Summary

Oxytocin is a peptide hormone produced in hypothalamus and released systemically via the posterior pituitary. Oxytocin has *in vitro* been shown to exert positive effects on the proliferation of human vaginal mucosal cells and vaginal administration of oxytocin has been suggested to be an approach to treat vaginal atrophy.

The present population pharmacokinetic analysis aims at characterizing the population pharmacokinetics (PopPK) of vaginally and intravenously administered oxytocin in the target population based on PK data from study OXYPEP002 (**Fel! Hittar inte referenskälla.**) and OXYPEP003 (**Fel! Hittar inte referenskälla.**).

OXYPEP002 was a parallel, placebo controlled dose-response study in 64 healthy postmenopausal women. The patients were administered vaginally with Vagitocin 400IU, Vagitocin 100IU, or placebo once daily for 7 weeks. PK sampling was performed for 24 patients with sampling at baseline (pre-dose) and after 2 weeks of treatment (pre-dose and at 30, 60 and 90 min post-dose).

OXYPEP003 was an open-label, two-period study in 12 healthy postmenopausal women. Each subject was administered vaginally with Vagitocin 400IU once daily for 15 days (period I) and, after a washout period, a single intravenous dose of oxytocin, 10 IU Syntocinon® (period II). Rich blood sampling was collected on Day 1, 15 and 22. In addition, single blood samples were collected on Day 5, 8, 12, 16, 19, 23 and 26.

A total of 33 individuals were included in the analysis, 21 individuals from OXYPEP002 and 12 individuals from OXYPEP003. A total of 651 oxytocin plasma concentrations were included, of which 78 were baseline observations, 180 were observations following intravenous administration, and 393 were observations following intravaginal administration.

The final PopPK model described the pharmacokinetics of oxytocin with a two-compartment disposition model with a flexible parallel absorption model to account for double peaks in the concentration time profile following intravaginal administration. The clearance (CL), volume of distribution at steady state (Vss), distribution half-life ($t_{1/2\alpha}$) and terminal half-life ($t_{1/2\beta}$) was estimated to 28 L/h, 15 L, 5.4 min and 1.1 h, respectively.

The absorption following vaginal administration showed considerable variability both between and within individuals. The bioavailability (F) following vaginal administration was estimated to be 2.3% for the typical patient. There was no indication of any systematic change in endogenous oxytocin levels during the course of treatment. Based on a graphical exploration of covariate relationships, trends indicated a lower bioavailability with increasing bodyweight, age and years following menopause.

This analysis was conducted with consideration of the “Guidance for Industry: Population Pharmacokinetics” issued by FDA 1999 and “Guidance on Reporting the Results of Population Pharmacokinetic Analyses” issued by CHMP 2007.