Japan s-CEI Protocol

Drug Substance Budesonide/ formoterol (Symbicort Turbuhaler)

First edition

Revised on

Symbicort Turbuhaler
Special Clinical Experience Investigation(s-CEI) Protocol

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1. OBJECTIVE

The purpose of the investigation is to confirm the followings under the post-marketing actual use of Symbicort Turbuhaler 30/60 (hereinafter referred as Symbicort).

1. ADR development with long term use of Symbicort

2. Safety with the highest dosage (8 DF/day)

3. Level of asthma control under long-term use

2. TARGET NUMBER OF PATIENTS AND ITS RATIONALE

Target number of patients: 1200

Rationale: The number of eligible patients was 138 (the 52-week treatment was completed in 120 of 138 patients) in the study of long term administration in Japanese patients with asthma until the approval. In 37 of 138 patients, the dose was increased to the maximum (4 DF/dose, twice daily). Since the number was limited, we will collect further data of patients receiving the highest dose under actual drug use to assess the safety of the maximum dose.

This investigation will be conducted only with asthma specialists in university hospitals and regional centre hospitals. In Japan, the number of moderate to large sized hospitals with asthma specialists is estimated as about 1000. In this investigation, about 400 institutions are planned as the target. Target number of patients is set as 1200. It is expected to collect data in large portion from the patients receiving the maximum dose of Symbicort by collecting information of such patients as much as possible from these institutions.

3. PATIENTS TO BE ENROLLED

Patients treated with Symbicort for the first time possibly at the higher dose* due to bronchial asthma (in case of concomitant use of inhalation steroid and long-acting inhalation beta 2 stimulant is required), which is the indication of the drug.

* Give priority for registration to patients with severe continuous asthma categorized based on ‘classification of severity of asthma by pre-treatment clinical findings (adult)’ of Asthma Prevention and Management Guideline 2009, Japan.

4. NUMBER OF INVESTIGATION SITES WHERE THE INVESTIGATION WILL BE CONDUCTED

About 400 institutions mainly with asthma specialists such as the respiratory division and the allergy department of university hospitals or regional center hospitals.

5. METHOD

1) Target investigation medical institutions are hospitals where this drug has been delivered and started to use. Medical Representatives (hereinafter referred as MRs) will explain 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 CRF of the investigation to the physicians who will conduct the investigation.

3) After the drug is started, the physician fills the Case Registration Form, signs on it and sends it by fax to the Symbicort Turbuhaler 30/60 central registration center 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 for 1 year, fills the CRF within around 4 weeks, and hands it to the MR in charge.

6. INVESTIGATION PERIOD

Registration period: Jan 2010 (launch date) - Jun 2011

Investigation period: Jan 2010 (launch date) - Jun 2012

7. DATA ITEM TO BE COLLECTED

1) Patient identification

Identification number

2) Background factors

Age, sex, height, weight, inpatient/outpatient, Indication of Symbicort, severity prior to Symbicort, smoking history, with/without atopic disposition, duration of illness, with/without hospitalization due to asthma during one year prior to Symbicort and its frequency, with/without previous therapeutic drug of asthma (used during four weeks prior to Symbicort) (if with, the drug name, administration route, daily dose and daily frequency), past medical history, concomitant disease

3) Dosage and administration of this drug

Start date and dosage and administration change date of Symbicort, administration frequency/dose, administration frequency/day, the reason why treatment was changed in case whose dose of Symbicort was changed,
treatment continued/discontinued, date of 1 year observation in case of treatment continued, stop date and the reason for withdrawal in case of treatment discontinued

4) with/without pregnancy during the observation period, expected delivery date if pregnancy was confirmed

5) Dosage and administration of concomitant drug(s)

To confirm with/without concomitant drug(s) during Symbicort treatment. If any concomitant drug was used, confirm the drug name, the administration route, and the indication.

In case of the patient experienced AE(s), confirm the daily dose, regular use/use as required, and the dosing period.

6) Concomitant therapy

To confirm with/without concomitant therapy during Symbicort treatment. If any concomitant therapy was performed, the therapy name and the purpose of the therapy should be confirmed. In case the patient experienced AE(s), the therapy duration should be confirmed also.

7) Clinical course

Following items at the start/after 24 weeks/after one year/at discontinuation of Symbicort:

a) Asthma Control Questionnaire (hereinafter referred as ACQ)

b) Frequency of Short Acting Beta2 stimulant (hereinafter referred as SABA) administration: frequency of SABA administration during seven days prior to the observation day, total days of SABA administration confirmed.

c) Peak flow rate: peak flow rate during seven days prior to the observation day (average) and the measurement model

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 Symbicort, the details should be described in the section of Adverse event.

[Laboratory test item]

Thyroid function, adrenal cortex function, bone metabolism, blood sugar (fasting or as needed, HbA1c), CPK, K

9) Adverse event

Regarding all adverse events developed during the observation period, AE term, onset date, outcome, outcome date, causality with Symbicort/alternative contributing factor, seriousness; as to the clinical laboratory test associated with the adverse event, the data item, examination date, and value.

Regarding serious event, describe comment on the progress of the AE and the causality.

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

If the patient had bronchial asthma aggravation or serious* condition due to bronchial asthma aggravated, it should be handled as adverse event and the details should be described in this section.

* 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

a) Safety with the highest dosage (8 DF/day)

Rationale: In the domestic clinical study (long-term study), 37 of 138 patients received 4DF/dose X2/day. As the result, the tolerability of Symbicort including

higher dose (4DF/dose X2/day) was considered as satisfactory. No tendency suggesting increase of serious adverse events or decreased tolerability with dose increasing of Symbicort was recognized. However, considering that larger population will receive the drug in the post-marketing phase and that there is data suggesting the higher blood level of Symbicort after administration in Japanese patients than in foreign patients, the safety in long-term use of the highest dose under actual drug use should be investigate intensively. For the reason, it was decided as the key investigation item.

Investigation method:The section of Symbicort administration in the CRF includes administration change date, changed dose and frequency of daily administration to collect administration period by dose, and to grasp administration period and ADR with the highest dose in case of the patient received the highest dose (4DF/dose X2/day).

In addition, to limit the target investigator to asthma specialists in university hospitals and regional centre hospitals, and to prioritize patients with severe asthma (step 4, severe continuous asthma, categorized by Asthma Prevention and Management Guideline) for registration make it available to collect the patients receiving the highest dose in higher frequency.

b) Development of ADRs possibly related to pharmacological effect of beta2 stimulant (Palpitations, Tachycardia, Tremor, Muscle cramp, etc), aggravation of the underlying disease in patients with hyperthyroidism.

Rationale: In the domestic clinical study, adverse events related to the class effect of beta2 stimulant were recognized as main ADRs such as Muscle cramp 2.9 % (9/314 patients) and Palpitations 2.5 % (8/314 patients). In these patients, the percentage of taking measures such as withdrawal of the drug due to the event was small. It was considered that the tolerability of Symbicort should be satisfactory as a whole. However, considering larger population will receive the drug in the post-marketing phase, these were decided as key investigation items to investigate the development.

Investigation method: The AEs possibly related to the pharmacological effect of beta2 stimulant should be described clearly with the AE terms (Palpitations, Tachycardia, Tremor, Muscle cramp, etc) in the section 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.

c) Development of systemic ADRs with steroid (Diabetes mellitus, and influence on the adrenal cortical function, bone metabolism and eyes), and serious infection (pulmonary infection).

Rationale: With all inhalation steroids, systemic ADRs may occur as well as local ADRs such as Dysphonia and Oral candida. Particularly, with higher dose for long term use, the incidence of systemic ADRs becomes higher. In the domestic

clinical study of Symbicort, the severity of the events possibly related to the class effect of ihalation steroid treatment was mild in general. However, considering larger population will receive the drug in the post-marketing phase, these were decided as key investigation items to investigate the development.

Investigation method: The AEs possibly related to the pharmacological effect of inhalation steroid should be described clearly with the AE terms [Hyperglycaemia, adrenal cortical function suppression, bone density decreased, cataract, glaucoma, serious infection (especially pulmonary infection)] in the section 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 Symbicort 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.

Schedule of the observation

	Start of treatment	**Observation day after 24 weeks****	**Observation day after one year or discontinuation****
Patients background factors	○		
Dosage and administration of Symbicort	←	—	→
Concomitant medications	←	—	→
Concomitant therapy	←	—	→
Clinical course *			
1) ACQ (Asthma Control Questionnaire)	○	○	○
2) Frequency of SABA administration	○	○	○
3) PFR	○	○	○
Laboratory test	←	—	→
Adverse event	←	—	→

* Only the patients treated under daily practice should be the subject.
Regarding 2) frequency of SABA administration and 3) PFR, the observation data for the seven days prior to the observation day should be recorded.

** The day after 24 weeks should be the nearest date to the last dose during 24 weeks +- 4 weeks.
The day after 1 year should be the nearest date to the last dose during 1 year +- 4 weeks.
'At discontinuation' should be the next day of the last dose or the last visit under the treatment.

8. DATA ANALYSIS: ITEM AND METHOD

Further details about definitions of target populations and analysis method are included in the analytic 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 efficacy evaluable patients, number of patients to exclude and the reason for exclusion

2) Items about structure of patient's background factors

   Age, sex, inpatient/outpatient, height, weight, BMI, duration of illness, severity prior to Symbicort, past medical history (allergy, cardiac disease, etc), concomitant disease (hepatic disorder, renal disorder, cardiac disease, allergy, etc), previous therapeutic drug of asthma (with/without, type, dose, etc)

3) Items about treatment

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

4) Safety items

   a) ADR/infection development by category

   b) 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 Symbicort.

   Particularly, regarding safety in elderly, development of ADR/infection should be reviewed by elderly/non-elderly and by age category.

   In addition, influence of concomitant drug(s), especially SABA, to the safety should be reviewed.

   c) ADR development by treatment period

   ADR development should be confirmed by treatment period to review the safety in long-term use.

   d) Development condition of serious adverse event by category

Particularly, regarding serious asthma-related events (asthma aggravated), development by patient's background factor and by treatment should be confirmed to review influencing factors to the development.

Regarding serious infections (pulmonary infection, etc), development should be confirmed by patient's demographics such as elderly/non-elderly, age category, and dose of Symbicort.

e) Development of serious AEs by treatment period Serious AE development should be confirmed by treatment period to review the safety in long-term use.

f) Safety with the highest dosage (8 DF/day)

ADR/infection development should be confirmed by dose, and the safety with the maximum dose (8DF/day) should be confirmed.

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

Regarding ADRs possibly related to pharmacological effect of beta2 stimulant (Palpitations, Tachycardia, Tremor, Muscle cramp, etc), development should be confirmed by patient's background factor and by treatment to review influencing factors to the development.

h) Underlying disease aggravated in patients with hyperthyroidism

In patients who had hyperthyroidism at the start of Symbicort, it should be confirmed if underlying disease aggravated occurred.

i) Systemic reaction with steroid (diabetes mellitus and influence on the adrenal cortical function, bone metabolism and eyes)

Development of diabetes mellitus, adrenal cortical function suppression, osteoporosis, glaucoma, cataract, and etc should be confirmed. In addition, in patients who had diabetes mellitus, adrenal cortical function suppression, osteoporosis, glaucoma, or cataract at the start of Symbicort, it should be confirmed if underlying disease aggravated occurred.

5) Efficacy items

a) Variation of asthma control level from the start of Symbicort (total of ACQ score) at treatment week 24 and treatment year 1

b) Variation of frequency of SABA administration from the start of Symbicort at treatment week 24 and treatment year 1

c) Variation of PFR from the start of Symbicort at treatment week 24 and treatment year 1

d) Asthma control level by patient's demographics and by treatment

9. ORGANISATION TO CONDUCT THE S-CEI

The organisation to conduct the s-CEI is same as that in Attachment 1 to PMS Basic Plan.

10. ORGANISATIONS TO WHICH THE OPERATIONS ARE TO BE OUTSOURCED, AND SCOPE OF THE CONTRACT

Name:

Address:

Scope of the contract:
Reception of patient enrollment, and operations of data management (data entry, CRF check/data lock, and request of re-investigation, database lock, and dataset compilation)

11. OTHER REQUIREMENTS

1. Revision of the protocol
Following information is always examined during the investigation; progress of the s-CEI, number of patients who discontinued the s-CEI, onsets of serious unexpected ADRs, large increase in the incidence of a specific ADR, and validity of the investigation items. The s-CEI protocol is to be reviewed and revised when necessary.
When a partial revision of "Dosage and Administration" or "Indication" is approved during the s-CEI period (other than new establishment of the re-examination period), necessity of the revision of the s-CEI protocol is examined, and the document is revised as required.

2. Process when any issue or query is provided
Necessity of additional s-CEI or post-marketing clinical study is examined to detect or identify any factors of ADRs, or to verify the estimation obtained after data analysis of the s-CEI if there is any of followings: a significant ADR which is not expected from "Precautions for Use" of Symbicort JPI is suggested, frequency of an ADR has significantly increased, there is a safety or efficacy issue compared to the data before marketing, or development of ADRs of a different nature is suggested.