

# Use Histology to Confirm Endometriosis Diagnosis

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SAN DIEGO — When it comes to diagnosing endometriosis, visual inspection is not enough, Dr. Georgine Lamvu said at the annual meeting of the International Pelvic Pain Society.

“We need to be more careful to use excisional biopsies during laparoscopies and careful about the thorough evaluation of the pelvic structures, to record these so we

can keep track of the infiltration, size, and distribution of the lesions,” said Dr. Lamvu of the department of obstetrics and gynecology at the Florida Hospital, Orlando.

She went on to note that not all endometriosis causes chronic pelvic pain. In one study of 15 patients with presumed endometriosis who went on to have conscious laparoscopic pain mapping, endometriotic lesions reproduced pain in 7 patients, all of whom had histologic con-

firmation of the diagnosis. Endometriotic lesions did not reproduce pain in eight cases.

“Seven of nine cases with histologically confirmed endometriosis mapped their pain to endometriotic lesions but none of the six cases in which the visual diagnosis of endometriosis was not histologically confirmed mapped their pain to ‘endometriotic’ lesions,” she said. “So although it’s very important to confirm [the diagnosis with] histology, we should not

always assume that because you have pathology you’ll have pain.”

Level A evidence suggests that endometriosis is associated with chronic pelvic pain in 50%-70% of patients. “This still does not answer the question: Is endometriosis the source of their pain?” Dr. Lamvu said. “Eighty percent of women with chronic pelvic pain also end up being diagnosed with endometriosis at some point. That does not mean that the endometriosis is the source of pain.”

## Viramune® (nevirapine) Tablets Viramune® (nevirapine) Oral Suspension

Rx only

Brief Summary of Prescribing Information: see full Prescribing Information for complete product information.

### WARNING

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. These events are often associated with rash. Female gender and higher CD4 counts at initiation of therapy place patients at increased risk; women with CD4 counts >250 cells/mm<sup>3</sup>, including pregnant women receiving VIRAMUNE in combination with other antiretrovirals for the treatment of HIV infection, are at the greatest risk. However, hepatotoxicity associated with VIRAMUNE use can occur in both genders, all CD4 counts and at any time during treatment. 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 (see WARNINGS).

Severe, life-threatening skin reactions, including fatal cases, have occurred in patients treated with VIRAMUNE. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction. Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions must discontinue VIRAMUNE and seek medical evaluation immediately (see WARNINGS).

It is essential that patients be monitored intensively during the first 18 weeks of therapy with VIRAMUNE to detect potentially life-threatening hepatotoxicity or skin reactions. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of these events. Do not restart VIRAMUNE following severe hepatic, skin or hypersensitivity reactions. In some cases, hepatic injury has progressed despite discontinuation of treatment. In addition, the 14-day lead-in period with VIRAMUNE 200 mg daily dosing must be strictly followed (see WARNINGS).

### CONTRAINDICATIONS

VIRAMUNE (nevirapine) is contraindicated in patients with clinically significant hypersensitivity to any of the components contained in the tablet or the oral suspension.

### WARNINGS

#### General

The most serious adverse reactions associated with VIRAMUNE (nevirapine) are hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Hepatitis/hepatic failure may be associated with signs of hypersensitivity which can include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction.

The first 18 weeks of therapy with VIRAMUNE are a critical period during which intensive clinical and laboratory monitoring of patients is required to detect potentially life-threatening hepatic events and skin reactions. The optimal frequency of monitoring during this time period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, would include monitoring of liver function tests at baseline, prior to dose escalation and at two weeks post-dose escalation. After the initial 18 week period, frequent clinical and laboratory monitoring should continue throughout VIRAMUNE treatment. In addition, the 14-day lead-in period with VIRAMUNE 200 mg daily dosing has been demonstrated to reduce the frequency of rash.

#### Hepatic Events

Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, have been reported in patients treated with VIRAMUNE. In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4% (range 0% to 11.0%) of patients who received VIRAMUNE and 1.2% of patients in control groups.

The risk of symptomatic hepatic events regardless of severity was greatest in the first 6 weeks of therapy. The risk continued to be greater in the VIRAMUNE groups compared to controls through 18 weeks of treatment. However, hepatic events may occur at any time during treatment. In some cases, patients presented with non-specific, prodromal signs or symptoms of fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels. Rash was observed in approximately half of the patients with symptomatic hepatic adverse events. Fever and flu-like symptoms accompanied some of these hepatic events. Some events, particularly those with rash and other symptoms, have progressed to hepatic failure with transaminase elevation, with or without hyperbilirubinemia, hepatic encephalopathy, prolonged partial thromboplastin time, or eosinophilia. Rhabdomyolysis has been observed in some patients experiencing skin and/or liver reactions associated with VIRAMUNE use. Patients with signs or symptoms of hepatitis must be advised to discontinue VIRAMUNE and immediately seek medical evaluation, which should include liver function tests.

Liver function tests should be performed immediately if a patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity reaction. Liver function tests should also be obtained immediately for all patients who develop a rash in the first 18 weeks of treatment. Physicians and patients should be vigilant for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. The diagnosis of hepatotoxicity should be considered in this setting, even if liver function tests are initially normal or alternative diagnoses are possible (see PRECAUTIONS, Information for Patients and DOSAGE AND ADMINISTRATION).

If clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur, VIRAMUNE should be permanently discontinued. Do not restart VIRAMUNE after recovery. In some cases, hepatic injury progresses despite discontinuation of treatment.

The patients at greatest risk of hepatic events, including potentially fatal events, are women with high CD4 counts. In general, during the first 6 weeks of treatment, women have a three fold higher risk than men for symptomatic, often rash-associated, hepatic events (5.8% versus 2.2%), and patients with higher CD4 counts at initiation of VIRAMUNE therapy are at higher risk for symptomatic hepatic events with VIRAMUNE. In a retrospective review, women with CD4 counts >250 cells/mm<sup>3</sup> had a 12 fold higher risk of symptomatic hepatic adverse events compared to women with CD4 counts <250 cells/mm<sup>3</sup> (11.0% versus 0.9%). An increased risk was observed in men with CD4 counts >400 cells/mm<sup>3</sup> (6.3% versus 1.2% for men with CD4 counts <400 cells/mm<sup>3</sup>). However, all patients, regardless of gender, CD4 count, or antiretroviral treatment history, should be monitored for hepatotoxicity since symptomatic hepatic adverse events have been reported at all CD4 counts. Co-infection with hepatitis B or C and/or increased liver function tests at the start of therapy with VIRAMUNE® are associated with a greater risk of later symptomatic events (6 weeks or more after starting VIRAMUNE) and asymptomatic increases in AST or ALT.

In addition, serious hepatotoxicity (including liver failure requiring transplantation in one instance) has been reported in HIV-uninfected individuals receiving multiple doses of VIRAMUNE in the setting of post-exposure prophylaxis, an unapproved use.

Because increased nevirapine levels and nevirapine accumulation may be observed in patients with serious liver disease, VIRAMUNE should not be administered to patients with severe hepatic impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations: Hepatic Impairment; PRECAUTIONS, General).

### Skin Reactions

Severe and life-threatening skin reactions, including fatal cases, have been reported, occurring most frequently during the first 6 weeks of therapy. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction including hepatic failure. Rhabdomyolysis has been observed in some patients experiencing skin and/or liver reactions associated with VIRAMUNE use. In controlled clinical trials, Grade 3 and 4 rashes were reported during the first 6 weeks in 1.5% of VIRAMUNE recipients compared to 0.1% of placebo subjects.

Patients developing signs or symptoms of severe skin reactions or hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and/or hepatitis, eosinophilia, granulocytopenia, lymphadenopathy, and renal dysfunction) must permanently discontinue VIRAMUNE and seek medical evaluation immediately (see PRECAUTIONS, Information for Patients). Do not restart VIRAMUNE following severe skin rash, skin rash combined with increased transaminases or other symptoms, or hypersensitivity reaction.

If patients present with a suspected VIRAMUNE-associated rash, liver function tests should be performed. Patients with rash-associated AST or ALT elevations should be permanently discontinued from VIRAMUNE.

Therapy with VIRAMUNE must be initiated with a 14-day lead-in period of 200 mg/day (4 mg/kg/day in pediatric patients), which has been shown to reduce the frequency of rash. If rash is observed during this lead-in period, dose escalation should not occur until the rash has resolved (see DOSAGE AND ADMINISTRATION). Patients should be monitored closely if isolated rash of any severity occurs. Delay in stopping VIRAMUNE treatment after the onset of rash may result in a more serious reaction.

Women appear to be at higher risk than men of developing rash with VIRAMUNE. In a clinical trial, concomitant prednisone use (40 mg/day for the first 14 days of VIRAMUNE administration) was associated with an increase in incidence and severity of rash during the first 6 weeks of VIRAMUNE therapy. Therefore, use of prednisone to prevent VIRAMUNE-associated rash is not recommended.

### Resistance

VIRAMUNE must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors, resistant virus emerges rapidly when nevirapine is administered as monotherapy. The choice of new antiretroviral agents to be used in combination with nevirapine should take into consideration the potential for cross resistance. When discontinuing an antiretroviral regimen containing VIRAMUNE, the long half-life of nevirapine should be taken into account; if antiretrovirals with shorter half-lives than VIRAMUNE are stopped concurrently, low plasma concentrations of nevirapine alone may persist for a week or longer and virus resistance may subsequently develop.

### St. John's wort

Concomitant use of St. John's wort (*Hypericum perforatum*) or St. John's wort containing products and VIRAMUNE is not recommended. Co-administration of non-nucleoside reverse transcriptase inhibitors (NNRTIs), including VIRAMUNE, with St. John's wort is expected to substantially decrease NNRTI concentrations and may result in sub-optimal levels of VIRAMUNE and lead to loss of virologic response and possible resistance to VIRAMUNE or to the class of NNRTIs.

### PRECAUTIONS

#### General

The most serious adverse reactions associated with VIRAMUNE (nevirapine) are hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Hepatitis/hepatic failure may be isolated or associated with signs of hypersensitivity which may include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction (see WARNINGS).

Nevirapine is extensively metabolized by the liver and nevirapine metabolites are extensively eliminated by the kidney. No adjustment in nevirapine dosing is required in patients with CrCl ≥ 20 mL/min. In patients undergoing chronic hemodialysis, an additional 200 mg dose following each dialysis treatment is indicated. Nevirapine metabolites may accumulate in patients receiving dialysis; however, the clinical significance of this accumulation is not known (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations: Renal Impairment; DOSAGE AND ADMINISTRATION, Dosage Adjustment).

It is not clear whether a dosing adjustment is needed for patients with mild to moderate hepatic impairment, because multiple dose pharmacokinetic data are not available for this population. However, patients with moderate hepatic impairment and ascites may be at risk of accumulating nevirapine in the systemic circulation. Caution should be exercised when nevirapine is administered to patients with moderate hepatic impairment. Nevirapine should not be administered to patients with severe hepatic impairment (see WARNINGS; CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations: Hepatic Impairment).

The duration of clinical benefit from antiretroviral therapy may be limited. Patients receiving VIRAMUNE or any other antiretroviral therapy may continue to develop opportunistic infections and other complications of HIV infection, and therefore should remain under close clinical observation by physicians experienced in the treatment of patients with associated HIV diseases.

When administering VIRAMUNE as part of an antiretroviral regimen, the complete product information for each therapeutic component should be consulted before initiation of treatment.

#### Drug Interactions

Nevirapine is principally metabolized by the liver via the cytochrome P450 isoenzymes, 2A6 and 2B6. Nevirapine is known to be an inducer of these enzymes. As a result, drugs that are metabolized by these enzyme systems may have lower than expected plasma levels when co-administered with nevirapine.

The specific pharmacokinetic changes that occur with co-administration of nevirapine and other drugs are listed in CLINICAL PHARMACOLOGY, Table 1. Clinical comments about possible dosage modifications based on these pharmacokinetic changes are listed in Table 3. The data in Tables 1 and 3 are based on the results of drug interaction studies conducted in HIV-1 seropositive subjects unless otherwise indicated.

In addition to established drug interactions, there may be potential pharmacokinetic interactions between nevirapine and other drug classes that are metabolized by the cytochrome P450 system. These potential drug interactions are listed in Table 4. Although specific drug interaction studies in HIV-1 seropositive subjects have not been conducted for the classes of drugs listed in Table 4, additional clinical monitoring may be warranted when co-administering these drugs.

The *in vitro* interaction between nevirapine and the antithrombotic agent warfarin is complex. As a result, when giving these drugs concomitantly, plasma warfarin levels may change with the potential for increases in coagulation time. When warfarin is co-administered with nevirapine, anticoagulation levels should be monitored frequently.

### Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and “cushingoid appearance” have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Table 3  
Established Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies (See CLINICAL PHARMACOLOGY, Table 1 for Magnitude of Interaction)

Drug Name	Effect on Concentration of Nevirapine or Concomitant Drug	Clinical Comment
Clarithromycin	↓ Clarithromycin ↑ 14-OH clarithromycin	Clarithromycin exposure was significantly decreased by nevirapine; however, 14-OH metabolite concentrations were increased. Because clarithromycin active metabolite has reduced activity against <i>Mycobacterium avium-intracellulare</i> complex, overall activity against this pathogen may be altered. Alternatives to clarithromycin, such as azithromycin, should be considered.
Efavirenz	↓ Efavirenz	Appropriate doses for this combination are not established.
Ethinyl estradiol and Norethindrone	↓ Ethinyl estradiol ↓ Norethindrone	Oral contraceptives and other hormonal methods of birth control should not be used as the sole method of contraception in women taking nevirapine, since nevirapine may lower the plasma levels of these medications. An alternative or additional method of contraception is recommended.
Fluconazole	↑ Nevirapine	Because of the risk of increased exposure to nevirapine, caution should be used in concomitant administration, and patients should be monitored closely for nevirapine-associated adverse events.
Indinavir	↓ Indinavir	Appropriate doses for this combination are not established, but an increase in the dosage of indinavir may be required.
Ketoconazole	↓ Ketoconazole	Nevirapine and ketoconazole should not be administered concomitantly because decreases in ketoconazole plasma concentrations may reduce the efficacy of the drug.
Lopinavir/Ritonavir	↓ Lopinavir	KALETRA 400/100 mg tablets can be used twice-daily in combination with nevirapine with no dose adjustment in antiretroviral-naïve patients.  A dose increase of KALETRA tablets to 600/150 mg (3 tablets) twice daily may be considered when used in combination with nevirapine in treatment-experienced patients where decreased susceptibility to lopinavir is clinically suspected (by treatment history or laboratory evidence).  A dose increase of lopinavir/ritonavir oral solution to 533/133 mg twice daily with food is recommended in combination with nevirapine.  In children 6 months to 12 years of age, consideration should be given to increasing the dose of lopinavir/ritonavir to 13/3.25 mg/kg for those 7 to < 15 kg; 11/2.75 mg/kg for those 15 to 45 kg; and up to a maximum dose of 533/133 mg for those > 45 kg twice daily when used in combination with nevirapine, particularly for patients in whom reduced susceptibility to lopinavir/ritonavir is suspected.
Methadone	↓ Methadone	Methadone levels were decreased; increased dosages may be required to prevent symptoms of opiate withdrawal. Methadone maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
Nelfinavir	↓ Nelfinavir M8 Metabolite ↓ Nelfinavir C <sub>max</sub>	The appropriate dose for nelfinavir in combination with nevirapine, with respect to safety and efficacy, has not been established.
Rifabutin	↑ Rifabutin	Rifabutin and its metabolite concentrations were moderately increased. Due to high intersubject variability, however, some patients may experience large increases in rifabutin exposure and may be at higher risk for rifabutin toxicity. Therefore, caution should be used in concomitant administration.
Rifampin	↓ Nevirapine	Nevirapine and rifampin should not be administered concomitantly because decreases in nevirapine plasma concentrations may reduce the efficacy of the drug. Physicians needing to treat patients co-infected with tuberculosis and using a nevirapine-containing regimen may use rifabutin instead.
Saquinavir	↓ Saquinavir	Appropriate doses for this combination are not established, but an increase in the dosage of saquinavir may be required.

### Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including VIRAMUNE. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indole or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

### Information for Patients

Patients should be informed of the possibility of severe liver disease or skin reactions associated with VIRAMUNE that may result in death. Patients developing signs or symptoms of liver disease or severe skin reactions should be instructed to discontinue VIRAMUNE and seek medical attention immediately, including performance of laboratory monitoring. Symptoms of liver disease include fatigue, malaise, anorexia, nausea, jaundice, acholic stools, liver tenderness or hepatomegaly. Symptoms of severe skin or hypersensitivity reactions include rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema and/or hepatitis.

Other potential causes of pelvic pain to rule out include urinary sources such as interstitial cystitis, gastrointestinal sources such as irritable bowel syndrome, and musculoskeletal trigger points.

"It's important to explain to patients with chronic pelvic pain that they may have symptomatic endometriosis or that they may have been misdiagnosed with endometriosis," she said. "It's also important to explain to them that endometriosis can be inadequately treated and can exacerbate pain from other sources."

The pathophysiology of endometriosis remains unclear but one concept developed in 1949 called the composite theory

has gained the attention of researchers in recent years.

This theory suggests that a variety of immunologic and genetic factors may mediate endometriosis, including direct extension into myometrium and adjacent organs, exfoliation of viable endometrial cells through tubes, and implantation of these cells into the peritoneum and adjacent organs.

"There [are] a lot of convincing data that retrograde menstruation and implantation of endometrial fragments are the primary mode of developing endometriosis in the peritoneal cavity, but it's definitely not the only process," Dr.

Lamvu said. "Research is now focusing on mechanisms that are involved in the attachment and the clearance of viable endometrium from the pelvic cavity. So the focus has come to alterations in the immune system."

Current treatment for endometriosis associated with pelvic pain includes observation with palliative treatment with NSAIDs, hormonal suppression with continuous oral contraceptives, and gonadotropin-releasing hormone agonists (GnRH), excision, ablation, or cystectomy, and definitive extirpating surgery such as hysterectomy or bilateral salpingo-oophorectomy.

"A lot of us are now doing a combination of medical and surgical therapies," Dr. Lamvu said.

Which surgical technique is best for managing endometriosis remains unclear. "There have been no comparison trials," she said. "Some experts suspect that excision may be more effective for pain management in deep lesions, but for the general population of gynecologists superficial ablation with some type of medical therapy afterwards will be less risky."

She added that pain improvement in the postoperative period "may be best for patients who have extensive disease. There may be some correlation between the extent of disease and response to treatment."

Pain usually recurs within a year in 40% of patients who undergo surgical therapy and within 1-2 years in 30%-40% of patients who receive medical therapy.

"This is a frustration for all of us," said Dr. Lamvu, who is also assistant director of the Florida Hospital Family Practice Residency program. "There is no telling

**Table 4: Potential Drug Interactions: Use With Caution, Dose Adjustment or Co-administration of Drug May Be Needed Due to Possible Decrease in Clinical Effect**

Drug Class	Examples of Drugs
Antiarrhythmics	Amiodarone, disopyramide, lidocaine
Anticonvulsants	Carbamazepine, clonazepam, ethosuximide
Antifungals	Itraconazole
Calcium channel blockers	Diltiazem, nifedipine, verapamil
Cancer chemotherapy	Cyclophosphamide
Ergot alkaloids	Ergotamine
Immunosuppressants	Cyclosporin, tacrolimus, sirolimus
Motility agents	Cisapride
Opiate agonists	Fentanyl

**Examples of Drugs in Which Plasma Concentrations May Be Increased by Co-administration With Nevirapine**

Antithrombotics	Warfarin Potential effect on anticoagulation. Monitoring of anticoagulation levels is recommended.
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Intensive clinical and laboratory monitoring, including liver function tests, is essential during the first 18 weeks of therapy with VIRAMUNE to detect potentially life-threatening hepatotoxicity and skin reactions. However, liver disease can occur after this period, therefore monitoring should continue at frequent intervals throughout VIRAMUNE treatment. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of hepatic events and skin reactions. Patients with signs and symptoms of hepatitis should discontinue VIRAMUNE and seek medical evaluation immediately. If VIRAMUNE is discontinued due to hepatotoxicity, do not restart it. Patients, particularly women, with increased CD4+ cell count at initiation of VIRAMUNE therapy (>250 cells/mm<sup>3</sup> in women and >400 cells/mm<sup>3</sup> in men) are at substantially higher risk for development of symptomatic hepatic events, often associated with rash. Patients should be advised that co-infection with hepatitis B or C and/or increased liver function tests at the start of therapy with VIRAMUNE are associated with a greater risk of later symptomatic events (6 weeks or more after starting VIRAMUNE) and asymptomatic increases in AST or ALT (see WARNINGS, Hepatic Events).

The majority of rashes associated with VIRAMUNE occur within the first 6 weeks of initiation of therapy. Patients should be instructed that if any rash occurs during the two-week lead-in period, the VIRAMUNE dose should not be escalated until the rash resolves. Any patient experiencing a rash should have their liver function evaluated immediately. Patients with severe rash or hypersensitivity reactions should discontinue VIRAMUNE immediately and consult a physician. VIRAMUNE should not be restarted following severe skin rash or hypersensitivity reaction. Women tend to be at higher risk for development of VIRAMUNE associated rash. Oral contraceptives and other hormonal methods of birth control should not be used as the sole method of contraception in women taking VIRAMUNE, since VIRAMUNE may lower the plasma levels of these medications. Additionally, when oral contraceptives are used for hormonal regulation during VIRAMUNE therapy, the therapeutic effect of the hormonal therapy should be monitored (see PRECAUTIONS, Drug Interactions).

VIRAMUNE may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Narcotic withdrawal syndrome has been reported in patients treated with VIRAMUNE and methadone concomitantly. Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly. VIRAMUNE may interact with some drugs, therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

Patients should be informed that VIRAMUNE therapy has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination. The long-term effects of VIRAMUNE are unknown at this time.

VIRAMUNE is not a cure for HIV-1 infection; patients may continue to experience illnesses associated with advanced HIV-1 infection, including opportunistic infections. Patients should be advised to remain under the care of a physician when using VIRAMUNE.

Patients should be informed to take VIRAMUNE every day as prescribed. Patients should not alter the dose without consulting their doctor. If a dose is missed, patients should take the next dose as soon as possible. However, if a dose is skipped, the patient should not double the next dose. Patients should be advised to report to their doctor the use of any other medications. Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long term health effects of these conditions are not known at this time.

The Medication Guide provides written information for the patient, and should be dispensed with each new prescription and refill.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term carcinogenicity studies in mice and rats were carried out with nevirapine. Mice were dosed with 0, 50, 375 or 750 mg/kg/day for two years. Hepatocellular adenomas and carcinomas were increased at all doses in males and at the two high doses in females. In studies in which rats were administered nevirapine at doses of 0, 3.5, 17.5 or 35 mg/kg/day for two years, an increase in hepatocellular adenomas was seen in males at all doses and in females at the high dose. The systemic exposure (based on AUCs) at all doses in the two animal studies were lower than that measured in humans at the 200 mg BID dose. The mechanism of the carcinogenic potential is unknown. However, in genetic toxicology assays, nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* studies. These included microbial assays for gene mutation (Ames; Salmonella strains and *E. coli*), mammalian cell gene mutation assay (CHO/HGPRT), cytogenetic assays using a Chinese hamster ovary cell line and a mouse bone marrow micronucleus assay following oral administration. Given the lack of genotoxic activity of nevirapine, the relevance to humans of hepatocellular neoplasms in nevirapine treated mice and rats is not known. In reproductive toxicology studies, evidence of impaired fertility was seen in female rats at doses providing systemic exposure, based on AUC, approximately equivalent to that provided with the recommended clinical dose of VIRAMUNE.

**Pregnancy: Pregnancy Category B**

No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits. The maternal and developmental no-observable-effect level dosages produced systemic exposures approximately equivalent to or approximately 50% higher in rats and rabbits, respectively, than those seen at the recommended daily human dose (based on AUC). In rats, decreased fetal body weights were observed due to administration of a maternally toxic dose (exposures approximately 50% higher than that seen at the recommended human clinical dose).

There are no adequate and well-controlled studies of VIRAMUNE in pregnant women. The Antiretroviral Pregnancy Registry, which has been surveying pregnancy outcomes since January 1989, has not found an increased risk of birth defects following first trimester exposures to nevirapine. The prevalence of birth defects after any trimester exposure to nevirapine is comparable to the prevalence observed in the general population.

Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic VIRAMUNE therapy as part of combination treatment of HIV infection. Regardless of pregnancy status women with CD4 counts >250 cells/mm<sup>3</sup>

should not initiate VIRAMUNE unless the benefit outweighs the risk. It is unclear if pregnancy augments the risk observed in non-pregnant women (see Boxed WARNING).

VIRAMUNE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Antiretroviral Pregnancy Registry**  
To monitor maternal-fetal outcomes of pregnant women exposed to VIRAMUNE, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling (800) 258-4263.

**Nursing Mothers**  
The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Nevirapine is excreted in breast milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving VIRAMUNE.

**Pediatric Use**  
The pharmacokinetics of nevirapine have been studied in two open-label studies in children with HIV-1 infection (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations). For dose recommendations for pediatric patients see DOSAGE AND ADMINISTRATION. The most frequently reported adverse events related to VIRAMUNE in pediatric patients were similar to those observed in adults, with the exception of granulocytopenia, which was more commonly observed in children receiving both zidovudine and VIRAMUNE (see ADVERSE REACTIONS, Pediatric Patients). The evaluation of the antiviral activity of VIRAMUNE in pediatric patients is ongoing.

**Geriatric Use**  
Clinical studies of VIRAMUNE did not include sufficient numbers of subjects aged 65 and older to determine whether elderly subjects respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

**ADVERSE REACTIONS**

The most serious adverse reactions associated with VIRAMUNE (nevirapine) are hepatitis/hepatic failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions. Hepatitis/hepatic failure may be isolated or associated with signs of hypersensitivity which may include severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction (see WARNINGS).

**Adults**  
The most common clinical toxicity of VIRAMUNE is rash, which can be severe or life-threatening (see WARNINGS). Rash occurs most frequently within the first 6 weeks of therapy. Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. In controlled clinical trials, Grade 1 and 2 rashes were reported in 13.3% of patients receiving VIRAMUNE compared to 5.8% receiving placebo during the first 6 weeks of therapy. Grade 3 and 4 rashes were reported in 1.5% of VIRAMUNE recipients compared to 0.1% of subjects receiving placebo. Women tend to be at higher risk for development of VIRAMUNE associated rash. In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4.0% (range 0% to 11.0%) of patients who received VIRAMUNE and 1.2% of patients in control groups. Female gender and higher CD4 counts (>250 cells/mm<sup>3</sup> in women and >400 cells/mm<sup>3</sup> in men) place patients at increased risk of these events (see WARNINGS).

Asymptomatic transaminase elevations (AST or ALT > 5X ULN) were observed in 5.8% (range 0% to 9.2%) of patients who received VIRAMUNE and 5.5% of patients in control groups. Co-infection with hepatitis B or C and/or increased liver function tests at the start of therapy with VIRAMUNE are associated with a greater risk of later symptomatic events (6 weeks or more after starting VIRAMUNE) and asymptomatic increases in AST or ALT.

Treatment related, adverse experiences of moderate or severe intensity observed in >2% of patients receiving VIRAMUNE in placebo-controlled trials are shown in Table 5.

**Table 5: Percentage of Patients with Moderate or Severe Drug Related Events in Adult Placebo Controlled Trials**

	Trial 1090 <sup>1</sup>		Trials 1037, 1038, 1046 <sup>2</sup>	
	VIRAMUNE (n=1121)	Placebo (n=1128)	VIRAMUNE (n=253)	Placebo (n=203)
Median exposure (weeks)	58	52	28	28
Any adverse events	14.5%	11.1%	31.6%	13.3%
Rash	5.1	1.8	6.7	1.5
Nausea	0.5	1.1	8.7	3.9
Granulocytopenia	1.8	2.8	0.4	0
Headache	0.7	0.4	3.6	0.5
Fatigue	0.2	0.3	4.7	3.9
Diarrhea	0.2	0.8	2.0	0.5
Abdominal pain	0.1	0.4	2.0	0
Myalgia	0.2	0	1.2	2.0

<sup>1</sup>Background therapy included 3TC for all patients and combinations of NRTIs and PIs. Patients had CD4+ cell counts <200 cells/mm<sup>3</sup>.  
<sup>2</sup>Background therapy included ZDV and ZDV+ddI; VIRAMUNE monotherapy was administered in some patients. Patients had CD4+ cell count ≥200 cells/mm<sup>3</sup>.

**Laboratory Abnormalities:** Liver function test abnormalities (AST, ALT) were observed more frequently in patients receiving VIRAMUNE than in controls (Table 6). Asymptomatic elevations in GGT occur frequently but are not a contraindication to continue VIRAMUNE therapy in the absence of elevations in other liver function tests. Other laboratory abnormalities (bilirubin, anemia, neutropenia, thrombocytopenia) were observed with similar frequencies in clinical trials comparing VIRAMUNE and control regimens (see Table 6).

**Post Marketing Surveillance:** In addition to the adverse events identified during clinical trials, the following events have been reported with the use of VIRAMUNE in clinical practice:

- Body as a Whole:** fever, somnolence, drug withdrawal (see PRECAUTIONS: Drug Interactions), redistribution/accumulation of body fat (see PRECAUTIONS, Fat Redistribution)
- Gastrointestinal:** vomiting
- Liver and Biliary:** jaundice, fulminant and cholestatic hepatitis, hepatic necrosis, hepatic failure
- Hematology:** anemia, eosinophilia, neutropenia
- Musculoskeletal:** arthralgia, rhabdomyolysis associated with skin and/or liver reactions
- Neurologic:** paraesthesia
- Skin and Appendages:** allergic reactions including anaphylaxis, angioedema, bullous eruptions, ulcerative stomatitis and urticaria have all been reported. In addition, hypersensitivity syndrome and hypersensitivity reactions with rash associated with constitutional findings such as fever, blistering, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, fatigue or significant hepatic abnormalities (see WARNINGS) plus one or more of the following: hepatitis, eosinophilia, granulocytopenia, lymphadenopathy and/or renal dysfunction have been reported with the use of VIRAMUNE.

**Table 6: Percentage of Adult Patients with Laboratory Abnormalities**

Laboratory Abnormality	Trial 1090 <sup>1</sup>		Trials 1037, 1038, 1046 <sup>2</sup>	
	VIRAMUNE (n=1121)	Placebo (n=1128)	VIRAMUNE (n=253)	Placebo (n=203)
<b>Blood Chemistry</b>				
SGPT (ALT) >250 U/L	5.3%	4.4%	14.0%	4.0%
SGOT (AST) >250 U/L	3.7	2.5	7.6	1.5
Bilirubin >2.5 mg/dL	1.7	2.2	1.7	1.5
<b>Hematology</b>				
Hemoglobin <8.0 g/dL	3.2	4.1	0	0
Platelets <50,000/mm <sup>3</sup>	1.3	1.0	0.4	1.5
Neutrophils <750/mm <sup>3</sup>	13.3	13.5	3.6	1.0

<sup>1</sup>Background therapy included 3TC for all patients and combinations of NRTIs and PIs. Patients had CD4+ cell counts <200 cells/mm<sup>3</sup>.  
<sup>2</sup>Background therapy included ZDV and ZDV+ddI; VIRAMUNE monotherapy was administered in some patients. Patients had CD4+ cell count ≥200 cells/mm<sup>3</sup>.

**Pediatric Patients**  
Safety was assessed in trial BI 882 in which patients were followed for a mean duration of 33.9 months (range: 6.8 months to 5.3 years, including long-term follow-up in 29 of these patients in trial BI 892). The most frequently reported adverse events related to VIRAMUNE in pediatric patients were similar to those observed in adults, with the exception of granulocytopenia, which was more commonly observed in children receiving both zidovudine and VIRAMUNE. Serious adverse events were assessed in ACTG 245, a double-blind, placebo-controlled trial of VIRAMUNE (n = 305) in which pediatric patients received combination treatment with VIRAMUNE. In this trial two patients were reported to experience Stevens-Johnson syndrome or Stevens-Johnson/toxic epidermal necrolysis transition syndrome. Cases of allergic reaction, including one case of anaphylaxis, were also reported. In post-marketing surveillance anemia has been more commonly observed in children although development of anemia due to concomitant medication use cannot be ruled out.

**OVERDOSAGE**  
There is no known antidote for VIRAMUNE (nevirapine) overdose. Cases of VIRAMUNE overdose at doses ranging from 800 to 1800 mg per day for up to 15 days have been reported. Patients have experienced events including edema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting and weight decrease. All events subsided following discontinuation of VIRAMUNE.

**DOSAGE AND ADMINISTRATION**

**Adults**  
The recommended dose for VIRAMUNE (nevirapine) is one 200 mg tablet daily for the first 14 days (this lead-in period should be used because it has been found to lessen the frequency of rash), followed by one 200 mg tablet twice daily, in combination with other antiretroviral agents. For concomitantly administered antiretroviral therapy, the manufacturer's recommended dosage and monitoring should be followed.

**Pediatric Patients**  
The recommended oral dose of VIRAMUNE for pediatric patients 2 months up to 8 years of age is 4 mg/kg once daily for the first 14 days followed by 7 mg/kg twice daily thereafter. For patients 8 years and older the recommended dose is 4 mg/kg once daily for two weeks followed by 4 mg/kg twice daily thereafter. The total daily dose should not exceed 400 mg for any patient. VIRAMUNE suspension should be shaken gently prior to administration. It is important to administer the entire measured dose of suspension by using an oral dosing syringe or dosing cup. An oral dosing syringe is recommended, particularly for volumes of 5 mL or less. If a dosing cup is used, it should be thoroughly rinsed with water and the rinse should also be administered to the patient.

**Monitoring of Patients**

Intensive clinical and laboratory monitoring, including liver function tests, is essential at baseline and during the first 18 weeks of treatment with VIRAMUNE. The optimal frequency of monitoring during this period has not been established. Some experts recommend clinical and laboratory monitoring more often than once per month, and in particular, would include monitoring of liver function tests at baseline, prior to dose escalation, and at two weeks post dose escalation. After the initial 18 week period, frequent clinical and laboratory monitoring should continue throughout VIRAMUNE treatment (see WARNINGS). In some cases, hepatic injury has progressed despite discontinuation of treatment.

**Dosage Adjustment**  
VIRAMUNE should be discontinued if patients experience severe rash or a rash accompanied by constitutional findings (see WARNINGS). Patients experiencing rash during the 14-day lead-in period of 200 mg/day (4 mg/kg/day in pediatric patients) should not have their VIRAMUNE dose increased until the rash has resolved (see PRECAUTIONS, Information for Patients).

If a clinical (symptomatic) hepatic event occurs, VIRAMUNE should be permanently discontinued. Do not restart VIRAMUNE after recovery (see WARNINGS).

Patients who interrupt VIRAMUNE dosing for more than 7 days should restart the recommended dosing, using one 200 mg tablet daily (4 mg/kg/day in pediatric patients) for the first 14 days (lead-in) followed by one 200 mg tablet twice daily (4 or 7 mg/kg twice daily, according to age, for pediatric patients).

An additional 200 mg dose of VIRAMUNE following each dialysis treatment is indicated in patients requiring dialysis. Nevirapine metabolites may accumulate in patients requiring dialysis; however, the clinical significance of this accumulation is not known (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations: Renal Impairment). Patients with CrCl ≥20 mL/min do not require an adjustment in VIRAMUNE dosing.

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**Endometriosis seen laparoscopically needs to be histologically confirmed.**

whether these numbers will [improve] now that we are incorporating so many different therapies for the management of pain."

Future therapies include selective progesterone receptor modulators such as asoprisnil, which induce amenorrhea without side effects of hypoestrogenism and control uterine prostaglandins. Doses of 5, 10, or 25 mg per day may be effective in reducing pelvic pain.

The progesterone antagonist RU486 (mifepristone) also holds promise. A dose of 50 mg every day for 6 months may lead to a decrease in the number of endometriotic lesions.

"These are experimental therapies," Dr. Lamvu emphasized. "They may not work for some patients. Most of these therapies are recommended for only 3-6 months."

Other future therapies include selective nonsteroidal aromatase inhibitors such as anastrozole and letrozole.

"The nice thing about these is that they're heavily studied in other disease processes such as cancer, so we have a lot more data as far as long-term side-effect profile and safety profile," she said. "In pelvic pain these have only been studied for up to 6 months."

Dr. Lamvu said she is most optimistic about the potential for new GnRH antagonists to make a significant improvement in chronic pelvic pain associated with endometriosis.

These agents "may work faster and have fewer side effects than the GnRH agonists that we now use," she said.

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