Nevirapine (Viramune, NVP)

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Animal Studies

Carcinogenicity

Nevirapine (NVP) showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. Hepatocellular adenoma and carcinomas are increased at all doses of NVP in mice and rats; however, given the lack of genotoxic activity of NVP, it is unclear if this is relevant to humans.[1]

Reproduction/Fertility

Female rats showed impaired fertility at systemic NVP exposures comparable to human therapeutic exposures.[1]

Teratogenicity/Adverse Pregnancy Outcomes

In studies of rats and rabbits, no teratogenic effects of NVP have been observed other than a significant decrease in fetal weight in rats at systemic concentrations 50% higher than human therapeutic exposure.[1]

Human Studies in Pregnancy

Pharmacokinetics

The pharmacokinetics (PKs) studies of NVP in pregnant women who received NVP as part of antiretroviral therapy (ART) during pregnancy demonstrate varied results. A study of 26 women during their second and third trimesters did not find altered PK parameters compared to the postpartum period;[2] however, two other studies found up to 30% lower exposure in pregnancy.[3,4] No dose adjustment is currently recommended for NVP during pregnancy.

Placental and Breast Milk Passage

NVP demonstrates rapid and effective placental transfer, achieving near-equivalent concentrations in maternal and cord blood (cord blood-to-maternal-plasma ratio ranges from 0.60 to 1.02).[5,6]

NVP also has been shown to be excreted into human breast milk, with breast milk-to-maternal plasma ratios of 0.27 to 0.6 and detectable NVP concentrations in breastfeeding infants.[7–9]

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to NVP to detect at least a 1.5-fold increase in risk of overall birth defects and a twofold increase in risk of birth defects in the cardiovascular and genitourinary systems (the most common classes of birth defects in the general population). No such increase in the risk of birth defects has been observed with NVP. Among the cases of first-trimester NVP exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.0% (35 of 1,169 live births; 95% confidence interval [CI], 2.1% to 4.1%) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[10] Similarly, the French Perinatal Cohort reported no association between exposure to NVP and birth defects, with 71% power to detect a 1.5-fold increase.[11] During 2013–2014, at one KwaZulu hospital, one-time nurse-performed exams found a significantly higher risk ratio of total congenital malformations in infants with first-trimester NVP exposure (relative risk [RR] = 9.28, 2.27–37.94); 2 out of 52 infants with NVP exposure vs. 29 out of 7,592 without NVP exposure.[12]

Other Safety Information

The risk of NVP-associated severe, life-threatening, and (in some cases) fatal hepatotoxicity—including fulminant and cholestatic hepatitis; hepatic necrosis; hepatic failure; and severe, life-threatening hypersensitivity skin reactions, including Stevens-Johnson syndrome ranges—from 0.04% to 0.40%.[1,13] The greatest risk of

severe rash or hepatic events occurs during the first 6 to 18 weeks of therapy, although the risk of toxicity continues past this period and patients should be regularly monitored for signs of toxicity.

Incidence of severe NVP-associated skin rash has been reported to be 5.5 times to 7.3 times more common in women than men. In 17 clinical trials of NVP therapy, women with CD4 counts >250 cells/mm³ were 9.8 times more likely to experience symptomatic, often rash-associated, NVP related hepatotoxicity than women with lower CD4 counts.[13] Higher CD4 counts also have been associated with an increased risk of severe, NVP-associated skin rash.[14]

Rates of hepatotoxicity and rash similar to those in U.S. studies have been seen in international cohorts of nonpregnant women, although not all studies have reported an association between rates of hepatotoxicity and rash and CD4 counts >250 cells/mm³. Some researchers have suggested that genetic variation in drug metabolism polymorphisms (e.g., CYP2B6 variants), tumor necrosis factor receptor–associated factor (TRAF) proteins, and immune human leukocyte antigen loci may be associated with a higher risk of NVP-associated adverse events and that the relationship between genetic variants and adverse events may vary by race.[15–18] Published literature reports rash and hyperbilirubinemia in infants exposed to NVP through breast milk.[1]

Data are conflicting regarding the increased risk of hepatotoxicity in pregnant women receiving NVP.[19] In a systematic review of 20 studies that included 3,582 pregnant women from 14 countries who initiated NVP while pregnant, the pooled proportion of women who experienced a severe hepatotoxic event was 3.6% (95% CI, 2.4% to 4.8%), and the proportion of women who experienced severe rash was 3.3% (95% CI, 2.1% to 4.5%); overall, 6.2% of women stopped taking NVP because of an adverse event (95% CI, 4.0% to 8.4%).[20] These results were comparable to published frequencies in the general adult population and comparable to frequencies in nonpregnant women within the same cohorts; publications by Ouyang and colleagues echo these results.[21,22] In contrast, an analysis of data collected in the United Kingdom and Ireland from 2000 to 2011 evaluated 3,426 women, one-quarter of whom were pregnant, and found that pregnant women who were taking efavirenz, maraviroc, or NVP had an increased risk of liver enzyme elevation.[23]

Two systematic reviews and a small case-control study additionally indicate that pregnancy appears to increase the risk of cutaneous events, such as Stevens-Johnson. The systematic review discussed above also reported nonsignificant trends toward increased risk of cutaneous events (odds ratio [OR] 1.1; 95% CI, 0.8–1.6) and severe cutaneous adverse events in pregnant women with CD4 counts ≥250 cell/mm³ (OR 1.4; 95% CI, 0.8–2.4).[20] Another systematic review reported a significant association between increased toxicity risk and the initiation of NVP-based therapy during pregnancy in women with CD4 counts ≥250 cells/mm³.[24] A case-control study (6 cases, 30 controls) in South Africa reported that pregnancy increased the risk of Stevens-Johnson syndrome (OR 14.28; $P = 0.006$; 95% CI, 1.54–131.82).[25] NVP (as a component of a combination regimen) should be initiated in pregnant women with CD4 counts ≥250 cells/mm^3 only if the benefit clearly outweighs the risk. Women with CD4 counts <250 cells/mm^3 can receive NVP-based regimens, and women who become pregnant while taking NVP and who are tolerating their regimens well can continue using those regimens, regardless of their CD4 counts.

Because pregnancy itself can mimic some of the early symptoms of hepatotoxicity (i.e., pregnancy-related nausea and vomiting), health care providers caring for pregnant women who are receiving NVP should be aware of this potential complication. Frequent and careful monitoring of clinical symptoms and hepatic transaminases (i.e., alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) is necessary, particularly during the first 18 weeks of therapy. Some clinicians measure serum transaminases at baseline, every 2 weeks for the first month, and then monthly for the first 18 weeks; in patients with pre-existing liver disease, monitoring should be performed more frequently when initiating therapy and monthly thereafter.[26] Transaminase levels should be checked in all women who develop a rash while receiving NVP. Patients who develop suggestive

clinical symptoms accompanied by elevation in serum transaminase levels (ALT and/or AST) or who have asymptomatic but severe transaminase elevations should stop taking NVP and not receive the drug in the future.

In a retrospective study at eight government hospitals in Botswana, women who received ART regimens that contained NVP were more likely to experience certain adverse events than women on ART regimens that did not contain NVP, including hypertension (30% vs. 16%), severe hypertension (3.3% vs. 1.2%), gestational hypertension (18% vs. 10%), and early gestational hypertension (12% vs. 7%).[27]

Excerpt from Table 10

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
Nevirapine (NVP) *Viramune* *Viramune XR* **Note:** Generic products are available for some formulations.	**NVP (Viramune)** *Tablet:* • 200 mg[d] *Oral Suspension:* • 50 mg/5 mL[d] **Viramune XR** *Tablets:* • 100 mg • 400 mg[d]	**Standard Adult Doses** • NVP 200 mg once daily (using Viramune immediate release) for a 14-day lead-in period; thereafter, NVP 200 mg twice daily or 400 mg (using Viramune XR tablet) once daily, without regard to food. • Repeat lead-in period if therapy is discontinued for >7 days. • In patients who develop mild-to-moderate rash without constitutional symptoms during the lead-in period, continue lead-in dosing until rash resolves, but administer for ≤28 days total. **Pregnancy** *PKs in Pregnancy:* • PKs of immediate-release tablets not significantly altered in pregnancy. • No data available on extended-release formulations in pregnancy. *Dosing in Pregnancy:* • No change in dose indicated.	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects and twofold increase in cardiovascular and genitourinary defects). There is an increased risk of symptomatic liver toxicity when first initiating therapy in women with CD4 counts ≥250/mm^3. Liver toxicity is often associated with a rash and can be fatal. Pregnancy does not appear to increase this risk. NVP should be initiated in pregnant women with CD4 counts ≥250 cells/mm^3 only if benefit clearly outweighs risk. There is a potential increased risk of life-threatening hepatotoxicity in women with high CD4 counts. Elevated transaminase levels at baseline may increase the risk of NVP toxicity. Women who become pregnant while taking NVP-containing regimens and who are tolerating their regimens well can continue taking those regimens, regardless of their CD4 counts.

[a] Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 10).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:
High: >0.6
Moderate: 0.3–0.6
Low: <0.3
[d] Generic product available

Key: ARV = antiretroviral; CD4 = CD4 T lymphocyte; NVP = nevirapine; PK = pharmacokinetic; XR = extended release

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