The case for pre-approval access to bedaquiline

Nathan Geffen
Treatment Action Campaign
Global TB Community Advisory Board
Legitimate concerns

• Testing is incomplete:
  – We only have phase II trial data.

• Setting a precedent for industry pressure:
  – Companies are pushing the MCC to register drugs that are far from properly tested

• Making medicines available pre-approval is not something to be done at a whim!
If there’s one book you read ...
Drug-resistant TB outcomes are poor

- Meta-analysis 9,000 MDR TB patients: 46% died, relapsed, defaulted or failed treatment
- Durban cohort of 60 people: 25 died, 12 cured
- Tugela Ferry 2007-2009: 82% XDR TB mortality, 69% MDR TB mortality

Sources: Gandhi 2009, O’Donnell 2009, Ahuja 2012
Side effects of the current regimens

• Colisle Lushaba
  – MSF project, Swaziland
Evidence for bedaquiline 1

• Phase II trial of 47 patients:
  – Standard background therapy + placebo vs Standard background therapy + bedaquiline
    • Bedaquiline significantly reduced time to sputum conversion (nearly half vs less than 10%)
    • Two year follow-up data confirms effect
    • Side effect: nausea

Sources: Diacon 2009, 2012
Evidence for bedaquiline 2

• Open label safety trial
  – Over 200 patients
  – 24 weeks bedaquiline
  – Well tolerated
  – 81% sputum culture conversion

Source: Pipeline Report 2012
Evidence for bedaquiline 3

• Phase I data
  – Well tolerated with efavirenz
  – Side effect: QT prolongation

Source: Dooley 2012
3.1 In the treatment of patients with MDR-TB, a fluoroquinolone should be used (strong recommendation, ☑️☀️☀️☀️/very low quality evidence).

3.2 In the treatment of patients with MDR-TB, a later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used (conditional recommendation, ☑️☀️☀️/very low quality evidence).

3.3 In the treatment of patients with MDR-TB, ethionamide (or prothionamide) should be used (strong recommendation, ☑️☀️☀️/very low quality evidence).

3.4 In the treatment of patients with MDR-TB, four second-line antituberculosis drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, should be included in the intensive phase³ (conditional recommendation, ☑️☀️☀️/very low quality evidence).

3.5 In the treatment of patients with MDR-TB, regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or PAS (p-aminosalicylic acid) if cycloserine cannot be used (conditional recommendation, ☑️☀️☀️/very low quality evidence).
Bedaquiline vs current treatment

• SA MDR TB guidelines:
  – Pyrazinamide, kanamycin, ethionamide, levofloxacin, terizidone and sometimes linezolid

• Pyrazinamide: Often patients resistant

• All others:
  – Evidence is worse than bedaquiline!
  – Side effects are worse than known bedaquiline ones.
There are precedents

• 35,000 people with HIV took didanosine in the early 1990s in the US and Europe before it was approved.
• Thousands with HIV took another adefovir.
• There are risks: Didanosine was approved, but not adefovir.
• In South Africa, lopinavir/ritonavir was available pre-approval.
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