Reviewer No. 1
checklist for application of: Procaine benzylpenicillin
In the WHO Essential Medicines List

(1) Have all important studies that you are aware of been included?
   Yes ☐  No  √

(2) Is there adequate evidence of efficacy for the proposed use?
   Yes ☐  No  √ *1

(3) Is there evidence of efficacy in diverse settings and/or populations?
   Yes ☐  No  √ *2

(4) Are there adverse effects of concern?
   Yes  √ *3  No  ☐

(5) Are there special requirements or training needed for safe/effective use?
   Yes  √ *4  No  ☐

(6) Is this product needed to meet the majority health needs of the population?
   Yes  √ *5  No  ☐

(7) Is the proposed dosage form registered by a stringent regulatory authority?
   Yes  √  No  ☐

(8) What action do you propose for the Committee to take?

To retain procaine benzylpenicillin in the WHO Essential Medicines List without age restriction, but with a remark for neonates to be used only in community settings where the health system is weak, care seeking is low, and the burden of neonatal mortality is high, for home-based care if other facilities and options are unavailable.

(9) Additional comment, if any.

The review of the efficacy and safety of procaine benzylpenicillin has brought following information:

- There is very little reliable evidence on the efficacy and safety of procaine benzylpenicillin and penicillin preparations generally in neonates. Much of the available evidence is several decades old and not derived from randomised, placebo controlled trials.
The available data show that penicillin levels achieved in the CSF are lower with procaine benzylpenicillin than with aqueous penicillin G. The limited clinical data from one relatively small trial showed no difference in efficacy of the two penicillin preparations.

- The serum penicillin levels achieved from the administration of intramuscular procaine benzylpenicillin are substantially lower than those achieved with aqueous penicillin G.
- There are no clinical trials examining the efficacy of procaine benzylpenicillin in the treatment of severe neonatal infection and sepsis.
- The evidence from the studies of effectiveness of home and community management strategies for reducing neonatal mortality and morbidity suggests improved mortality and morbidity outcomes for neonates. However, while the use of intramuscular procaine benzylpenicillin appears to be an integral component of these successful strategies, it is not possible to separate the effect of procaine benzylpenicillin from that of other components. Consequently, further research is necessary to ascertain the effectiveness of intramuscular procaine benzylpenicillin in the home and community based management of serious neonatal infection and sepsis.

- In terms of safety, none of the identified studies have reported an analysis of the incidence of adverse events, over this time it has generally been reported that procaine benzylpenicillin has been well tolerated. Despite published case reports of serious adverse events, it appears that both aqueous and procaine benzylpenicillin are relatively safe when viewed in context of the number of newborns treated.
- The use of procaine benzylpenicillin in neonates appears to provide a long acting, once daily administered antibiotic therapy that can be effectively and safely managed in the community setting by appropriately trained community health workers when access to preferred antibiotic therapy is not available. Safety data available do not provide a compelling case for recommending that procaine benzylpenicillin should not be used in neonates.

*1 the available evidence is not strong to support the use of procaine benzylpenicillin in the treatment of neonatal infections (there is not statistical significance in the efficacy between aqueous penicillin and procaine benzylpenicillin; in contrary, the CSF penetration is better for other penicillins, i.e. aqueous crystalline penicillin)

*2 in neonatal population the evidence is very week for its efficacy and compared with other antimicrobials; but in settings with low income and restricted availability of medical services, the intramuscular procaine benzylpenicillin incorporated in other strategies is efficient in reducing the neonatal mortality

*3 the adverse effects are more frequent in neonates, especially in those born prematurely and with low birth weight. This data restrict its use and inclusion only for clinical guidelines developed for settings where other antimicrobials and route of administration are unavailable

*4 training is necessary for intramuscular administration of the medicine
this medicine meets the needs of the population in low income settings for treatment of penicillin sensitive infections only in cases when other aqueous penicillins or antimicrobials are unavailable