

Statistical Memorandum

NDA: 20-634/S-047 (tablets) (dated 7.30.07)
20-635/S-051 (injection)
21-721/S-015 (oral solution)

PRODUCT NAME: Levaquin® (levofloxacin)
(250 mg, 500 mg, 750 mg, 25 mg/ml, 5 mg/ml)

INDICATION: Pediatric use in inhalational anthrax (post-exposure)

APPLICANT: J&JPRD

REVIEWER: LaRee A. Tracy, MA

Levofloxacin tablets, injection and oral solution, sNDAs 20-634/S-035, sNDA 20-635/S-035 and sNDA 21-721/S-003 respectively, are approved for the indication of post-exposure prophylaxis (PEP) for inhalational anthrax in adults (approval **11.24.04** under 21 CFR 314 Subpart H). Under subpart H, marketing approval may be granted by the FDA “...on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.” Due to the ethical requirement and disease prevalence constraints an alternate means of evaluating levofloxacin efficacy for the treatment of post-inhalational anthrax in humans is required. As stated in the FDA’s guidance document on the development of treatment for post-inhalational anthrax exposure, a non-human primate model that models the drug disposition in humans is considered an adequate surrogate for human disease and objective endpoints such as mortality, time of death relative to antimicrobial use, pathology, and bacteremia in the macaque are key endpoints in the determination of efficacy for humans. The approved dose and duration is 500 mg q24h for 60 days. The sponsor is now seeking approval for this indication in pediatric patients.

The approval of levofloxacin in adults for PEP for inhalational anthrax was primarily based on results from a single animal efficacy challenge study using the rhesus monkey model, pharmacokinetic and microbiologic data.. In this study, thirty (30) rhesus monkeys were treated twice daily, with levofloxacin, ciprofloxacin, or placebo for 30 days following exposure to lethal doses of inhalational anthrax in a controlled setting. Following the 30 day treatment period, animals were observed for death or morbidity for an additional 70 days. Survival was 90% (9/10) in the levofloxacin group, 80% (8/10) in the ciprofloxacin group, and 10% (1/10) in the placebo group. Survival was significantly better ($p=0.0011$, two-sided Fishers exact test) and time to death was significantly longer ($p<0.0001$, log rank test) in the levofloxacin group compared to the placebo group. All deaths in the placebo group occurred by day 8 following anthrax exposure while deaths in the levofloxacin ($n=1$) and ciprofloxacin ($n=2$) groups occurred on day 39 and

days 58/67 respectively. ***The complete statistical review is available in DFS (date submitted 11.1.04).***

The Division was not comfortable approving this indication in pediatric patients during the original review for adults because the sponsor was still conducting pediatric studies under a Pediatric Written Request (WR) and collecting pediatric safety data. (b) (4)

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Upon completion of the pediatric studies, the sponsor submitted pediatric safety and PK data to NDA 20-634/S-043, NDA 20-635/S-046, and NDA 21-721/S-011 on December 20, 2006. Review of these supplemental NDAs, particularly results from a long-term surveillance study, LTSS-001, led to labeling changes noting an increased risk of musculoskeletal disorders in pediatric patients. ***The modified label was approved on 9.11.07 and the statistical review is available in DFS (submitted on 6.21.07).***

Both the efficacy and safety data for levofloxacin for the use in PEP of inhalational anthrax in pediatrics has already been reviewed under separate sets of supplemental NDAs. The new applications contain proposed labeling and cross-references to NDA 20-634/S-035, NDA 20-635/S-035, and NDA 21-721/S-003 (adult inhalational anthrax PEP indication) and NDA 20-634/S-043, NDA 20-635/S-046, and NDA 21-721/S-011 (pediatric safety and PK submitted under Pediatric WR).

This current review pertains to NDA 20-634/S-047 (tablets), NDA 20-635/S-051 (injection), and NDA 21-721/S-015 (oral solution) and cross-referenced pediatric safety and PK data (previously reviewed) for levofloxacin for inhalational anthrax PEP in pediatrics. No new clinical data were provided within these submissions and therefore a statistical review is not required. Refer to previous statistical reviews (noted above) of cross-referenced submissions.

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/s/

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