Pharmacokinetics of Nalbuphine Hydrochloride Extended Release Tablets in Hemodialysis and Healthy Subjects following Multiple Escalating Oral Doses

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Abstract

Purpose: Uremic pruritus (UP) is a chronic itch disorder common in end-stage renal patients or hemodialysis. The disease can be a disabling and distressing condition with significant impact on the patient with no approved therapies in the US or EU.

Methods: Uremic pruritus (UP) is neuropathic and is believed to be transmitted by activation of independent neural circuit via opioid kappa agonist and direct antagonism of mu opioid receptor. Nalbuphine PK in HD patients was well described by a one compartment model with first order elimination, and a dialysate compartment for nalbuphine. A one compartment PK model, driven by nalbuphine in the central compartment, with first order elimination, and a dialysate compartment for nalbuphine was selected to describe the PK of nalbuphine. A one compartment PK model for M3, which was driven by nalbuphine in the central compartment, with first order elimination, and a dialysate compartment for nalbuphine was selected to describe M3 concentrations in plasma and nalbuphine dialysate concentrations in dialysis and non-dialysis study. PK model for M3 was appropriate for describing M3 concentrations in plasma and nalbuphine dialysate concentrations necessary for interpatient and intrapatient variability analysis in efficacy studies with nalbuphine PK sampling.

Results: Nalbuphine PK in HD patients was well described by a one compartment model with first order elimination, and a dialysate compartment for nalbuphine. A one compartment model for M3, which was driven by nalbuphine in the central compartment, with first order elimination, and a dialysate compartment for nalbuphine was selected to describe the PK of M3. Nalbuphine removed by dialysis is described by the dialysate compartment. Interindividual and intrapatient variability were included in the model. Final model PK profile in HD patients was evaluated using goodness-of-fit and visual predictive check (VPC). Estimated parameter uncertainty was less than 30% of the parameter estimate.

Conclusions: Nalbuphine 30 mg BID can safely administered in HD subjects without significant PK interaction. Additional PK studies in UP patients will facilitate exposure-response analysis in efficacy studies with nalbuphine PK sampling.

Study Information

Male or female (19) and female (5) subjects with an average age of 47 years and a BMI of 29.7. Clinical PK data was collected during escalating doses of nalbuphine hydrochloride extended release tablets over 13 days or 15 days in HD and healthy subjects. No clinical PK data on subjects with small volume of distribution.

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