

MANAGEMENT OF RASH WITH VIRAMUNE® (nevirapine)

Time to Onset of Rash²

- The risk of rash of any severity is greatest in the first 6 weeks

Incidence of Rash²

- In controlled clinical trials, the frequency of rash was 14.8% compared with 5.9% in controls
- The overall frequency of severe rash is 1.5%
- Stevens-Johnson syndrome (SJS) is estimated to occur in 0.3% (C.I. 0–0.5%)

Risk Factors for Rash Development²

- Women appear to be at higher risk of developing rash than men

Definitions

- Mild or moderate rash may include:
 - Erythema
 - Diffuse erythematous or maculopapular rash
- Severe rash may include:
 - Extensive erythematous or maculopapular rash
 - Rash with moist desquamation
 - Rash with angioedema
 - Serum sickness-like reaction
 - Stevens-Johnson syndrome
 - Toxic epidermal necrolysis (TEN)

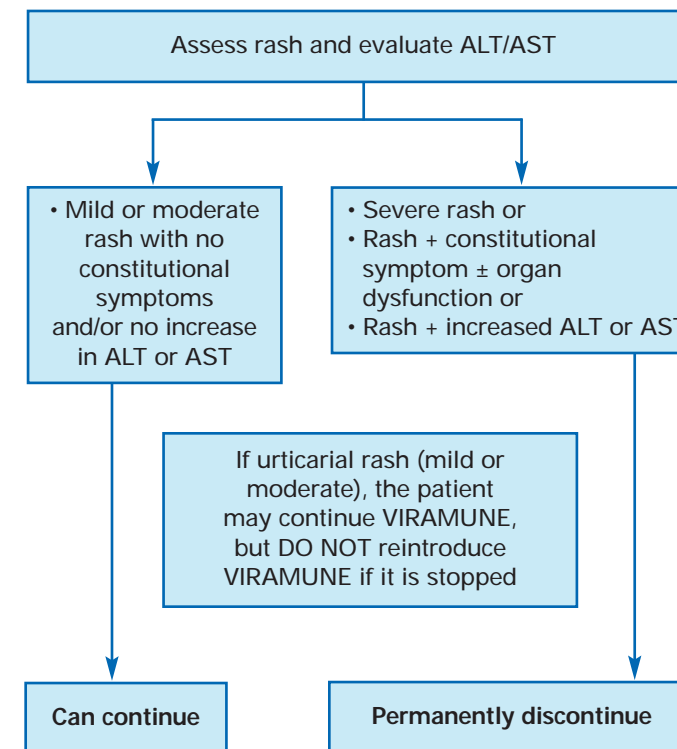
Patient Management

- The 200-mg once-daily lead-in dose prior to escalation to 200 mg twice daily after day 14 has been shown to reduce the frequency of rash and must be strictly followed
- Do not increase the dose of VIRAMUNE in the presence of rash
- If VIRAMUNE is interrupted for >7 days, reintroduce with the 14-day, 200-mg once-daily lead-in dose
- Initiation of VIRAMUNE and other medications that often cause rash (e.g., abacavir, trimethoprim-sulfamethoxazole) can make the identification of the responsible drug difficult. Where possible concurrent initiation should be avoided
- Prednisone should not be used to prevent rash. Prednisone administration during the first 2 weeks of therapy with VIRAMUNE appears to increase the incidence of rash
- Antihistamines do not appear to be effective in preventing rash with VIRAMUNE

Definitions (cont'd)

- Urticaria: pruritic raised rash with welts (may be mild, moderate, or severe)
- Constitutional symptoms include fever, blistering, oral erosive lesions, conjunctivitis, facial edema, and myalgia/arthritis

Rash Management Algorithm



VIRAMUNE is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with VIRAMUNE. These have included severe cases of SJS, TEN, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs and symptoms of severe skin reactions or hypersensitivity reactions must discontinue VIRAMUNE as soon as possible.

MANAGEMENT OF HEPATIC EVENTS WITH VIRAMUNE® (nevirapine)

Important Usage Information

- Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled studies, VIRAMUNE should not be initiated in adult females with CD4+ cell counts greater than 250 cells/mm³ or in adult males with CD4+ cell counts greater than 400 cells/mm³ unless the benefit outweighs the risk

Time to Onset of Hepatic Events^{1,2}

- In controlled clinical trials, the risk of hepatic events regardless of severity was greatest in the first 6 weeks of therapy. The risk continued to be greater in the groups receiving VIRAMUNE compared with controls through 18 weeks of treatment

Incidence of Hepatic Events^{1-3*}

- All antiretroviral drugs have been associated with hepatotoxicity
- VIRAMUNE is associated with asymptomatic ALT/AST >5X ULN[†] in 5.8% of patients compared with 5.5% of controls
- Symptomatic hepatic events are observed in 4.0% (range: 2.5%–11%) vs 1.2% of controls
 - About half of these cases were associated with rash
 - Symptomatic hepatic events occurred in 5.8% of women and 2.2% of men during the first 6 weeks of therapy
 - Symptomatic hepatic events occurred in 0.42% of women and 0.08% of men during week 7 through week 18
 - Women with CD4+ cell counts >250 cells/mm³ at initiation of VIRAMUNE therapy had an 11% rate of these events compared with 0.9% for women with CD4+ cell counts <250 cells/mm³
 - Men with CD4+ cell counts >400 cells/mm³ at initiation of VIRAMUNE therapy had a 6.3% rate of these events compared with 1.2% for men with CD4+ cell counts <400 cells/mm³

* Hepatic events include symptomatic hepatitis and/or ALT/AST >5X ULN.

[†] ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

[‡] Risk factors associated with regimens with and without VIRAMUNE.

[§] Signs and symptoms of hepatitis may include anorexia, malaise, jaundice, nausea/vomiting, hyperbilirubinemia, acholic stools, hepatomegaly, and hepatic tenderness. Other constitutional symptoms may include fever, arthralgia, fatigue, and findings of generalized organ dysfunction. The presence of one or more of these findings does not necessarily indicate hepatitis. Diagnosis should be based on sound clinical judgment.

^{||} If VIRAMUNE has been interrupted for >7 days, reinitiate with 200-mg once-daily lead-in dose.

Risk Factors for Symptomatic Hepatic Events^{1,2}

- Higher CD4+ cell count at initiation of VIRAMUNE therapy
- Female gender
- Women with CD4+ cell counts >250 cells/mm³ are at the greatest risk for hepatic events at the initiation of VIRAMUNE therapy

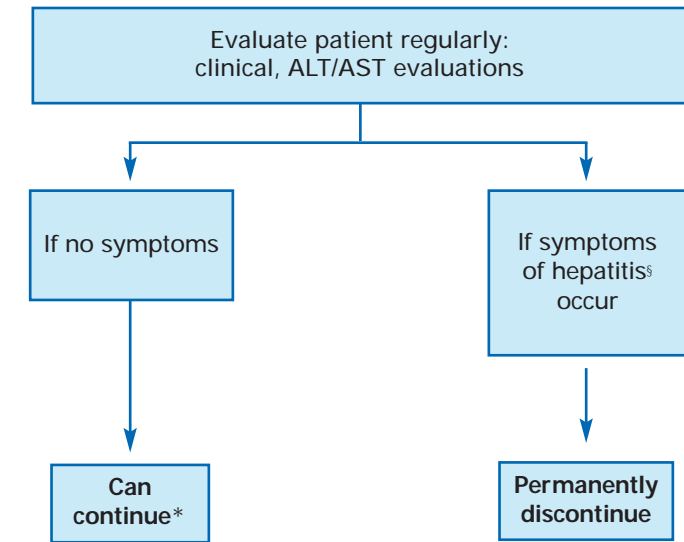
- Although hepatic events have occurred in pregnant women it is unclear how pregnancy affects risk
- Elevated pretreatment ALT or AST[†]
- HBV and/or HCV coinfection[†]

Patient Management

- Counsel patients that if signs or symptoms of hepatitis[§], severe skin reactions, or hypersensitivity occur, then discontinue VIRAMUNE and seek medical evaluation immediately
- Frequent clinical and laboratory monitoring is essential, especially during the first 18 weeks of treatment—extra vigilance is warranted during the first 6 weeks
- Baseline assessments should include LFTs and HBV/HCV status
- If hepatic symptoms or elevated LFTs with rash occur:
 - Permanently discontinue VIRAMUNE
 - Consider stopping all potential hepatotoxins, including concomitant antiretrovirals
 - Evaluate patient for other causes, including HBV/HCV coinfection, alcohol use, and coadministered medications
 - Continue to monitor patient until symptoms resolve
- In some cases, hepatic injury has progressed despite discontinuation of treatment

Severe, life-threatening, and in some cases fatal hepatotoxicity, particularly in the first 18 weeks, has been reported in patients treated with VIRAMUNE. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. Patients with signs or symptoms of hepatitis, or with increased transaminases combined with rash or other systemic symptoms, must discontinue VIRAMUNE and seek medical evaluation immediately.

Hepatic Event Management



* Patients who are doing well on VIRAMUNE therapy can continue with appropriate monitoring regardless of CD4 count.

Other Important Information

- The 14-day lead-in period with VIRAMUNE 200 mg daily must be strictly followed^{||}
- VIRAMUNE should not be used for multiple-dose postexposure prophylaxis. Serious hepatotoxicity, including hepatic failure, has occurred in this setting

VIRAMUNE is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection.

References: 1. Stern JO, Love JT, Robinson PA, et al. Hepatic Safety of Nevirapine: Results of the Boehringer Ingelheim Viramune® Hepatic Safety Project. XIV International AIDS Conference; July 7–12, 2002; Barcelona, Spain. Abstract LBO15. 2. Data on file. Boehringer Ingelheim Pharmaceuticals, Inc. 3. Reisler K. High hepatotoxicity rate seen among HAART patients. *AIDS Alert*. 2001;16:118–119.