# Development of new FDCs for children

Cécile Macé

# Treatment of TB in children

- Previously recommended treatment doses in2006
- Rational for review:
  - Previously recommended dosing extrapolated from adult dosing leading to lower serum concentration
  - Long standing appreciation that doses prescribe for children require adaptation to yield the same exposure as in adults
- Serie of systematic reviews of literature related to:
  - pharmacokinetics,
  - hepatotixicity,
  - efficacy and safety of intermittent treatment
  - efficacy, safety and pharmacokinetics on 1st line TB medicines for children less than 3 months
- Cochrane review published in 2010

# Rapid Advice published in 2010

- Change in dosages proposed based on reviews and modelling:
  - Isoniazid (H) - 10mg/kg (range 10-15mg/kg); maximum dose 300mg/day
  - Rifampicin (R) - 15mg/kg (range 10-20mg/kg); maximum dose 600mg/day
  - Pyrazinamide (Z) - 35mg/kg (30-40mg/kg)
  - Ethambutol (E) - 20mg/kg (15-25mg/kg)
- Introduction of E for the intensive phase for children leaving in high prevalence HIV settings or where INH resistance is high

# Impact on Procurement

- The quality-assured FDCs available on the market cannot deliver the required doses
  - Dispersible (RHZ 60/30/150, RH 60/30)
  - Non dispersible (RH 150/75, RHE 150/75/275, RHZE, RH 150/150)
- WHO removed the existing FDCs from the WHO EML for children in 2009 (only loose products are available)
- Interim dosing guidelines using currently available fixed dose combination developed by WHO in August 2009
- But difficult to implement at country level: multiple tablets and additional loose products. Lot of countries don’t implement it!
- Need for the development of adapted FDCs
- Formulations proposed: Practically not feasible, too big!
  - R250/H150/Z400/E250 as dispersible tablet for children

# Consultation meeting in July 2011

- Objectives:
  - To discuss the regulatory aspects of potential new FDCs (efficacy aspect)
  - To identify problems to be solved to get TB FDCs in the right dose and form for children and identify solutions and key actors
- Outcome
  - Paediatric effectiveness can be extrapolated from adequate and well-controlled efficacy studies in adults supplemented by other info on paediatric patients such as PK and safety studies
  - Studies not needed in each paediatric group (except for specific group such as below 2 years)
  - Modelling will be enough for regulatory requirements in children over 2 years

# Consultation meeting in July 2011

- Outcome
  - No clear guidance for manufacturers on the composition of the new FDCs
  - Not clear if further studies are needed to begin FDC development for children over 2 years
  - No committment pharmacokinetic studies for children below 2 years will be carried out rapidly
- Manufacturers understandably unwilling to invest in the development of new FDCs until unequivocal guidance is provided by WHO
- It will take 3 to 5 years to get quality-assured adapted FDCs available to treat children
- Discussion on possibility to develop kits according to interim dosing guidelines

# Questions

- Which countries have switched to new WHO recommendations?
- What is their feedback on the use of the interim instructions using existing FDCs?
- Position from The Union when advising countries on treatment for children

# Feedback from GDF meeting with TB manufacturers in August 2011

Cécile Macé

# Objectives

- Outline main challenges to secure and increase global TB drug supply in the public sector
- Share experiences of the India TB programme
- Generate ideas on collaboration to enhance TB medicine procurement and quality assurance (consolidating demand and providing realistic forecast with confirmed funding)
- Initiate the process of developement of a realistic action plan addressing the challenges on TB drug supply in the public sector

# Key points

- Consolidation needed for Active Pharmaceutical Ingredients (API) and finished products from WHO prequalified sources: critical for continued development and ultimate sustainability of the TB drug market
- Steps must be taken to rapidly increase the number of patients to be put on treatment: in conjunction with demand consolidation this will result in reduction of cost of treatment for MDR TB
- India’s role: Could play an important role to leverage the number of patients on MDR-TB

# Key points

- Need for process reforms within GDF to increase quality of services to keep current clients and potentially attract some others
- Funding committment is necessary: joint meeting with donors highly recommended to guarantee money is available and disbursed at the right time and make sure donors are supportive of the purchase of quality assured products
- Importance of involving national regulatory authorities in setting

# Next steps

- Development of an action plan for 2nd line TB medicines and establishment of a permanent working group to implement the agreed plan (The Union being part of it)
- A plan of action still te be developed for 1st line TB medicines
- Meeting in Lille on Friday 28 October as a starting point for prioritizing among the objectives for 2nd line TB medicines and have a document to be circulated largely
- Commitment from GDF management to improve quickly their services but quid of the