Evaluate Vantage

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Event – J&J drug for resistant TB speeds towards US approval

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A unanimous FDA advisory committee vote for Johnson & Johnson's bedaquiline is a reflection of the importance health regulators are placing on treating multidrug-resistant tuberculosis. The diarylquinoline has the first new mechanism in 40 years for treating TB, and met with expert panellists' backing based on phase II data in 500 patients; it appears headed for US approval by December 28.

Approval of the anti-infective would potentially ease the burden of the disease, treatment of which can require the use of five second-line drugs for up to two years. Bedaquiline also has the potential to become a steady earner for the New Jersey group, with consensus sales forecast at $231m in 2018, according to *EvaluatePharma*.

Product	bedaquiline
Company	Johnson & Johnson
Market cap	$192bn
Product NPV	$642m
% of market cap	0%
Event type	PDUFA date
Indication	Multi-drug resistant TB
Date	December 28, 2012

Global view

Multidrug-resistant TB is defined as infections resistant to isoniazid and rifampicin, two of the four drugs that make up the first-line treatment regimen. It emerged as a result of incomplete treatment of TB, and once resistant bacteria develop they can spread to other people.

Treatment of multidrug-resistant infections involves use of multiple drugs, some of them off-label and with significant toxicity, such as levofloxacin, or injectables like capreomycin, which require greater intervention by healthcare providers.

The World Health Organization estimates 3.7% of new cases and 20% of previously treated patients have multidrug-resistant strains; an estimated 8.4 million patients worldwide were estimated to be infected with TB worldwide in 2011. In the US, 98 multidrugresistant cases were identified in 2011 – by comparison, in Eastern Europe 20% of all new cases are, while China and India also have a high percentage of cases.

Thus, US approval will not drive significant sales in itself, but will signify an important first step towards regulatory endorsement in higher-burden countries.

New mechanism

The J&J drug, with the proposed name Sirturo, blocks the protein pump of adenosine triphosphate synthase, inhibiting energy production and causing bacterial cell death. It is selective for the mitochondria of mycobacteria, and thus has little effect on the energy production in human cells. By comparison, isoniazid blocks synthesis of cell walls and rifampicin inhibits RNA synthesis.

Two phase II trials tested a 24-week regimen of bedaquiline with a background of other anti-tubercular drugs. One was placebo controlled; the compound significantly improved the rate of treatment success at eight

weeks.

Accepting the New Jersey group’s application on the strength of phase II data – and granting accelerated review – was a sign of the importance the FDA assigned to finding treatments for the condition. Briefing documents cautioned about heartbeat abnormalities and elevated liver enzymes, and panellists expressed concern about a mortality imbalance; a separate vote on safety generated seven negative votes.

Should the agency follow through on the panel’s recommendation next month, bedaquiline could represent the leading edge of a new generation of TB treatments targeting multidrug-resistant strains. Otsuka has filed delamanid, or OPC-67683, in Europe, where J&J has also filed bedaquiline. In phase II, Novartis has rights to PA-824, a project emerging from the Global Alliance for TB Drug Development.

Approval of the first agent specifically targeting multidrug-resistant infections would be an important advance for TB patients. Despite a low incidence in the biggest drug markets, it appears that the draw of emerging economies has been sufficient to attract the attention of major drug developers.

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