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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for revision of the guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus

Agreed by Cardiovascular Working Party	11 May 2016
Adopted by the Committee for Medicinal Products for Human Use for release for consultation	23 June 2016
Start of public consultation	28 July 2016
End of consultation (deadline for comments)	31 October 2016

The proposed guideline will replace 'Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 1).

Keywords	<i>treatment or prevention of diabetes, prediabetes, cardiovascular safety, cardiovascular risk, insulin products, definition of hypoglycaemia, fixed dose combinations, oral treatments for type 1 diabetes</i>
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1. Introduction

This concept paper (CP) refers to the need for revision of the *Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus* (1).

2. Problem statement

The current guideline was adopted by the CHMP in May 2012 and came into effect 15 November 2012. The main reason for a revision of the guideline is to update the section on cardiovascular safety to align it with the recently adopted *Reflection paper on assessment of cardiovascular safety profile of medicinal products* (7).

At the same time, some additional changes to the guideline are proposed to be considered based on recent developments and queries from different stakeholders. These issues include outcome measures to assess benefit of new products, safety issues associated with higher insulin concentrations, definitions of hypoglycaemia, guidance with respect to delay in onset/prevention of diabetes and oral treatments for type 1 diabetes (see further below).

3. Discussion (on the problem statement)

A Reflection paper on assessment of cardiovascular safety profile of medicinal products (7) has recently been published. Reference to this paper is intended to replace the majority of the text in section 4.4.3 (long term safety and cardiovascular safety). This section is intended to be consistent with the corresponding sections of the guidelines on products for weight control, treatment of hypertension and treatment of lipid disorders. This is the main reason for the update of the guideline. However, some other areas have been identified that could benefit from revisions.

- Patient groups have expressed concerns that HbA1c may be insufficient to establish benefit of glucose lowering therapies and that additional measures need to be evaluated to characterize benefit. Depending on further assessment of this issue, it may be considered to include additional guidance with respect to potential endpoints others than those directly associated with glycaemic control, e.g. patient reported outcome measures.
- During the last years, insulins with different concentrations (200 U/ml, 300 U/ml) have been approved. An addendum to the good practice guide on risk minimisation and prevention of medication errors reflecting risk minimisation strategy for high-strength and fixed-combination insulin products has been published in November 2015 (8), and some wording and reference should be included in the guideline reflecting specific safety issues associated with higher insulin concentrations.
- Since the last revision of the guideline, no Marketing Authorisation Application has been received and only limited advice has been given with respect to “delay in onset/prevention of type 2 diabetes”. However, in such a potential scenario, proposed study designs may rather suggest “treatment of prediabetes” as possible consequential indication. For the claim of “prevention of type 2 diabetes” preferably a population with no glycaemic abnormalities would need to be followed for a very long time leading to feasibility issues with such a study design. Therefore some changes in that section may be proposed to clarify these aspects.
- With respect to definition of hypoglycaemia, the following statement is included in section 7 of the current guideline: *The definitions of hypoglycaemia in individual protocols and across protocols within the development program should be standardized. One recommended approach for such*

standardization is to use classifications of severity from well-accepted sources, such as the ADA for adults. Since the EMA has received input from external stakeholders considering the ADA definition may not be appropriate in all cases, another example for the definition of hypoglycaemia representing a lower cut off could be added.

- Scientific advices recently given by CHMP on the development of oral treatments for patients with type 1 diabetes, primarily with the class of SGLT 2 inhibitors, suggest the need for advice on this topic in the GL. While these products potentially can provide beneficial effects (insulin sparing, reduced risk of hypoglycaemia), there are also safety concerns, e.g. with respect to risk of atypical presentation of ketoacidosis which has been reported in patients with type 2 diabetes. This warrants new text in the guideline as this development is not yet reflected in the current version of the GL.

4. Recommendation

The CVS Working Party and CHMP recommend revising the *Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus* (1).

Points that will be addressed are listed in sections 2 and 3 of this CP.

5. Proposed timetable

This CP will be released for 3 months public consultation. Following this it is planned to release the draft Guideline within 6 months after the completion of the public consultation on the CP. The draft Guideline will be released for 6 months public consultation and following the receipt of comments it will be finalised within approximately 6 months.

6. Resource requirements for preparation

The drafting process will be done internally at the CVS WP. Contribution from the Scientific Advice Working Party, Biostatistics Working Party and Geriatric Experts Group will be requested.

7. Impact assessment (anticipated)

The document is intended to update methodological aspects when performing trials to develop medicinal products for the treatment or prevention of diabetes. It should also provide a clear basis for the CHMP when assessing primary safety data and secondary efficacy and safety data of clinical relevance from studies for medicinal products in this indication and providing advice in this field.

8. Interested parties

The interested parties in the guideline include the Industry, Academia, EASD (European Association for the Study of Diabetes), ESE (European Society of Endocrinology), European Society of Cardiology (ESC), European Federation of Internal Medicine (EFIM), ADA (American Diabetes Association) and clinical trialists in diabetes.

9. References to literature, guidelines, etc.

1. Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus

- http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129256.pdf
2. Draft reflection paper on the wording of the indication for medicinal products for the treatment of type-2 diabetes
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/03/WC500162192.pdf
 3. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Inzucchi SE, Bergenstal RM, Buse JB et al. *Diabetologia*. 2015;58:429-442.
 4. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Authors/Task FM, Rydén L, Grant PJ et al. *Eur Heart J*. 2013;34:3035-3087.
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http://www.who.int/cardiovascular_diseases/report-hba1c_2011_edited.pdf
 6. American Diabetes Association – Standards of care in diabetes – 2016. *Diabetes Care*, January 2016, Volume 39, Suppl. 1
http://care.diabetesjournals.org/content/suppl/2015/12/21/39.Supplement_1.DC2/2016-Standards-of-Care.pdf
 7. Reflection paper on assessment of cardiovascular safety profile of medicinal products
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/03/WC500203804.pdf
 8. Risk minimisation strategy for high-strength and fixed combination insulin products (Addendum to the good practice guide on risk minimisation and prevention of medication errors)
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/11/WC500196980.pdf