# MANAGEMENT OF RASH WITH VIRAMUNE® (nevirapine)

## Time to Onset of Rash[2]

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

## Incidence of Rash[2]

- 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%)

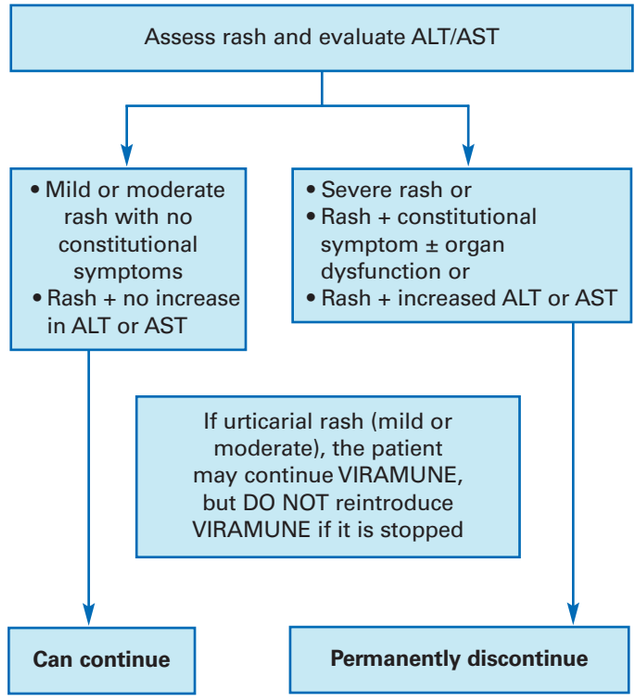
## Risk Factors for Rash Development[2]

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

## Patient Management

- The recommended 14-day, 200-mg once-daily lead-in dose, prior to escalation to 200 mg twice daily, 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
- It is suggested that VIRAMUNE and other medications that often cause rash (e.g., abacavir, trimethoprim-sulfamethoxazole) should not be started simultaneously
- 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

## Rash Management Algorithm




## 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)

## 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/arthralgia

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.**

These Guidelines, although not approved by the FDA, were produced by Boehringer Ingelheim Pharmaceuticals, Inc., to assist you in managing these events. Please consult enclosed Prescribing Information before prescribing VIRAMUNE® (nevirapine) tablets or oral suspension.

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# MANAGEMENT OF HEPATIC EVENTS WITH VIRAMUNE® (nevirapine)

## 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 8.8% of patients compared with 6.2% 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 occur in 5.8% of women and 2.2% of men during the first 6 weeks of therapy
  - Women with CD4+ cell counts >250 cells/mm$^3$ at initiation of VIRAMUNE therapy had an 11% risk of these events compared with 0.9% for women with CD4+ cell counts <250 cells/mm$^3$
  - Men with CD4+ cell counts >400 cells/mm$^3$ at initiation of VIRAMUNE therapy had a 6.3% risk of these events compared with 2.3% for men with CD4+ cell counts <400 cells/mm$^3$

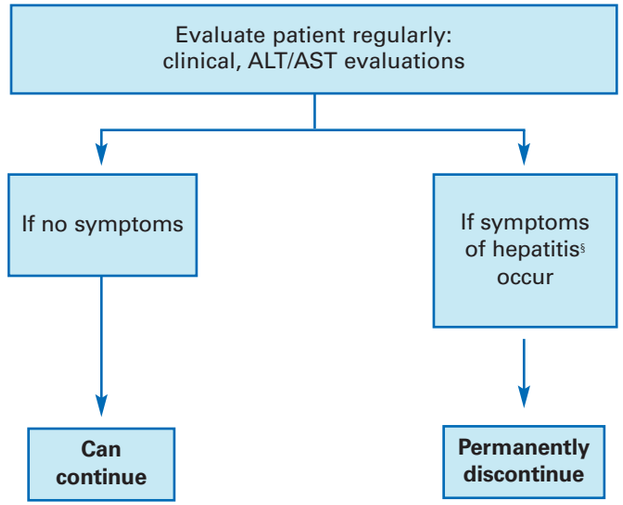
## Risk Factors for Symptomatic Hepatic Events[1,2]

- Elevated pretreatment ALT or AST
- HBV and/or HCV coinfection[‡]
- Higher CD4+ cell count at initiation of VIRAMUNE therapy
- Female gender
- **Women with CD4+ cell counts >250 cells/mm$^3$, including pregnant women receiving chronic treatment for HIV infection, are at considerably higher risk of hepatotoxicity, including fatal events**

## 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 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

## Hepatic Event Management




## 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

* 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, bilirubinemia, acholic stools, hepatomegaly, and hepatic tenderness. Other constitutional symptoms may include fever, arthralgia, fatigue, and other 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, reintroduce with 200-mg once-daily lead-in dose.

**Severe, life-threatening, and in some cases fatal, hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure, has been reported in patients treated with VIRAMUNE. In some cases, patients presented with nonspecific prodromal signs or symptoms of hepatitis and progressed to hepatic failure. Patients with signs and symptoms of hepatitis must seek medical evaluation immediately and should be advised to discontinue VIRAMUNE.**

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 LBOr15. **2.** Data on file. Boehringer Ingelheim Pharmaceuticals, Inc. **3.** Reisler K. High hepatotoxicity rate seen among HAART patients. *AIDS Alert.* 2001;16:118–119.

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