(1) Does the application adequately address the issue of the public health need for the medicine?
   Yes  X

Five per cent of TB cases were estimated to have had MDR-TB in 2013 (3.5% of new and 20.5% of previously treated TB cases). Drug resistance surveillance data show that an estimated 480,000 people developed MDR-TB in 2013 and 210,000 people died. Extensively drug resistant TB (XDR-TB) has been reported by 100 countries in 2013. On average, an estimated 9% of people with MD-TB have XDR-TB. Curing patients with drug-resistant TB and interrupting the spread of these strains of TB bacteria requires a wide range of resources, including effective antibiotics.

(2) Have all important studies that you are aware of been included in the application?
   Yes  X

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?
   Yes  X

The evidence for terizidone efficacy is very limited. More clinical evaluation is needed however the possible benefits of using terizidone outweigh the potential risk.

(4) Is there evidence of efficacy in diverse settings and/or populations?
   Yes  X

A typical MDR-TB regimen is composed of pyrazinamide plus at least 4 second line anti-TB drugs considered to be effective, including a later-generation fluoroquinolones, a second-line injectable, ethionamide (or prothionamide) and cycloserine or PAS. Terizidone, which is a Group 4 drug, can be used in the place of cycloserine. It can also be used in XDR-TB regimens in the place of cycloserine.
(5) Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?
   Yes  X

Terizidone showed no better to moderately better safety than CS in a systematic review of the available literature. Greater attention to the patients' mental health is thus essential.

ADDITIONAL CONSIDERATIONS:

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?
   Yes  X

Adequate information on possible ADRs should be provided to patients, their families and attending health care workers. Greater attention to MDR-TB patients' mental health is essential. Baseline and monthly depression screening should be done.

It is recommended that terizidone is administered by DOT.

The use of terizidone requires that countries agree to implement it under the 5 conditions recommended by the WHO, including: 1) careful selection of patients; 2) close monitoring of patients; 3) use in a regimen that follows WHO recommendations; and 4) active pharmacovigilance.

(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)
   No  X

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?
   No  X

(9) Please comment briefly on issues regarding cost and affordability of this medicine.

First marketed in Germany 1 January 1978. Only quality assured supplier is Fatol, in Germany. However, it is a scheduled medication in South Africa, regulated by the Medicines Control Council. Sanofi manufactures terizidone in South Africa under the trade name Terivalidin® and has plans for future expansion.
Macleods in India manufactures terizidone capsules 250 mg and 300 mg but it is not a WHO/SRA/ERP Approved Product. Cost should be around 900 to 2000 US dollars per six months.

(10) Any additional comments?

Although the approval of terizidone for the treatment of MDR TB represents a critical step forward in eliminating TB, we need to continue to develop treatment options for TB.

(11) Please summarise the action you propose the Expert Committee takes.

I will recommend the addition of TERIZIDONE oral administration (Capsule: 250 mg) to the EM Complementary List, Reserve second-line drugs for the treatment of multidrug-resistant tuberculosis (MDRTB).