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Proprietary Intelligence

Antibiotic sales struggling to reach market projections to see reimbursement woes read through to upcoming launches, experts say

- FDA approvals do little to boost uptake confidence
- Recent sales fall far short of prior analyst projections
- UK explores alternative payment model, but still in pilot stage

Flawed reimbursement dynamics are significantly hurting recent antibiotic sales, which are failing market projections, and similar repercussions are expected for upcoming launches, said experts. While discussions around implementing alternative payment models for these drugs are active, efforts to alleviate price pressures are unlikely to materialize soon.

Some companies with Phase III trials or approvals in the next 12 months include **Iterum Therapeutics** (NASDAQ:ITRM), **Spero Therapeutics** (NASDAQ:SPRO), **Nabriva Therapeutics**, (NASDAQ:NBRV) and **Tetraphase Pharmaceuticals** (NASDAQ:TTPH).

The difficult reimbursement trend has particularly amplified in recent years due to increased efforts to conserve and preserve use of novel antibiotics through stewardship programs, and the availability of cheaper generics which hospitals prefer over more expensive novel ones, experts said.

Experts anticipated upcoming antibiotics in development to face similar challenges that have led to lower than calculated sales for manufacturers and subsequent loss of market caps, unless companies and payers pursue alternative payment models or follow success in the anti-fungal space.

Casualties of the current system

There has been an increased push for stewardship programs in hospitals that advocate conservation of potent novel antibiotics, said experts. This has increased over the last five years due to the growing problem of antibiotic resistance, said Kevin Outterson, professor of Law, Boston University, and executive director of Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X). He and other experts emphasized the need for such stewardship programs, but that along with a genericized market, especially for gram negative infections, has led to lower antibiotics sales, which also threaten the outlook for future antibiotics.

As per GlobalData figures, the top selling anti-infective drugs in 2017 that had been approved since January 2014 are **Astellas Pharma's** (TYO:4503) **Cresemba** (isavuconazonium sulfate) making USD 90m and **Allergan's** (NYSE:AGN) **Avycaz** (avibactam sodium/ ceftazidime) which made USD 61m in 2017. Allergan's **Dalvance** (dalbavancin) made USD 56m, **Almirall's** (BME:ALM) **Acticlate** (doxycycline hyclate) and **Otonomy's** (NASDAQ:OTIC) **Otiprio** (ciprofloxacin) made a mere USD 8m and USD 1m in 2017, respectively.

There has been a negative impact of current reimbursement dynamics on market caps of antibiotic manufacturers despite FDA approvals, said Outterson, pointing to **Achaogen** (NASDAQ:AKAO) and **Melinta Therapeutics** (NASDAQ:MLNT). The total sales for Achaogen's **Zemdri** (plazomicin) in 2018 have been less than USD 1m, and the company's stock price has also been hammered in the last few months, he said. Achaogen's stock has dropped by approximately 94% since 26 June 2018, the date Zemdri got an FDA approval to treat complicated urinary tract infections. Prior to the approval, analyst peak sales projections were as high as USD 500m.

Dr David Shlaes, president, Anti-Infectives Consulting, Norwich, Connecticut, pointed to hospitals not stocking Avycaz—even though it has been proven to be a superior antibiotic with lower mortality—due to its high cost compared to generics. Avycaz costs approximately USD 8,000 for a 10-day course. The drug was approved to treat complicated urinary tract infections (cUTIs) and complicated intra-abdominal infections (cIAIs) in combination with metronidazole in February 2015, when it was estimated to yield USD 360m in 2024, as per a report from November that year. But now GlobalData estimates peg them at a lower USD 140m in 2024, with actual 2018 global sales only reaching USD 94.6m, as per Allergan's 4Q18 report.

Currently, experts said Medicare and private payers reimburse antibiotics as a part of a bundled payment for in-patient treatments under Diagnosis Related Groups (DRG) payments. A hospital would get a fixed amount, around USD 15,000-20,000 per patient, which covers all ancillary costs including drugs except physician costs, said Outterson. If novel antibiotics of around USD 10,000 are to be used, then hospitals will likely lose money on the patient, he added. Furthermore, new antibiotics, including novel ones, require prior authorization from infectious disease pharmacists, said Dr Amesh Adalja, senior scholar, Johns Hopkins University Center for Health Security, Baltimore, Maryland.

Even in cases where CMS has granted a new technology add-on payment (NTAP), which allows hospitals to get up to 50% of the drug cost, like with **Merck's** (NYSE:MRK) **Dificid** (fidaxomicin), the uptake after launch was quite slow, said Peter Bak PhD, vice president, Back Bay Life Sciences Advisor. Dificid was approved in May 2011 to treat *Clostridium difficile*-associated diarrhea. Due to its cost, it did not do as well as expected, especially since there were cheaper—though less effective—generics available, he added. When approved, its peak sales were expected to be USD 250m, as per an analyst report, while its sales were USD 190m in 2018.

Allergan, Achaogen and Merck did not respond to a request for comment.

Considering these circumstances, all interviewed experts expect any upcoming antibiotics to

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Company

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face the same set of reimbursement challenges. A radical reform in the reimbursement system may not be possible in the near term, but if the system is not fixed soon, the field may lose its ability to have an adequate pipeline of antibiotics, said Outterson.

An FDA approval decision is expected for Nabriva's lefamulin and Tetrphase's Xerava (eravacycline) in 2H19, which are projected to yield USD 265m and USD 206 in respective sales by 2024, as per GlobalData. Phase III pivotal data is expected from Spero's SPR994 and Iterum's sulopenem, both oral penems, in 2H19, and 2024 sales for these drugs are pitted at USD 375m and USD 307m, respectively.

However, Bak pointed to one exception—Cresemba. This was the highest selling anti-infective drug in 2017, as per GlobalData. Its reimbursement economics are different compared to other anti-infectives, he said. It is usually used in severely immunosuppressed patients like transplant or oncology patients with fungal infections where reimbursements are comparatively more generous, said Bak. Cresemba sales touched USD 61m in 2017. It was approved to treat invasive aspergillosis and invasive mucormycosis in 2015. Companies with antibiotics for gram-negative bacteria could look at the anti-fungal space where reimbursement dynamics are somewhat different, to strategize their launches, he added.

Attractiveness of alternative payment models

While there are several alternative payment models proposed to delink payments from the volume of antibiotics used, most are just in the discussion phase, said Joanna Buckle, principal and consulting actuary, Milliman, London.

The UK has proposed a pilot program to study the potential of such a program in 2Q19 that explores an alternative payment model for antibiotics, said Colin Garner PhD, founder Antibiotic Research UK. The pilot project, which will include marketed and upcoming antibiotics, is trying to reimburse companies based on their value to society, he explained. However, this pilot project will not be adequate and in order to successfully combat this issue, such models will have to be adopted in other countries as well, Garner added.

A bill may need to be introduced in US Congress to modify CMS reimbursements for antibiotics, said Outterson. However, Bak and Adalja said it would be difficult to get all the stakeholders on the same page to allow for such a bill to pass. Furthermore, it's not clear if a legislative measure will be required, but pharmaceutical companies may be able to negotiate with payers on an individual basis, said Adalja. There have been alternate models proposed; a "Netflix-like" subscription model, for example, has been proposed with **Gilead Sciences'** (NASDAQ:GILD) hepatitis C drugs wherein the state would pay Gilead for unlimited access to the drugs for patients under Medicaid or in state correctional systems, said Adalja. While the challenge in that instance is the high cost, it has allowed reimbursement by State Medicaid to allow access, said Adalja.

by Manasi Vaidya in New York

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