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How Can Migraine Drugmakers Avoid the PCSK9 Debacle?

Luke Timmerman / 0 /

All, Drugs, Payers

One of the big ideas in biotech today is that you can prevent severe, chronic migraine headaches. This story has a lot of juicy ingredients: **intriguing biology**, bona fide medical value, and a potentially broad impact on millions of people.

But if the drugmakers in this emerging category overplay their hand, and don't pay careful attention to the new drug pricing reality, it could become a train wreck.

Think about the PCSK9 drugs. Not long ago, biologists and cardiologists were raving about the cholesterol-lowering power of these antibodies from Amgen and Sanofi/Regeneron Pharmaceuticals.

Both drugs won FDA approval to much fanfare last summer. Months later, sales of these drugs are barely a rounding error for either company. The vast majority of prescriptions (about 75 percent by estimates from Amgen) are being denied by payers via prior authorization procedures. And the denials keep coming on appeal. Payers want to see whether these $14,000 list-priced drugs are any better than cheap generic statins at what really counts – reducing heart attack and stroke. Until cardiovascular outcomes data rolls in from clinical trials in 2017, and data accumulates on their long-term safety, payers have tucked these drugs in a tidy little box. They are limited to small genetically defined populations where statins aren't cutting it, and the need for LDL cholesterol lowering is urgent and obvious.

Josh Ofman, Amgen's senior vice president of global value and access and policy, said doctors are "exhausted" by the hoops payers

are making them jump through to prescribe the medicines.

“It’s an extraordinary cautionary tale,” said **Roger Longman**, CEO of Real Endpoints, a pharmaceutical value consulting firm. “The PCSK9s were one of the great case studies in how not to develop and launch drugs in a payer-dominated environment.”

Roger Longman, CEO, Real Endpoints

There are some similarities between this category and the new emerging class of migraine drugs directed at calcitonin gene-related peptide (**CGRP**). Both classes have compelling underlying biology. Both classes rely on targeted antibodies, which must be injected and are more costly to manufacture than small molecules. Antibodies like these have traditionally been priced high. Both the cholesterol-lowering antibodies, and migraine antibodies, have the potential to reach high-volume markets with millions of patients. Each class has intense competition from drugs that appear to offer similar efficacy. Payers, in this kind of dynamic, will be super-motivated to drive hard bargains, extract steep discounts, and play one drugmaker off against the other for the coveted slot at the top of a formulary.

For those unfamiliar with the CGRP class,

here's a little background. Four drugmakers – Amgen, Alder Biopharmaceuticals, Eli Lilly and Teva Pharmaceuticals – are racing through the final stages of development with their CGRP-directed antibodies for chronic migraine. Amgen is technically going after the receptor and everyone else is aiming for the ligand itself.

The societal impact here is potentially huge. About **14 million people** in the U.S. are thought to have chronic migraine headaches, defined as 15 or more episodes per month. About 3 million people in the U.S. are thought to be the most severe patients who are candidates for intravenous infusion therapy, Alder has estimated. These are people who end up with migraines so bad they go to the emergency room. Headaches accounted for 2.1 million emergency room visits annually, according to a 2012 report by the **U.S. Agency for Healthcare Research and Quality**. Leerink analyst Jason Gerberry pegs the market for CGRP migraine antibodies at $4 billion to $6 billion a year.

The CGRP drugs represent something truly new. Today, some people get cheap beta-blockers, anti-depressants, Botox, or triptans. Those are drugs people take when they have a migraine, by which time they're already in a lot of pain and suffering. The CGRP-directed antibodies are different because they can prevent the migraine. They keep the

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headaches at bay by keeping a certain amount of antibody on board in the bloodstream for a full month, a quarter, or maybe longer. Last week, **Alder reported** from a Phase 2b clinical trial that showed it could cut the number of migraine episodes in half for 57 percent of patients on a once-a-quarter IV infusion, compared with 41 percent on a placebo.

I've never had a migraine, but I know people who suffer, and anything that can help is a big deal on an individual level. If you take migraine sufferers who get 15 headaches a month, and half suddenly get 7-8, and a third get only 4-5, that's a big difference. Someone with that many migraines per month must find it hard to hold a job, live an active life, or be even remotely happy. It's not hard to imagine that drugmakers with such products could make a strong argument to payers based on their value, as defined by not just hard costs like hospitalizations and medical procedures, but also on economic impact through fewer sick days and greater productivity. As the drugmakers will have you know, the Migraine Research Foundation estimates U.S. employers lose more than $13 billion each year as a result of 113 million lost work days from migraines.

For sure, the companies are gathering information on patient-reported outcomes and productivity in addition to the hard

clinical endpoints that physicians and the FDA want to see on migraines per month. But if the drugmakers can't, or don't bother, to make a truly compelling value proposition, this could get ugly. Payers will have to think in broad budgetary terms, not just in terms of cost-effectiveness at the individual patient level. Drugmakers complain that the payers are being short-sighted, not seeing the long-term benefit of the medicine. But let's also not forget that these drugs will need to be taken on a chronic basis for the rest of a patient's life. That could add up to a lot of money over time. The burden of proof is on the drugmaker to show that an expensive drug in the short-term will really save money in the long-term.

It's not clear to me whether the drugmakers are loaded for bear, and truly ready to make an overwhelming case in favor of the CGRP antibodies for migraine. They have encouraging clinical trial data. It's still a couple years away from coming to a head in the marketplace, but **Chronis Manolis**, the vice president of pharmacy at the UPMC Health Plan, an integrated health provider and payer in Pittsburgh, called this category a "brewing storm."

"I know migraine specialists are super-excited about these drugs, but the price has to be within reach, and has to provide value," Manolis said. "It can't just be bucketed into

the $15,000 a year price because that's the new standard set by the PCSK9s."

There are ways drugmakers could approach this situation. Surely, each will seek to differentiate in hopes of being the best-in-class option. If none stand above in terms of efficacy, then dosing could a source of competitive advantage. Alder is seeking to hang its hat on the fewest injections, with a once-a-quarter option, either through IV, intramuscular, or subcutaneous injection. Teva executives told Leerink's Gerberry last week that they think the market is small for an intravenous migraine drug because not many clinics are set up to handle patients that way, and many will prefer a subcutaneous shot. Alder's Phase 2b trial, at first glance, suggests it may be able to go the subcutaneous route as well.

Alder CEO Randy Schatzman didn't respond to my requests for an interview about pricing, and learnings from the PCSK9 debacle. But I quoted him **four years ago** saying that biotech companies should embrace cost-effectiveness evaluations. In 2013, Alder told me it could imagine pricing its migraine drug **at $5,000 to $7,000 a year** based on the value it delivers to the healthcare system.

Grounding the price in "value," of course, is now a much more popular concept today than it was three or four years ago. Longman,

the CEO of Real Endpoints, said another way forward might be for the migraine drugmakers to focus on a smaller population with the absolute highest medical need, and charge a higher price based on the obvious value delivered. Later, once a drug can prove its value to a wider swath of the patient population, it can bring the price down to a level that a high-volume market can absorb. Employers, who pay for health insurance and PBM services, also might have some influence if they understand the productivity benefits that come from good migraine drugs, Longman said.

Amgen's Ofman said his company wants to start talking with payers earlier in the game before commercialization, and bring multiple stakeholders at the bargaining table, such as physicians and patient advocates. Right now, companies feel constrained by FDA rules against promoting experimental medicines, which puts tight limitations around what can be said in such pre-market negotiations. Ofman said he's hopeful that Lilly and Anthem will make some headway with their recent **proposal**.

There's still time for the migraine story to turn out positive. It could be an example of a better way forward. I'd like to think if you take millions of sick people and significantly improve their lot in life, that will be richly rewarded. Advancements start with great

biology and clinical data. But drugmakers can't stop there. The burden of proof is on them to show the value of their medicines, in more ways than one. Let's all hope the drugmakers start wising up to the new reality, and find a way to avoid shooting themselves in the feet.

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