Paris, 17 December 2012
Open letter

To Patricia Brunko,
Head of Unit, Medicinal Products – Authorisations
European Commission

Copy to Guido Rasi, Executive Director,
and to the members of the CHMP
European Medicines Agency (EMA)

Copy to Dominique Maraninchi, General Director
French national agency for medicines and health products safety (ANSM)

Copy to Susanne Keitel, Director
Council of Europe/European Directorate for the Quality of Medicines (EDQM)
Copy to the WHO Expert Committee on Biological Standardization
and to the Department of Medicines Policy and Standards (HTP/PSM) (Dr Hans V. Hogerzeil)

Is there a need for insulin at 200 units per ml?
Why use a new and poorly established analogue?

● In an open letter, *Prescrire* alerts the European Commission to the dangers of over-hasty authorisation of *insulin degludec* at twice the concentration of other available insulins, which is liable to cause medication errors with serious consequences for patients.
● If a tangible need for a more concentrated *insulin* could outweigh the risk of serious errors inherent in the coexistence of two concentrations, why is the European Union implementing this difficult change using a new substance, whose risks are relatively unknown, rather than a better established *insulin*?

Dear Mrs Brunko,

In October 2012, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) issued a recommendation to the European Commission in favour of the authorisation of the first *insulin* at a strength of 200 units per millilitre for self-injection by patients with type 1 or type 2 diabetes (**a**,**b**) (1–4). The recommendation concerned a new "next-generation" *insulin* analogue: *insulin degludec* (TRESIBA°). This analogue is also offered at the standard concentration of 100 U/ml. The CHMP has also recommended the authorisation of a fixed combination of *insulin degludec* 100 U/ml and *insulin aspart* (RYZODEG°).

In support of its recommendation to approve *insulin* at a concentration of 200 U/ml, the CHMP cited a growing need for higher-strength *insulin* to enable the administration of high doses in a single injection, particularly for very obese diabetic patients (1–3).

Prescrire* wishes to alert the European Commission to the dangers of over-hasty authorisation of double-strength *insulin degludec.

Packaging: an essential aspect of harm–benefit balance

The coexistence of two concentrations of *insulin* has long been denounced as a source of error (4). Cases of severe hypoglycaemia are foreseeable, from injecting *insulin degludec* 200 U/ml with a syringe intended for use with *insulin* 100 IU/ml.

The CHMP offered reassurance over the safety of TRESIBA°, by pointing out that *insulin degludec* will only be available in prefilled pens graduated in units of *insulin* and that the pack design of the two strengths has been clearly differentiated.

Prescrire has some questions however that the CHMP press release does not address:

1) If a tangible need to treat diabetic patients with more concentrated *insulin* could outweigh the risk of serious errors inherent in the coexistence of two concentrations, why is the European Union implementing this difficult change using a new drug rather than a better established and better standardised *insulin*?
2) Does the differentiation of the labelling apply only to the two concentrations of TRESIBA°? Has consideration also been given to the labelling of RYZODEG°, which contains *insulin degludec* at a concentration of 100 U/ml only? Has the labelling of the boxes and the pens, as well as the package leaflets of the three medicinal products been tested by a group of patients and carers representative of the population likely to use the products?
3) Is the pen suitable for visually impaired patients? Many patients who are visually impaired (diabetes being one of the causes) rely on the number of audible clicks when selecting their dose; but how will they manage to count the number of clicks required for doses of 100, 120, 140 or 160 units? Is the pen equipped with a device to confirm the dose selected by means of an audible message?
4) *Insulin degludec* is one of the insulins that is quantified in in-house units. How do they correlate with international units of *insulin*? Why is the concentration not in standard units? Why do the European and US drug regulatory agencies (EMA and FDA) accept a standard different from international units of insulin? Have the EMA and FDA taken account of the opinion of the WHO (its expert committee on the standardisation of biological medicinal products (ECBS) and its department for the standardisation of medicines (HTP/PSM/QSM)) and the European Pharmacopoeia (EDQM), which is responsible for the quality of medicines in Europe? What are the consequences of this difference?
5) The FDA noticed a higher incidence of medication errors with *insulin degludec* than with the comparator in trials, to which the pharmaceutical company responded simply by offering mollifying suggestions as to why this might have occurred (5). What measures are planned for quantifying and analysing the risk of errors once the product is marketed?
6) Can we be sure that in real-life use, patients will be unable to open the pens, remove the contents (probably a cartridge, since these are often used in pens), then extract the *insulin* using a syringe designed for the administration of insulin 100 IU/ml? Will patients be able to extract *insulin degludec* 200 U/ml using a syringe designed for the administration of *insulin* 100 U/ml by piercing the rubber membrane of the TRESIBA° prefilled pen?

A safety signal for cardiovascular risk overlooked in the CHMP opinion

The licensing process in the US is more transparent than in the European Union, where secrecy reigns until the CHMP has issued an opinion (**c**).

On 8 November 2012, the FDA convened a public advisory committee meeting to discuss a possible safety signal for serious cardiovascular risks with *insulin degludec* (deaths, strokes). The signal emerged on analysis of the data on adverse effects reported during clinical trials (5). But, as is often the case, the pharmaceutical company was given the benefit of the doubt: 8 of the 12 members of the FDA Advisory Committee recommended the approval of *insulin degludec*, provided that the company conducts a postmarketing cardiovascular outcomes trial. While the company carries out this postmarket requirement trial, patients using *insulin degludec* might be exposed to unjustified cardiovascular risks. In contrast, the CHMP opinion of October 2012 makes absolutely no mention of this serious safety signal (**d**).

Prescrire asks the European Commission, and especially the committee charged with assisting it, to check that the recommendation by the CHMP on *insulin degludec* has taken into account all of the risks inherent in the introduction of a new concentration of *insulin* using *insulin degludec*.

Furthermore, *Prescrire* requests that all communications and all the meetings that take place during the period between publication of CHMP opinions and publication of the Commission's Decisions (Standing Committees (**e**), Appeal Committees) be published in detail on the Commission website. This is currently not the case. This lack of transparency damages the public's confidence in the decisions of the European Commission's Directorate General of Health and Consumers.

Thanking you in advance for the consideration you will give to our requests, we look forward, Mrs Brunko, Head of Unit 'Medicinal Products' of the European Commission, to receiving your responses.

Yours sincerely,

Bruno Toussaint
Editorial Director
For Prescrire Editorial Team

• • • • •

a- *For some years, the only insulin concentration available in the European Union has been* ***100*** *units per millilitre. This harmonisation had been recommended by the World Health Organization (WHO) to prevent dosing errors in patients travelling to a different country (refs. 3,4).*

b- *The company Novo Nordisk applied to the FDA and the EMA for marketing authorisation (MA) for insulin degludec in 2011 (ref. 6). By 15 November 2012, the EMA, the FDA and the PMDA, Japan's pharmaceuticals and medical devices agency, had recommended the approval of insulin degludec (refs. 7,8).*

c- *In the US, when internal FDA assessors detect safety signals, especially adverse effects that require detailed analysis, an Advisory Committee is convened to discuss the issue before deciding whether or not to recommend approval of the drug. The Committee's briefing documents, including the FDA's assessment, and the votes cast by the committee members, are made publicly accessible to ensure the transparency of the decision-making process.*

In contrast, apart from a vague statement that an MA application is under evaluation, the EMA releases nothing to the public: it publishes none of the conclusions of the rapporteurs' day 80, 120, 150 or 180 assessment reports, and none of the pharmaceutical company's answers to the EMA's questions at the end of each of these stages. This lack of transparency means that available scientific information that would be useful to prescribers and patients is lost. Releasing it would increase European citizens' confidence in the EMA's decision-making processes.

d- *Insulin degludec is intended for use in patients with type 1 or type 2 diabetes. In the US, the guidelines on drugs developed for the treatment of type 2 diabetes advise pharmaceutical companies to provide data on long-term cardiovascular risks (ref. 9). The European guidelines have similar requirements for oral antidiabetic drugs, but are ambiguous regarding insulins (ref. 10).*

e- *When the European Commission receives a positive opinion on an MA from the CHMP, before making a decision, the MA department of the Directorate General for Health and Consumers is required to seek the opinion of each member state on the draft MA in question (Article 10 of Regulation 726/2004/EC). These opinions are generally given in writing (ref. 11). A "Standing Committee" is then formed, including representatives from each member state, who vote for or against the draft MA decision. But the composition of Standing Committees is not made public, and it is therefore impossible to find out the conflicts of interest declared by these representatives. The opinions and the questions asked are not made public either. In some cases, for example if a member state maintains an objection to an MA, the Standing Committee meets physically to discuss and vote on the MA. Some brief information is posted on the European Commission's Comitology Register (http://ec.europa.eu/transparency/regcomitology/index.cfm), but detailed minutes of Standing Committee meetings are not released to the public.*

An Appeal Committee is the last resort in the European Union for anyone wishing to challenge the conclusions of a specialised committee such as a Standing Committee.

● ● ● ● ●

1- EMA-CHMP "Insulin degludec-TRESIBA°-Summary of opinion" 18 October 2012.
2- EMA-CHMP "Insulin degludec/insulin aspart-RYZODEG°-Summary of opinion" 18 October 2012.
3- EMA "European Medicines Agency recommends approval of first higher-strength insulin for treatment of patients with diabetes mellitus in the EU" 19 October 2012.
4- Prescrire "Insuline: harmonisation à 100 UI/ml au 30 mars 2000" *Prescrire Rédaction*; 2000 (204): 197.
5- FDA "FDA Briefing Document-NDA 203313 and NDA 203314: Insulin Degludec and Insulin Degludec/Aspart" 8 November 2012: 272 pages + erratum 1 page + "Draft questions to the Committee": 3 pages.
6- Scrip "Novo Nordisk to file Lantus rival Degludec in US after EU" 27 September 2011: 1 page.
7- Scrip "US FDA advisers back Novo Nordisk genetic insulins, despite worries" 9 November 2012: 2 pages.
8- Scrip "Latest Japanese recommendations include first nod for Novo's insulin degludec" 4 September 2012: 2 pages.
9- FDA "Guidance for Industry. Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes" December 2008: 8 pages.
10- EMA "Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus" 14 May 2012: 28 pages.
11- European Commission "Standing Committee, Appeal Committee" Response to Prescrire 03 April 2012: 2 pages.

Prescrire is a non-profit continuing education organisation that works to improve the quality of patient care. *Prescrire* publishes reliable 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. english.prescrire.org

Contact: Pierre Chirac, contact@prescrire.org)