September 03, 2012

Oxis 9mcg Turbuhaler
Clinical Experience Investigation Protocol

１．！ Purpose of the investigation:

The purpose of the investigation is to confirm the followings under the post-marketing actual use of Oxis 9 mcg Turbuhaler (hereinafter referred to as Oxis).

(1) ADR development

Development of ADRs possibly related to pharmacological class effect of beta2 stimulant (Palpitations, Tachycardia, Tremor, Muscle cramp, etc).

Serious cardiovascular adverse events (Arrhythmia, Atrial fibrillation, Supraventricular tachycardia, Extrasystole, Angina pectoris, etc.)

(2) Contributing factors possibly having an impact on the safety

２．！ Target number of patients and the ground

Target number of patients: 300

Ground: AEs reported in the domestic and overseas clinical studies were considered as common health problems in COPD* patients or class effect recognized with beta2 stimulant.

However, considering that the drug is used more broadly in the post-marketing phase, the safety under actual drug use, especially development of ADRs possibly related to pharmacological effect of beta2 stimulant should be confirmed. The incidence of ADRs related to the beta2 stimulant effect (Palpitations, Tachycardia, Tremor, Muscle cramp, etc) was about 1-10 %. If the incidence of these ADRs is hypothesized as 1 %, the number of patients can be estimated as 300 that the ADR reported from at least one patient can be detected with 95 % power.

*COPD： Chronic obstructive pulmonary disease

３．！ Subject of the investigation

Patients treated with Oxis for the first time due to ‘relief of various symptoms associated with airway obstructive disorders of chronic obstructive pulmonary disease (Chronic bronchitis, Pulmonary emphysema), which is the indication of this drug.

４．！ Observation period

12 weeks

５．！ Number of investigation centres (by department)

About 100 institutions, mainly internal medicine and respiratory division.

6. ! Investigation method

(1) Target investigation medical institutions are hospitals where Oxis has been delivered and started to be used. Medical Representatives (hereinafter referred to as MRs) will explain the objectives, target and method of the investigation to physicians of the hospitals who will conduct the investigation, and will request the investigation to the head of the hospital. Written contract must be obtained before the investigation is started.

(2) The investigation is carried out with central registration method. After the contract is obtained, MRs deliver Case Registration Form and Case Report Form (CRF) of the investigation to the physicians who will conduct the investigation.

(3) After Oxis is started, the physician fills the Case Registration Form, signs on it and sends it by fax to the central registration centre to be received within 14 days after the drug start date (the start date is considered as Day 1).

(4) After a patient is registered, MR communicates completion of registration to the physician.

(5) The physician monitors the patient according to '4. Observation period', fills the CRF within around 4 weeks after the observation period, and hands it to the MR in charge.

7. ! Investigation period

Registration period: January 1, 2013 - December 31, 2014

Investigation period: January 1, 2013 - March 31, 2015

8. ! Data Items

(1) Patient identification

Identification number

(2) Patient's background factors

Age, gender, indication of Oxis, COPD staging classification at baseline, smoking history, height, weight, inpatient/outpatient, duration of illness, episode of COPD exacerbation during one year prior to the start of Oxis (with/without hospitalisation, with/without treatment with systemic steroid), with/without previous therapeutic drug for COPD (used during four weeks prior to Oxis)(if with, the drug name and the administration route), past medical history/concomitant disease (if with, the disease)

(3) Dosage and administration of Oxis

Start date and date of dose change, dose, daily frequency of administration, the reason for change in case the dosage and administration were changed, treatment continued/discontinued, stop date and the reason for withdrawal in case Oxis was stopped

(4) With/without pregnancy during the observation period (expected delivery date if pregnancy was confirmed)

(5) Respiratory function test (forced vital capacity [FVC], forced expiratory volume [FEV_1]),

PFR

(6) Dosage and administration of concomitant drug(s)

With/without concomitant drug(s) during treatment with Oxis (if with, the drug name, the administration route, and the indication)

In case with AE, the daily dose and the treatment duration.

(7) Concomitant therapy (other than drugs)

With/without concomitant therapy during treatment with Oxis (if with, the therapy name and the purpose of the therapy)

In case with AE, the therapy duration.

(8) Blood pressure, pulse, laboratory test

If blood pressure and pulse were measured or any laboratory test described below was performed during the observation period, the date of measurement or test and the value should be described in the CRF. If any adverse event was recognised after the start of Oxis, the details should be described in the section of Adverse Event.

[Laboratory test item]

Blood sugar (fasting or as needed, HbA1c), serum potassium

(9) Adverse event

Regarding all adverse events developed during the observation period, AE term, onset date, outcome, outcome date, seriousness*, causality with Oxis, alternative contributing factor, clinical laboratory test associated with the adverse event (the data item, reference value of the institution, examination date, and value)

Regarding serious event*, comment on the progress of the AE and the causality should be described.

If the outcome of the adverse event was 'death', the date of death, the cause of death, existence of the causality between the death and Oxis, and with/without autopsy (if autopsy was conducted, the findings should be described.)

If the underlying COPD symptoms or signs (Bronchitis, Cough, Sputum expectoration, Increase of sputum, Dyspnea and Wheezing, etc) worsened and met any of the followings, describe it as AE. In addition, as to COPD exacerbation, with/without treatment with systemic steroid and with/without hospitalization should be described.

-If it meets the definition of serious* AE

-If Oxis was discontinued

-If the investigator considered it as newly developed or different from the history of COPD (within one year prior to the start of observation period)

*:The definition of serious is based on 'serious' criteria by ICH (Yakushokuan No 0328007, 28 Mar 2005) as follows:

Patient died, life threatening, involved or prolonged inpatient hospitalization, involved

persistence or significant disability or incapacity, congenital anomaly, other medically important condition

(10) Rationale and practical investigation method for key investigation items

Development of ADRs possibly related to pharmacological class effect of beta2 stimulant (Palpitations, Tachycardia, Tremor, Muscle cramp, etc).

Serious cardiovascular adverse events (Arrhythmia, Atrial fibrillation, Supraventricular tachycardia, Extrasystole, Angina pectoris, etc.)

Ground: The adverse events reported in the domestic clinical studies were considered as common health problems in COPD patients or class effect recognized with beta2 stimulant. However, considering that the drug is used more broadly in the post-marketed phase, development of AEs under actual drug use should be investigated. Cardiovascular AEs such as arrhythmia (Atrial fibrillation, Supraventricular tachycardia, Extrasystole, etc) and angina pectoris have been reported for Oxis although they were rare. It was decided to set these events as key investigation items of this investigation for attracting special attention as the symptoms may become serious.

Investigation method: The AEs possibly related to the pharmacological effect of beta2 stimulant (Palpitations, Tachycardia, Tremor, Muscle cramp, etc.) and serious cardiovascular AEs (Arrhythmia, Atrial fibrillation, Supraventricular tachycardia, extrasystole, Angina pectoris, etc.) should be described clearly as 'key investigation item' with the case examples in the sections of adverse event of CRF and the implementation guideline. It is instructed to fill the Adverse Event section without fail if any of these events occurred.

(11) Others

If it is confirmed that Oxis was used for a pregnant woman during the observation period of this investigation, follow-up investigation should be performed for the delivery and the neonate.

<Observation schedule>

	Start of treatment	End of observation period (Observation day after Week 12* or discontinuation**)
Patient's background factors	○	
Dosage and administration of Oxis	←	→
Concomitant medications	←	→
Concomitant therapy	←	→
Clinical course		
Forced Vital Capacity(FVC)	○	○
Forced expiratory volume(FEV_1)	○	○
PFR	○	○
Blood pressure, pulse, laboratory test	←	→
Adverse event	←	→

* Observation day after Week 12 should be the nearest date to the last dose during Week 12 +- 4 weeks. If the patient did not visit during the period of Week 12 +- 4 weeks, the observation day should be the last visit before Week 12.

**Discontinuation should be the day of the last visit under the treatment or the last dose.

９．！ Items and method for analysis

Further details about conditions of target populations and analysis method are included in the statistical analysis plan.

(1) Items about structure of patients to analyse

Number of registered patients, number of patients whose CRF was collected, number of safety evaluable patients, number of patients to exclude and the reason for exclusion

(2) Items about patient's background factors

Age, gender, COPD staging classification at baseline, smoking history, height, weight,BMI, inpatient/outpatient, duration of illness, episode of COPD exacerbation during one year prior to the start of Oxis (with/without hospitalisation, with/without treatment with systemic steroid), with/without previous therapeutic drug for COPD (with/without, the type), past medical history (with/without, the type), concomitant disease (with/without, the type, including with/without concurrent asthma)

(3) Items about treatment

Dose, daily frequency of administration, concomitant drug (with/without, the type), concomitant therapy (with/without, the type)

(4) Safety items

1) ADR/infection development by category
2) Development of serious adverse event by category
3) Development of ADRs possibly related to pharmacological class effect of beta2 stimulant (Palpitations, Tachycardia, Tremor, Muscle cramp, etc).
4) Development of serious cardiovascular adverse events (Arrhythmia, Atrial fibrillation, Supraventricular tachycardia, Extrasystole, Angina pectoris, etc.)
5) ADR/infection development by patient's background factor and by treatment
ADR/infection development by patient's background factor and by treatment should be confirmed to review factors affecting the safety of this drug.
In addition, influence of concomitant drug(s) to the safety should be reviewed.

(5) Other items
COPD exacerbation should be confirmed.

10. Organisation to conduct the investigation

The organisation to conduct the investigation is same as that in the attachment 1) of the PMS Basic Plan.

11. In case of entrusting investigational operation partially, the name and address of the contractor and the entrusted operations

Contractor:
Address:
Name:
Entrusted operations:
Request to and contract with medical institutions, promotion of case registration, collection of CRFs and follow-up investigation, progress management, etc.

Address:
Name:
Entrusted operations:

12. Other necessary items

(1) Amendment of the protocol
During the investigational period, the number of withdrawal, development of unexpected serious ADRs, remarkable increase of incidence of specific ADRs, and validity of investigational items should be grasped constantly. If needed, the protocol should be reviewed and revised.
In case of s-NDA is approved for dosage and administration or indications during the investigation period of this drug (except the case when the re-examination period is

established newly), the protocol should be reviewed and revised appropriately.

(2) Actions when issues/questions are recognized

Conducting Specific Clinical Experience Investigation and Post-marketing Clinical Studies is to be examined to detect/confirm their factors and to verify discussion outcome in following conditions: when development of a significant ADR unexpected from the Precautions for use is suggested, when the frequency of an ADR is excessively increased, when an issue was recognized in safety and efficacy compared to their condition before launch, and when development of a different kind of ADR is suggested.

Attachment

A. Contract (draft)

B. Implementation Guidance of the investigation (draft)

C. Case Registration Form of the investigation (draft)

D. Case Report Form of the investigation (draft)