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Bydureon subcutaneous injection 2 mg

Bydureon SC Pen 2 mg

Protocol of S-CEI for long-term use

1. Objective

To confirm the safety and efficacy of Bydureon subcutaneous injection 2 mg and Bydureon SC Pen 2 mg (hereinafter referred to as Bydureon) in long-term use in Japanese patients with type 2 diabetes mellitus under actual drug use.

(1) Primary Objective

To confirm the safety profile in Japanese patients with type 2 diabetes mellitus receiving Bydureon under daily practices.

(2) Secondary objective

As the secondary objective of this S-CEI, the following items are to be investigated.

- Frequencies of AEs related to cardiovascular events, hypoglycaemia, digestive symptoms, and injection site reaction.
- Development of pancreatitis, renal impairment (especially acute renal failure), hypersensitivity reaction, and malignant tumour (especially thyroid tumour and pancreatic malignancy)
- Safety in patients with mild or moderate renal impairment
- Changes of weight, blood pressure, pulse rate, fasting blood sugar, fasting insulin, HbA1c, and blood lipids
- Bydureon administration under daily practices focusing on the patient's demographics and clinical characteristics of diabetes mellitus (duration of diabetes mellitus, treatment duration, complications, Bydureon administration, etc)
- Anti-exenatide antibody titer in AE cases (hypersensitivity, loss of control of blood sugar)

2. Target number of patients and its rationale

(1) Target number of patients

1,000 safety evaluable patients

(2) Rationale

When the number of safety evaluable patients is 1000, the two-sided 95% confidential interval (CI) width for AE frequency is about 6.2% at a maximum.

When the frequency of cardiovascular ADRs in this S-CEI is estimated at 4.5% based on the data of the Japan Diabetes Complication Study (JDCS)[1)], an epidemiology study in Japan, the two-sided 95% CI width is about 2.6% with the data of 1000 patients.

When the frequency of gastrointestinal disorders is estimated at 27.7% based on the results of Bydureon studies in Japan, the two-sided 95% CI width is about 5.5%; in the same way, when the

frequency of hypoglycaemia in this S-CEI is estimated at 8.6% without concomitant use of sulfonylurea and 22.3% with concomittant use of sulfonylurea, the two-sided 95% CI width is about 3.5% and about 5.2%, respectively. When the frequency of injection site reaction is estimated at 28.3%, the two-sided 95% CI width is about 5.6%.

As above, the target number of safety evaluable patients in this S-CEI is determined as 1000.

3. Patients to be enrolled

The patients with type 2 diabetes mellitus who will be given Bydureon for the first time and who inadequately respond to sulfonylurea, biuguanides, and/or thiazolidines (monotherapy or combination use) in addition to diet and exercise.

<Conditions for enrolment>

The patients who meet the following conditions:

- The patients with type 2 diabetes mellitus who inadequately respond to sulfonylurea, biuguanides, and/or thiazolidines (monotherapy or combination use) in addition to diet and exercise.

  The patient who will receive Bydureon in any of the following combinations:

  - Bydureon + sulfonylurea
  - Bydureon + biguanides
  - Bydureon + thiazolidines
  - Bydureon + sulfonylurea + biguanides
  - Bydureon + sulfonylurea + thiazolidines
  - Bydureon + biguanides + thiazolidines
- No past history of hypersensitivity to the components of Bydureon.
- Not the patient with diabetic ketoacidosis, diabetic coma/precoma, and/or type 1 diabetes mellitus.
- Bydureon will not be administered to the patient in an emergency situation such as severe infection and operation.
- Not the patient with severe renal impairment, including those receiving dialysis.

4. Observation period

Maximum 3 years from the start to completion (or discontinuation) of Bydureon administration.

In case that a cardiovascular AE occurred, if administration of Bydureon was discontinued, follow-up investigation should be conducted as far as possible for approximately 10 weeks after the discontinuation.

5. Number of investigation sites where the investigation is conducted

Medical institutions providing treatment for diabetes mellitus (mainly department for endocrine/metabolic disorders and diabetes internal medicine department)

Number of investigation centres: 300

6. Methods

(1) AZKK Medical Representatives (MRs) explain objectives, target patients and methods of this S-CEI to the physicians in charge of the S-CEI at the medical institutions which decided to issue prescriptions of Bydureon, and request conduct of the S-CEI to the head of the medical institution. Written contract must be concluded prior to the start of the S-CEI.

(2) Method of the S-CEI is central registration. After the contract is concluded, MR in charge of the investigation site sends Case Registration Forms and CRF1 (observation period: 12 months) to the physician in charge of the S-CEI.

(3) The physician in charge of the S-CEI enters the required information into the Case Registration Form and sends it to the Registration Centre by fax within 14 days after Bydureon is started in the patient defined as '3. Patients to be enrolled' as the above (the start date should be Day 1). If the Case Registration Form is sent to the Registration Centre on and after 15 days after Bydureon was started or the next day of the end of registration period and after, it is not acceptable.

(4) After the registration is completed, MR communicates the completion of the case registration to the physician in charge of the S-CEI in writing.

(5) The physician in charge of the S-CEI follows up the patient according to '4. Observation period' above. The physician enters data of the patient in CRF1 within around 4 weeks from 12 months after the start of Bydureon, and hands it to the MR.

(6) MR requests the physician to enter data in CRF2 (observation period: 24 months) after CRF1 is collected,when the data in CRF1 shows that Bydureon has been continued. In the same way, MR requests the physician to enter data in CRF3 (observation period: 36 months).

7. Investigation period

Registration period: 01 Oct 2013 to 31 Aug 2016 (2 years and 11 months)

Investigation period: 01 Oct 2013 to 31 Aug 2019 (5 years and 11 months)

However, enrolment will not be accepted when the target number of patients is achieved by the number of enrolled patients.

8. Data to be collected

The following observation and examinations should be performed at the discretion of the physician in charge of the S-CEI (See Attachment 1).

(1) Information required for patient identification

ID Number

(2) Patients demography data (the condition at the start of Bydureon)

Age, sex, duration of diabetes mellitus, inpatient/outpatient, smoking habit, drinking habit and daily alcohol intake, past history, and complication.

(3) Physical findings, observation items (blood pressure, pulse rate), and ECG prior to the start of Bydureon

Height, weight, waist circumference, pelvic circumference, blood pressure, and pulse rate.

ECG measurement (yes/no) (if yes, date of measurement, and abnormality [yes/no]. If any abnormality is found, the abnormal findings).

(4) Bydureon administration

Bydureon start date, unit dose/week

Product name, or when dose was changed, product name, product name and date of the dose change, unit dose/week after the change, and product name and the reason of the dose change.

(5) Whether Bydureon was continued or stopped

If Bydureon was continued, the last observation date by CRF (CRF1: 12 months ±4 weeks, CRF 2: 24 months ±4 weeks, CRF 3: 36 months ±4 weeks).

If Bydureon was stopped, the last administration date and the reason of discontinuation.

(6) Administration of previous medications and concomitant drugs (medications for type 2 diabetes mellitus)

Medications for type 2 diabetes mellitus given just before (within 4 weeks) and during Bydureon treatment (yes/no)(if yes, name of drug, administration route, indication, daily dose [unit], start date, and stop date)

(7) Administration of concomitant drugs other than those for treatment of type 2 diabetes mellitus

Drugs given during Bydureon treatment other than those for treatment of type 2 diabetes mellitus (yes/no) (if yes, drug name, administration route, and indication. In AE cases,daily dose [unit], start date, and stop date).

(8) Concomitant therapy (other than drugs)

Therapy given during Bydureon treatment (yes/no) (if yes, name of therapy and purpose of therapy. In AE cases, start date and stop date.)

(9) Items to be observed

If the following clinical test items are measured, all data should be entered in the CRF regardless of whether any AE is present.

Date of measurement, weight, blood pressure (systolic blood pressure/diastolic blood pressure), and pulse rate.

(10) ECG

ECG measurement (yes/no) (if yes, date of measurement, and abnormality [yes/no]. If any abnormality is found, the abnormal findings).

(11) Pregnancy during the observation period (yes/no) (if yes, expected delivery date)

When a patient becomes pregnant during the observation period of this S-CEI, the pregnancy case is to be followed up to investigate the influence of Bydureon administraton on the pregnancy, delivery, and neonate.

(12) Laboratory tests

If the following clinical test items are measured, all data should be entered in the CRF regardless of whether any AE is present.

Fasting blood sugar, fasting insulin, HbA1c (NGSP), blood lipids (total cholesterol, LDL-cholesterol, HDL-cholesterol, and fasting triglyceride), ALT, AST, gamma-GTP, serum urea nitrogen, serum creatinine, urinary albumin, calcitonin, lipase, and amylase.

- Anti-exenatide antibody

If the physician in charge of the S-CEI considers formation of anti-exenatide antibody as the possible cause of an AE (hypersensitivity, loss of control of blood sugar) and decides the need, the antibody levels should be measured.

- Other clinical test items

Regarding the clinical test items related to AEs, the measured values over time should be entered.

(13) Adverse event

Adverse event during the observation period of this S-CEI (yes/no)(regardless the causality with administration of Bydureon, all undesirable or unintended signs [including abnormal clinical laboratory tests], symptoms, and disease)(if yes, the items below should be confirmed.)

AE term, onset date, outcome, outcome date, seriousness*, causality with Bydureon (yes/no), alternative contributing factors (yes/no), clinical laboratory test associated with the AE (the data item, reference value of the institution, unit, 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 Bydureon, and with/without autopsy (if autopsy was conducted, the findings should be described.)

*Definitions of 'serious' follow the ICH definitions (PFSB/SD No 0328007 of 28 Mar 2005): Death, Life threatening, Results in persistent or significant disability/incapacity, Requires inpatient hospitalization or prolongation of existing hospitalization, Other medically important, Congenital anomaly/birth defect

**Cardiovascular events:

Cardiovascular events are defined as coronary heart diseases (angina pectoris and myocardial infarction) and stroke and should be investigated for reviewing by comparing the data with the frequencies in diabetic patients in Japan[1)-2)]. In case that a cardiovascular AE occurred, if Bydureon was discontinued, follow-up investigation should be conducted as far as possible for approximately 10 weeks after the discontinuation.

9.Data analysis: item and method

Further details about definitions of the target population and the analysis method are included in the case handling guideline and the statistical analysis plan separately.

(1) Target populations

1) Safety analysis set

2) Efficacy analysis set

(2) Analysis items

1) Case constitution

Number of patients enrolled in the investigation, Number of CRFs collected, Number of safety evaluable patients, Number of efficacy evaluable patients, Number of excluded patients and the number of those by reason of the exclusion, Number of patients withdrew from the study treatment and the number of those by reason of withdrawal

2) Patients' background factors

Age, sex, duration of diabetes mellitus, inpatient /outpatient, smoking habit , drinking habit and daily alcohol intake (in sake), physical findings (height, waist circumference, and pelvic circumference), past history, and complication

3)Treatment factor

Bydureon administration (treatment duration, dose/week), number of patients who stopped Bydureon and the reason of discontinuation, administration of concomitant drugs (drugs for type 2 diabetes mellitus, drugs not for type 2 diabetes mellitus), and concomitant therapy (other than drugs)

4) Safety items

- Adverse event
- Serious Adverse Event
- Factors possibly having an impact on the safety (patient's background factors, factors related to Bydureon administration, and concomitant treatment factors, etc).
- Changes of blood pressure and pulse rate

5) Efficacy items

- Variations from the baseline of fasting blood sugar and HbA1c (NGSP)
- Achievement rates of HbA1c (NGSP) < 6.0% and < 7.0%
- Changes of weight and blood lipids(total cholesterol, HDL-cholesterol, LDL-cholesterol, and fasting triglyceride)
- Variations from the baseline of index for insulin endocrine secretion (HOMA-beta) and insulin resistance index (HOMA-R)

10.Organisation to conduct the S-CEI

The organisation to conduct the S-CEI is the same as that in the attachment 2) of the PMS Basic Plan.

11.Contract partners of the operations to be outsourced, and scope of each contract

Contract partners

Address:

Name:

Entrusted operations: Processing operations of contract with medical institutions, case registration process, data management (data input, check and fixation of CRF data, preparation of follow-up investigation form, data base fixation, preparation of data set)

12.Other required items

(1) Amendment of the protocol

During the investigation period, the progress, the number of withdrawal, development of unexpected serious ADRs, remarkable increase of incidence of specific ADRs, and validity of investigational items should be grasped continuously. 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

Conduct of Specific Clinical Experience Investigation and/or Post-marketing Clinical Studies is to be examined to detect or confirm their factors and to verify discussion outcome in following conditions: when development of an 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.

13. References

1)H.Sone et al: Japan Diabetes Complication Study (JDCS) - Characteristics and the current situation of Japanese patients with type 2 diabetes mellitus Medical Progress 220(3), 263-271, 2007.

2) H.Sone.et al. : Long-term lifestyle intervention lowers the incidence of stroke in Japanese patients with type 2 diabetes : a nationwide multicentre randomised controlled trial (the Japan Diabetes Complications Study). Diabetologia 53, 419-428, 2010

Attachments

A. Contract template (draft)

B. Specific Clinical Experience Investigation guidance (draft)

C. Specific Clinical Experience Investigation patient enrolment form (draft)

D. Specific Clinical Experience Investigation CRF (draft)

CRF 1 (12 months), CRF 2 (24 months), CRF 3 (36 months)

Attachment 1Data to be collected

	Entry form	CRF 1							CRF 2				CRF 3				At withdrawal
		Before initiation of the drug(-4 weeks to 0)	2 months(±4 weeks)	4 months(±4 weeks)	6 months(±4 weeks)	8 months(±4 weeks)	10 months(±4 weeks)	12 months(±4 weeks)	15 months(±4 weeks)	18 months(±4 weeks)	21 months(±4 weeks)	24 months(±4 weeks)	27 months(±4 weeks)	30 months(±4 weeks)	33 months(±4 weeks)	36 months(±4 weeks)	
1) Enrollment information	○																
2) Background factors		○															
3) Laboratory tests[*1)] Fasting blood sugar, HbA1c, etc.		○ [*2)]	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
ECG		○		○				○				○				○	○
Weight, blood pressure, pulse rate		○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Anti-exenatide antibody*[3)]			→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Other clinical test items[*4)]		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
4) Adverse event			→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
5)Bydureon administration			→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
6) Whether Bydureon was continued or stopped								○				○				○	○
7) Concomitant medications		○	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
8) Concomitant therapy			→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
9) Pregnancy								○				○				○	○

*1)If measured, it should be described in the CRF with or without AE.

*2) Regarding serum creatinine, if it was not measured four weeks before the start of Bydureon, the value measured within three months prior to the start is acceptable.

*3)If the physician in charge of the S-CEI considers formation of anti-exenatide antibody as the possible cause of an AE (hypersensitivity, loss of control of blood sugar) and decides the need, the antibody levels should be measured.

*4)Only when it was determined as an AE. Regarding the test items related to the AE, if the value measured prior to the start of the drug exists, it should be described in the CRF.