Etravirine has no effect on fetal development in rats and rabbits

Araz Raoof, Sophie Lachau-Durand, Johan Verbeeck, Graham Bailey, Mark Martens
Tibotec BVBA, Mechelen, Belgium; Johnson & Johnson Pharmaceutical Research and Development, Division of Janssen
Pharmaceutica N.V., Beerse, Belgium

Presenting author: Mark Martens
Tibotec BVBA
Generaal de Wittelaan L11 B3
B2800, Mechelen
Belgium
mmartens@tibbe.JNJ.com

Abstract

Background
The effect of etravirine (ETR; TMC125) on embryo-fetal and pre and postnatal development was assessed in pregnant rats and rabbits.

Methods
In the embryo-fetal study, ETR was administered at several oral doses up to 1000mg/kg/day in rats and 375mg/kg/day in rabbits during the period of fetal organogenesis (Gestation Day [GD] 6 to Day 16 in rats and Day 19 in rabbits). The uterus was examined and the number of implantations, live fetuses, fetal weight and sex distribution were analyzed. Fetuses were subjected to external and visceral examination. In the pre and postnatal study, ETR was administered (up to 500mg/kg/day) to pregnant rats from Day 7 of gestation through Day 21 of lactation. The clinical conditions, sensory functions, and behavior and reproductive performance of the first generation were assessed.

Results
ETR showed no adverse effect on embryo-fetal development at any doses tested in rats or rabbits. ETR also had no effect on offspring development and maturation during lactation or postweaning in rats. In these studies, maternal systemic exposure to ETR was equivalent to the clinical exposure (area under the plasma concentration-time curve from time of administration to 24 hours after dosing; AUC0–24h=7.4µg•h/mL) at the end of treatment and was 2–3-fold higher at the beginning of dosing during the early stages of organogenesis.

Conclusions
These studies confirm that ETR was safe in pregnant rats and rabbits.

Background and aims
- ETR is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that acts by binding to the HIV-1 gp120 gp41 protein (or envelope protein) and blocking membrane fusion
- ETR was developed because current NNRTIs are not active against all NNRTI resistant HIV strains
- The aim of this study was to evaluate the safety of ETR in pregnant rats and rabbits

Effect of ETR on embryo-fetal development in rats and rabbits

- ETR was administered during the period of organogenesis in rats and rabbits
- The uterus was examined and the number of implantations, live fetuses, fetal weight and sex distribution were analyzed
- Fetuses were subjected to external and visceral examination
- In the pre and postnatal study, ETR was administered from Day 7 of gestation through Day 21 of lactation
- The clinical conditions, sensory functions, and behavior and reproductive performance of the first generation were assessed

Results
ETR showed no adverse effect on embryo-fetal development at any doses tested in rats or rabbits. ETR also had no effect on offspring development and maturation during lactation or postweaning in rats. In these studies, maternal systemic exposure to ETR was equivalent to the clinical exposure (area under the plasma concentration-time curve from time of administration to 24 hours after dosing; AUC0–24h=7.4µg•h/mL) at the end of treatment and was 2–3-fold higher at the beginning of dosing during the early stages of organogenesis.

Conclusions
These studies confirm that ETR was safe in pregnant rats and rabbits.

Toxicokinetic data in female rats

- ETR was administered during the period of organogenesis in rats and rabbits
- The uterus was examined and the number of implantations, live fetuses, fetal weight and sex distribution were analyzed
- Fetuses were subjected to external and visceral examination
- In the pre and postnatal study, ETR was administered from Day 7 of gestation through Day 21 of lactation
- The clinical conditions, sensory functions, and behavior and reproductive performance of the first generation were assessed

Results
ETR showed no adverse effect on embryo-fetal development at any doses tested in rats or rabbits. ETR also had no effect on offspring development and maturation during lactation or postweaning in rats. In these studies, maternal systemic exposure to ETR was equivalent to the clinical exposure (area under the plasma concentration-time curve from time of administration to 24 hours after dosing; AUC0–24h=7.4µg•h/mL) at the end of treatment and was 2–3-fold higher at the beginning of dosing during the early stages of organogenesis.

Conclusions
These studies confirm that ETR was safe in pregnant rats and rabbits.

Conclusions
- ETR use was not associated with adverse effects on embryo-fetal development in:
  - pregnant Wistar rats at levels up to 1000mg/kg/day
  - pregnant NZW rabbits at levels up to 375mg/kg/day
- In both species, maternal exposure at the end of treatment was equivalent to human exposure at the recommended therapeutic dose:
  - exposure levels in the rabbit, however, exceeded clinical exposure at the beginning of dosing (during organogenesis), but subsequently declined due to autoinduction.
- ETR had no effect on offspring development in rats, during lactation and postweaning at doses ≤ 500mg/kg/day (equivalent to clinical exposure levels).
- Clinical data in pregnant humans are limited, and ETR should not be used during pregnancy unless the potential benefit justifies the potential risk.

Supported by Tibotec
Presented at the XVIIth International AIDS Conference, Mexico City, Mexico, August 3–8 2008.

This poster is available on-line at www.tibotec.com