The Impact of Bedaquiline's Approval on the Laboratory

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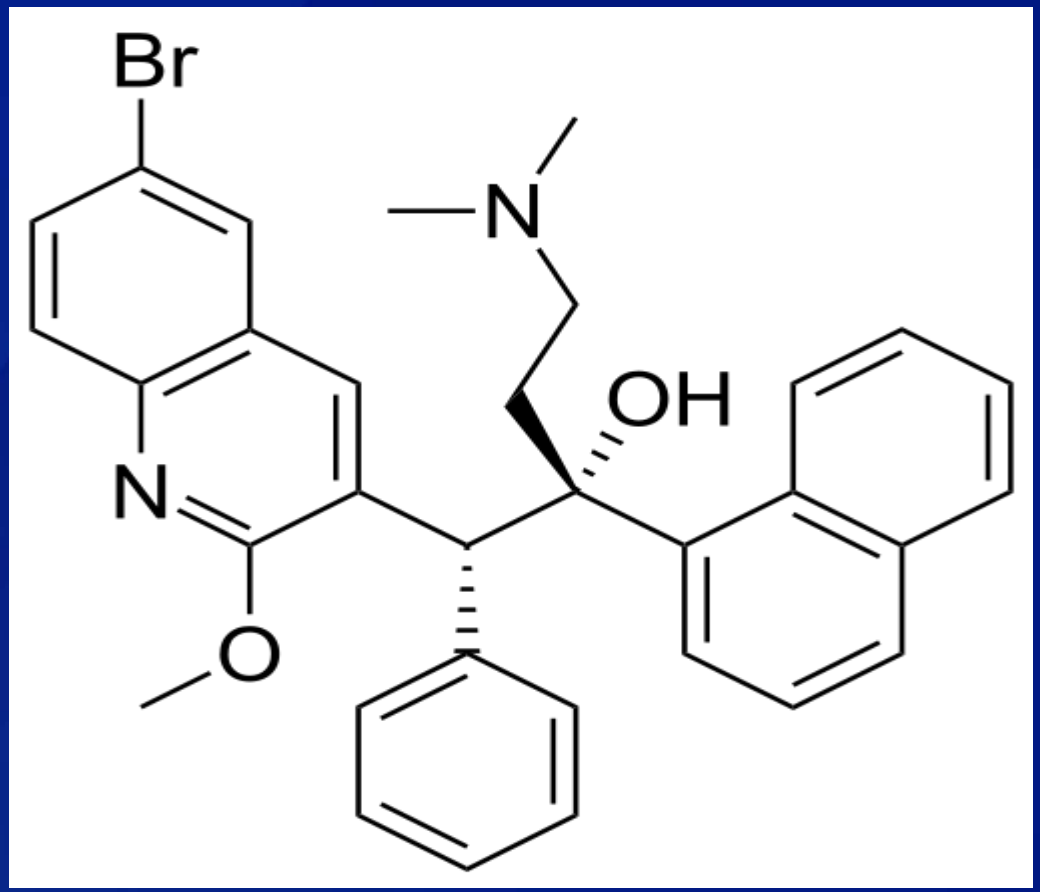
Bedaquiline (SIRTURO™) First Novel Anti-TB Drug in 40 Years



How do you pronounce it?

- Bedaquiline
  - bed ak'wi leen
- "BDQ"

Bedaquiline fumarate

- Diarylquinoline (DARQ)
- Molecular formula:
  $C_{32}H_{31}BrN_2O_2 \cdot C_4H_4O_4$
- Molecular weight: 671.58 (555.5)
- Practically insoluble in aqueous media
- Other names: TMC207, R207910

Bedaquiline

- Broad antimycobacterial activity
- First described at ICACC 2004; had been in development for >7 years
- Drug developed by Tibotec
- Tibotec acquired by J&J / Janssen
- J&J kept rights for DR TB
- TB Alliance has rights for DS TB ("universal regimens" and drug-shortening regimens)

Mechanism

- OF ACTION
  - Inhibits mycobacterial ATP synthase, an enzyme that is essential of the generation of energy in MTBC
  - Active on DS TB and DR TB
  - Kills both replicating and non-replicating bacilli
  - Extracellular and intracellular activity; intracellular activity > extracellular activity
  - In mice, increases bactericidal and sterilizing activity of first and second-line regimens
- OF RESISTANCE
  - Modification of the *atpE* target gene
  - Unknown

FDA Priority (Accelerated) Review

- FDA grants priority review to medicines that may offer major advances in care or to provide a treatment option where no adequate therapy exists
- June 29, 2012; Janssen submitted New Drug Application (NDA)
- November 28, 2012; FDA Anti-Infective Drugs Advisory Committee meeting
- December 28, 2012; FDA approval as part of combination therapy to treat adults with MDR TB
  - Indication for use based on analysis of time to sputum culture conversion for 2 controlled Phase 2 trials in patients with pulmonary MDR TB

BLACK BOX Warning

- An increased risk of death was seen in the SIRTURO treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial. Only use SIRTURO when an effective treatment regime cannot otherwise be provided.
- QT prolongation can occur with SIRTURO. Use with drugs that prolong the QT interval may cause additive QT prolongation.

Dosage and Administration (100 mg tablets)

- 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks with food. Swallow SIRTURO tablets whole with water.
- Only use in combination with at least 3 other drugs to which to patient's MDR TB isolates has been should to be susceptible in vitro. If DST results unavailable, treatment may be initiated in combination with at least 4 other drugs to which the patient's MDR TB isolates is likely to be susceptible.

TB Laboratory-Related Postmarketing Requirements (PMR)

- PMR 002: Patient registry to include Minimum Inhibitory Concentration (MIC) data for baseline and any subsequent MDR TB isolate
- PMR 003 / 004: Conduct studies to define QC ranges of BDQ for MDR TB isolates using standard proportion methods / MIC methods
- PMR 005: Conduct prospective in vitro study (5 year) after introduction to the market to determine MICs of MDR TB isolates to BDQ

http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/204384Orig1s000ltr.pdf

Manufacturer's Studies (CDC in negotiations)

- PMR 003 / 004: Define QC parameters (CLSI Tier II QC study)
  - 10 DST vs. H37Rv by 7H10 agar AP MIC, 7H11 agar AP MIC, and 7H9 broth (TREK frozen broth MIC panels); 3 lots of each medium
  - 8 laboratories world-wide
- PMR 002: Act as reference laboratory for registry; test prospectively collected MDR TB isolates (broth MIC; AP MIC)
- PMR 005: Worldwide drug resistance surveillance (AP MIC and broth MIC)

- In vitro DST of recently collected well-defined MDR TB isolates

So, BDQ is available to use in US.

Jenssen is working on the system and development of the registry.

CDC hopes to publish interim guidelines for the use of and safety monitoring of bedaquiline for the treatment of pulmonary MDR TB.

TB Laboratory-Related Issues
BDQ Prescribing Information

- DST should be performed according to published methods
  - AP (agar proportion) or REMA (resazurin microtiter assay) test range from 0.008 —1.0 µg/mL
  - Actual MIC should be reported. (A specialist in drug-resistant TB should be consulted in evaluating therapeutic options)
- For 9 patients who failed to convert or relapsed, post-baseline isolates had MICS with 4-fold to >8-fold higher than baseline (AP) and 4-fold to >16-fold higher than baseline (REMA)

Question: How should isolates be identified as MDR TB?

- Need rapid identification
  - Molecular vs. culture-based testing vs. combination
- Once MDR TB is diagnosed, need rapid and comprehensive FLD and SLD DST results
  - Molecular vs. culture-based testing vs. combination for comprehensive testing
  - Which laboratories?

Question: What about testing of companion drugs?

- Comprehensive SLD panel
- Drugs without CLSI guidance?
  - (Linezolid)
  - Cycloserine
  - Clofazimine
  - Macrolides
  - Imipenem
  - Amoxicillin / clavulanic acid

Question: What about testing of BDQ?

- Which laboratories?
- Critical concentration not determined; FDA recommending MIC testing
- Will commercially prepared MIC panels be available?
- Are baseline MIC results required in real-time?
- Baseline and follow-up isolates need to be stored
- Resistance will emerge and will need to be studied in a coordinated fashion

Susceptibility Testing

- Suggested (proposed) interpretive criteria
  - Agar proportion
    - ≤ 0.5 µg/mL = Susceptible
    - >0.5 µg/mL = ?
  - REMA (broth microdilution)
    - ≤ 0.25 µg/mL = Susceptible
    - >0.25 µg/mL = ?

CDC guidelines will propose that "Because of FDA's post market requirements, one isolate per month, including one before treatment initiation with bedaquiline, should be referred to a laboratory for surveillance of bedaquiline resistance in consultation with the state public health laboratory. CDC will assist inidentifying a laboratory that can perform bedaquiline susceptibility testing for this purpose."

Stay Tuned!