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Regulators clear incretin mimetics – for now

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With positive signals emerging from regulators on both sides of the Atlantic, drugmakers can draw a sigh of relief that there will not be any immediate new restrictions on the use of incretin mimetic drugs for diabetes such as Merck & Co's Januvia or Novo Nordisk's Victoza. The risks of pancreatitis are well-known, and are called out on the labels of all the drugs approved so far in the DPP-IV inhibitor and GLP-1 agonist classes; the elevated risk of pancreatic cancer, meanwhile, cannot be determined based on existing evidence, regulators have concluded.

That risk may become clearer as data from seven post-marketing trials, encompassing nearly 60,000 patients, begin to mature in coming months and years – a cardiovascular study of Takeda's Nesina is due very soon (*Roche's long-odds aleglitazar bet points to others chasing the cardio dream, July 11, 2013*). Incretin mimetics represent the biggest growth drivers for Merck, Novo Nordisk, and Takeda, and are leading ones for Novartis and Bristol-Myers Squibb, so the data will be closely watched for any cancer signal.

Small numbers, limited evidence

Worries first emerged with publication of analysis, based on data from FDA's Adverse Event Reporting System, suggesting a link between GLP-1 agonists like Victoza and an elevated risk of pancreatic cancer – patients taking them were 23.3 times more likely to have developed the particularly deadly tumour type (*Diabetes drug safety controversy grows with new analysis, April 19, 2013*).

Last week, the European Medicines Agency concluded that the analyses so far have been "methodologically limited" and subject to potential bias. There have been too few cases of pancreatic cancer to draw any statistical conclusions, but because of the mechanism of action – stimulation of pancreatic beta cells and suppression of alpha cells – there are "uncertainties" about the potential effects of long-term use, the EMA stated.

On pancreatitis, the risk has already been identified on the labels, although there could be better harmonisation of the language of the warnings between products to aid in communication with physicians and patients, according to the agency.

The go-ahead was given at the same time as the EMA supported approval of Nesina, to be sold in the European Union as Vipidia.

The FDA has not formally published a statement on the pancreatic cancer statement, but agency spokeswoman Lisa Kubaska confirmed in an email to *EP Vantage* that the EMA's conclusions are "consistent with our current understanding of the data." She wrote that regulators will be watching the pancreatitis and pancreatic cancer data from the ongoing post-marketing cardiovascular trials.

Looking for an edge

The trials will conclude between now and 2019, and aim to largely to show a cardiovascular benefit on top of the glycaemic control offered by the two drug classes. One, the Savor trial of Bristol-Myers Squibb and AstraZeneca's DPP-IV Onglyza, found no cardiovascular benefit, but topline readout was short on pancreatic safety data – more detail is expected at the European Society of Cardiology meeting later this month in Amsterdam (*Move along, nothing to see here: Onglyza Savor trial result leaves diabetes world unrocked, June 19, 2013*).

The five-biggest non-insulin drugs fit into the two categories, so the implications of any safety restrictions are enormous – not just to the companies selling them, but to patients who in many cases have failed to achieve glycaemic control on metformin or sulfonylurea. The new SGLT-2 class, which includes the recently US approved Invokana from Johnson & Johnson, is a new alternative, although it has safety worries of its own – namely genitourinary infections.

At the same time, companies selling the DPP-IV drugs have been trying to protect themselves from the better efficacy of the GLP-1 class – and with its newest insulin on hold for years in the US, Novo has probably been pushing Victoza sales hard. Merck disclosed in its second quarter earnings Januvia had a rough quarter in which prescription volume grew 1%; most of the sales growth occurred because of pricing increases, which are

only achievable in the US right now.

In their analyst call, Merck executives acknowledged that there was not much class growth in DPP-IVs right now, but that the agents are continuing to take share from the genericised sulphonylurea class. This is a tactic shared by Boehringer Ingelheim, whose Tradjenta is the most recent to launch in the Western markets – its 14,000-patient post-marketing programme includes the head-to-head trial against sulphonylurea, the only such study for a DPP-IV.

Still, with diabetes prevalence expected to grow by nearly two-thirds globally there should be room for quite a few drug classes. However, the sellers of incretin mimetics need to hope that as trials continue to report the pancreatic cancer profile remains benign if they are to defend or even expand their market share – or indeed, stay on the market.

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