DOM-18-0404-IC Commentary Bailey

Commentary to:

DOM-17-0964-RA.R2 Blind et al

The European Medicines Agency´s Approval of New Medicines for Type 2 Diabetes

European Medicines Agency: approval of new glucose-lowering medicines for type 2 diabetes

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The author declares no specific conflict of interest for this commentary but records previously holding representative positions on various committees of EMA .

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Since 2005 all new glucose-lowering medicines to be used in Europe have required approval by the European Medicines Agency (EMA) through a centralised procedure [1]. This involves assessment of a detailed file of data generated during the preclinical studies and phase 1-3 clinical trials, along with the proposed product label. The file is subject to internal review and some aspects may also receive external review, giving rise to questions that are referred back to the sponsor and may lead to additional studies. The assessment is considered by the Committee for Medicinal Products for Human Use (CHMP) and if approval is recommended then a marketing authorisation is usually granted by the European Commission. Use within individual countries may also involve the competent authority of that country to implement the conditions of the marketing authorisations as well as the price setting. Further endorsements may be required by other national bodies such as NICE in the UK. Meanwhile post-approval studies mandated by the regulators or undertaken on the initiative of the sponsor, such as cardiovascular outcome trials, will be monitored and considered for any amendments to the label. At the same time the Eudravigilance system will collect safety reports and consider signals for adverse effects.

New drug assessments take account of unmet need, existing therapies, properties of the new agent, the quality and extent of information submitted, and the intended use - with safety as a crucial element. The review by Blind et al documents the variety of new glucose-lowering agents for type 2 diabetes approved by EMA since 2005 [2]. These agents conform to guidance set out by EMA in 2002 and 2012 [3], and are predated by metformin, sulfonylureas, meglitinides, pioglitazone, alpha-glucosidase inhibitors and insulins that were already available before 2005. An updated guidance document from EMA on agents to treat or prevent diabetes mellitus is planned for introduction in 2018.

Risk-benefit is the guiding principle of the assessment process. It is often a delicate and sometimes unquantifiable balancing exercise which includes what (in another context) Donald Rumsfeld described as the known unknowns and the unknown unknowns [4]. The former might include an aspect not tested in the human trials such as overdose or use in pregnancy, while the latter could be a drug interaction not encountered during the pre-approval trials and not anticipated on theoretical grounds. Some risks such as hypoglycaemia are well recognised and must be commensurate with the benefits. With regard to insulins for example hypoglycaemia is an accepted risk for this essential life-support therapy, appreciating that reasonable cautions are undertaken to minimise such risk.

The need for a variety of differently acting glucose-lowering agents is consistent with the many different causative and exacerbating components of type 2 diabetes that contribute to its heterogeneous and progressive pathophysiology [5]. Treatment often requires more than one agent, hence the variety of combination products approved by EMA which include fixed-dose combination tablets and fixed-ratio injectable combinations. Several studies have demonstrated the potential benefits of a combination approach to achieve early, effective and sustained glycaemic control in type 2 diabetes, as acknowledged in the treatment algorithms [6, 7].

The use of HbA1c as a surrogate marker of metabolic effectiveness to mitigate diabetic complications comes under the spotlight periodically, but seems set to stay. Other measures of glycaemic control including glucose variability are informative but they are more difficult to assess with consistency, and waiting for complications in pre-approval trials is ethically unpalatable given current knowledge of the detriments of glucotoxicity.

Guidance for sponsors is under review at EMA, but the record of agents approved since 2005 indicates a thorough and responsive review process with follow-up amendments to the drug label as new evidence arises, enabling safer and/or wider use of agents in a timely manner [8]. It is noted that EMA and FDA do not always derive the same conclusions from the same information: opinions of advisory committees can differ, and regulators may take account of the availability of other medicines, the requirements of different populations, historical factors and levels of uncertainties. Consultation with experienced reviewers is important to help to interpret new data.

For the future the regulatory process may expand attention on preventative measures, take advantage of advances in pharmacogenomics to refine drug labels and consider further opportunities for the integration of comprehensive glucose monitoring and automated drug delivery.

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