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LETTERS

BAD MEDICINE: THE WAY WE MANAGE DIABETES

European Medicines Agency must take account of cardiovascular harm associated with degludec insulin

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The way we manage diabetes is bad medicine and, with the increasing use of analogue insulin, type 2 diabetes is pharma's lottery win.[1] Degludec insulin (Tresiba), Novo Nordisk's novel analogue, may be viewed in this context. Our concerns about its marketing led us to submit a letter to the European Medicines Agency (EMA) (available at: www.bmj.com/content/346/bmj.f2695/rr/648949).

The EMA approved degludec in September 2012, but the US Food and Drug Administration asked the manufacturer to conduct further cardiovascular safety studies (February 2013) on the basis of a meta-analysis of studies to date. The analogue increased the risk of major adverse cardiovascular events (hazard ratio 1.67, 95% CI 1.01 to 2.75).[2] These data were available to EMA, but because its prespecified analysis used a different definition of events, the hazard ratio was 1.097 (0.681 to 1.768).[3] For all five definitions of major adverse cardiovascular events, the point estimate corresponds to an increase in risk from 9.7% to 61.4%. Like the FDA, we argue that any questionable benefit over existing long acting insulin analogues through claimed lower risk of hypoglycaemia does not outweigh the additional cardiovascular risk.

Type 2 diabetes more than doubles the risk of cardiovascular disease, with little or no benefit from glucose lowering,[4] and cardiovascular disease continues to be patients' major cause of death. Changes in glycated haemoglobin are a poor surrogate for cardiovascular risk reduction, with a 1% reduction associated with only 10-15% improvement.[4] Because the risks of cardiovascular complications in these patients far exceed those of patient relevant microvascular complications, glucose lowering treatments must show beneficial, or at worst neutral, cardiovascular effects.

We call on EMA to amend its summary of products characteristics for degludec to state that the FDA found sufficient evidence of cardiovascular harm not to register degludec insulin.

Competing interests: TAS holds Novo Nordisk stock.

1 Spence D. Bad medicine: the way we manage diabetes. *BMJ* 2013;346:f2695. (29 April.)
2 Food and Drug Administration Endocrine and Metabolic Drugs Advisory Committee Meeting 8 November 2012. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM330923.pdf.
3 European Medicines Agency. CHMP assessment report: Tresiba. 2012. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002498/WC500139010.pdf.
4 Control Group, Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009;52:2288-98.

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