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NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF DIABETES MELLITUS

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NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF DIABETES MELLITUS

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 Expert report. They should be read in conjunction with Directive 75/318, 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)

1. INTRODUCTION

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**.,** Global treatment of diabetes mellitus should not only aim at lowering blood glucose to near normal levels but also at correcting metabolic abnormalities and cardiovascular risk factors.

Diabetes is currently defined (WHO/ADA) as symptoms of diabetes plus random plasma glucose concentration ≥ 11.1 mmol/L, or fasting plasma glucose ≥ 7.0 mmol/L, or 2-h plasma glucose concentration after 75 g anhydrous glucose in an oral glucose tolerance test ≥ 11.1 mmol/L [Alberti KG, Zimmet PZ. Diabet Med 1998;15:539-553]. In the absence of symptoms, diabetes should not be diagnosed on a single glucose measurement but needs confirmation.

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 with an only partly understood pathogenesis. It 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. Eventually, even in spite of current combination therapy and/or insulin treatment, an important group of the patients is not well controlled. Although several international trials have shown that any decrease in the level of blood glucose monitored by the glycated fraction of haemoglobin (HbA_{1C}) reduces the risk of microangiopathy, multiple cardiovascular risk factor intervention is the key issue in type 2 diabetes. Overweight, hypertension

and hyperlipidaemia are often associated with diabetes mellitus, and are important factors to consider in a global therapeutic approach of the disease.

Prevention of diabetes, fixed combination of oral antidiabetic agents, and new insulin delivery systems, will not be part of this guideline because of limited experience in this field.

2 DEVELOPING AND LICENSING ORAL ANTIDIABETIC AGENTS FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

2.1 Specific considerations on study designs

2.1.1 Washout period

Monotherapy studies are optimally conducted in patients who have previously failed on diet and exercise. In case patients already treated with oral antidiabetic 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 oral antidiabetic 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 be underestimated, i.e. 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 considering the size of the anti-hyperglycaemic effect in comparison to starting values, particularly when HbA_{1C} is the primary outcome measure.

For therapeutic confirmatory studies using HbA_{1C} as an endpoint (see section 2.3.3.3), a washout period is usually not necessary for previously treated patients, as the final HbA_{1C} level will not be influenced by the former therapy. However, as the baseline HbA_{1C} level will be influenced by the previous treatment in patients directly switched from this treatment, the relative fractions of drug-naive patients and previously treated patients should be carefully considered to assess the 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 full dose of an established treatment.

2.1.2 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. less than 10%) may be enrolled in 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 support for efficacy assessment.

2.1.3 Dosage

The dossier should contain well-designed dose-finding and dose-ranging studies in order to justify the dosage used in confirmatory clinical trials and claimed in the SPC. The hypotheses on doses made at the early stages of development should be carefully tested in therapeutic confirmatory trials.

In monotherapy as well as in add-on situations, it is current clinical practice, when several doses are available, to titrate a new oral antidiabetic agent until an optimal effect is seen or until maximal tolerated dose is reached or up to the maximal doses allowed. 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.

2.1.4 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 oral antidiabetic agent.

2.1.5 Specific populations

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 unrestricted indication. Depending on the data, specific efficacy and safety trials in this population may be needed.

As type 2 diabetes might tend to become prevalent in obese adolescents, it is recommended that trials in adolescents diagnosed with type 2 diabetes be carried out.

2.1.6 Associated cardiovascular risk factors

Diabetes, especially type 2, is a multifaceted disease. It is highly desirable for an oral antidiabetic agent to show neutral or beneficial effects on associated cardiovascular risk factors (e.g. central adiposity, blood pressure, lipid level).

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 most 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 (e;g a demonstration of non-inferiority of the tested drug in the lipid profile compared to the combination of an antidiabetic and a hypolipidaemic agents).

Furthermore, as the goal of treatment is to reduce the risk of complications, not just to lower HbA_{1C}, a new agent could not be approved based on a reduction in HbA_{1C} if there is evidence that it increased the risk of diabetic complications directly.

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 antiobesity agent has a pharmacologic rationale, is sustained, and clinically relevant, over and above that explained by effects on weight. Moreover it should be of the same order of magnitude as oral antidiabetic agents currently marketed.

2.1.7 Outcome studies

Long term complications include macrovascular (coronary, cerebrovascular, and peripheral vascular diseases) and microvascular complications (retinopathy, nephropathy, and partly neuropathy). Positive effect on 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.

2.2. Assessment of efficacy

The primary purposes of the therapeutic confirmatory studies involving the tested agent are usually to demonstrate a favourable effect on blood glucose control.

Efficacy parameters pertaining to the complications of diabetes are detailed in section 4.

2.2.1 Measures of glycaemic control

2.2.1.1 Glycohaemoglobin (Haemoglobin A_{1C})

Glycohaemoglobin (HbA_{1C}) is the most widely accepted measure of overall, long-term blood glucose control in type 1 and type 2 diabetes, and therefore an appropriate primary endpoint. Moreover, reduction of HbA_{1C} is directly related to a reduced risk of development of vascular complications.

The primary analysis of HbA_{1C} should evaluate the difference in evolution from baseline HbA_{1C} between the test compound and the active comparator/placebo. Baseline HbA_{1C} 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 justified by the applicant.

A well-validated assay for HbA_{1C} should be used, i.e. reference methods recommended by scientific bodies involved in the international standardisation of HbA_{1C} measurement. Centralised analyses are strongly recommended, at least for therapeutic confirmatory studies.

2.2.1.2 Plasma glucose

Changes 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 may be used as primary endpoints in short term studies (under 8 to 12 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.

2.2.2 Other measures of metabolic control/status

A reduction in insulinaemia in patients treated with oral antidiabetic agents, or a reduction in insulin dose itself in insulin-treated type 2 diabetic patients, is usually not considered a measure of efficacy unless accompanied by a favourable evolution of HbA_{1C}. However this could be taken as evidence of improvement in insulin resistance.

In insulin-treated type 2 diabetic patients, the elimination of the need for insulin entirely, or a reduction in insulin dose accompanied by a clinically significant improvement in the evolution of body weight could be considered a measure of efficacy 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 (see 2.1.6). The effects of the tested product on LDL and HDL cholesterol should be specifically documented in type 2 diabetes, as available evidence supports benefit of reduction of LDL and increase in HDL.

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 may not be 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 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.

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

2.3.1 Pharmacodynamic data

Although there are no specific requirements for pharmacodynamic testing of oral antidiabetic 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.

2.3.2 Pharmacokinetics

The pharmacokinetic information required is stated in detail in the appropriate guidelines on 'Pharmacokinetic Studies in Man'. Although initial PK studies can be done in healthy volunteers, it is important that PK studies also be performed in the types of patients for whom treatment is intended. Indeed it may not be assumed that the PK properties observed in healthy subjects will be the same in diabetics. Factors such as delayed gastric emptying or altered renal function can be expected to complicate drug absorption and disposition in a significant number of type 2 diabetic patients.

2.3.3 Methodology of clinical studies

2.3.3.1 Study population and selection of patients

The patients enrolled into clinical trials must be representative of the target population in terms of demography, ethnic differences, co-morbidity (especially cardiovascular disease) and severity of diabetes. The usual clinical distinctions between type 1 and type 2 diabetes based on history of ketoacidosis, age of onset, etc. will be adequate in most cases.

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

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 severity of the disease (e.g. HbA_{1C} ≤8% / >8%) and on pre-study treatment (e.g. diet alone, monotherapy, combination therapy). Specific populations should also be considered (see 2.1.5 and 2.1.6).

2.3.3.2 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 2.1.1). In dose-ranging studies, at least 3 dosages should be studied with a total therapy phase of at least 8 weeks and usually up to 3 months.

The endpoints in dose ranging studies are usually changes in plasma glucose (see 2.2.1.2). However HbA_{1C} should be the primary evaluation criterion in the dose-ranging studies of more than 8 to 12 weeks duration (see 2.2.1.1).

2.3.3.3 Therapeutic confirmatory studies

Parallel-group, randomised, double-blind, placebo and comparator-controlled studies are necessary. The therapeutic confirmatory trials should normally aim at demonstrating (i) 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 HbA_{1C} as the primary endpoint, or a three arm trial with a short placebo period at the beginning of an active control trial (see ICH E10), and (ii) the non-inferiority of the new agent to an active comparator, 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. Further advice is given in the ICH E9 ('Statistical Principles for Clinical Trials') and ICH E10 ('Choice of Control Group in Clinical Trials') guidelines.

Regarding the non-inferiority design of the pivotal studies, it has recently been confirmed that even an apparently small reduction in HbA_{1C} is considered clinically relevant in terms of risk reduction of diabetic complications. It is therefore 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 be equated to the loss of efficacy in some sense.

Monotherapy studies comparing the test drug to normal standards of practice are always needed to obtain a marketing authorisation for monotherapy, and should always be considered for a marketing authorisation in 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 oral antidiabetic agents with an original mechanism of action, a 12 month controlled overall duration may be required. Concomitant background treatment should be kept as similar as possible during the study.

Run-in (baseline) period

As normally no washout period is necessary in confirmatory studies (see 2.1.1), a run-in period of appropriate duration (usually 2 weeks) is generally sufficient during which the investigator must carry out baseline evaluation of the patient, including full clinical and laboratory assessment.

Titration period

The demonstrated optimal dose range should be used for both products. In the usual case where several doses are available, the dose should be progressively up-titrated as described in 2.1.3, by evaluating the drug effect on fasting and/or post-prandial plasma glucose, and if necessary blood glucose self-monitoring.

Maintenance period

A 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 therapy with established treatment. It is recognised that no one single agent may result in normal HbA_{1C} in a large number of patients: when blood glucose control is not adequate with monotherapy, the usual standard of care is to resort to combination therapy.

A study in such patients comparing the established agent as monotherapy against the combination of the new agent and the established agent is mandatory. Add-on studies are carried out by adding the test drug to non-responders to the first drug. Dose titration will usually be indicated (see 2.1.3). It is desirable (i) to select patients not meeting therapeutic targets (i.e. non responders) with this previous medication 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 observed and that HbA_{1C} is stabilised at baseline, (iii) during the study, to avoid dose adaptation of the concomitant antidiabetic agent(s), unless they are necessary due to interactions. 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 products should be kept stable.

Usually a 16 week duration of the maintenance period is sufficient to demonstrate efficacy, which seems acceptable from an ethical viewpoint, since , in this situation, the placebo group is not untreated.

It is necessary to demonstrate a statistically significant and clinically relevant additional HbA_{1C} reduction (or improvement in blood glucose control). Improvement in responder rates with the combination in these patients is also desirable.

Depending on the results of placebo-controlled trials, active-controlled data are advisable against a commonly used combination.

Regarding combination with insulin, efficacy on glycaemic control should be documented vs. placebo i.e. insulin alone. Studies should be carried out in patients already treated with insulin 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 insulin dose will be maintained unchanged as far as possible during the double-blind period (unless

necessary for safety reasons), and the efficacy will primarily be evaluated on the evolution of HbA_{1C} (see 2.2.2).

A comparative evaluation versus the combination of insulin plus an oral antidiabetic agent currently licensed in this indication may be required.

Whatever the situation (monotherapy, add-on therapy or combination with insulin), continuation or extension of the studies to at least 12 months is desirable to assess the maintenance of efficacy and safety in the long term.

2.4 Safety aspects

2.4.1 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 oral antidiabetic 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 a definitive assessment of the safety of a new compound. Pharmacodynamic interactions almost always occur with oral antidiabetic 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) outcome of adverse events/adverse drug reactions) do not outweigh the additional benefit of the combination.

2.4.2 Hypoglycaemia

In type 2 diabetes, episodes of 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. 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.

There are several definitions of 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 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.

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.

2.4.3 Cardiovascular function

Cardiovascular disease is the main cause of morbidity and mortality in type 2 diabetes. Any new medicinal product in this area must have well documented data regarding effects on blood pressure, hyperlipidaemia, and clinical indicators of cardiac function (e.g. ECG, QT). If warranted by preclinical findings, controlled studies of cardiac function, e.g. with echocardiography may be necessary.

2.4.4 Long-term safety

The total clinical experience must generally include data on a large and representative group of patients (see ICH E1). Trials focusing on long-term clinical safety are expected for agents claiming a novel mode of pharmacological activity (see 2.3.3.3). Depending on the safety profile of the product (see 2.1.7) outcome studies may be required in pre- or post-marketing.

3 DEVELOPING AND LICENSING INSULIN PREPARATIONS FOR THE TREATMENT OF TYPE 1 AND TYPE 2 DIABETES MELLITUS MELLITUS

3.1 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 (see 3.3.3.3 and 3.4). For premixed combination of insulins already individually licensed, pharmacokinetic/ pharmacodynamic data form the basis of the dossier (see 3.3.2); clinical data are supportive, and essentially needed for safety assessment.

Clinical studies in type 1 diabetic children are usually required pre-licensing, unless otherwise justified, as tested insulin preparations are to be used in this population (see guideline ICH topic E11).

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.

3.2. Assessment of efficacy

The measures of glycaemic control detailed in the section pertaining to oral antidiabetic agents also apply to insulin preparations (see 2.2.1).

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.
- 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 an obstacle that diabetic patients face in trying to implement a programme of 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.

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

3.3.1 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.

3.3.2 Pharmacokinetics

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

For the evaluation of a new insulin or insulin analogue, the comparator drug should be an 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 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 and in children, 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 desirable to have steady-state PK data (multiple-dose concentration-time profiles), particularly with long-acting insulin preparations.

It is desirable 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.

Good 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 differences in occurrence of long-term vascular complications.

3.3.3 Methodology of clinical studies

3.3.3.1 Study population and selection of patients

General considerations pertaining to oral antidiabetic agents (see 2.3.3.1) 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 3.1).

3.3.3.2 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.

3.3.3.3 Therapeutic confirmatory studies

General considerations regarding the design of these studies, envisaged in section 2.3.3.3, 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 oral antidiabetic agents in type 2 diabetes. Studies should be carried out in patients already treated, respectively, with long-acting insulin or oral antidiabetic agents. Recommendations in 2.2.2 and 2.3.3.3 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, preferably in separate trials, 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.

3.4 Safety aspects

3.4.1 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 2.4.2 should be followed. In particular, a detailed analysis of hypoglycaemic episodes noted in clinical trials should be provided.

3.4.2 Local reactions / toxicity

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

3.4.3 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.

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

Further advice is given in the CPMP/SWP documents on the preclinical development of insulin analogues.

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.

4 EFFICACY ENDPOINTS PERTAINING TO THE COMPLICATIONS OF TYPE 1 AND TYPE 2 DIABETES MELLITUS

An antidiabetic 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 CPMP. In designing such trials, the means for patients to achieve adequate glycaemic and blood pressure control will have to be provided.

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

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 way 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 acceptable surrogate endpoints.

For nephropathy, hard endpoints are time for 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.