Necessity of any changes to the content of the plan for this investigation, including the presence or absence of new safety considerations, will be considered.
- Necessity of adopting risk minimization measures to new safety considerations will be considered

### **14. Publication of Study Results**

The information regarding the results of this investigation will be provided to clinical sites as interim and final reports as appropriate for the purpose of "proper use" and "safety securing", considering a proper timing and number of patients whose CRF is collected, etc., by means of presentation at an academic conference and papers.

In addition, the summary of plan and results in this investigation will be disclosed in GSK Clinical Study Register.

### **15. Other Requirements**

#### **1) Protocol Revision**

During the study period, the progress of the investigation, the number of patients excluded from the analysis sets, occurrence of unknown/serious ADRs, a significant increase in the incidence of specific ADRs, validity of study items, etc. should be monitored accordingly, and the study protocol should be reviewed and revised if necessary.

In case of making changes to the protocol for this investigation, a change notification should be submitted to the Pharmaceuticals and Medical Devices Agency in advance, except for minor changes.

<Examples of minor changes>

- (1) Any change in the planned number of medical institutions (by department)
- (2) EDC system

- [1] Any change in layout of the study items (movement in the position of described items, enlargement/reduction of field size)
- [2] Any change in the explanation of study items
- [3] Any addition of examples of ADRs resulting from revision to the precautions and addition of appreciable ADRs
- (3) Any addition, change and deletion of the items NOT affecting analysis of the whole investigation, specially effectiveness and safety
- (4) Study period
  - [1] Any change in the start date of the investigation resulting from delay of sales launch
  - [2] Prolongation of the study period to correspond to a short-term (within 3 months) prolongation, if necessary, of the registration period
  - [3] Reduction of the study period in case no change has been made to the planned sample size
- 2) Measures taken in detecting an issue or concern

If any problem is found during the study period or in the evaluation and analysis results, etc. after completion of the investigation, implementation of an additional special drug use investigation or post-marketing clinical study will be considered according to need.

## 16. Attachments

- 1) Contract Document for the Drug Use Investigation of ENCRUSE<sup>®</sup>ELLIPTA<sup>®</sup>  
Attachment 1
- 2) Implementation Guidance for the Drug Use Investigation of ENCRUSE<sup>®</sup>ELLIPTA<sup>®</sup>  
Attachment 2
- 3) Registration Form for the Drug Use Investigation of ENCRUSE<sup>®</sup>ELLIPTA<sup>®</sup>  
Attachment 3
- 4) Case Report Form for the Drug Use Investigation of ENCRUSE<sup>®</sup>ELLIPTA<sup>®</sup>  
Attachment 4
- 5) CAT for the Drug Use Investigation of ENCRUSE<sup>®</sup>ELLIPTA<sup>®</sup>  
Attachment 5