Physiological modeling of uric acid in man: application to assess benefit-risk of lesinurad in gout

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Objectives: Lesinurad (Zurampic) is a novel selective uric acid reabsorption inhibitor (SURI) recently approved in combination with xanthine oxidase inhibitors (XOI) for chronic treatment of hyperuricemia in gout patients who have not achieved target serum uric acid (sUA) with an XOI alone. Modeling of clinical data can help quantify benefit-risk of alternative dose regimens and treatment strategies [1]. The objectives of this work were to provide further justification of a once daily regimen of lesinurad supported by Phase 3 clinical data; and for using lesinurad in combination with increased allopurinol dosing.

Methods: A model was developed to describe the physiologic turnover of uric acid in man including its production and intestinal and renal clearance. The stimulatory effect of lesinurad on renal clearance of uric acid and the inhibitory effect of allopurinol on its production were described by saturable functions of drug plasma concentration. The model was developed using serial uric acid data in serum and urine in 278 subjects from 9 Phase 1 studies and qualified using data from 6 Phase 3 studies. The model predicts population mean of sUA concentration and excretion of uric acid in urine (uUA).

Results: Simulation showed that twice daily lesinurad results in higher uUA concentration (and the potential to cause adverse events via uric acid precipitation) after the evening than the morning dose because of slower urine flow and lower urine pH at night thus confirming the decision to use once daily dosing in the morning in the lesinurad Phase 3 program. Adding 200 mg lesinurad once a day to allopurinol results in greater lowering of sUA than allopurinol monotherapy. Additional lowering is similar across the range of allopurinol doses used in clinical practice.

Conclusions: Modeling supports improved benefit-risk of once daily over twice daily dosing and additional sUA lowering by lesinurad regardless of the allopurinol dose.

Reference: