Health Canada Santé Canada

September 24, 2007

NOTICE

Our file number: 07-122151-509

Release of final Health Canada document: Standards for Clinical Trials in Type 2 Diabetes in Canada

The final version of the Health Canada guidance document *Standards for Clinical Trials in Type 2 Diabetes in Canada* is now available. This guidance document replaces the *Draft Guidance for Industry: Clinical Trials in Type 2 Diabetes in Canada (Oral Agents)* published for consultation on July 19, 2006. The effective date for this document is November 1, 2007.

Health Canada is issuing this guidance for clinical trials in type 2 diabetes to provide clarification on the interpretation of the Canadian Diabetes Association Clinical Practice Guidelines (CDA-CPG) in relation to clinical trial applications under Part C, Division 5 of the *Food and Drug Regulations*.

Comments and suggestions received from the consultation on the draft version of the guidance were reviewed and considered in the finalization of this document. A tabulation summarizing the comments received during the external consultation and the outcome of the Health Canada discussion of these comments is available on request.

Should you have any questions or comments regarding the content of this guidance, please contact:

Office of Clinical Trials
Therapeutic Products Directorate
5th Floor, Holland Cross, Tower B
1600 Scott Street, A.L.: 3105A
Ottawa, ON K1A 0K9
Fax: (613) 946-7996
E-mail: OCT_BEC_Enquiries@hc-sc.gc.ca

Canada

Health Canada Santé Canada

GUIDANCE DOCUMENT

Standards for Clinical Trials in Type 2 Diabetes in Canada

Published by authority of the
Minister of Health

Date Adopted	2007/06/28
Effective Date	2007/11/01

Health Products and Food Branch

Canada

Our mission is to help the people of Canada maintain and improve their health. *Health Canada*	HPFB's Mandate is to take an integrated approach to managing the health-related risks and benefits of health products and food by: • minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and, • promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. *Health Products and Food Branch*

Également disponible en français sous le titre : Normes applicables aux essais cliniques sur le diabète de type 2 au Canada

FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

TABLE OF CONTENTS

1. INTRODUCTION

1.1 Policy Objectives

Health Canada is issuing this guidance for clinical trials in type 2 diabetes to provide clarification on the interpretation of the Canadian Diabetes Association Clinical Practice Guidelines (CDA-CPG)[1] in relation to clinical trial applications under Part C, Division 5 of the *Food and Drug Regulations*.

1.2 Policy Statements

Clinical practice guidelines ensure the best standard of care based on current science and consensus in the medical and scientific communities. From the regulatory perspective, they are one of the measures against which the safety of the subjects is assessed during the review of clinical trial applications. The consistent interpretation of CDA-CPG in relation to the management of subjects with type 2 diabetes in clinical trials for new drugs for the treatment of type 2 diabetes will contribute to the safety of subjects.

1.3 Scope and Application

This guidance is written primarily for oral pharmaceuticals being developed for the treatment of type 2 diabetes, but it is also applicable to pharmaceuticals delivered by other routes, and to novel insulin formulations.

The guidance focuses on five areas for clinical trials in with type 2 diabetes: inclusion/exclusion criteria, concomitant treatments, monitoring, withdrawal criteria, and informed consent. Guidance is presented separately for Phase II and Phase III trials because the trial objectives, design and duration usually differ between the two phases.

1.4. Background

The Canadian Diabetes Association Clinical Practice Guidelines (CDA-CPG) published in December 2003 recommended more aggressive management of type 2 diabetes. The revised guidelines were based on published studies reporting an association between higher levels of glycosylated haemoglobin (HbA1c) and an increased risk of complications related to diabetes, including death, myocardial infarction, and micro- and macro-vascular disease[2-4]. Based on the available evidence, the CDA-CPG Expert Committee recommended targets for glycemic control of a HbA1c $\leq$7%, a fasting plasma glucose (FPG) of 4.0 - 7.0 mmol/L (International Federation of Clinical Chemistry and Laboratory Medicine (IFCC): 4.3 - 7.3 mmol/L) and a 2-hour postprandial plasma glucose of 5.0 - 10.0 mmol/L (IFCC: 5.3 - 10.3 mmol/L) in patients in whom these targets could be safely met. For type 2 diabetes mellitus it was recommended that the management regimen be tailored to aim for glycemic targets as close to normal as possible, and as early as possible, with the target HbA1c attained within 6 to 12 months.

Division 5 of the *Food and Drug Regulations* defines good clinical practice as generally accepted practices that are designed to ensure the protection of the rights, safety and well-being of clinical trial subjects and other persons. A clinical trial application may be refused if (A) the use of the drug endangers the health of a clinical trial subject or other person, or (B) the clinical trial is contrary to the best interests of the subject. Current scientific evidence indicates that inadequate glycemic control increases the risk of mortality and macro- and micro-vascular disease. Thus, maintaining clinical trial subjects on suboptimal glycemic control solely to demonstrate superior efficacy or to collect safety data is clearly not in the best interests of the subject, and is contrary to the ethical principles outlined in the Declaration of Helsinki[5], ICH E6[6], and the Tri-Council Policy Statement[7].

2. GUIDANCE FOR IMPLEMENTATION

2.1 Concomitant Medications

Lifestyle management with diet and exercise can improve glycemic control, and is an integral part of the treatment of diabetes mellitus and patient self-management. Because the majority of patients with type 2 diabetes are overweight or obese, lifestyle interventions that combine dietary modification, and increased and regular physical activity, are recommended in the CDA-CPG. Thus, it is expected that subjects in all clinical trials for type 2 diabetes will receive dietary and lifestyle counselling consistent with the CDA-CPG.

Patients with type 2 diabetes often have coexisting diseases or conditions, including cardiovascular and other metabolic disorders. All subjects should receive adequate treatment for other coexisting diseases and conditions in accordance with appropriate treatment guidelines. In long-term trials the protocol should allow adjustment of treatment for co-existing diseases and conditions as medically indicated.

2.2 Placebo-Controlled Phase II Proof-of-Concept Trials

Phase II trials are generally short term, placebo-controlled, proof-of-concept dose-ranging studies with the experimental agent as monotherapy or add-on to another agent. These trials are usually 12 to 24 weeks in duration with a run-in period during which subjects receive only a placebo or single agent therapy. The objective is to show superiority of one or more dose levels to the placebo arm.

2.2.1 Inclusion/Exclusion Criteria

In short-term Phase II proof of concept studies, subjects are usually treatment naive or inadequately controlled type 2 diabetes patients with a HbA1c of 6.5 - 10%. The CDA-CPG recommend that patients who do not achieve glycemic targets within 2 - 3 months using lifestyle management should be treated with a single antihyperglycemic agent if the HbA1c <9%. An HbA1c ≥9% is considered marked hyperglycemia, and the CDA-CPG

recommend that patients with an HbA1c ≥9%, despite lifestyle management, be treated with 2 antihyperglycemic agents from different classes, or with insulin. Thus, a HbA1c ≥9% should only be allowed if the subject has not previously attempted lifestyle management

For placebo-controlled monotherapy trials, lifestyle management is an established effective therapy. However, consideration should be given to the ability of the subject to maintain or improve glycemic control with more intense lifestyle management prior to enrollment in a placebo-controlled, monotherapy phase II proof-of-concept trial.

2.2.2 Monitoring

The CDA-CPG guidelines recommend that most patients with type 2 diabetes self monitor blood glucose at least once daily, with more frequent monitoring as needed. Health Canada is recommending that subjects enrolled in clinical trials in Canada self monitor blood glucose at least once daily. HbA1c should be monitored by the investigator at 3 month intervals. Because some antihyperglycemic agents have been associated with weight gain and water retention, subjects should also be advised to self monitor body weight at frequent intervals and inform the investigator of sudden or consistent increases in body weight. The protocol should specify weight monitoring by the investigator at treatment visits.

2.2.3 Withdrawal Criteria

In short term, placebo-controlled, proof-of-concept trials with a placebo run-in, the primary risk is loss of glycemic control. Subjects should monitor blood glucose daily. If the FPG is >12 mmol/L (IFCC: 12.3 mmol/L) more than half of the days in a week (i.e. ≥4 days), the subject should be assessed by the investigator. If the laboratory values exceed 15/15.5 mmol/L (IFCC: 15.3/15.8 mmol/L) and there are no other explanations for the elevation, the subject should be withdrawn from the study. Subjects with symptomatic hyperglycemia or hypoglycemia should be withdrawn if the symptoms are severe.

2.3 Phase III Trials

Phase III trials are longer term, typically 6 months to 2 years in duration, and usually have an active control arm with an accepted treatment. The test arm, or arms, are placebo-controlled, add-on therapy to the accepted treatment, or direct comparisons to the accepted treatment. The objective is usually non-inferiority or equivalence to the accepted treatment. The CDA-CPG recommend a target HbA1c of <7% within 6 to 12 months, therefore the protocol for any trial of >3 months duration should contain procedures to meet the CDA-CPG target and withdrawal criteria for inadequate glycemic control. The procedures to meet the CDA-CPG target include dose escalation and the addition of other therapies.

2.3.1 Inclusion/Exclusion Criteria

The subjects enrolled in phase III trials should be representative of the target patient population as reflected in International Conference on Harmonization (ICH) E8[8]. Thus, the inclusion/exclusion criteria should allow subjects with higher HbA1c and more severe medical problems than would be allowed in phase II trials.

2.3.2 Monitoring

The CDA-CPG guidelines recommend that HbA1c be monitored every three months and that most patients with type 2 diabetes self monitor blood glucose at least once daily, with more frequent monitoring as needed. Health Canada is recommending that subjects enrolled in clinical trials in Canada self monitor blood glucose daily, with more frequent monitoring as needed. HbA1c should be monitored at a maximum of 3 month intervals.

Some antihyperglycemic agents have been associated with weight gain and water retention leading to congestive heart failure, therefore subjects should be advised to self monitor body weight at frequent intervals and to inform the investigator of sudden or consistent increases in body weight. The maximum intervals for monitoring body weight and other measures should conform to the intervals prescribed in the sample patient care plan in the CDA-CPG.

2.3.3 Withdrawal Criteria

In long term phase III trials the risks are loss of glycemic control and lack of efficacy over time.

Loss of glycemic control may occur at any time during the trial, but is of greatest concern during the run-in period and early stages of the trial. When the baseline HbA1c is <9%, the criteria based on FPG for short-term placebo-controlled trials (Section 2.2.3) should apply during the run-in period and the early stages of the trial. If the baseline HbA1c is ≥9%, increases in FPG of ≥2 mmol/L (IFCC: 2.3 mmol/L) over baseline on more than half of the days in a week (i.e. ≥ 4 days), the subject should be assessed by the investigator. During the later stages of the trial increases in FPG of ≥3 mmol/L (IFCC: 3.3 mmol/L) , or >30 - 40%, over the value recorded at the last visit on more than half of the days in a week should be assessed by the investigator.

Lack of efficacy during long term trials may result in subjects being maintained on sub-optimal treatment for extended periods. To protect subjects against lack of efficacy, the withdrawal criteria should be tightened by progressive lowering of HbA1c towards the CDA-CPG target of ≤7%. After 12 weeks of treatment, the withdrawal criteria for FPG should be tightened and HbA1c should be increasingly used to determine the clinical trial endpoints. Dose escalation or the addition of other therapies should be instituted if the

HbA1c >7% (≈FPG > 9.5 mmol/L) after 6 to 12 months of treatment. Criteria for dose escalation, the addition of other therapies, or subject withdrawal should be clearly defined in the protocol for subjects with a HbA1c ≥8% (≈FPG ≥11.5 mmol/L (IFCC: 11.8 mmol/L)) at 52 weeks.

2.4 Informed Consent

Every effort should be made to maintain subjects on a therapy that would not delay optimal treatment. However, if the clinical trial protocol may delay optimal treatment this should be written in the Informed Consent Form. The subjects should be clearly informed of the situation, and of possible risks to their health.

3. REFERENCES

1. Canadian Diabetes Association. 2003. Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Canadian Journal of Diabetes. 27 (Suppl. 1): 1-152.

2. Diabetes Control and Complications Research Group. 1995. Effect of intensive diabetes management on macrovascular events and risk factors in the diabetes control and complications trial. American Journal of Cardiology 75: 894- 903.

3. UK Prospective Diabetes Study Group. 1998. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352: 837-853.

4. Stratton, I.M.. et al. 2000. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. British Medical Journal (BMJ) 321: 405-412.

5. World Medical Association. 2004. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.

6. International Conference on Harmonisation. 1997. E6: Good Clinical Practice: Consolidated Guideline.

7. Tri-Council Policy Statement. 1998. Ethical Conduct for Research Involving Humans.

8. International Conference on Harmonisation. 1998. E8: General Considerations for Clinical Trials.