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Novartis's Entresto Voyage: Hindsight Is 20/20

15 May 2017 | **ANALYSIS**

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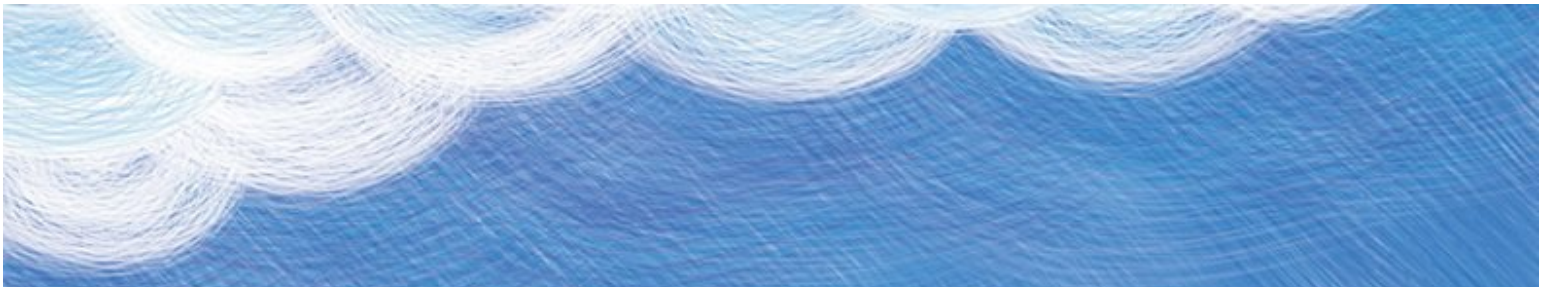
Executive Summary

What caused Novartis's innovative heart failure drug to falter, missing sales targets by $30m in 2016, and how is it expected to bounce back in 2017? *Scrip* explores Entresto's journey and what this experience shows about the changing face of pharma's customers.



WHAT LESSONS CAN PHARMA LEARN FROM NOVARTIS'S ENTRESTO VOYAGE IN HEART FAILURE?

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As a novel treatment for heart failure coming into a marketplace that had seen little innovation in recent years, with a proven effect on morbidity and mortality, *Entresto* should have been a groundbreaking US launch in 2015 for **Novartis AG** – a region where nearly 5 million people are currently living with congestive heart failure (CHF) and approximately 550,000 new cases are diagnosed each year. But the drug suffered a slower-than-expected start in its biggest market and missed out on sales targets in 2016 despite Novartis introducing new value-based reimbursement methods to tempt US payers.

In light of these unusual circumstances, *Scrip* has taken a look back at Entresto's story to piece together why a successful product with a large target market missed the mark in its first 18 months post-launch.

Only now, after the close of 2017's first full quarter, is Entresto beginning to earn its keep for Novartis. The drug saw sales of $84m in the first quarter compared with just $17m in the year-ago quarter. Paul Hudson, who heads Novartis' pharmaceuticals operations, said in the company's 1Q 2017 earnings call this stark revenue rise is because of doctors' increased familiarity with the drug and a stronger sales force.

Quarter By Quarter Entresto Sales

4Q 2015: $5m

1Q 2016: $17m

2Q 2016: $32m

3Q 2016: $53m

4Q2016: $68m

1Q 2017: $84m

Hudson said the full deployment of the Novartis sales force for the product "happened at the beginning of [this] year and the true operational impact will come late summer or autumn. So, we feel good about that progression." He is predicting a dramatic acceleration for Entresto this year.

Jefferies analysts have joined Novartis's optimistic bandwagon – a May 15 note from the group highlights that Entresto has seen a recent upturn in the US. They point out that Entresto saw one round of acceleration in spring 2016 when new treatment guidelines were introduced, but that this was mostly swallowed by a poor launch performance (*see box*). Now they predict this second wave of acceleration will hold steadfast for Entresto "as payer hurdles continue to fall and enthusiasm builds among cardiologists."

Still, consensus estimates remain mostly conservative for the drug at 3.1bn by 2021. Jefferies now estimates that Entresto revenues will reach $4.7bn by that time.

What Went Wrong?

First approved in the US in July 2015 as a treatment for CHF, Entresto (valsartan/sacubitril) was predicted to be a prominent growth driver for Novartis's pharmaceutical unit. However, the launch got off to a slow start and sales for its first full year on the market missed the big pharma's own target: Entresto's 2016 sales were $170m, while Novartis had forecast $200m for the period. However, the company believes its full year sales target for 2017 of $500m is still "very achievable."

First-in-class Entresto, an angiotensin receptor blocker/neutral endopeptidase (ARB/NEP) inhibitor, is a fixed dose combination comprising valsartan (Novartis's angiotensin receptor blocker *Diovan*, a mega-blockbuster franchise that faced generic competition in 2014) and the NEP inhibitor prodrug sacubitril.

Slow uptake of the drug in the US was unexpected, but is understandable because of a set of circumstances. While its efficacy and safety as a treatment for CHF were not questioned by payers, the groups responsible for reimbursing Entresto in the US were reluctant to embrace the new product. Unlike the oncology space, which has faced increasing price scrutiny for new drugs, the main complaint about Entresto was not its price but its relevance.

The cardiology market is well served by generic drugs as most the stalwart therapies, angiotensin-converting enzyme (ACE) inhibitors or ARBs, have lost patent protection. In parallel, innovation in the sector has been fleeting and R&D for heart therapies is notoriously a risky business with a high threshold

for clinical failure. Despite the odds, Entresto won approval with a strong label to treat heart failure patients – but doctors were not immediately convinced of its benefits over available drugs. (Also see "*Entresto* Label: Strong Efficacy, Complex Dosing" - Pink Sheet, 13 Jul, 2015.)

Roger Longman, CEO of Real Endpoints, a reimbursement analytics and advisory firm, told *Scrip* that Entresto's disappointing launch in 2015 resulted largely from two key factors.

Novartis first had to convince doctors to switch stabilized CHF patients from ARBs and ACEs to a new therapy. “These are relatively delicate patients,” Longman said. “Why try something new when what you’re doing is working?” Moreover, as with any new drug, Novartis had no real-world data. "Novartis won this fabulous label for Entresto but it was based on data from randomized clinical studies. Convincing doctors to use the product was a big hurdle for Novartis."

The second major challenge for Novartis was convincing payers to reimburse the medication. "One thing that has become clear in the last couple of years is that payers are increasingly going their own way when it comes to coverage – not merely following the label," Longman said. "They are using their own evidence and valuations and making their own restrictions – not infrequently based on the economic incentives specific to their lines of business. What works for one insurance company, or line of business at a payer, does not necessarily work for another."

JANUARY 2015

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Novartis appeared to offer a deal payers couldn't refuse – increasing the rebates if the drug didn't reduce hospitalization rates. But while such deals would work for health plans responsible for both the drug and medical costs, like many commercial plans, that type of performance-based agreement isn't as interesting to plans responsible only for the drug costs. One of the major problems for Novartis, Longman said, was that most of its patients fell into Medicare plans, and many of those belonged to Medicare stand-alone prescription drug plans (PDPs). And PDPs make money solely by keeping their drug costs lower than their premiums – they get no benefit from saving the system money in other areas, Longman noted.

Adding to this complex reimbursement scenario, heart failure is an area where new treatments are not common. "Cardiologists are not used to having to fill out prior-authorization forms or lobby for the use of new drugs like oncologists or rheumatologists," said Longman. "Most of the drugs used for heart conditions are generics; cardiologists don't have the reimbursement infrastructure to campaign for new drugs."

The drug, usually administered in conjunction with other heart failure therapies, is recommended as an alternative to ACE inhibitors or ARBs to reduce morbidity and mortality in patients with chronic CHF with reduce ejection fraction. Updated treatment guidelines now specifically recommend switching patients from ACEs and ARBs to Entresto, due to its superior effects. (Also see "Entresto US Sales Barriers Set To Be Removed By Strong Guidance" - Scrip, 23 May, 2016.)

Novartis has since upped its salesforce in the US for Entresto and has provided stronger support packages to payers including more data for the product. Over time the drug's use has increased, but it is still a way off Novartis's target peak sales figure of $5bn. The company has keenly emphasized that a $500m worldwide sales target for the full year 2017 is achievable – but some analysts still have doubts considering the drug has repeatedly fallen short of its quarterly and full year sales goals in 2015 and 2016.

"Health care providers have gained considerably more experience prescribing Entresto, and insurance providers in the US continue to expand coverage," a spokesperson for Novartis told *Scrip*. "Overall, uptake in the US this year is meeting expectations, and we are making progress with approvals and reimbursement in many other countries as well," the spokesperson said, noting that Entresto is now approved in 78 countries around the world.

Datamonitor Healthcare analyst Sita Indrakumar highlighted that in Europe, "Entresto experienced stronger uptake than in the US due to the European single-payer, government-funded healthcare systems being more accepting of its clinical benefits." But the product is still working its way through individual reimbursement bodies in Europe. The drug has recently been given the green light by payers in Italy and Germany, with the latter country's pricing agency agreeing a 'pay for performance' agreement with Novartis.

Knowing The Customer

Longman highlighted that the key lesson for the wider pharmaceutical industry from Entresto's reimbursement struggle is that the industry is still lacking in knowledge and understanding of its US customers.

"In hindsight, this case highlights that pharma companies still need to do a better job understanding their customers. They need to understand the different incentives that are of interest to different businesses," Longman said.

He added that it is critical that US payers are thought of as businesses first and foremost. "Currently, pharma companies often only offer a one-size-fits-all approach to insurers in the US. These groups are

industrial buyers with significant incentives that are diverse," he said – adding that in the US insurers are now the focal customer base for pharma, overtaking physicians.

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Competition In Heart Failure

Novartis is steadily growing Entresto's consumer base and the drug is expected to bring in significant profits to the Swiss company in the coming years. Novartis also continues to trial the drug in other cardiovascular indications, such as heart failure in patients with preserved ejection fraction (HFpEF). With the increasing prevalence of hypertension, obesity, atrial fibrillation and diabetes, as well as the growing elderly segment of the general population, the number of patients diagnosed with HFpEF is expected to rise significantly in the coming years. Indrakumar highlighted that "there is no set treatment plan for preserved ejection fraction HF, which could result in Entresto fulfilling an unmet need in this population."

Novartis is investing heavily in the cardiovascular field and its FortiHFy program is the largest global clinical program in heart failure with more than 40 active or planned clinical studies.

The FortiHFy program has been designed to generate additional data on Entresto’s clinical outcomes, quality of life benefits and real-world evidence within HF. Datamonitor Healthcare notes in its analysis of Entresto that "the outcomes of these trials are likely to greatly enhance the understanding of HF and provide additional information on the patient populations which may benefit from Entresto treatment. It is likely that Novartis will use these data to submit applications for Entresto’s use in wider HF patient populations, enhancing the drug’s commercial potential within this indication."

Major trials in the FortiHFy program include: PARAGON-HF, examining the efficacy of Entresto in patients with preserved ejection fraction; and PARADISE-MI, investigating the long-term benefit of Entresto in high-risk patients following a myocardial infarction

Despite Entresto starting to make its mark on the CHF market, there are other products moving up the pipeline. Novartis's drug will face competition imminently from marketed metabolic drugs broadening their reach. The sodium-glucose cotransporter-2 (SGLT-2) class, used to treat type 2 diabetes, is the biggest incoming threat to Entresto.

See Related Story

For more on competition in the heart failure market: (Also see "Entresto Facing Pressure From Diabetes Drugs" - Scrip, 15 May, 2017.)