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Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus

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Comments should be provided using this template. The completed comments form should be sent to EWPSecretariat@ema.europa.eu

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Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus

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Executive summary

This guideline intends to address the EU regulatory position on the main topics of the clinical development of new medicinal products in the treatment of patients with diabetes.

1. Introduction (background)

Diabetes mellitus is a metabolic disorder characterised by the presence of hyperglycaemia due to defective insulin secretion, insulin action or both. The chronic hyperglycaemia of diabetes mellitus is associated with significant long term sequelae, particularly damage, dysfunction and failure of various organs – especially the kidney, eye, nerves, heart and blood vessels.

Type 1 diabetes is the result of pancreatic beta cell destruction and is prone to acute complications, such as ketoacidosis. In type 1 diabetes the main goal is optimal blood glucose control to be achieved by optimal insulin replacement therapy, extensive education and disease self management. Prevention of complications and management of pregnancy are important issues.

Type 2 diabetes is a complex disorder which involves various degrees of decreased beta-cell function, peripheral insulin resistance and abnormal hepatic glucose metabolism. Glucose control in type 2 diabetes deteriorates progressively over time, and, after failure of diet and exercise alone, needs on average a new intervention with glucose-lowering agents every 3-4 years in order to obtain/retain good control. Despite combination therapy and/or insulin treatment, a sizeable proportion of patients remains poorly controlled.

Overweight, hypertension and hyperlipidaemia are often associated with diabetes mellitus and multiple cardiovascular risk factor intervention is the key issue in type 2 diabetes. Therefore, global treatment aims in management of diabetes mellitus cover both lowering of blood glucose to near normal levels and correcting metabolic abnormalities and cardiovascular risk factors. Indeed, it has been shown that normalisation or near normalisation of glucose levels (assessed by changes in HbA1c) in patients with type 1 and type 2 diabetes significantly reduces the risk of microvascular complications (retinopathy, nephropathy and neuropathy); the macrovascular risk reduction in patients with type 2 diabetes is less certain.

In children and adolescents, the diagnosis of diabetes type 1 and type 2 is similar to that in adults, however, the discrimination between them may not always be straightforward. Type 1 diabetes is the predominant form in children. Type 2 diabetes has been recently emerging among – mostly obese - children in puberty and may present with ketoacidosis as the first manifestation of the disease; an obese adolescent with hyperglycaemia may have either type 1 or type 2 diabetes. An important feature of type 2 diabetes in adolescence is the higher insulin resistance and faster beta cell destruction rate relative to adults.

ADA recommendations for the diagnosis of diabetes in children are based on presence or absence of:

- obesity,
- family history,
- fasting insulin and C-peptide levels,
- auto-antibodies (Diabetes Care, 23(3):381, 2000)
- age of onset

and may help discriminating between type 1 and 2 diabetes in children and adolescents.

2. Scope

These notes describe the type of clinical development programme that should support the registration of new medicinal products for the indication treatment of diabetes mellitus.

These notes are intended to assist applicants during the development phase and for guidance only. Any deviation from guidelines should be explained and discussed in the Clinical Overview.

Insulin delivery systems are outside the scope of this document.

3. Legal basis

This guideline has to be read in conjunction with the introduction and general principles (4) and part I and II of the Annex I to Directive 2001/83 as amended and other pertinent elements outlined in current and future EU and ICH guidelines, especially those on:

- Studies in Support of Special Populations: Geriatrics (ICH topic E7).
- Dose Response Information to Support Drug Registration (ICH topic E4).
- Statistical Principles for Clinical Trials (ICH topic E9).
- Choice of the control group in clinical trials (ICH topic E10).
- Fixed combination medicinal products (EU).
- Pharmacokinetic Studies in Man.
- Note for Guidance on the Investigation of Drug Interactions (CPMP/EWP/560/95).
- Clinical investigation of medicinal products in children (ICH topic E11).
- Points to Consider on the Need for Reproduction Studies in the Development of Insulin Analogues (CPMP/SWP/2600/01) and on the Non-Clinical Assessment of the Carcinogenic Potential of Human Insulin Analogues (CPMP/SWP/372/01).
- Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications (EMEA/CHMP/SWP/169215/2005).
- E7 Geriatric Studies: Questions and Answers.
- Evaluation of Medicinal Products for cardiovascular disease prevention (CHMP/EWP/311890/07).

4. Developing and Licensing Glucose Lowering Agents for the Treatment of Type 2 Diabetes Mellitus

4.1 Specific considerations on study designs

4.1.1 Washout period

Monotherapy studies are optimally conducted in patients who have previously failed on diet and exercise. In case patients already treated with glucose lowering agents participate in monotherapy studies, the need for a washout period should be carefully considered:

- For therapeutic exploratory studies with a treatment period up to around 3 months, a washout period is recommended in patients previously receiving glucose lowering agents which are not to be used in the study. The aim of this washout period is two-fold: (i) to decrease the influence of previous treatment on the parameters of blood glucose control, that could last for a large part of short-term studies (to a certain extent, depending on the mode of action of the treatment previously received), (ii) to decrease the placebo effect resulting from the extra attention provided by more frequent visits during the study. Furthermore, unless the washout period is long (2-3 months), the HbA_{1C} level at the end of the washout period may still be influenced by the previous treatment, since HbA_{1C} gives a quantitative index of blood glucose control over the past 2 to 3 months. The washout period can be shorter than 2 to 3 months, but this should be taken into account when estimating the size of the anti-hyperglycaemic effect in comparison to baseline values, particularly when HbA_{1C} is the primary outcome measure.

- For therapeutic confirmatory studies using HbA_{1C} as the primary endpoint, a washout period is usually not necessary for previously treated patients. However, as the baseline HbA_{1C} level will be influenced by the previous treatment in patients directly switched to study drug, both previously drug-naive patients and pre-treated patients should be assessed for efficacy of the tested drug. For example, a favourable evolution will be a decrease in HbA_{1C} in drug-naïve

patients, whereas at least maintenance of the baseline HbA_{1C} level is expected in patients previously treated with an optimal dose of an established treatment.

4.1.2 Use of placebo

Placebo-controlled trials are necessary to get relevant information on the glucose-lowering effect of the investigational drug. However, placebo-controlled trials may be viewed as unethical in certain circumstances. Placebo-controlled studies of three to six months duration should therefore be reserved for patients at an early stage of the disease. Candidates for these trials should have a relatively low starting HbA_{1C} (e.g. less than 8.5%, normal <6%). Patients with higher HbA_{1C} (e.g. up to 10%) may be enrolled in placebo-controlled trials of less than three months duration. Protocols will need to stipulate that patients will be withdrawn from the study if their glucose control consistently deteriorates over a pre-set target. A drug-related reduction in the proportion of patients who are withdrawn due to lack of efficacy may be used to provide additional support for efficacy.

4.1.3 Dosage

The dossier should contain well-designed dose-ranging studies in order to justify the dosage used in confirmatory clinical trials. In monotherapy as well as in add-on situations, it is current clinical practice, when several doses are available, to titrate a new glucose lowering agent until an optimal effect is seen or until the maximal tolerated or recommended dose is reached. The therapeutic confirmatory drug trials should be as close as possible to these clinical principles. Titration steps should in most cases last for at least 2-4 weeks unless otherwise justified. In the maintenance period the dose of the test drug should be kept stable whenever possible.

4.1.4 Predictive factors of response to treatment

Applicants should be encouraged to determine if there are demographic, genetic, metabolic (e.g. C-peptide or other measure of beta-cell function) or other factors which may predict the response to a particular glucose lowering agent. Internal consistency of estimated treatment effects across important subgroups should be investigated.

4.1.5 Associated cardiovascular risk factors

Any new glucose-lowering agent should show at least neutral or beneficial effects on associated cardiovascular risk factors (e.g. obesity, blood pressure, lipid levels).

Before concluding on possible additional benefits or risks, the influence of changes in blood glucose control itself on the changes in the other risk factors should be carefully addressed. For example hypertriglyceridaemia reported commonly in type 2 diabetic patients reverts to normal with good glycaemic control in the majority of patients. Any specific claim regarding improvement in lipid profile will require evidence of efficacy over and above this and should be of documented clinical relevance.

Furthermore, as the goal of treatment is to reduce the risk of diabetic complications, not just to lower HbA1C, a new agent could not be approved based on a reduction in HbA1C if there is evidence that it directly increases the risk of diabetic complications.

Weight-lowering agents are also likely to lower mean glucose levels in patients with type 2 diabetes. Given the impact that even small degrees of weight reduction can have on diabetes, these agents could potentially be considered glucose-lowering agents. Improvement in hyperglycaemia related to weight loss in obese diabetics is certainly desirable and could potentially be a labelled indication. However, it will not be accepted as the sole basis for approval unless the glucose lowering effect of the weight-loss agent has a pharmacologic rationale, is sustained, and clinically relevant, over and above that explained by effects on weight. This could be demonstrated by either including non-obese diabetics as separate arm in the study or in comparison with an accepted glucose lowering agent.

4.1.6 Outcome studies

Long term complications include macrovascular (coronary, cerebrovascular, and peripheral vascular diseases) and microvascular complications (retinopathy, nephropathy, and partly neuropathy). Beneficial effect of the drug on development of these complications can only be evaluated properly in large scale and long term controlled clinical trials. These trials will only be mandatory when specific

claims are made or when there are suspicions of a detrimental effect of the tested drug (see also section 4.5.3).

4.2 Assessment of glucose lowering efficacy

The primary purpose of the therapeutic confirmatory studies with the tested agent is to demonstrate a favourable effect on blood glucose control. Efficacy parameters pertaining to the complications of diabetes are detailed in section 6.

4.2.1 Measures of glycaemic control

4.2.1.1 Glycohaemoglobin (Haemoglobin A1C)

Glycohaemoglobin (HbA1C) is the most widely accepted measure of overall, long-term blood glucose control in type 1 and type 2 diabetes. It reflects a beneficial effect on the immediate clinical consequences of diabetes (hyperglycaemia and its associated symptoms). Moreover, reduction of HbA1C is known to reduce the long-term risk of development of microvascular complications. Therefore, HbA1c is an appropriate primary endpoint to support a claim based on glycaemic control.

The primary analysis of HbA1C should evaluate the difference in evolution from baseline HbA1C between the test compound and the active comparator/placebo. Baseline HbA1C should be included as a covariate in the analysis. The applicant should also justify the clinical relevance of the effect size observed. One method of justification might be a responder analysis comparing the proportion of patients who reached (and/or maintained, in the case of therapeutic confirmatory studies with no washout period) an absolute value of ≤ 7% (for normal values <6%) across the different treatment groups. Other definitions of a responder should be prospectively identified and justified by the applicant.

A well-validated assay for HbA1C should be used, i.e. reference methods recommended by scientific bodies involved in the international standardisation of HbA1C measurement. Centralised analyses are strongly recommended, at least for therapeutic confirmatory studies.

4.2.1.2 Plasma glucose

Change in fasting plasma glucose is an acceptable secondary efficacy endpoint. Changes in average plasma glucose recorded at regular intervals (mean of at least seven measurements, before and after each of three meals and at bedtime; capillary glucose is acceptable, provided that there is confidence in the quality of the glucose measurements) or glucose AUC are also acceptable endpoints. Parameters based on plasma glucose might be used as primary endpoints in short term studies (under 8 weeks), where the use of HbA_{1C} is not or less appropriate. In addition, a reduction of post-prandial hyperglycaemia, which may be an independent risk factor for macrovascular complications, can be used as a secondary endpoint. Future use of devices allowing continuous glucose level measurement is also encouraged; currently, these measurements are always confirmed through plasma glucose levels.

4.2.2 Other measures of metabolic control/status

A reduction in insulinaemia in patients treated with glucose lowering agents, or a reduction in insulin dose itself in insulin-treated type 2 diabetic patients, is of clinical interest but is not considered as a sufficient measure of efficacy unless accompanied by a favourable evolution of HbA_{1C}.

In insulin-treated type 2 diabetic patients, the entire elimination of the need for insulin, or a relevant reduction in insulin dose accompanied by a clinically significant improvement in the evolution of body weight could be considered a measure of efficacy even in the absence of improvement in HbA_{1C} provided that studies had appropriate controls.

Serum lipids (LDL and HDL cholesterol, triglycerides) levels should be documented regarding short and long-term effects. The effects of the tested product on LDL and HDL cholesterol should be specifically documented in type 2 diabetes.

Body weight should be documented regarding short- and long-term effect. In the natural history of diabetes, obesity increases insulin resistance and cardiovascular risk. It is not known whether the relationship is the same for weight increase induced by antidiabetic therapy. If a novel agent causes weight increase in association with a decrease in HbA_{1C} it should be established that the beneficial effect on HbA_{1C} is maintained long term in spite of the weight increase and the nature of the weight increase should be addressed.

4.3 Strategy and steps in the development. Methodology of the clinical studies

4.3.1 Pharmacodynamic data

Although there are no specific requirements for pharmacodynamic testing of glucose lowering agents, the mechanism of action of the drug should be evaluated and discussed in relation to that of relevant drugs already available. When possible, the direct pharmacodynamic effect should be evaluated independently of the effect on blood glucose level. The pharmacological activity of the main metabolites should be quantified, in diabetic patients when possible (in relevant animal models otherwise), and studied in detail if they are likely to contribute substantially to the therapeutic or toxic effects.

4.3.2 Pharmacokinetics

The pharmacokinetic information required is stated in detail in the appropriate guidelines. Although initial PK studies can be done in healthy volunteers, it is important that PK studies also be performed in all types of patients for whom treatment is intended (including children and elderly). Indeed it may not be assumed that the PK properties observed in healthy subjects will be the same in diabetics and at different age groups. Factors such as delayed gastric emptying and gastrointestinal transit time or altered renal function can be expected to complicate drug absorption and disposition in a significant number of type 2 diabetic patients.

4.3.3 Methodology of clinical studies

4.3.3.1 Study population and selection of patients

The patients enrolled into clinical trials must be representative of the target population in terms of demography, ethnic background, co-morbidity (especially cardiovascular disease) and type and severity of diabetes. Groups should be sufficiently balanced with respect to age, gender, body mass index, severity and duration of disease. Stratified allocation may be desirable, particularly on the pre-existing metabolic control (e.g. HbA_{1C} □8% / >8%) and on pre-study treatment (e.g. diet alone, monotherapy, combination therapy). Studies in specific populations should also be considered (see 4.4 and 5.4).

Patients enrolled in the trials should be given similar instructions with regard to diet and exercise. To the extent possible, study designs should attempt to simulate ordinary clinical practice.

4.3.3.2 Therapeutic exploratory studies

Dose ranging studies should thoroughly assess the lower end of the effective dose range, as well as the optimal dose. A parallel, fixed-dose, double-blind placebo-controlled design has proven useful in evaluating new drugs. A washout period is recommended in previously treated patients (see 4.1.1). In dose-ranging studies, at least 3 dosages should be studied with a total treatment phase of at least 8 weeks and usually up to 3 months.

The endpoints in dose ranging studies are changes in plasma glucose (see 4.2.1.2). However HbA1C should be the primary evaluation criterion in the dose-ranging studies of more than 8 to 12 weeks duration (see 4.2.1.1).

4.3.3.3 Therapeutic confirmatory studies

Parallel-group, randomised, double-blind, placebo and comparator-controlled studies are necessary. The therapeutic confirmatory trials should aim at demonstrating:

- the superiority of the new agent over a placebo in at least one study of no less than 3 months duration, which could be a dose-ranging study using $HbA1_C$ as the primary endpoint, or a three arm trial with a short placebo period at the beginning of an active controlled trial (see ICH E10), and
- the non-inferiority of the new agent to an active comparator (or standard therapeutic regimen), the efficacy of which has previously been clearly established in well-designed trials. The choice of the comparator may depend on the pharmacological properties of the test compound and the type of patients recruited in the studies (e.g. metformin in obese patients).

Criteria for equivalence/non-inferiority must be predefined and well discussed regarding their clinical relevance. Even apparently small reductions in HbA_{1C} have been shown to be clinically relevant in terms of risk reduction of diabetic complications. This should be considered when selecting the non-inferiority margin; it is necessary to balance the degree of potential inferiority against some other clinical advantage such as safety, tolerability, compliance, and improvement in cardiovascular risk profile. The applicant should demonstrate that this advantage can outweigh a potentially reduced efficacy.

Monotherapy studies comparing the test drug to normal standards of practice (active comparator) are always needed to obtain a marketing authorisation for monotherapy, and should also be performed for a marketing authorisation for combination therapy as add-on studies alone do not allow a definitive assessment of the genuine antidiabetic effect of a new compound.

They should include a run-in period, a titration period and a maintenance period. The overall duration of therapeutic confirmatory comparator controlled monotherapy studies should not be less than 6 months, including a maintenance period of at least 16 weeks. For glucose lowering agents with an original mechanism of action, a 12 month controlled duration may be required. Concomitant background treatment should be kept stable during the study unless adjustment is necessary for safety reasons. Any change in background treatment that may affect the efficacy or safety evaluation should be appropriately documented and reported.

Run-in (baseline) period

As normally no washout period is necessary in confirmatory studies (see 4.1.1), a 2-week run-in period is generally sufficient during which the investigator must carry out the baseline evaluation of the patient, including full clinical and laboratory assessment. Longer run-in period may be necessary in some situations (see combinations with insulin)

Titration period

The demonstrated optimal dose should be used for both products. In the usual case where several doses are available, the dose should be progressively up-titrated by evaluating the drug effect on fasting and/or post-prandial plasma glucose, and if necessary blood glucose self-monitoring.

Maintenance period

16-week duration of double blind treatment is usually considered relevant to assess short term efficacy.

Add-on (or combination) studies aim at determining the efficacy of the investigational drug used as add-on therapy in patients insufficiently controlled despite monotherapy with established treatment.

There are many possible therapeutic combinations of glucose lowering agents. A choice of new combination must be made based on recommendations for diabetes treatment as well as on known contra-indications for some combinations.

For add-on studies it is mandatory to compare the combination of the new agent and the established agent to the established agent alone. Dose titration will usually be indicated (see 4.1.3). It is recommended:

(i) to select patients not meeting therapeutic targets (non-responders) on the established agent alone even at maximal tolerated dose, as recommended in current therapeutic guidelines,

(ii) to select patients who did not need any change and/or adjustment in previous medication during the 8 to 12 weeks preceding the study to ensure that the maximal effect of the

previous medication has been achieved and that HbA_{1C} is stabilised at baseline; some products may need longer than 12 weeks to reach their maximal effect

(iii) during the study, to avoid dose adaptation of the concomitant glucose lowering agent(s), unless they are necessary for safety reasons. If dose adaptations in the concomitant antidiabetic therapy are expected to occur, the optimal dose may be predefined. In the maintenance period the test and concomitant medications should be kept stable.

Usually 16 week duration of the maintenance period is sufficient to demonstrate efficacy in the add-on situation, where a statistically significant and clinically relevant additional HbA_{1C} reduction should be demonstrated. Improvement in responder rates with the combination in these patients is also desirable.

Depending on the results of placebo-controlled trials, and especially if the HbA1c improvement obtained with the new combination is of doubtful clinical relevance, active-controlled data are advisable against a commonly used combination in order to put into perspective the improvement obtained with the new combination.

Fixed dose combinations

In most cases, general guideline on fixed dose combinations will apply.

Current developments of FDC in the treatment of type 2 diabetes cover add-on and substitution indications. The MAA for an FDC product is generally based on the content of the files submitted for each of its active substances as monotherapies, together with the comparison of the free combination of both active substances to the first line monotherapy. In addition, bioequivalence and interaction studies should be provided in support of the FDC.

If no data are available on the efficacy and safety of the free combination, an add-on trial in non-responders or in patients insufficiently controlled with the maximally tolerated doses of the established first line monotherapy should be performed to support the 2nd line (add-on) indication; patients should be randomised to the FDC versus optimised monotherapy; an active comparator arm may be necessary.

Any potential acceptability of an initial (1st line) combination therapy (in drug-naïve patients failing on diet and exercise) will require a scientific consensus on this, as reflected in recommendations in treatment guidelines issued by Learned Societies in the field. Currently, initial combination therapy is not recommended for patients with diabetes.

Combinations with insulin

Combination therapy of a glucose-lowering agent with insulin may occur in different clinical situations and patient populations. This should be taken into account when planning clinical trials.

i) One approach to optimizing treatment in patients with type 2 diabetes inadequately controlled with one or two (oral) glucose lowering agents is to continue the GL agents and to add insulin. Published data suggests that this may reduce insulin requirements by 20% (with one GL drugs) to 40% (with 2 GL drugs).

Patients on one or two GL agents (one of 2 agents being a test drug) should be randomised to:

- GL plus insulin,
- insulin alone and
- insulin + metformin (reference treatment arm).

Insulin may be given open label and freely titrated in all treatment arms to obtain good glycaemic control throughout the trial. An 8-week, single blind run-in phase may be necessary in order to ensure inclusion of patients inadequately controlled despite maximally dosed OGL bitherapy. Both improved glycaemic control (change in HbA1c from baseline to end of treatment), **and** decrease in daily insulin doses should be demonstrated and may be co-primary endpoints. Decrease in body weight (linked to decrease in insulin doses) and hypoglycaemic events should be assessed as key secondary endpoints (see also 4.2.2).

ii) Another approach in patients with inadequately controlled type 2 diabetes on insulin alone is to introduce the experimental drug in add on to insulin. Studies should be carried out in patients put on optimised insulin doses for a time sufficient to ensure that HbA_{1C} levels are stable before the test drug is added to insulin (i.e. at least 2 to 3 months). The efficacy of a test drug in combination with insulin will be compared to insulin alone. A comparison to the reference treatment arm (e.g. insulin + metformin) may also be needed. Insulin dose will be maintained stable as far as possible during the

double-blind period (unless down-titration is necessary for safety reasons), and the efficacy will be evaluated on the evolution of HbA_{1C}. Patients should be stratified based on type of diabetes and duration of insulin treatment (long-standing treatment or current switch to insulin).

Therapeutic approaches, trial designs/aims and responses to treatment differ in situations described under i) and ii). Therefore, it is recommended to perform two trials (one in each clinical situation) in order to support the general claim "combination with insulin". If only one trial has been performed, an indication with a specific wording reflecting the corresponding clinical situation may be granted.

4.4 Studies in specific populations

4.4.1 Elderly

Regarding the elderly, it is important to determine whether or not the pharmacokinetic behaviour of the drug in this population is different from that in younger adults. Safety of the tested product, especially occurrence of hypoglycaemia, is a matter of concern in the elderly and very elderly. Therefore a reasonable number of such patients (>65 years and >75 years) should be included in the therapeutic confirmatory studies to get an unrestricted indication. Depending on the data, specific efficacy and safety trials in this population may be needed.

4.4.2 Children and adolescents

Due to important differences between adolescents and adults in several aspects of the disease and its management (e.g. stage of the disease, increased insulin resistance at puberty, more rapid beta cell destruction rate, neurologic vulnerability to hypo- and hyperglycaemia, sensitivity to the compound, adherence to therapy, lifestyle, as well as doctors` approach), it is recommended that trials in adolescents diagnosed with type 2 diabetes be carried out.

The prevalence of type 2 diabetes in children and adolescents is increasing worldwide in parallel with the prevalence of childhood obesity.

In clinical practice, however, a diagnosis of type 2 DM in a child is made only when other forms of DM have been ruled out. Rapid and acute manifestation, insulin deficiency (C-peptide values less than 1.5ng/ml), presence of autoantibodies against beta cells or insulin, ketosis and total permanent insulin dependence point towards type 1 DM.

Persisting C-peptide levels, absent auto antibodies (ICA,IA2, IAA,anti GAD ab) , together with obesity or overweight point in children/adolescents to the diagnosis of type 2 DM . When children are not obese/overweight , and have no detectable antibodies, MODY genetic syndromes and secondary diabetes should be excluded. Overweight/obese children with auto antibodies (ICA, IA2, IAA,anti GAD ab) should be considered type 1 DM , as their insulin secretion will disappear faster than is observed in type 2 DM.

Insulin is required initially in children with dehydratation and keto-acidosis; other children are treated with change in lifestyle and metformin as an initial OGL agent. If monotherapy with metformin is not successful, bitherapy with OGL agents, insulin or insulin and metformin are recommended. Currently, metformin and insulin are the only drugs approved in EU.

Despite these recommendations, prospective data on the management of type 2 childhood diabetes are still sparse.

As the mean age of type 2 DM development in children is 13 – 14 years, it is recommended that trials be performed in patients 10 to 18 yr old, since type 2 diabetes in this population emerges generally at or after onset of puberty, and is extremely rare in childhood.

The studies in adolescents are proposed to be carried out during or after the late phase 3 adult trials, when new drug candidates have shown sufficient efficacy and a favourable benefit/risk balance in adult therapeutic confirmatory trials. Applicants may perform either separate trials or include pubertal patients with type 2 diabetes as a subgroup in late adult trials with stratification based on age.

Monotherapy

Placebo and metformin controlled 3-arm study (see 4.3.3.3) is recommended to support monotherapy indication. Alternatively, a 2-arm active-controlled trial demonstrating superior efficacy to metformin may be performed.

In the first case (3-arm placebo and metformin controlled study), a scientific advice from the EMEA and/or national authorities may be useful. In particular, a trial powered to show superiority of each active drug to placebo but not adequately powered to show non-inferiority should be thoroughly discussed.

In any case, a decision to grant a first-line or a second-line monotherapy indication will be taken on the case by case basis and will take into account the observed efficacy of the drug in the target population, delta HbA1c (or differences in HbA1c between active treatments and compared to placebo), as well as the safety profile in adolescents and adults.

Add-on therapy

As the disease progresses, adolescents may no longer be controlled adequately on monotherapy and a second active treatment may be needed. This can happen while the patient is still in the adolescent age range. If add-on studies are considered necessary, (a test drug is intended to be added to an established agent), the combination of both should be compared to the established agent given as monotherapy. Patients enrolled in such studies should be insufficiently controlled with the maximally tolerated doses of the established agent (see add-on studies in adults) should be enrolled in such studies.

4.5 Safety aspects

4.5.1 General considerations

As for any other medicinal product, the occurrence of blood, liver or skin disorders should be carefully monitored and documented in detail for glucose lowering agents. Regarding liver function, special attention should be paid to elevated activities of liver enzyme, which are observed more frequently in type 2 diabetes. Follow-up should be careful in order to differentiate drug-induced effects on liver function from the spontaneous fluctuations of liver enzyme activities observed in diabetes.

Special efforts should be made to assess potential adverse events that are characteristic of the class of products being investigated, depending on the mechanism(s) of action and on the pharmacodynamic properties.

Add-on studies alone do not allow for a definitive assessment of the safety of a new compound. Therefore, safety data for the test agent in the monotherapy setting are necessary in addition to add-on trials. Pharmacodynamic interactions almost always occur with glucose lowering agents, and other effects might occur (e.g. PK interactions, additive toxic effects). It may therefore be difficult to determine the relative contribution of these changes to the observed effect. It is also usually difficult to determine whether an adverse event could be specifically attributed to the product under evaluation. However, it is necessary to show that any additional safety concerns (incidence/seriousness/severity) do not outweigh the additional benefit of the combination.

In children, at least one year safety data are needed and specific attention should be paid to assess potential adverse effects on growth, bone density, neurobehavioural and sexual maturation. Possible influence on immune status, interference with humoral or T-cell linked immune processes should also be carefully investigated. If a specific mechanism of action predicts interference with development then two year data may be needed.

4.5.2 Hypoglycaemia

In type 2 diabetes, episodes of severe hypoglycaemia associated with severe CNS dysfunction are rare. However, hypoglycaemia is a deterrent to effective glycaemic control, and is of particular concern in the elderly and very elderly. There is no definite definition of the less severe episodes, which are usually diagnosed on symptoms and/or measures of capillary blood glucose (see section 7). A definition for these less severe episodes of hypoglycaemia should therefore be established by the applicant to include a set of symptoms and a given level of self-monitored blood glucose. As a high level of specificity is needed to make claims, the definition needs to be more rigorous than in clinical practice, e.g. only blood glucose levels less than 3 mmol/L would be considered. The likelihood of the

diagnosis will be based on the measure of capillary or plasma glucose level at the time of symptoms whenever possible, the description of the symptoms and their evolution following sugar intake, the time of occurrence from last food intake, and the lack of another more likely diagnosis. There should be confidence in the quality of the glucose measurements.

In children, hypoglycaemia is described as severe (with or without seizures), and non-severe (symptomatic and asymptomatic). Severe hypoglycaemia episodes are considered clinically relevant and must be assessed in all trials with children (see section 3.5).

A detailed analysis of hypoglycaemic episodes noted in clinical trials should be provided (i.e. analysis stratified for age: ≤ 65 years, > 65 years, >75 years, timing of the episodes in relation to drug exposure, diurnal distribution, and for each episode: time of onset, time after last drug administration, time after meal, severity, duration, outcome of hypoglycaemia, dose of treatment).

Short-term studies which measure blood glucose occurrences during the night can be considered as a surrogate for the assessment of nocturnal hypoglycaemia, provided that studies had appropriate controls.

Use of continuous glucose monitoring, providing more information on night profiles, may be considered especially in children and adolescents.

4.5.3 Long-term safety and cardiovascular safety

The target population for glucose lowering agents includes to a large degree patients with co-morbidities and concomitant medications. Different safety aspects should therefore be evaluated in a dataset representative of this population. In addition to an assessment of overall safety data in multiple organ systems, it is essential to, as far as possible, exclude that the new drug increases the risk of macrovascular complications, e.g. cardiovascular disease.

In the past, the assessment of cardiovascular safety in the context of the clinical development of glucose lowering agents has not been possible; the generally benign baseline CV risk profile of patients recruited in confirmatory studies presented for licensure and the limited treatment or diabetes duration have played a major role. For future developments, it is expected that the development programme provides sufficient data supporting the lack of a drug-induced excess cardiovascular risk both from a clinical and regulatory perspective.

4.5.3.1 Study Population

Every effort should be undertaken to include an adequate number of high risk patients that mimics as much as possible the target population with regards to comorbidities, e.g CV risk factors, and concomitant drugs (see further 4.5.3.2). This refers to, though not limited to, duration of diabetes, prevalence of known cardiovascular risk factors and an adequate representation of elderly patients. The database should include a sufficient number of subjects with long duration of the disease (at least a mean duration of diabetes > 5 years) and presence of micro- and/or macro vascular complications (e.g. renal dysfunction). A significant proportion of elderly patients (aged 65 to 74 as well as aged 75 and older) should be included as well as subjects with cardiovascular risk factors (e.g hypertension, hyperlipidemia), high annual risk for cardiovascular complications (e.g. 3%) and confirmed history of ischemic heart disease and congestive heart failure. Detailed clinical information allowing a proper characterisation of the baseline characteristics, including ischemic heart disease and congestive heart failure, for patients enrolled in controlled studies must be collected and summarised.

4.5.3.2 Type of studies

The complete development program will be taken into account in order to detect potential signals that may suggest an increased risk for CV events. The following general elements should be considered:

- Non-clinical data

Non-clinical data in relevant animal models evaluating the potential effect of the test drug on different safety aspects, and especially CV risk, should be conducted and provided as an instrumental element of the safety evaluation. Animal studies should focus on athero-thrombotic findings, fluid retention, blood pressure, renal function, electrolytes homeostasis, cardiac functionality, repolarisation and conduction abnormalities (pro-arrhythmic effects), etc.

- Clinical data

There are two important aspects to consider in terms of detecting signals of adverse events; the size of the database and the time needed to detect the signal.
The size of database is expected to be adequate to detect signals for serious and uncommon events, including CV events. Long-term controlled clinical study, with at least 18 – 24 months follow up (depending on the characteristic of a drug and baseline risk of the studied population) would be expected as a part of the clinical development program of new oral glucose lowering agents. It is recommended that the follow-up period be long enough to collect slowly occurring events.

Patients with high risk for cardiovascular events (3% annual cardiovascular risk), representing qualitatively and quantitatively the actual prevalence of the whole cardiovascular risk spectrum in the diabetic population (according to validated cardiovascular risk scoring systems), are strongly recommended to be included either in the phase II and phase III studies or in a specific study in a high risk population of sufficient size to allow a sufficient CV safety assessment. In addition, recognising that conventional CV risk scoring systems may underestimate risk in diabetics, care should be taken to use systems that are applicable to this specific population.[1][2][3]

Particular attention should be given to assure that enough data of sufficient duration with the **final therapeutic dose(s)** is provided. The potentially deleterious CV effect of the test drug should not be biased downward in the statistical analysis, by including the data of an inactive or insufficiently active dose. Therefore, should the data not support the overall efficacy of the lower dose, it should not be used to demonstrate the CV safety of the upper/final (therapeutic) dose.

An overall plan for the detection and evaluation of potential adverse events, including justification of the size and duration of the studies with respect to the possibility of detecting safety signals, should be prospectively designed early during the clinical development, optimally before starting phase II studies. This program should take into consideration key elements of the primary and secondary pharmacology as well as key toxicological findings from non-clinical studies.

The safety evaluation should include a prospective definition of adverse events, particularly cardiovascular safety outcomes of interest that is common for all phase II-III program, facilitating pooled analysis strategies. Furthermore, applicants should foresee a consistent central adjudication system for all CV and other adverse events of interest during the entire clinical development. Detailed statistical analysis plan for the pooled CV safety data should be prospectively designed

4.5.3.3 Cardiovascular safety outcomes

Concerning CV events, the emphasis will be on major cardiovascular events (MACE) (CV death, non fatal myocardial infarction and stroke) but other events such as myocardial ischaemia, hospitalisation for acute coronary syndrome, revascularisation and/or worsening of heart failure will also be evaluated.

Additional parameters such as increase in body weight, oedema/ fluid retention, clinically relevant changes in cardiac function (echography, change in BNP/NT-pro BNP), occurrence of hypertension and arrhythmia should be systematically collected.

Use of relevant terms for coding AEs should be properly defined and homogenised across clinical development, allowing an efficient analysis of safety.

4.5.3.4 Evaluation of the results

A detailed statistical analysis plan for assessing safety signals, including uncommon events, in both general and high risk populations, including CV safety signals, should be prospectively designed. This evaluation is expected to include a meta-analysis including all phase II and phase III studies and / or a specific study in a high risk population (see 4.5.3.2) of sufficient size to detect less common adverse events. Due consideration should be given to the range of analyses presented as in the field of signal

[1] Ruth L Coleman, Richard J Stevens, Ravi Retnakaran, and Rury R Holman.
Diabetes Care (2007); **30**: 1292-1293.
[2] Score project. European Heart Journal 2003 24(11):987-1003; doi:10.1016/S0195-668X(03)00114-3
[3] Stevens R, Kothari V, Adler AI, Stratten IM, Holman RR.
Clinical Science (2001); **101**: 671-679

detection no single approach to the analysis of data is sufficient to guarantee that relevant signals can be captured.

At the time of the MAA, the overall results of this safety program should be submitted and discussed in terms of internal and external validity and clinical justification of the safety outcome. Acceptability of the data presented will be decided based on its overall quality, the point and interval estimates obtained for the calculation of specific risks, including cardiovascular risk compared to controls, and the reliability of these estimations. A summary of what is known about CV risk should be proposed for the SPC.

Indications of increased risk of certain adverse events or unacceptable lack of precision are an important concern and may trigger the request for additional specific CV outcome trials to exclude an unacceptable increase in CV risk associated with the new agent before granting of MA.

Showing cardiovascular benefit

See Section 6.2

5. Developing and licensing insulin preparations for the treatment of type 1 and type 2 diabetes mellitus

5.1 Specific considerations

Insulin preparations differ mainly by their kinetic/pharmacodynamic profiles. They are usually classified as short-, rapid-, intermediate-, and long-acting preparations, and are used alone or as free mixtures or premixed preparations of fast/rapid acting insulin and long-acting insulin in various proportions. The same classification is used for insulin analogues, which differ from human insulin preparations by the substitution of amino-acids or other chemical changes, e.g. adding a fatty acid chain, within the insulin molecule.

For insulin preparations with novel pharmacokinetic and pharmacodynamic properties (e.g. insulin analogues), long term efficacy and safety data are essential. For premixed combination of insulins already individually licensed, pharmacokinetic/ pharmacodynamic data form the basis of the dossier; clinical data are supportive, and essentially needed for safety assessment.

5.2 Assessment of efficacy

The measures of glycaemic control detailed in the section pertaining to other glucose lowering agents also apply to insulin preparations (see 4.2.1).

However, the rapid changes in plasma glucose levels that occur in type 1 diabetes call for some specific considerations:

- Evolution of fasting plasma glucose is not a sufficient secondary measure of outcome in type 1 diabetes, whereas it might be used in type 2 diabetes.
- In addition to the evaluation of the overall blood glucose control by HbA_{1C}, compliance of patients to providing capillary blood samples for at least 7-point capillary-blood glucose profiles (before and after each meal and at bedtime) at regular intervals is necessary in type 1 diabetic patients. In order to assess nocturnal hypoglycaemia, the use of continuous glucose monitoring devices may be considered in children and adolescents.
- Reduction in the amplitude between hyperglycaemic peaks and low blood glucose values in type 1 diabetes is probably desirable, but will not be accepted as a claim of efficacy unless accompanied by improvement in other measures of blood glucose control such as HbA_{1C}.

Weight gain is frequent in diabetic patients trying to implement intensive glucose control. The evolution of body weight, in appropriately controlled studies, will also be taken into account in the global evaluation of the efficacy, particularly in type 2 diabetic patients.

5.3 Strategy and steps in the development. Methodology of the clinical studies

5.3.1 Pharmacodynamic data

Due to the wide intra- and inter-subject variability in the response to insulin in type 1 diabetes, pharmacodynamic data are of primary importance to demonstrate therapeutic equivalence or differences between insulin preparations, including their use in mixtures. Data on the time-action profiles using the euglycaemic clamp technique should be available, providing data based on the glucose infusion rate and the exogenous insulin serum concentrations.

5.3.2 Pharmacokinetics

Although initial PK studies can be done in healthy volunteers, it is required that PK studies also be performed in all types of patients for whom treatment is intended.

For the evaluation of a new insulin or insulin analogue, the comparator drug should be insulin or an analogue with a pharmacological profile similar to the product under consideration. Comprehensive data should be provided on the insulin bioavailability based on peak insulin concentration, time to peak concentration and area under the insulin-time curves. Apart from the kinetic studies in healthy volunteers, studies should be performed in type 1 and in type 2 diabetic patients, adults and children (stratified by age), and in various situations associated with PK variability: insulin dose, site of injection and thickness in fat layer contribute to the rather considerable variation in the PK parameters seen with insulin even in the same individual over time, and this should be addressed in clinical trials. Age and conditions such as impaired renal or liver function may also contribute to PK variability, particularly with long-acting preparations.

It is recommended to have steady-state PK data (multiple-dose concentration-time profiles), particularly with long-acting insulin preparations.

It is necessary to show that pharmacokinetic characteristics remain the same if the insulin is used in mixtures. Furthermore, in studying mixtures, fresh mixtures should be tested versus mixtures made several hours prior to administration to mimic actual use.

Pharmacokinetic studies are particularly important for short/rapid- and long-acting insulin analogues whose very reason for being is their novel pharmacokinetic properties. Differences in parameters of PK/PD activity should however not be used to claim superiority unless these parameters have been validated to be associated with better HbA1c and differences in occurrence of long-term vascular complications.

5.3.3 Methodology of clinical studies

5.3.3.1 Study population and selection of patients

General considerations pertaining to other glucose lowering agents (see 4.3.3) also apply to insulin preparations. Type 1 and type 2 diabetic patients should be studied. Groups should be balanced with respect to types of insulin regimens. Stratified allocation on pre-study treatment may also be desirable (e.g. previous insulin preparation, type of insulin regimen). Specific populations should also be considered (see 4.4).

5.3.3.2 Therapeutic exploratory studies

Given the wide intra- and inter-subject variability, crossover designs may be useful to compare glucose excursions and insulin profiles with different insulin preparations, as well as incidence of hypoglycaemia. Study duration should be of at least 4 weeks with each insulin preparation with crossover designs, and usually up to 3 months in parallel design. The main end-point is usually 24-h blood glucose profiles (delta AUC, Cmax, Cmin) in short-term studies.

For pre-mixed insulins, the demonstration that the combination product is different (onset / duration of glucose-lowering activity) from each of its components taken separately is required. The demonstration that it is different from other combinations already available (e.g. 90/10 versus 70/30) in ways which are clinically relevant is also desirable.

5.3.3.3 Therapeutic confirmatory studies

General considerations regarding the design of these studies, envisaged in section 4.3.3, also apply here. However the use of a placebo is not ethically justifiable in monotherapy. Therefore the active comparator will be an insulin preparation, or an insulin regimen, with a pharmacological profile similar to that of the tested agent.

The use of placebo can be justifiable in the add-on situation, e.g. when studying the effect of the combination of a short/rapid-acting insulin given at meal time with longer-acting insulins, or in combination with other glucose lowering agents in type 2 diabetes. Studies should be carried out in patients already treated, respectively, with long-acting insulin or other glucose lowering agents. Recommendations in 4.2.2 and 4.3.3.3 apply here.

In type 1 diabetic patients, the run-in period is important to assess the variability in blood glucose profiles and the baseline number of hypoglycaemic episodes. It should be of sufficient duration to properly assess the baseline efficacy and safety parameters.

Therapeutic confirmatory studies should assess the safety and efficacy of the insulin preparation in type 1 and type 2 diabetes, usually of up to 6 months duration. For insulin analogues, a duration of the comparative period of 6 months may be sufficient, and an adequate amount of follow-up data covering a period of at least 12 months should also be available.

For premixed combination of insulin preparations already individually licensed, (see section 3.1), controlled trials of shorter duration (i.e. at least 3 months) may be appropriate, essentially for safety reasons.

The efficacy and safety of transferring patients from one insulin preparation to another should also be addressed, for example by subgroup analysis based on pre-study therapy.

5.4 Studies in special populations

5.4.1 Elderly

A reasonable number of elderly patients (□65 years and >75years) should be included in the therapeutic confirmatory studies, and attention should be particularly paid to tendency to develop hypoglycaemia with long acting insulin preparations in the elderly and very elderly.

5.4.2 Children

Clinical studies in type 1 diabetic children are usually required, unless otherwise justified, as insulin preparations are to be used in this population. Type 1 diabetes is a childhood disease in many cases; in addition, there are numerous other factors varying with age like PK, PD (glycaemic variability is higher than in adults and different in the various age groups, "physiological" insulin resistance in puberty, response to insulin is different), immunogenicity (anti-insulin response), susceptibility to hypoglycaemic episodes and neurobehavioural consequences of hyperglycaemia.

Paediatric patients should be stratified by age group: < 1 year, 1 – 6y, below 6y, 6-12y, 12-18y.

Efficacy assessment: HbA1c is a recommended primary endpoint (see 4.2.1.1). Reduction of glycaemic variability and hypoglycaemic episodes are important secondary endpoints (see 4.2.2).

5.5 Safety aspects

5.5.1 Hypoglycaemia

Severe hypoglycaemia is the biggest obstacle that diabetic patients face in trying to implement a programme of intensive glucose control. Reduction of documented episodes of severe hypoglycaemia, in appropriately controlled studies, could of itself form the basis of approval of a new treatment, provided that this is not achieved with simply allowing HbA_{1C} to rise. To be considered severe, a hypoglycaemic episode needs to be associated with severe CNS dysfunction without any other apparent cause, in which the patient was unable to treat himself/herself, and where there is reversal of CNS dysfunction by glucagon or iv glucose. This mostly pertains to type 1 diabetes. For type 2 diabetes, the recommendations detailed in 4.5.2 should be followed. In particular, a detailed analysis of hypoglycaemic episodes noted in clinical trials should be provided.

5.5.2 Local reactions / toxicity

Pain at the injection site and any type of local reaction should be carefully monitored, particularly on long term treatment.

5.5.3 Product immunogenicity / affinity

The antibody status of patients included in long-term trials with new insulin preparations should be monitored, and compared to that observed with existing products. In addition, detailed information on auto-antibody status and endogenous insulin production should be assessed and reported for all patients entering into clinical trials.

For analogues of insulin, comparative data to human insulin should be available on the insulin receptor and IGF1 receptor binding (affinity and dissociation rate), receptor autophosphorylation, phosphorylation of signalling elements, and promotion of mitogenesis.

In case of higher affinity to IGF-1 receptor of insulin analogues compared to human insulin, it is recommended that fundus photographs are taken during long term trials to detect possible retinal adverse events.

In children, in addition to severe hypoglycaemia episodes, immunogenicity, auxological development, sexual maturation and neuropsychological development for at least 1 year (as in adults) should be assessed. If there are specific concerns (e.g. long acting insulin derivative, immunogenicity, tumorigenicity) 2 year follow up may be indicated.

6. Other potential claims

6.1 Delay in onset of type 2 diabetes mellitus

Subjects with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) are at increased risk for developing type 2 diabetes. In addition, there is an increased risk for vascular complications in subjects with IGT and/or IFG.

However, there are no conclusive studies to date that show that lowering of fasting or postprandial glucose in subjects with IGT and/or IFG reduces cardiovascular risk.

Lifestyle measures are clearly recommended as first line intervention. However, additional drug therapy may be beneficial in individuals with particularly high risk, for example, those with worsening glycaemia, cardiovascular disease, or non-alcoholic fatty liver disease when lifestyle interventions are unsuccessful.

Medicinal products aiming at delaying type 2 diabetes may directly or indirectly affect glucose metabolism (e.g. glucose lowering vs. weight loss drugs). So far, no medications have been approved for the prevention of or delay in onset of type 2 diabetes.

Confirmatory studies intended to demonstrate benefit of pharmacotherapy in the delay in onset of type 2 diabetes should include the following considerations.

The study population should consist of subjects who are considered at high risk for developing diabetes and who do not respond sufficiently to intensive life style interventions. Risk definition and criteria need to be pre-defined and tools used for diabetes risk assessment validated. The type and enforcement of appropriate life style interventions should be well documented and (non)response pre-defined. Treatment groups should be balanced for risk factors (such as control of blood pressure, control of blood cholesterol and stopping smoking) known or suspected to convey a different magnitude of risk for progression to type 2 diabetes and for confounding concomitant therapy.

Trials should be randomized, double-blind, placebo-controlled. In addition, appropriate life style interventions (i.e. diet and exercise) should be reinforced in all subjects throughout the study. The treatment phase may vary depending on the mechanism of action of the drug but should always be followed by a wash-out phase which is sufficiently long to exclude a masking effect on diabetes. Overall, the studies will likely be of substantial duration (years) and size.

Cumulative diabetes incidence according to established diagnostic criteria is considered an appropriate primary endpoint. However, the effect needs to be statistically significant as well as clinically relevant. Delaying the onset of diabetes may be important but the value of this endpoint as surrogate for clinical outcome needs further validation. Therefore, demonstration of additional benefit with regard to microvascular and/or macrovascular complications will likely be needed. Assessment of markers/tests of beta-cell function/decline may be included to further support the preventive nature of any observed effect.

6.2 Slowing the progression of diabetic complications

A glucose lowering agent or an agent acting independently of a glucose-lowering effect may seek to slow the progression of diabetic complications.

Overall a clearly documented and clinically significant change in the natural history of a diabetic complication would be considered as a primary measure of efficacy. Unfortunately, valid intermediate markers of most of the long term complications of diabetes which could be used in clinical trials are currently lacking. Before undertaking such studies, sponsors are invited to seek scientific advice from the CHMP. In designing such trials, the means for patients to achieve adequate glycaemic and blood pressure control will have to be provided.

Hard endpoints are required for claims relating to macrovascular disease (*i.e.* morbidity / mortality trials).

In order to show cardiovascular benefit, applicants should assess both major cardiovascular events (MACE) and overall and cardiovascular mortality in long-term trials (e.g. at least 3 years) (cf. Guideline on the Evaluation of Medicinal Products for Cardiovascular Disease Prevention). The primary analysis of a composite endpoint may be based on a 'time-to' first event (survival) analysis. To provide supportive information, analyses of each separate component of the composite endpoint should be presented. For overall mortality and cardiovascular mortality both confidence intervals and point estimate are relevant for assessment. Other secondary endpoints may include relevant cardiovascular morbidity measures.

For retinopathy, endpoints based on the progression of diabetic retinopathy documented on well validated grading scales, are considered clinically meaningful. Dilated ETDRS (Early Treatment Diabetic Retinopathy Study) standard seven-standard field stereoscopic 30° fundus photography obtained by a skilled photographer, and compared to standard photographs by a skilled reader, are currently the only well validated tools to document the effect of treatment on non proliferative diabetic retinopathy. Progression may be defined as a change from baseline of 2 steps in patients without pre-existing retinopathy (3 steps in patients with pre-existing retinopathy) on the ETDRS scale. The ETDRS severity scale is unsuitable to evaluate diabetic macular oedema. Progression of macular oedema to the centre of the fovea, i.e. to imminently sight-threatening macular oedema is a clinically meaningful outcome; the definition of progression should be justified by the applicant. Recent technologies may provide a means to standardise the photographs and document other aspects (e.g. leakage) of diabetic retinopathy. The images they provide still have to be demonstrated to be acceptable surrogate endpoints.

For nephropathy, hard endpoints are time to doubling of baseline serum creatinine, or sustained increase in serum creatinine, e.g. to greater than 250 µmol/L, and the evolution to end-stage renal failure defined as need for maintenance dialysis or transplantation. Regarding intermediate endpoints, delay of progression to macroalbuminuria is a relevant measure, particularly if supported by long-term

data (of at least 24 months) indicating a favourable evolution of glomerular filtration rate. Delaying the progression to diabetic nephropathy in a clinically relevant manner over and above that explained by effects on blood pressure and/or glycaemic control would be sufficient for a specific claim.

Diabetic neuropathy is not a single entity but a number of different syndromes, and no gold standard exists for its assessment. There are markers of progression, but the extent of specific improvement to provide evidence of clinically relevant benefit has not been fully evaluated. The evaluation of efficacy should be based on clinical signs and symptoms. Efficacy variables based upon electrodiagnostic tests (assessing nerve conduction velocity or amplitudes), quantitative sensory tests (for vibration, tactile, thermal warming and cooling thresholds), and quantitative autonomic function tests (assessing heart rate variation with deep breathing, valsalva manoeuvre and postural testing) may be supportive. Composite measures that combine information from the above-mentioned evaluations may be used within a single score. The reliability and validity of the methods used must be justified.

7. Definitions

7.1 Diabetes

Diabetes is currently defined (WHO/ADA) as symptoms of diabetes plus:

- random plasma glucose concentration ☐ 11.1 mmol/L *[200mg/dl*], or
- fasting plasma glucose ☐ 7.0 mmol/L [*126mg/dl*], or
- 2-h plasma glucose concentration after 75 g anhydrous glucose in an oral glucose tolerance test ☐ 11.1 mmol/L [*200mg/dl*].

In the absence of symptoms, diabetes should not be diagnosed on a single glucose measurement but needs confirmation.

Impaired glucose[, *200mg/dl*] tolerance (IGT): plasma glucose concentration ☐ 7.8 mmol/l [*140mg/dl*] but less than 11.1 mmol/l at 2-h in the oral glucose tolerance test

Impaired fasting glucose (IFG): fasting plasma glucose ☐ 5.6 mmol/l [*100mg/dl*] but less than 7.0 mmol/l [*126mg/dl*]

7.2 Hypoglycaemia

Hypoglycaemia could be described as:

i) Major hypoglycaemic episodes, defined as symptomatic episodes requiring external assistance due to severe impairment in consciousness or behaviour, with blood glucose level below 3 mmol/L and prompt recovery after glucose or glucagon administration,

(ii) Minor episodes defined as either a symptomatic episode with blood glucose level below 3 mmol/L [*54mg/dl*] and no need for external assistance, or an asymptomatic blood glucose measurement below 3 mmol/L, and

(iii) Episodes suggestive of hypoglycaemia, where blood glucose measurement were not available.

Severe hypoglycaemic episode:

Needs to be associated with severe CNS dysfunction without any other apparent cause, in which the patient was unable to treat himself/herself, and where there is reversal of CNS dysfunction by glucagon or iv glucose. There is no definite definition of the less severe episodes, which are usually diagnosed on symptoms and/or measures of capillary blood glucose.

In children, hypoglycaemia is described as:

i) severe (with or without seizures):

- in need for help, irrespective of age,
- unconsciousness,
- unconsciousness and seizure,

ii) non-severe (symptomatic and asymptomatic).