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Amid rising concern, need for novel antibiotics

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Singapore: Recent worries over antibiotics losing their effectiveness will only be exacerbated by the FDA's latest drug safety update which stated that the commonly prescribed antibiotic Azithromycin can cause abnormal changes in the electrical activity of the heart.

Azithromycin, currently marketed as Zithromax by Pfizer, is indicated for a large range of bacterial infections, such as chronic obstructive pulmonary disorder (COPD), acute bacterial sinusitis, nosocomial pneumonia, and certain skin structure infections. The drug's wide-ranging use, improved safety profile, and short treatment duration of just five days, compared to the 10 days required by many competing antibiotics, have made Azithromycin a popular choice among physicians.

These detrimental effects were linked with potentially fatal heart arrhythmias in patients who already exhibited risk factors such as QT interval prolongation, low blood levels of potassium or magnesium, and slower heart rates. They were also indicated in patients currently being treated for heart arrhythmias with certain drugs.

A study, first published in the *New England Journal of Medicine* in May 2012, showed that patients treated with azithromycin displayed a higher likelihood of developing complications of the heart in comparison to patients treated with amoxicillin, ciprofloxacin, or levofloxacin, or left untreated. The updated safety information is likely to have been delayed by the manufacturers' own studies to corroborate this evidence.

Dr Brad Tebbets, GlobalData's analyst covering infectious diseases, does not expect FDA's announcement to dramatically affect the sales of Zithromax, but states, "The news could decrease its uptake among patients at risk of cardiac complications, and these adverse events could also make Zithromax more susceptible to competition from novel antibiotics."

Some pharmaceutical and biotech companies are attempting to address the rising demand for novel antibiotics, in a pharmaceutical field currently in a state of flux. "Most currently, prescribed antibiotics are produced by generic manufacturers, and there is little incentive for pharmaceutical or biotech players to launch new products into the market," says Dr Ramya Kartikeyan, GlobalData's senior analyst covering infectious diseases. "The GAIN Act in the US and the Innovative Medicines Initiative in the EU both reflect acknowledgement by governmental, regulatory and research bodies alike of the need to

increase research efforts to develop cures against drug-resistant bacterial infections."

The UK's chief medical officer, Sally Davies, recently stated that the antibiotics market has stagnated over the past 20 years.

However, a recent deal between Cubist Pharmaceuticals and Astellas showed Cubist putting up as much as $25m for an antibiotic pipeline candidate ceftolozane. Ceftolozane, in combination with tazobactam, has come out with impressive and encouraging results in late-stage trials. The drug combination is currently set to be used against the gram-negative bacteria, Pseudomonas aeruginosa, one of the causative agents of nosocomial pneumonia and urinary tract infections.

As regulators continue to provide incentives for the development of novel antibiotics, they must also address the issue of antibiotic stewardship both in companies and clinics, says Dr Tebbets. If novel antibiotics are not used responsibly, resistant pathogens are bound to emerge, which would decrease the sales of the drug and limit treatment options. In addition, Dr. Kartikeyan argues that public awareness of resistance is also required to enhance the effects of these initiatives.

Dr Tebbets explains, "Big Pharma's abandonment of antibiotic R&D is not the sole reason for the escalation of drug-resistant strains. Physicians and patients also bear responsibility. These parties, as well as government regulators, have been complacent with a lapse of antibiotic stewardship. For example, poor compliance with antibiotic therapy has enabled drug-resistant pathogens to emerge and spread."

"However," states Dr Kartikeyan, "the recent EU financial crisis and US sequestration cuts make it difficult to predict how and when governmental bodies might be able to exercise this auxiliary role. Without a doubt, the severity of the issue is not lost amongst researchers and policy makers today; most are aware of the writing on the wall, which spells a clear message to all that dramatic regulatory reform and drug development initiatives are not all that is needed to quell the growing burden of drug-resistant."