EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 October 2016

Submission of comments on "Concept paper on the need for revision of the guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus" (EMA/317855/2016)

Comments from:

Name of organisation or individual
Prescrire is a non-profit continuing education organisation that works to improve the quality of patient care. Prescrire publishes evidence-based information about treatments and treatment strategies, in total independence, as a basis for truly informed decision-making. Prescrire is funded exclusively by its subscribers. It receives no other financial support whatsoever and carries no advertising. It has no shareholders or sponsors. More info: english.prescrire.org; contact@prescrire.org

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The European Medicines Agency (EMA) has released a concept paper for public consultation on the revision of its guideline on the clinical evaluation required to apply for European marketing authorisation for antidiabetic drugs. In its response to this consultation, *Prescrire* reminds the EMA of the importance of evaluating the efficacy of antidiabetics using clinical endpoints useful to patients, and of evaluating their risks properly, in particular their cardiovascular risks, before authorisation rather than afterwards. *Prescrire* supports this initiative by the European Medicines Agency (EMA) to revise its guideline on antidiabetic drugs, adopted in 2012 by the European Commission's Committee for Medicinal Products for	

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	Human Use (CHMP) (1,2). *Prescrire* encourages the EMA to adopt more meaningful efficacy endpoints for the evaluation of antidiabetic drugs, and to raise the standard of evaluation required of marketing authorisation applicants, especially with regard to the adverse effects of certain classes of antidiabetic. *Prescrire* has several times warned of the risks associated with the coexistence of insulins of different concentrations, and demands that the EMA publish regular detailed pharmacovigilance reports on insulins and injectable antidiabetic products containing an insulin and a GLP-1 agonist in the same autoinjector. **Base efficacy evaluation on clinical endpoints that are useful to patients.** The primary goal of treatment for type 2 diabetes is to prevent or delay the sometimes fatal complications of the disease, such as: myocardial	

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	infarction, stroke, renal disease, neuropathy, and impaired visual acuity or even blindness (3). A reduction in blood glucose concentration is only useful if accompanied by a reduction in the clinical complications of diabetes or increased survival. If the efficacy of an antidiabetic drug is determined solely on the basis of a surrogate endpoint such as glycaemic control, by measuring glycated haemoglobin (HbA1c), there is no guarantee that the drug will be useful to patients (4). **Demand a reduction in cardiovascular risk before authorisation rather than ruling out an increased risk after authorisation.** Cardiovascular events are the main cause of death in patients with type 2 diabetes (3,5). The least one can expect from an antidiabetic is that it does not increase cardiovascular mortality. Yet two glucose-lowering drugs of the glitazone class have	

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	been shown to increase this risk (3,5). Since 2008, the US Food and Drug Administration (FDA) asks pharmaceutical companies to conduct trials to determine the cardiovascular risk of new glucose-lowering drugs. The guideline on antidiabetic drugs adopted by the CHMP in 2012 contained a sub-section on cardiovascular risk (2). In 2015, the CHMP adopted common recommendations on the evaluation of the cardiovascular risk associated with drugs for diabetes, obesity, hypertension and hypercholesterolaemia (6). These are the recommendations the EMA intends to incorporate into the proposed revised guideline on antidiabetic drugs (1). These recommendations include performing a meta-analysis of the frequency of cardiovascular events observed during the clinical trials conducted before authorisation, and conducting a dedicated cardiovascular outcome trial if the meta-	

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	analysis does not rule out an increased cardiovascular risk (6). Based on our experience of analysing numerous marketing authorisation applications evaluated by the EMA, *Prescrire* is concerned that these dedicated trials might be largely conducted after authorisation. Postponing the evaluation of cardiovascular risk until after the drug is marketed, when it is already being used by a large group of patients, means gambling with patients' health and trusting pharmaceutical companies to honour their post-authorisation commitments, which they rarely do (7,8,9). **Do not authorise drugs with an unfavourable harm-benefit balance.** One of the EMA's proposed revisions to the guideline on antidiabetic drugs is to add information on the adverse effects of gliflozins, in	

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	particular the risk of ketoacidosis (1). However, in the absence of any clear demonstration of the benefits of gliflozins in preventing the clinical complications of diabetes, their adverse effects are disproportionate and their harm-benefit balance is unfavourable (3,10,11). Instead of warning those concerned of the risk of atypical diabetic ketoacidosis, the EMA would better fulfil its role of protecting patients by accepting no more marketing authorisation applications for gliflozins. The same applies to dipeptidyl peptidase 4 inhibitors (gliptins) and glitazones, which again have no proven benefits, yet expose diabetic patients to disproportionate risks: an increased risk of bladder cancer with *pioglitazone*, and an increased risk of cardiovascular events with *rosiglitazone*, which led to its withdrawal from the European market in 2010 (3,12). The EMA should learn from these public health problems	

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	by imposing much stricter pre-authorisation requirements on new drug classes. It is essential that the revised guideline provides more information on the whole issue of the adverse effects of antidiabetic drugs than the 2012 guideline, which left far too many gaps, overlooking for example the risks of glitazones. And that the riskiest classes of antidiabetics are monitored more closely, that pharmaceutical companies provide full and robust data, and that the EMA publishes detailed public pharmacovigilance reports and applies restrictions on or revokes marketing authorisations as necessary (2,3). **Avoid high-concentration insulins and fixed-dose combinations of insulin + other glucose-lowering drugs.** Until 2012, all the insulins available in the European Union for subcutaneous self-injection were	

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	marketed at the same concentration of 100 units per millilitre, in order to limit the risk of confusion and protect patients. But in 2013, the CHMP approved the first *insulin* containing 200 units per millilitre, followed by a second one in 2014, then an *insulin* containing 300 units per millilitre in 2015. These new insulin concentrations add to an already overcrowded insulin market. Rather than benefiting diabetic patients, they create the risk of healthcare professionals or patients confusing the different concentrations and administering an overdose that could cause severe hypoglycaemia (13,14). Such cases have been reported in the US and the Netherlands for example (15-17). Their introduction on the market generally appears to be a corporate strategy to keep generics at bay. In 2016, the CHMP authorised an autoinjector containing	

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	a fixed-dose combination of *insulin degludec* + *liraglutide* (a GLP-1 analogue). Yet combining these two drugs in the same autoinjector precludes individual dose adjustment, and because the autoinjector is graduated only in units of insulin, patients and healthcare professionals could forget that the product also contains *liraglutide* (18). The same risks will probably apply to the *insulin glargine* + *lixisenatide* combination currently under development. The guidance documents published by the EMA suggest that it is aware of the dangers (19-21). Will it be able to prevent them? The revision of the guideline on antidiabetic drugs is a great opportunity for the EMA to put patients' interests first, by offering them the maximum possible protection from the adverse effects of antidiabetic drugs. A	

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	worthwhile challenge for an agency whose mission is to protect patients' health.	

References:

1- European Medicines Agency - Committee for Medicinal Products for Human Use "Concept paper on the need for revision of the guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus" London, 23 June 2016 (ref. EMA/317855/2016): 4 pages.

2- European Medicines Agency - Committee for Medicinal Products for Human Use "Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus" London, 14 May 2012 (ref. CPMP/EWP/1080/00 Rev.1): 28 pages.

3- Prescrire Rédaction "Traitement hypoglycémiant du diabète de type 2 (suite). Première partie. En dehors de la metformine, aucun hypoglycémiant n'a d'effet démontré sur les complications" + "Deuxième partie. Choisir un hypoglycémiant après la metformine: dans l'incertitude, et selon les effets indésirables" *Rev Prescrire* 2014; **34** (374): 911-923.

4- Prescrire Rédaction "Déterminer la balance bénéfices-risques d'une intervention: pour chaque patient" *Rev Prescrire* 2016; **36** (394): 596-601.

5- Prescrire Rédaction "Trompe-l'œil" *Rev Prescrire* 2015; **35** (379): 327.

6- European Medicines Agency - Committee for Medicinal Products for Human Use "Reflection paper on assessment of cardiovascular safety profile of medicinal products" London, 25 February 2016 (ref. EMA/CHMP/50549/2015): 7 pages.

7- Prescrire Rédaction "AMM "fractionnées": projet dangereux de l'EMA" *Rev Prescrire* 2016; **36** (390): 293-299.

8- Prescrire Rédaction "Autorisations de mise sur le marché des médicaments: un dossier clinique souvent indigent" *Rev Prescrire* 2015; **35** (384): 782.

9- HAI, ISDB, IRCCS, MIEF, Cochrane, WEMOD ""Adaptive licensing" or "adaptive pathways": Deregulation under the guise of earlier access" *Joint consultation response*; October 2015: 12 pages.

10- Prescrire Rédaction "4-1-10. Patients sous dapagliflozine ou canagliflozine" *Rev Prescrire* 2015; **35** (386 suppl. Interactions médicamenteuses).

11- Prescrire Rédaction "empagliflozine-Jardiance°. Diabète de type 2: pas d'emballement" *Rev Prescrire* 2016; **36** (389): 168-173.

12- Prescrire Rédaction "Pour mieux soigner, des médicaments à écarter: bilan 2016" *Rev Prescrire* 2016; **36** (388): 138-146.

13- Prescrire Rédaction "insuline lispro-Humalog Kwikpen° en stylo à concentration double (200 unités/ml): gare aux confusions" *Rev Prescrire* 2015; **35** (384): 743.

14- Prescrire Rédaction "insuline glargine à 300 U/ml- Toujeo°. Une stratégie anticopie source de confusions" *Rev Prescrire* 2016; **36** (390): 251.

15- ISMP "ISMP Medication safety alert" 16 June 2016; **21** (12): 6 pages.

16- Centrale Medicatie-incidenten Registratie "CMR Nieuwsbrief" N° 2, 2016: 3 pages.

17- Centrale Medicatie-incidenten Registratie "CMR Nieuwsbrief" May 2016: 3 pages.

18- Prescrire Rédaction "insuline dégludec + liraglutide-Xultophy° et diabète de type 2" *Rev Prescrire* 2016; **36** (398): 896

19- European Medicines Agency "Guidance on prevention of medication errors with diabetes medicines containing insulin and a non-insulin active substance" London, 27 November 2015 (ref. EMA/134144/2015): 2 pages.

20- European Medicines Agency "Guidance on prevention of medication errors with high-strength insulins" London, 27 November 2015 (ref. EMA/134145/2015): 3 pages.

21- European Medicines Agency - PRAC "Risk minimisation strategy for high strength and fixed combination insulin products - draft addendum to the good practice guide on risk minimisation and prevention of medication errors" London, 14 April 2015 (ref. EMA/686009/2014): 14 pages.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Comment: Proposed change (if any):	
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Please add more rows if needed.