The case for pre-approval access to bedaquiline

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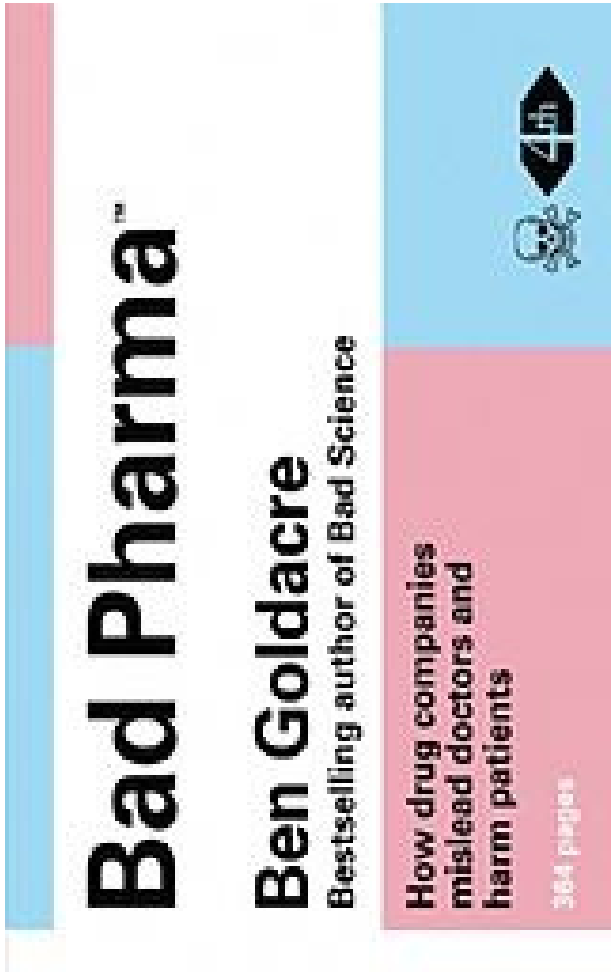
Legitimate concerns

- 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
  - Only 12 cured
- Tugela Ferry 2007-2009
  - XDR TB mortality: 82%
  - MDR TB mortality: 69%

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

Recommendations

Source: WHO

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 anti-tuberculosis drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, should be included in the intensive phase[3] (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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