

Administrative Notice¹
July 9, 2010

To: Pharmaceutical Affairs Divisions,
Prefectural Public Health Bureaus (Departments)

From: Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

On Release of Questions and Answers (Q&As) regarding the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents

The official adoption of the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents has been notified in the PFSB/ELD Notification No. 0709 issued by the Director, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare dated July 9, 2010. Questions and Answers (Q&As) regarding the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents are provided in the attachment. Please inform relevant manufacturers under your jurisdiction of the Q&As.

¹ This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the Japanese text shall prevail.

(Attachment)

Q&As regarding the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents

General

Q1

Explain the concept and the points to be considered regarding development of an oral hypoglycemic agent (OHA) based on a bridging study or a global clinical trial.

A1

The ICH E5 guidelines and “Basic Principles on Global Clinical Trials” (PFSB/ELD Notification No. 0928010, dated September 28, 2007) are applied to development of an OHA based on a bridging study or a global clinical trial. Consult the Pharmaceuticals and Medical Devices Agency (PMDA) for details specific to individual drugs.

Q2

Does the scope of the guideline include only OHAs, or does it include injections such as insulin preparations and GLP-1 analogues?

A2

Development of medicinal products to treat diabetes mellitus other than OHAs (not including insulin preparations) needs to be planned appropriately according to the guideline. Insulin preparations are not included in the scope of the guideline.

Efficacy evaluation method for OHAs

Q3

Define “standard meal” or explain the concept of it.

A3

A standard meal should be comprised with the same nutritional components and calories within a study to ensure appropriate efficacy evaluation. While the standard meal ideally consists of the standard food eaten by Japanese in general, its nutritional components may be determined based on the objective of the study or the characteristics of the investigational drug.

Phase III study

Q4

The guideline specifies, “long-term treatment, specifically, 300 or more patients treated for at least six months and 100 or more patients treated for at least one year, is required” Is this the total number of the patients who received long-term treatment for monotherapy counted with those who received long-term treatment for concomitant therapies?

A4

In principle, the number refers to patients who received long-term treatment for monotherapy.

Q5

The guideline specifies, “the drug-drug interaction study to evaluate the effect of the concomitant therapy on the blood concentration is recommended when using the investigational drug concomitantly with a drug with a higher hypoglycemia risk compared with other OHAs (e.g., SU).” Does the drug-drug interaction study with other OHAs not need to be studied?

A5

Drug interactions need to be studied in accordance with “Method of Drug Interaction Studies” (PMSB/ELD Notification No. 813; dated June 4, 2001) when using an investigational drug concomitantly with other OHAs.

Study for monotherapy (double-blind, randomized controlled study)

Q6

The guideline recommends the treatment duration to be “at least 12 weeks, or ideally 24 weeks in principle.” A 24-week treatment period will be reasonable if an approved drug is used as a control. Does the guideline recommend a 24-week treatment period in placebo-controlled studies in terms of HbA1c assessment period and safety evaluation of six-month treatment?

A6

In order to assess efficacy and safety, a 24-week treatment period is recommended. Since drugs with various characteristics are in development, specific points depending on the characteristics of a drug may be taken into consideration with regards to the treatment period. Consult the PMDA for details specific to individual drugs.

Long-term study for concomitant therapies (open-label, long-term study for concomitant therapies)

Q7

Regarding the term “all groups of concomitant drugs expected to be administered to patients in clinical practice,” please specify, not exemplify, all possible groups of concomitant drugs. In addition, is it acceptable to use any of the drugs with the same mechanism of action unspecified in a study as a concomitant drug?

A7

SU, glinide, biguanide, α -glucosidase inhibitor, thiazolidine and DDP-4 inhibitor are the possible concomitant drug groups at the moment. However, use of other drugs as concomitant drugs will be at the discretion of manufacturers depending on future change in the field of medicinal products to treat diabetes mellitus. It is not required to limit the concomitant drug to a single agent. Since background factors need to be uniform to a certain extent for appropriate safety and efficacy evaluation, however, concomitant drugs used in a group should be limited to two to three.

Q8

Regarding “drugs with higher hypoglycemia risk compared with other OHAs (e.g., SU)” used in long-term studies for concomitant therapies, may both patients treated with a SU and those treated with a glinide be included in the sample size of 100?

A8

It is appropriate to evaluate the safety and efficacy of the concomitant use with a SU or a glinide separately in a long-term study for concomitant therapies. The sample size of 100 patients treated with a SU is required in principle, considering possible hypoglycemia risk.

Description of the indication

Q9

Regarding “an appropriate description of the indication is ‘type 2 diabetes’,” does the statement intend to recommend to provide the results of a study for concomitant therapies conducted in accordance with the guideline in the sections of PRECAUTIONS and CLINICAL STUDIES and describe the indication only as “type 2 diabetes”?

A9

The statement intends to recommend “type 2 diabetes mellitus” as the indication for the drug evaluated in all possible combinations with other medicinal products to treat type 2 diabetes mellitus in accordance with the guideline. Results of clinical studies should be provided in the package insert section of CLINICAL STUDIES, and precautions should be included in the section of PRECAUTIONS as necessary depending on the study results.

Q10

A regulatory approval should basically be granted to an indication for monotherapy. Is it mandatory to file an application for an approval for an indication for monotherapy? Or is it possible to file an approval for concomitant therapy alone?

A10

Drug therapies for diabetic treatment in Japan are basically monotherapies. Monotherapy studies are therefore required in principle.

Q11

The guideline recommends type 2 diabetes mellitus as the indication for OHAs. Is it enough to provide a description such as “Concomitant use of XXX with YYY has not been evaluated.” in the section of PRECAUTIONS to raise caution about the OHAs inappropriate for combined use based on the properties of the investigational drug?

A11

For “all combinations with possible concomitant drug groups expected to be used in patients,” type 2 diabetes mellitus should be the indication based on a long-term study for concomitant therapies. However, appropriate precautions need to be included in the package insert sections such as “Contraindications for Coadministration” to make people more cautious about use of the OHAs inappropriate for combined use.

Q12

The guideline recommends type 2 diabetes mellitus as the indication for OHAs. Is the conventional way of describing the indications not accepted any longer? Do the results of a long-term study for concomitant therapies need to be submitted? What is the submission deadline if the results of a long-term study for concomitant therapies are required?

A12

In application for marketing authorization of an OHA developed and applied in accordance with the guideline, type 2 diabetes mellitus should be the indication based on the required clinical studies including a long-term study for concomitant therapies. The clinical data package submitted with the NDA needs to include the results of the long-term study for concomitant therapies. A long-term study for concomitant therapies intends to evaluate the safety and efficacy of a concomitant therapy with the investigational drug and an approved OHA for a long-term. Since the safety and efficacy of the new drug cannot be evaluated unless the long-term study for concomitant therapies is completed and all the results are included, it is not acceptable to first file an application with data from studies other than the long-term study for concomitant therapies and submit the data from the long-term study afterwards.

Q13

Is the evaluation specified in the guideline required for drugs to “improve postprandial blood glucose in type 2 diabetes mellitus” such as α -glucosidase inhibitors?

A13

The same evaluation is required for α -glucosidase inhibitors because it is a type of OHAs.

Q14

Will the descriptions of package inserts of the approved drugs be changed by the guideline? Will the guideline also be applied to the approved drugs?

A14

It is not intended to require revision of the package inserts for the currently approved OHAs. Applications for approval of partial changes may be filed for unapproved drug combinations based on the long-term study for concomitant therapies. Consult the PMDA for details specific to individual

drugs.

Combination drug

Q15

The main objective of a long-term study for concomitant therapies regarding a new active ingredient is to evaluate the safety of the treatment. Is a confirmatory study for efficacy required for development of a fixed dose combination drug containing the new active ingredient?

A15

The significance of the combination and the evidence supporting the efficacy and safety need to be demonstrated for a fixed dose combination drug. Since the primary objective of a long-term study for concomitant therapies is to evaluate the safety of the treatment, a long-term study for concomitant therapies is not considered to be a confirmatory study to evaluate the efficacy of a fixed dose combination drug. A confirmatory study with an appropriate design will be separately required.