

Merck's Januvia raced to diabetes dominance in many countries. But it's a different game among combination products and in emerging markets, as competitors seize rostrum spots in their quest for gliptin gold. **Sarah Rickwood** and **Carolyn Gauntlett** reveal opportunities for competitive advantage



THE DIABETES OLYMPICS

The market for non-insulin diabetes treatments has experienced strong growth over the last decade, averaging 9.5% over the past five years. Epidemiology and unmet need have combined to generate demand for new product classes. The first of these, the DPP-IV class, is dominated by Merck's Januvia, but further launches are lining up in another major new class, the SGLT-2s.

Given the similarities in the competitive characteristics of this new class compared to the DPP-IVs, there may be significant learning opportunities from the successes and failures of recent oral diabetes agent launches—knowledge that companies can apply to gain advantage in a highly competitive field.

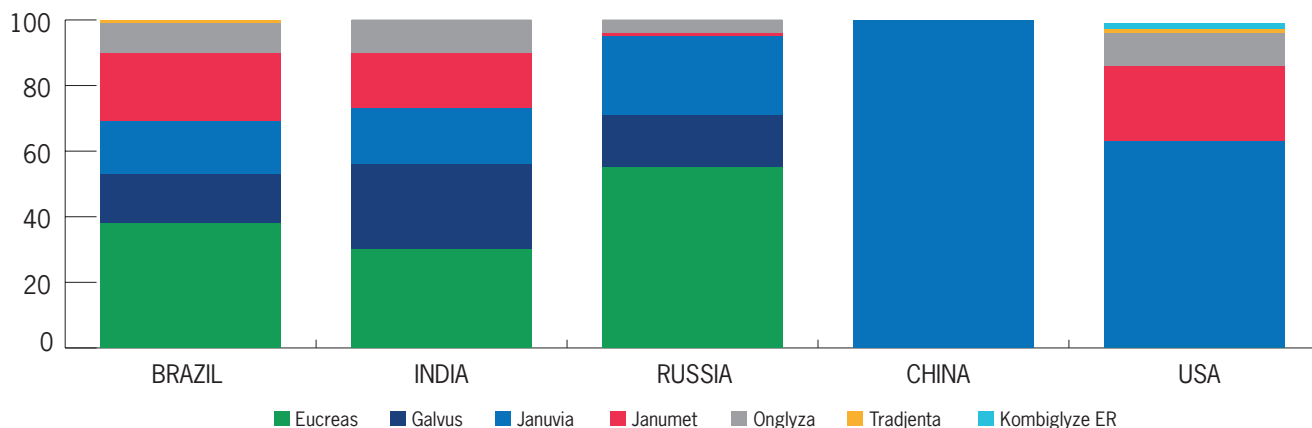
Type II diabetes, paradoxically, is dominated by old and off-patent drugs in the early stages of treatment, but remains a significant growth opportunity for new patented products because of the progressive nature of the disease, and considerable remaining unmet need. DPP-IVs, therefore, offered a new alternative in the treatment pathway, post metformin alone and prior to the later stages of treatment with insulins, or, latterly, GLP-1s pre-insulin.

These diabetes medicines have been the primary success story over the last five years, capturing 33% of worldwide value sales of non-insulin, anti-diabetic products. In the eight mature markets, DPP-IVs account for a significant percentage of value growth in diabetes treatments.

The first DPP-IV inhibitor to enter the market was Januvia (sitagliptin), introduced in 2006 in the US by Merck. Today, Januvia dominates sales of DPP-IV products in developed markets, with the brand accounting for about 80% of worldwide sales for single-compound products. Januvia's success can be attributed to both an excellent commercialization plan from Merck and a strong element of serendipity.

Fig. 1: A second chance to unseat the champ

In emerging markets, Novartis's Galvus and Eucreas account for more than 50% of the DPP-IV market. Share, by country, according to 2011 sales*



* Galvus launched Jan. 2012 in China, so no sales data as yet. Galvus and Eucreas not launched in US. Indian sales include all local brands.

Source: IMS Health MIDAS MAT Dec 2011

Januvia could have launched in direct competition to Novartis' Galvus (vildagliptin) in the US, but shortly before launch, Galvus was delayed, a consequence of side-effect concerns. This left the field open to Januvia, allowing it to enjoy three years of US exclusivity in its class before AstraZeneca/Bristol-Myers Squibb introduced Onglyza (saxagliptin).

During this time, Merck aggressively promoted Januvia to gain early buy-in from stakeholders and to build a positive brand image. Januvia secured its place as "the" gliptin, an image followers have found hard to challenge despite comparable promotional spending. Similar market dynamics occurred in Europe, where Januvia was launched in 2007. Galvus hit the European market in 2008, but has managed sales of just 9% compared to Januvia.

Fixed-dose combinations offer a second chance to be first

While it's been standard for single-compound oral agents to be followed by combinations of those agents, most frequently with metformin, these products have been follower, second brands—with less importance and potential than the original single agent. However, with the DPP-IVs, combination products have posed an opportunity to gain competitive advantage. In major European markets, Novartis launched its combination product, Eucreas (vildagliptin/metformin), concurrently with Galvus. While Galvus was the second-to-market single-compound product, Eucreas was the first launched combination DPP-IV product.

In contrast, Merck delayed launching its fixed-dose combination product, Janumet (sitagliptin/metformin), until a year after Januvia's launch.

This meant that Janumet was the second-to-market combination product. Although uptake of Eucreas did not match that of Janumet across the top five European countries—likely because Janumet benefited from Januvia's established patient base—Eucreas performed significantly better than Galvus in most European markets.

The competitive success of Eucreas versus Galvus raises questions about the relative importance of single-compound products versus combination products in overall diabetes brand success. After two years on the market in France, Germany and Spain, Eucreas represents 85-90% of vildagliptin family sales. In contrast, Janumet represents 40-60% of sitagliptin family sales. In the first quarter post launch, Novartis' promotional spending on Eucreas, as audited by IMS Health, was three times higher than it was for Galvus.

In the US, Merck was first to market with both Januvia and Janumet. The second combination product to come to market was Kombiglyze XR, which has not been able to compete with Janumet's first-mover advantage and has seen poor uptake. In 4Q 2011, Kombiglyze XR accounted for just 2% of the DPP-IV market, compared with 16% for Janumet.

Pharmerging markets: A different game

Pharmerging markets (a term coined by IMS to include 17 countries with income levels under \$25,000 per capita and relatively rapid growth) account for most of the volume potential of the diabetes market, driven by growing and aging populations acquiring Western habits. But they have, until now, accounted for very little diabetes market value, and less of the global sales of recently launched agents. This is starting to change with the battle among the DPP-IVs.



In Brazil, Russia and India, Merck's Januvia was launched before Novartis's Galvus. Nonetheless, Novartis' family of products accounted for more than 50% of the DPP-IV market in 2011 (see Fig. 1), mostly thanks to Eucreas, which has outperformed Janumet considerably. Meanwhile, Galvus has held its own against Januvia.

Pharmerging markets offer a new opportunity for diabetes launches, and the opportunity to overturn the competitive dynamics seen in the established markets. The first opportunity is one of size. In 2011, combined sales for non-insulin anti-diabetics (albeit both generic and branded) across BRIC were higher than sales in Germany, France and the UK.

Additionally, pharmerging markets experienced average annual growth of 26% for diabetes products from 2007-2011. The second opportunity is to employ different approaches to commercialization: winning in pharmerging markets is driven by adaptation to the local environment, not by mature market success.

Local issues and knowledge have had a significant impact on the success of DPP-IVs in pharmerging markets. In Brazil, Novartis heavily promoted Galvus and launched both plain and combination products together. This helped Novartis achieve sales for its DPP-IVs that were 40% higher than Merck's Januvia family in 2011.

Additionally, the importance of local knowledge means that "going it alone" may not be an effective strategy. In late 2008, Novartis joined forces with a local partner, USV, to co-promote Galvus in India. Local branding of the product as Jalra and a large sales force resulted in fast market penetration. In contrast, Merck waited until after Novartis launched Galvus to increase its sales force and partner with Sun Pharma to launch the local brand Istamet.

Differentiation: How much is enough?

IMS's research program of interviews with key opinion leaders (KOLs), providers and payers suggests that recent DPP-IV launches have lacked clear points of differentiation in these stakeholders' eyes, despite significant clinical investment. However, given the size of the global diabetes market, even small patient niches represent valuable opportunities and new products can be targeted to capture them.

Boehringer Ingelheim targeted a niche patient population—those with renal impairment—with Tradjenta (linagliptin), because the product is not excreted via the kidneys. While the jury is still out in the US on Tradjenta's market performance, the product is experiencing slow uptake in Europe due to differentiation not being achieved.

Additionally, Onglyza received supplementary approval for the same patient group; and the German Institute for Quality and Efficiency in Health Care (IQWiG) failed to find that Tradjenta provided an added benefit, resulting in Boehringer Ingelheim choosing not to launch in Germany rather than accept a sub-optimal price with wider European ramifications.

Several combination products that have recently launched have delivered lesser initial performance because their main differentiation, convenience and compliance, were simply not a strong enough sell. For example, Merck's Juvasynt (sitagliptin and simvastatin) has struggled because patients still have to take metformin with it.

Four more DPP-IV inhibitor products are in late-stage development. The lessons of the first four products strongly suggest that, unless there is true differentiation backed up with a very effective campaign across stakeholders, they are likely to chase ever-decreasing portions of the market in most countries, and at best achieve limited success in certain markets.

Lessons learned from long-distance launches

Four more DPP-IV inhibitor products are in late-stage development. The lessons of the first four products strongly suggest that, unless there is true differentiation backed up with a very effective campaign across stakeholders, they are likely to chase ever-decreasing portions of the market in most countries, and at best achieve limited success in certain markets. The next major class of diabetes drugs—sodium-glucose transporter inhibitors (SGLT-2s)—are likely to experience market dynamics that mirror those of the DPP-IV inhibitors. Here are some tips for new entrants

First-to-market products

1 Capitalize on the position—promoting heavily prior to the launch of competitors—and launch combination products quickly in mature markets to reduce the opening for rivals.

2 Leverage pharmerging markets. Form alliances with local companies and consider local branding. Local partners can help shield a product from negative attitudes directed toward the sponsor.

3 As competitive products enter, emphasize homogeneity in the class as a whole, since physicians tend not to switch patients off of existing therapy for a clinically comparable product.

Late-to-market products

1 Look beyond the largest markets for sales opportunities. Pharmerging markets may present opportunities to be first, especially for combination products.

2 Ensure that points of differentiation are really clinically relevant. This will be an issue for the follower DPP-IV and SGLT-2 brands, the majority of which KOLs have had trouble distinguishing.

3 Ensure that other differentiators, such as those that deliver patient convenience, will be recognized and appreciated by prescribers and patients.

Future diabetes classes: Sodium-Glucose Transporter Inhibitors (SGLT-2s)

With an abundance of treatments for Type II diabetes in the pipeline, companies should be looking to apply the lessons of recent launches (see sidebar). The next major class of drugs—sodium-glucose transporter inhibitors (SGLT-2s)—are likely to experience market dynamics that mirror those of the DPP-IV inhibitors.

A large number of these molecules are in late-stage development and are expected to launch around the same time. Like the DPP-IV inhibitors, IMS KOL interviews suggest the SGLT-2s may not be clearly differentiated from one another in the eyes of prescribers in terms of safety, efficacy or convenience. The first-to-market product will therefore, as with Januvia, have a significant advantage.

European approval for AstraZeneca/BMS's dapagliflozin suggests that this agent will be the beneficiary here; however it may still be possible for late-to-market products to succeed if they learn the lessons of the DPP-IVs. ■

Sarah Rickwood is director, European thought leadership group, and Carolyn Gauntlett is consultant, European thought leadership group, IMS Health.