Solubility and Bioavailability Improvement of Pazopanib Hydrochloride (PZH)

M. Herbrink, S. L. Groenland, N. Steeghs, A. D. Huitema, J. H. Schellens, J. H. Beijnen, B. Nuijen
Netherlands Cancer Institute

Purpose
PZH is currently marketed as Votrient® and is registered for treatment of advanced renal cell carcinoma and advanced tissue cell carcinoma. The absolute bioavailability (BA) of PZH is low (14-39%) and is mainly hindered by the low aqueous solubility of the drug. Furthermore, the exposure and plasma levels exhibit a similarly high inter- and intra-individual variability. Increasing the solubility of PZH may lead to an improved BA and exposure. Moreover, as the extent of the drug absorption increases, the variability thereof and of the resulting exposure may become less.

The objective of this study was to improve the solubility of PZH through the development of a new solid oral dosage form. Additionally, the effect of the solubility improvement on the BA and the pharmacokinetics, and the variability thereof, of PZH was studied.

Methods
The compatibility of PZH with a broad range of excipients was examined using thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), Fourier-transform infrared spectrometry (FTIR) and high performance liquid chromatography (HPLC). The solubility and dissolution behavior of PZH and of PZH-excipient combinations was tested using a pH-switch dissolution system to simulate the stomach and intestinal conditions along with the transfer region. The best performing formulation was physically characterized using dynamic light scattering (DLS), electron microscopy (EM) and X-ray powder diffraction (XRD). Additionally, the short- and long-term stability of the final formulation was analyzed.

Results
PZH exhibited an overall adequate compatibility with most of the studied excipients. An interaction was observed for the combinations PZH/PEG6,000, PZH/PEG35,000 and PZH/Lactose monohydrate. These combinations were not considered further in the formulation development. The solubility of PZH showed a pH-dependent profile, with a maximum at pH 3.0. The dissolution behavior of Votrient® displayed similar behavior; approximately 50% solubility in simulated gastric fluid (SGF), a small increase upon initial pH-increase and a collapse of solubility towards simulated intestinal fluid (SIF) at pH 6.8.

In 10% polymer solutions, the solubility of PZH was increased the most by Kollidon VA64, Kollidon 30, Soluplus® and Lutrol F68. Various ratios of these excipients and PH were produced by small-scale wet mixing with methyl-tert-butyl ether (MTBE). The powder mixtures all showed an initial increase in the solubility of PZH in SGF, as compared to Votrient®. Of these excipients, only Soluplus® was capable of maintaining >50% solubility of PZH after the transformation of SGF to SIF. The best performing formulation was 1/8 w/w binary mixture of PZH and Soluplus® (PazSol). DLS and EM show that PazSol powder consists of a fine distribution of PZH crystals in a more wide distribution of Soluplus® particles. PazSol forms micelles that solubilize PZH over extended time periods. The micelle formation is pH-sensitive with a favorable size distribution of 86 +/- 10 nm in SIF.

Patients receiving 100 mg PZH as PazSol in the form of powder-filled capsules exhibited lower-to-similar exposure (70 μg/mL*hr, N=3) as with 100 mg Votrient® (97 μg/mL*hr). Upon receiving 200 mg PazSol, the exposure more than doubled (192 μg/mL*hr, N=3), where Votrient® did not (105 μg/mL*hr). Patients that were administered 300 mg showed an exposure (379 μg/mL*hr, N=6) that was similar to 800 mg Votrient® (275 μg/mL*hr). The maximum and minimum plasma concentrations of PazSol (28.4 and 11.3 μg/mL, respectively) were also similar to the 800 mg Votrient® parameters (19.4 and 9.4 μg/mL, respectively).

Conclusion
The developed increased-solubility formulation both increases the BA of PZH in vivo and decreases the variability in PK parameters. Further scale-up and tablet-suitability and stability studies still need to be performed.