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Pre-Authorisation Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON THE NEED FOR REVISION OF THE NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF DIABETES MELLITUS

AGREED BY EFFICACY WORKING PARTY	May 2008
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This Concept Paper refers to a proposed revision of Note for Guidance of Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus CPMP/EWP/1080/00.

Comments should be provided using this template to EWPSecretariat@emea.europa.eu
Fax +44 20 74 18 86 13

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1 INTRODUCTION

The current CHMP Note for guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus CPMP/EWP/1080/00 was adopted by the CHMP in November 2002. New aspects have emerged since then including:

- Paediatric regulation has been implemented and a need for specific trials in children and adolescents with diabetes is considered.
- A number of new medicines for diabetes have been approved.
- Some medicines have only limited long-term safety data and may be associated with an increased cardiovascular risk.
- The possibility to develop medicines for the prevention of diabetes has been proposed.
- Combination treatment studies, especially with insulin, become more and more complex.

Therefore, the points mentioned above may deserve discussion and a need to update the guidance has been identified.

2 PROBLEM STATEMENT

It is proposed to consider introducing the following new chapters (or to amend the existing ones) in the revised guideline:

2.1 Paediatric Population

Taking into account a rise in the incidence of type 2 diabetes in adolescents, there might be an increasing need for evaluation of medicines for type 2 diabetes in this population. Guidance should be given with regard to age-specific requirements and possible study designs.

In addition, in order to better explore immunogenicity and pharmacodynamic profile of new insulin preparations (e.g. glycaemic variability in type 1 diabetes), a need for such trials in children with type 1 diabetes is proposed to be discussed.

Safety of antidiabetic medicines is also an important factor to take into account when discussing the need for specific trials in children.

2.2 Cardiovascular Outcome Studies

Recently, a series of publications in the NEJM, JAMA, and Lancet, have analysed the cardiovascular risk associated with the use of Avandia (rosiglitazone) (1-3), Actos (pioglitazone) (4), or both (5, 6).

The possibility of an increased cardiovascular risk associated with the use of Avandia, but to some degree also the lack of clear evidence of a benefit with regard to macrovascular complications for other currently approved antidiabetic agents in patients with type 2 diabetes, raised questions about the way medicines for type 2 diabetes are currently approved in the EU and US (7-12). This included some criticism of the predominant reliance on HbA1c as primary outcome parameter and an emphasis on the need for outcome studies.

Regulators have always acknowledged the high importance of the reduction of macrovascular complications in patients with type 2 diabetes. Currently, approval is based on studies with HbA1c as the primary outcome parameter, as a very well validated marker of glycaemic control. A correlation between glycaemic control achieved and microvascular complications (diabetic nephropathy, neuropathy, retinopathy) is relatively well established both for type 1 and type 2 diabetes, but to a lesser extent for macrovascular complications, particularly in type 2 diabetes.

Cardiovascular outcome studies have been performed in the past, in some cases to fulfill post-marketing commitments. An example is the ProActive study with Actos (13). Although this study failed in its primary outcome parameter, it showed that there was no increased risk of macrovascular events associated with its use.

Similarly, for some recently approved medicines for type 2 diabetes, cardiovascular outcome studies have been requested as post-marketing commitments in case there was suspicion of a detrimental effect on the cardiovascular system. Undertaking such studies is acknowledged to require extensive resources (typically > ~5000 patients, > ~3 yrs, even in high risk populations), and is further complicated by the multiplicity of co-medications influencing cardiovascular outcome, which these patients typically are on.

It is proposed to discuss the following scenarios:

- the need for pre-marketing CVS outcome studies for all new medicines (with a new mechanism of action);
- the need for post-marketing CVS outcome studies for all new medicines (except if they belong to a well-known class of drugs);
- the need for pre-marketing CVS outcome studies for new medicines whose mode of action and observed effects suggest a “detrimental effect” on CVS. Detrimental effect should be defined.

A design of such trials and the recommended study population should be specified.

2.3 Combination Studies of oral antidiabetic agents with insulin

Most of the currently performed trials inadequately reflect patient populations and clinical practice in situations where oral antidiabetic agents (OAD) are combined with insulin: in most cases, OAD (or placebo) is added to insulin in patients with type 2 diabetes mellitus, while the opposite is generally happening in clinical practice. Furthermore, in these trials where patients already on insulin are included, the oral antidiabetic treatment at inclusion currently ranges from no OAD to 1 or 2 OADs. These OADs are either stopped or continued at study entry, depending on study design.

Therefore, more specific guidance on the design of combination therapies with insulin in type 2 diabetes mellitus should be given.

2.4 Prevention of diabetes

There is no regulatory experience with any product for this indication in Europe at present; therefore, it may be difficult to give regulatory advice or recommendations in this field at this time.

Prevention of type 1 diabetes:

Prevention of type 1 diabetes or preservation of beta-cell function in recent-onset type 1 diabetes patients may be a possible claim for new medicines; metabolic outcomes and immune markers and the markers of cellular immune response are of interest in this setting; in addition, the ability of PPAR gamma agonists to protect and preserve beta cell function has also been advocated. These studies are still at a very early stage; no long-term study has been published. However, several studies are being launched and it would be important to give some recommendations on relevant endpoints and desired features of an approvable product.

Prevention of type 2 diabetes:

The aim of such trials would be to show that a medicinal product is capable of preventing/delaying type 2 diabetes in high-risk individuals (e.g. in patients with impaired glucose tolerance or impaired fasting glucose). It would be of importance to show that a product truly delays progression to diabetes

and not only masks emerging diabetes during treatment, and that there is a durable delay of the onset of diabetes after discontinuation of therapy. In long-term placebo-controlled trials, an improvement of glycaemic and clinical parameters, beyond those expected from glucose-lowering alone, should be demonstrated. This could be a clinical benefit with regard to microvasular or macrovascular complications reduction, thus requiring very sizable and long-term studies. For agents acting via weight loss, an effect on diabetes incidence independent from the effect on weight loss would have to be shown.

Foremost, it should be explored, whether at present enough data are available at all to propose any guidance on studies for the prevention of type 1 or type 2 diabetes, respectively.

2.5 Safety evaluation

Independently of the assessment of an increased cardiovascular risk, a large number of patients with diabetes should be exposed to a new medicine before granting MA. There may be a need to discuss both the patient exposure required (e.g. for 6 months, 1 year and more) to assess the safety of the new MP and the minimal percentage of elderly subjects (>65 y and >75 y) needed among the exposed patients.

3 DISCUSSION (ON THE PROBLEM STATEMENT)

The main topics to be addressed will be related to the design of efficacy studies and to safety evaluation in the following situations:

1. Studies in children: type 1 and type 2 diabetes;
2. Cardiovascular outcome studies;
3. Combination studies with insulin;
4. Prevention of diabetes indication (type 1 and type 2 diabetes).

4 RECOMMENDATION

In the light of the identified emerging regulatory issues, the Efficacy Working Party/CHMP recommends revising the guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus in order to address the above mentioned points.

5 PROPOSED TIMETABLE

- Writing of an outline of the key changes proposed and of the list of questions addressed to the Diabetes/Endocrinology SAG by the drafting group (June 2008);
- Discussion of the key issues and of the questions to the SAG at the July EWP (7-8 July 2008);
- Adoption of the CHMP list of questions to the Diabetes/Endocrinology SAG at the July CHMP (21-25 July 2008);
- Diabetes/Endocrinology SAG meeting (September 2008);
- Discussion at October EWP (14-15 October 2008);
- Drafting of the revision during 4. quarter 2008;
- Discussion at January EWP (12-13 January 2009);
- Release for 6-month consultation following CHMP adoption in February 2009.

6 RESOURCE REQUIREMENTS FOR PREPARATION

SAG Diabetes/Endocrinology, CVS drafting group, EWP.

7 IMPACT ASSESSMENT (ANTICIPATED)

The revised guideline will provide updated guidance to both industry and Regulatory Authorities regarding the clinical development and assessment of medicinal products for Diabetes and is expected to contribute to a consistent approach in development and assessment of these products.

8 INTERESTED PARTIES

EASD (European Association for the Study of Diabetes).

9 REFERENCES TO LITERATURE, GUIDELINES ETC

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