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LETTER TO THE EDITOR

Comment on: "Achieving Glycaemic Control with Concentrated Insulin in Patients with Type 2 Diabetes"

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Dear Editor,

Chatterjee et al. have written a potentially valuable article summarising the clinical profiles and use of some recently developed basal insulins [1]. As review articles in *Drugs* are widely regarded as useful reference guides by prescribers, I feel it important to point out some factual errors and misleading statements in the review that I believe prescribers should be made aware of. Specifically:

1. The title refers to *concentrated insulin*, and the introduction refers to "*second-generation ultra-long-acting highly concentrated basal insulins … degludec U100 and U200 … and insulin glargine U300"*. Much of the review discusses degludec U100, which is however not a concentrated insulin. It is a novel molecule formulated at the same unit/mL strength as standard insulin products.
2. In Sect. 2, the review refers to the ultra-long duration of action of degludec resulting from *"the stabilising action of low concentrations of phenol and increased albumin binding resulting in the formation of hexamers following subcutaneous injection"*, and *"… soluble multihexamers result from changes in the amino acid structure of insulin"*. This is a fundamental misrepresentation of the pharmacology of degludec. In the pharmaceutical formulation, degludec exists as dihexamers and these subsequently link together to form multihexamer chains in the injected depot as phenol diffuses away. The multihexamers break down slowly, releasing monomers, and this is the major mechanism of protraction. Albumin binding has a relatively minor influence on protraction, and does not contribute to self-association. Furthermore, none of these processes are the result of amino acid changes. The amino acid sequence of degludec is identical to human insulin except for one deletion at B30. At B29, a glutamic acid spacer is attached that bridges to a 16-carbon diacid. It is this acylated region of the molecule that bestows the unique self-association properties.
3. Figure 1 refers to an "*Increased window of administration (4–6 h)*". However, the degludec summary of product characteristics clearly states "*a minimum of 8 h should be ensured between doses"*, i.e. a window of administration of ± 16 h [2].
4. In Sect. 5.4 and Fig. 2, it is stated that "*Patients already on insulin therapy start at same unit dose as* [their previous] *total daily long or intermediate acting insulin unit dose"*. However, the SmPC (EU) states there should be a 20% dose reduction in the total dose for patients previously taking twice-daily basal insulin [2].

It is also unfortunate that this review is, in my opinion, weakened by the inclusion of the reference to insulin pricing in the introduction, particularly as this is subject to frequent review and has, in many countries, changed since the prices quoted in the old citation in the review. It is also highly unscientific to make comparisons across trials, as in Sect. 5.5, for very well-established reasons, not the least of which include the differences in study population, trial design and trial conduct. The only reliable way of comparing the effects of two different treatments is within the same trial.

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References

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