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ORIGINAL ARTICLE

Development of a population pharmacokinetic model for the novel long-acting injectable antipsychotic risperidone ISM®

Christian Laveille[1] | Eric Snoeck[2] | Lourdes Ochoa Díaz de Monasterioguren[3] | Javier Martínez-González[3] | Jordi Llaudó[3] | Lourdes Anta[3] | Ibon Gutierro[3]

[1]Calvagone SAS, Liergues, France

[2]Luccio bv, Retie, Belgium

[3]Laboratorios Farmacéuticos ROVI, S.A., Madrid, Spain

Correspondence
Lourdes Anta, Laboratorios Farmacéuticos ROVI, S.A., Alfonso Gómez 45, 28037 Madrid, Spain.
Email: lanta@rovi.es

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Abstract

Aims: The aims of this study were to develop a population pharmacokinetic (PK) model for risperidone ISM® and to investigate the relationships between active moiety exposure, as described by apparent clearance (CL_{40}), and several covariates using all data from five clinical studies.

Methods: A population PK model was developed using active moiety concentrations from a study in healthy volunteers and two studies in patients with schizophrenia. Data from a comparative bioavailability study in medically stable patients and a Phase III study in patients with acute exacerbation of schizophrenia were then incorporated, using empirical Bayesian feedback and model refinement in NONMEM. Finally, covariate analysis was performed on CL_{40}.

Results: The final model adequately described the pharmacokinetics of 6288 active moiety concentrations in 17 healthy volunteers and 430 patients with schizophrenia. This one-compartment disposition model had a complex absorption process, combining a small amount immediately entering the central active moiety compartment, two first-order absorption processes and a combined zero-order and first order process, with first-order elimination from the central compartment. Significant covariates on CL_{40} were BMI and sex. Goodness-of-fit (GOF) plots and visual predictive checks (VPC) confirmed acceptable description of the data.

Conclusions: The population PK model adequately described active moiety concentrations from five clinical studies after risperidone ISM® administration. Relationships between active moiety exposure and covariates were defined in order to facilitate simulations for future studies. The model showed that risperidone ISM® rapidly achieves therapeutic plasma levels within the first hours after the first injection that are maintained sustainedly throughout the whole dosing interval following once-monthly gluteal injections of 100 mg and 75 mg.

KEYWORDS

active moiety, atypical antipsychotic, ISM® technology, NONMEM, population pharmacokinetic analysis, schizophrenia, simulation