of all patients (3% severe) and in 52% (2% severe) of the patients without pre-existing neuropathy. The frequency of peripheral neuropathy increased with cumulative dose. Paresthesia commonly occurs in the form of hyperesthesia. Neurologic symptoms were observed in 27% of the patients after the first course of treatment and in 34 to 51% from course 2 to 10. Peripheral neuropathy was the cause of TAXOL discontinuation in 1% of all patients. Sensory symptoms have usually improved or resolved within several months of TAXOL discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for TAXOL therapy.

In the Intergroup first-line ovarian carcinoma study (see **TABLE 11**), neurotoxicity included reports of neuromotor and neurosensory events. The regimen with TAXOL 175 mg/m^2 given by 3-hour infusion plus cisplatin 75 mg/m^2 resulted in greater incidence and severity of neurotoxicity than the regimen containing cyclophosphamide and cisplatin, 87% (21% severe) versus 52% (2% severe), respectively. The duration of grade III or IV neurotoxicity cannot be determined with precision for the Intergroup study since the resolution dates of adverse events were not collected in the case report forms for this trial and complete follow-up documentation was available only in a minority of these patients. In the GOG first-line ovarian carcinoma study, neurotoxicity was reported as peripheral neuropathy. The regimen with TAXOL 135 mg/m^2 given by 24-hour infusion plus cisplatin 75 mg/m^2 resulted in an incidence of neurotoxicity that was similar to the regimen containing cyclophosphamide plus cisplatin, 25% (3% severe) versus 20% (0% severe), respectively. Cross-study comparison of neurotoxicity in the Intergroup and GOG trials suggests that when TAXOL is given in combination with cisplatin 75 mg/m^2, the incidence of severe neurotoxicity is more common at a TAXOL dose of 175 mg/m^2 given by 3-hour infusion (21%) than at a dose of 135 mg/m^2 given by 24-hour infusion (3%).

In patients with NSCLC, administration of TAXOL followed by cisplatin resulted in a greater incidence of severe neurotoxicity compared to the incidence in patients with ovarian or breast cancer treated with single-agent TAXOL. Severe neurosensory symptoms were noted in 13% of NSCLC patients receiving TAXOL 135 mg/m^2 by 24-hour infusion followed by cisplatin 75 mg/m^2 and 8% of NSCLC patients receiving cisplatin/etoposide (see **TABLE 15**).

Other than peripheral neuropathy, serious neurologic events following TAXOL administration have been rare (<1%) and have included grand mal seizures, syncope, ataxia, and neuroencephalopathy.

Autonomic neuropathy resulting in paralytic ileus has been reported. Optic nerve and/or visual disturbances (scintillating scotomata) have also been reported, particularly in patients who have received higher doses than those recommended. These effects generally have been reversible. However, reports in the literature of abnormal visual evoked potentials in patients have suggested persistent optic nerve damage. Postmarketing reports of ototoxicity (hearing loss and tinnitus) have also been received.

Convulsions, dizziness, and headache have been reported.

Arthralgia/Myalgia: There was no consistent relationship between dose or schedule of TAXOL and the frequency or severity of arthralgia/myalgia. Sixty percent of all patients treated experienced arthralgia/myalgia; 8% experienced severe symptoms. The symptoms were usually transient, occurred 2 or 3 days after TAXOL administration, and resolved within a few days. The frequency and severity of musculoskeletal symptoms remained unchanged throughout the treatment period.

Hepatic: No relationship was observed between liver function abnormalities and either dose or schedule of TAXOL administration. Among patients with normal baseline liver function 7%, 22%, and 19% had elevations in bilirubin, alkaline phosphatase, and AST (SGOT), respectively. Prolonged exposure to TAXOL was not associated with cumulative hepatic toxicity.

Hepatic necrosis and hepatic encephalopathy leading to death have been reported.

Renal: Among the patients treated for Kaposi's sarcoma with TAXOL, 5 patients had renal toxicity of grade III or IV severity. One patient with suspected HIV nephropathy of grade IV severity had to discontinue therapy. The other 4 patients had renal insufficiency with reversible elevations of serum creatinine.

Patients with gyneocological cancers treated with TAXOL and cisplatin may have an increased risk of renal failure with the combination therapy of paclitaxel and cisplatin in gynecological cancers as compared to cisplatin alone.

Gastrointestinal (GI): Nausea/vomiting, diarrhea, and mucositis were reported by 52%, 38%, and 31% of all patients, respectively. These manifestations were usually mild to moderate. Mucositis was schedule dependent and occurred more frequently with the 24-hour than with the 3-hour infusion.

In patients with poor-risk AIDS-related Kaposi's sarcoma, nausea/vomiting, diarrhea, and mucositis were reported by 69%, 79%, and 28% of patients, respectively. One-third of

patients with Kaposi's sarcoma complained of diarrhea prior to study start. (See **CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma**.)

In the first-line Phase 3 ovarian carcinoma studies, the incidence of nausea and vomiting when TAXOL was administered in combination with cisplatin appeared to be greater compared with the database for single-agent TAXOL in ovarian and breast carcinoma. In addition, diarrhea of any grade was reported more frequently compared to the control arm, but there was no difference for severe diarrhea in these studies.

Intestinal obstruction, intestinal perforation, pancreatitis, ischemic colitis, dehydration, esophagitis, constipation, and ascites have been reported. Neutropenic enterocolitis (typhlitis), despite the coadministration of G-CSF, was observed in patients treated with TAXOL alone and in combination with other chemotherapeutic agents.

Injection Site Reaction: Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently with the 24-hour infusion than with the 3-hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of TAXOL at a different site, ie, "recall," has been reported.

More severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis, and fibrosis have been reported. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to 10 days.

A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Other Clinical Events: Alopecia was observed in almost all (87%) of the patients. Transient skin changes due to TAXOL-related hypersensitivity reactions have been observed, but no other skin toxicities were significantly associated with TAXOL administration. Nail changes (changes in pigmentation or discoloration of nail bed) were uncommon (2%). Edema was reported in 21% of all patients (17% of those without baseline edema); only 1% had severe edema and none of these patients required treatment discontinuation. Edema was most commonly focal and disease-related. Edema was observed in 5% of all courses for patients with normal baseline and did not increase with time on study.

Skin abnormalities related to radiation recall as well as maculopapular rash, pruritus, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported.

Reports of asthenia and malaise have been received as part of the continuing surveillance of TAXOL safety. In the Phase 3 trial of TAXOL 135 mg/m^2 over 24 hours in combination with cisplatin as first-line therapy of ovarian cancer, asthenia was reported in 17% of the patients, significantly greater than the 10% incidence observed in the control arm of cyclophosphamide/cisplatin.

Conjunctivitis, increased lacrimation, anorexia, confusional state, photopsia, visual floaters, vertigo, and increase in blood creatinine have been reported.

Accidental Exposure: Upon inhalation, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported. Following topical exposure, events have included tingling, burning, and redness.

OVERDOSAGE

There is no known antidote for TAXOL (paclitaxel) overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity, and mucositis. Overdoses in pediatric patients may be associated with acute ethanol toxicity (see **PRECAUTIONS: Pediatric Use**).

DOSAGE AND ADMINISTRATION

Note: Contact of the undiluted concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted TAXOL solutions should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

All patients should be premedicated prior to TAXOL administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before TAXOL, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to TAXOL, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before TAXOL.

For patients with **carcinoma of the ovary**, the following regimens are recommended (see **CLINICAL STUDIES: Ovarian Carcinoma**):

1) For previously untreated patients with carcinoma of the ovary, one of the following recommended regimens may be given every 3 weeks. In selecting the appropriate regimen, differences in toxicities should be considered (see **TABLE 11** in **ADVERSE REACTIONS: Disease-Specific Adverse Event Experiences**).
   a. TAXOL administered intravenously over 3 hours at a dose of 175 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2; or
   b. TAXOL administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin at a dose of 75 mg/m^2.
2) In patients previously treated with chemotherapy for carcinoma of the ovary, TAXOL has been used at several doses and schedules; however, the optimal regimen is not yet clear. The recommended regimen is TAXOL 135 mg/m^2 or 175 mg/m^2 administered intravenously over 3 hours every 3 weeks.

For patients with **carcinoma of the breast**, the following regimens are recommended (see **CLINICAL STUDIES: Breast Carcinoma**):

1) For the adjuvant treatment of node-positive breast cancer, the recommended regimen is TAXOL, at a dose of 175 mg/m^2 intravenously over 3 hours every 3 weeks for 4 courses administered sequentially to doxorubicin-containing combination chemotherapy. The clinical trial used 4 courses of doxorubicin and cyclophosphamide (see **CLINICAL STUDIES: Breast Carcinoma**).

2) After failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, TAXOL at a dose of 175 mg/m^2 administered intravenously over 3 hours every 3 weeks has been shown to be effective.

For patients with **non-small cell lung carcinoma**, the recommended regimen, given every 3 weeks, is TAXOL administered intravenously over 24 hours at a dose of 135 mg/m^2 followed by cisplatin, 75 mg/m^2.

For patients with **AIDS-related Kaposi's sarcoma**, TAXOL administered at a dose of 135 mg/m^2 given intravenously over 3 hours every 3 weeks or at a dose of 100 mg/m^2 given intravenously over 3 hours every 2 weeks is recommended (dose intensity 45–50 mg/m^2/week). In the 2 clinical trials evaluating these schedules (see **CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma**), the former schedule (135 mg/m^2 every 3 weeks) was more toxic than the latter. In addition, all patients with low performance status were treated with the latter schedule (100 mg/m^2 every 2 weeks).

Based upon the immunosuppression in patients with advanced HIV disease, the following modifications are recommended in these patients:

1) Reduce the dose of dexamethasone as 1 of the 3 premedication drugs to 10 mg PO (instead of 20 mg PO);

2) Initiate or repeat treatment with TAXOL only if the neutrophil count is at least 1000 cells/mm^3;

3) Reduce the dose of subsequent courses of TAXOL by 20% for patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer); and

4) Initiate concomitant hematopoietic growth factor (G-CSF) as clinically indicated.

For the therapy of patients with solid tumors (ovary, breast, and NSCLC), courses of TAXOL should not be repeated until the neutrophil count is at least 1500 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3. TAXOL should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline or subsequent neutrophil count is less than 1000 cells/mm^3. Patients who experience severe neutropenia (neutrophil <500 cells/mm^3 for a week or longer) or severe peripheral neuropathy during TAXOL therapy should have dosage reduced by 20% for subsequent courses of TAXOL. The incidence of neurotoxicity and the severity of neutropenia increase with dose.

Hepatic Impairment: Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III–IV myelosuppression (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS: Hepatic**). Recommendations for dosage adjustment for the first course of therapy are shown in **TABLE 17** for both 3- and 24-hour infusions. Further dose reduction in subsequent courses should be based on individual tolerance. Patients should be monitored closely for the development of profound myelosuppression.

TABLE 17
RECOMMENDATIONS FOR DOSING IN PATIENTS WITH HEPATIC IMPAIRMENT BASED ON CLINICAL TRIAL DATA[a]

Degree of Hepatic Impairment			
Transaminase Levels		Bilirubin Levels[b]	Recommended TAXOL Dose[c]
24-hour infusion			
<2 × ULN	and	≤1.5 mg/dL	135 mg/m^2
2 to <10 × ULN	and	≤1.5 mg/dL	100 mg/m^2
<10 × ULN	and	1.6–7.5 mg/dL	50 mg/m^2
≥10 × ULN	or	>7.5 mg/dL	Not recommended
3-hour infusion			
<10 × ULN	and	≤1.25 × ULN	175 mg/m^2
<10 × ULN	and	1.26–2.0 × ULN	135 mg/m^2
<10 × ULN	and	2.01–5.0 × ULN	90 mg/m^2
≥10 × ULN	or	>5.0 × ULN	Not recommended

[a] These recommendations are based on dosages for patients without hepatic impairment of 135 mg/m^2 over 24 hours or 175 mg/m^2 over 3 hours; data are not available to make dose adjustment recommendations for other regimens (eg, for AIDS-related Kaposi's sarcoma).

[b] Differences in criteria for bilirubin levels between the 3- and 24-hour infusion are due to differences in clinical trial design.

[c] Dosage recommendations are for the first course of therapy; further dose reduction in subsequent courses should be based on individual tolerance.

Preparation and Administration Precautions

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1–4] To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing TAXOL Injection. If TAXOL solution contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure, events have included tingling, burning, and redness. If TAXOL contacts mucous membranes, the membranes should be flushed thoroughly with water. Upon inhalation, dyspnea, chest pain, burning eyes, sore throat, and nausea have been reported.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration (see **PRECAUTIONS: Injection Site Reaction**).

Preparation for Intravenous Administration

TAXOL (paclitaxel) Injection must be diluted prior to infusion. TAXOL should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5%

Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25° C) and room lighting conditions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. No significant losses in potency have been noted following simulated delivery of the solution through IV tubing containing an in-line (0.22 micron) filter.

Data collected for the presence of the extractable plasticizer DEHP [di-(2-ethylhexyl)phthalate] show that levels increase with time and concentration when dilutions are prepared in PVC containers. Consequently, the use of plasticized PVC containers and administration sets is not recommended. TAXOL solutions should be prepared and stored in glass, polypropylene, or polyolefin containers. Non-PVC containing administration sets, such as those which are polyethylene-lined, should be used.

TAXOL should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

The Chemo Dispensing Pin™ device or similar devices with spikes should not be used with vials of TAXOL since they can cause the stopper to collapse resulting in loss of sterile integrity of the TAXOL solution.

Stability

Unopened vials of TAXOL (paclitaxel) Injection are stable until the date indicated on the package when stored between 20°–25° C (68°–77° F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration, components in the TAXOL vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. There is no impact on product quality under these circumstances. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded. Solutions for infusion prepared as

Chemo Dispensing Pin™ is a trademark of B. Braun Medical Incorporated.

recommended are stable at ambient temperature (approximately 25° C) and lighting conditions for up to 27 hours.

HOW SUPPLIED

NDC 0015-3475-30 30 mg/5 mL multidose vial individually packaged in a carton.
NDC 0015-3476-30 100 mg/16.7 mL multidose vial individually packaged in a carton.
NDC 0015-3479-11 300 mg/50 mL multidose vial individually packaged in a carton.

Storage

Store the vials in original cartons between 20°–25° C (68°–77° F). Retain in the original package to protect from light.

Handling and Disposal

See **DOSAGE AND ADMINISTRATION: Preparation and Administration Precautions**.

REFERENCES

1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.

2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling occupational exposure to hazardous drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html.

3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm*. 2006;63:1172-1193.

4. Polovich M, White JM, Kelleher LO, eds. 2005. Chemotherapy and biotherapy guidelines and recommendations for practice. 2nd ed. Pittsburgh, PA: Oncology Nursing Society.

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Rev August 2010

Patient Information

TAXOL® (TAX all)
(paclitaxel)
Injection

Read this patient information leaflet before you start taking TAXOL. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about TAXOL?

TAXOL can cause serious side effects including death.

Serious allergic reactions (anaphylaxis) can happen in people who receive TAXOL. Anaphylaxis is a serious medical emergency that can lead to death and must be treated right away.

Tell your healthcare provider right away if you have any of these signs of an allergic reaction:

- trouble breathing
- sudden swelling of your face, lips, tongue, throat, or trouble swallowing
- hives (raised bumps) or rash

Your healthcare provider will give you medicines to lessen your chance of having an allergic reaction.

What is TAXOL?

TAXOL is a prescription medicine used to treat some forms of:

- ovarian cancer
- breast cancer
- lung cancer
- Kaposi's sarcoma

It is not known if TAXOL is safe or effective in children.

Who should not receive TAXOL?

Do not receive TAXOL if:

- you are allergic to any of the ingredients in TAXOL. See the end of this leaflet for a complete list of ingredients in TAXOL.
- are allergic to medicines containing Cremophor® EL* (polyoxyethylated castor oil).
- you have low white blood cell counts.

What should I tell my healthcare provider before receiving TAXOL?

Before receiving TAXOL, tell your healthcare provider about all your medical conditions, including if you:

- have liver problems
- have heart problems
- are pregnant or plan to become pregnant. TAXOL can harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- are breast-feeding or plan to breast-feed. It is not known if TAXOL passes into your breast milk. You and your healthcare provider should decide if you will receive TAXOL or breast-feed.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How will I receive TAXOL?

- TAXOL is injected into a vein (intravenous [IV] infusion) by your healthcare provider.

Your healthcare provider will do certain tests while you receive TAXOL.

What are the possible side effects of TAXOL?

Tell your healthcare provider right away if you have:

- severe stomach pain

- severe diarrhea

The most common side effects of TAXOL include:

- low red blood cell count (anemia) feeling weak or tired
- hair loss
- numbness, tingling, or burning in your hands or feet (neuropathy)
- joint and muscle pain
- nausea and vomiting
- hypersensitivity reaction - trouble breathing; sudden swelling of your face, lips, tongue, throat, or trouble swallowing; hives (raised bumps) or rash
- diarrhea
- mouth or lip sores (mucositis)
- infections - if you have a fever (temperature above 100.4°F) or other sign of infection, tell your healthcare provider right away
- swelling of your hands, face, or feet
- bleeding events
- irritation at the injection site
- low blood pressure (hypotension)

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of TAXOL. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of TAXOL.

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use TAXOL for a condition for which it was not prescribed. Do not give TAXOL to other people, even if they have the same symptoms that you have. It may harm them.

This patient information leaflet summarizes the most important information about TAXOL. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about TAXOL that is written for health professionals. For more information call 1-800-321-1335 or go to www.bms.com.

What are the ingredients in TAXOL?

Active ingredient: paclitaxel.

Inactive ingredients include: purified Cremophor® EL (polyoxyethylated castor oil) and dehydrated alcohol, USP.

What is cancer?

Under normal conditions, the cells in your body divide and grow in an orderly, controlled way. Cell division and growth are necessary for the human body to perform its functions and to repair itself, when necessary. Cancer cells are different from normal cells because they are not able to control their own growth. The reasons for this abnormal growth are not yet fully understood.

A tumor is a mass of unhealthy cells that are dividing and growing fast and in an uncontrolled way. When a tumor invades surrounding healthy body tissue, it is known as a malignant tumor. A malignant tumor can spread (metastasize) from its original site to other parts of the body if not found and treated early.

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

*Cremophor® EL is the registered trademark of BASF Aktiengesellschaft.
Cremophor® EL is further purified by a Bristol-Myers Squibb Company proprietary process before use.

Rev August 2010

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VIRAMUNE safely and effectively. See full prescribing information for VIRAMUNE.

VIRAMUNE® (nevirapine) tablets, for oral use
VIRAMUNE® (nevirapine) oral suspension, for oral use
Initial U.S. Approval: 1996

WARNING: LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXICITY and SKIN REACTIONS

See full prescribing information for complete boxed warning.

- **Fatal and non-fatal hepatotoxicity (5.1)**
- **Fatal and non-fatal skin reactions (5.2)**

Discontinue immediately if experiencing:

- **Signs or symptoms of hepatitis (5.1)**
- **Increased transaminases combined with rash or other systemic symptoms (5.1)**
- **Severe skin or hypersensitivity reactions (5.2)**
- **Any rash with systemic symptoms (5.2)**

Monitoring during the first 18 weeks of therapy is essential. Extra vigilance is warranted during the first 6 weeks of therapy, which is the period of greatest risk of these events. (5)

----------INDICATIONS AND USAGE----------

- VIRAMUNE is an NNRTI indicated for combination antiretroviral treatment of HIV-1 infection in adults and in pediatric patients 15 days and older. (1)

Important Considerations:

- Initiation of treatment is not recommended in the following populations unless the benefits outweigh the risks. (1, 5.1)
  - adult females with $CD4^+$ cell counts greater than 250 cells/mm^3
  - adult males with $CD4^+$ cell counts greater than 400 cells/mm^3
- The 14-day lead-in period must be strictly followed; it has been demonstrated to reduce the frequency of rash. (2.4, 5.2)

----------DOSAGE AND ADMINISTRATION----------

- If any patient experiences rash during the 14-day lead-in period, do not increase dose until the rash has resolved. Do not continue the lead-in dosing regimen beyond 28 days. (2.4)
- If dosing is interrupted for greater than 7 days, restart 14-day lead-in dosing. (2.4)

	Adults (≥16 yrs)	**Pediatric Patients*** (≥15 days)
First 14 days	200 mg once daily	150 mg/m^2 once daily
After 14 days	200 mg twice daily	150 mg/m^2 twice daily

*Total daily dose should not exceed 400 mg for any patient.

----------DOSAGE FORMS AND STRENGTHS----------

- 200 mg tablets (3)
- 50 mg per 5 mL oral suspension (3)

----------CONTRAINDICATIONS----------

- Patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment. (4.1, 5.1, 8.7)
- Use as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens, an unapproved use. (4.2, 5.1)

----------WARNINGS AND PRECAUTIONS----------

- Hepatotoxicity: Fatal and non-fatal hepatotoxicity has been reported. Monitor liver function tests before and during therapy. Permanently discontinue nevirapine if clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur. Do not restart nevirapine after recovery. (5.1)
- Rash: Fatal and non-fatal skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions, have been reported. Permanently discontinue nevirapine if severe skin reactions or hypersensitivity reactions occur. Check transaminase levels immediately for all patients who develop a rash in the first 18 weeks of treatment. (5.2)
- Monitor patients for immune reconstitution syndrome and fat redistribution. (5.5, 5.6)

----------ADVERSE REACTIONS----------

- The most common adverse reaction is rash. In adults the incidence of rash is 15% versus 6% with placebo, with Grade 3/4 rash occurring in 2% of subjects. (6.1)
- In pediatric subjects the incidence of rash (all causality) was 21%. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Co-administration of VIRAMUNE can alter the concentrations of other drugs and other drugs may alter the concentration of nevirapine. The potential for drug interactions must be considered prior to and during therapy. (5.4, 7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

- No dose adjustment is required for patients with renal impairment with a creatinine clearance greater than or equal to 20 mL per min. Patients on dialysis receive an additional dose of 200 mg following each dialysis treatment. (2.4, 8.6)
- Monitor patients with hepatic fibrosis or cirrhosis carefully for evidence of drug induced toxicity. Do not administer VIRAMUNE to patients with Child-Pugh B or C. (5.1, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LIFE-THREATENING (INCLUDING FATAL) HEPATOTOXICITY and SKIN REACTIONS

HEPATOTOXICITY:

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 $CD4^+$ cell counts at initiation of therapy place patients at increased risk; women with $CD4^+$ cell counts greater than 250 cells/mm^3, including pregnant women receiving VIRAMUNE in combination with other antiretrovirals for the treatment of HIV-1 infection, are at the greatest risk. However, hepatotoxicity associated with VIRAMUNE use can occur in both genders, all $CD4^+$ cell counts and at any time during treatment. Hepatic failure has also been reported in patients without HIV taking VIRAMUNE for post-exposure prophylaxis (PEP). Use of VIRAMUNE for occupational and non-occupational PEP is contraindicated *[see Contraindications (4.2)]*. 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 and Precautions (5.1)]*.

SKIN REACTIONS:

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. Transaminase levels should be checked immediately for all patients who develop a rash in the first 18 weeks of treatment. The 14-day lead-in period with VIRAMUNE 200 mg daily dosing has been observed to decrease the incidence of rash and must be followed *[see Warnings and Precautions (5.2)]*.

MONITORING:

Patients must 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 clinical hepatitis, or transaminase elevations combined with rash or other systemic symptoms, or following severe skin rash or hypersensitivity reactions. In some cases, hepatic injury has progressed despite discontinuation of treatment.

1 INDICATIONS AND USAGE

VIRAMUNE is indicated for combination antiretroviral treatment of HIV-1 infection in adults and in pediatric patients 15 days and older *[see Clinical Studies (14.1, 14.2)]*.

Additional important information regarding the use of VIRAMUNE for the treatment of HIV-1 infection:

- Based on serious and life-threatening hepatotoxicity observed in controlled and uncontrolled trials, VIRAMUNE should not be initiated in adult females with $CD4^+$ cell counts greater than 250 cells/mm^3 or in adult males with $CD4^+$ cell counts greater than 400 cells/mm^3 unless the benefit outweighs the risk *[see Boxed Warning and Warnings and Precautions (5.1)]*.
- The 14-day lead-in period with VIRAMUNE 200 mg daily dosing must be strictly followed; it has been demonstrated to reduce the frequency of rash *[see Dosage and Administration (2.4) and Warnings and Precautions (5.2)]*.

- If rash persists beyond the 14-day lead-in period, do not dose escalate to 200 mg twice daily. The 200 mg once-daily dosing regimen should not be continued beyond 28 days, at which point an alternative regimen should be sought.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Patients

The recommended dose for VIRAMUNE is one 200 mg tablet daily for the first 14 days, followed by one 200 mg tablet twice daily, in combination with other antiretroviral agents. The lead-in period has been observed to decrease the incidence of rash. For concomitantly administered antiretroviral therapy, the manufacturer's recommended dosage and monitoring should be followed.

2.2 Pediatric Patients

The recommended oral dose for pediatric patients 15 days and older is 150 mg/m^2 once daily for 14 days followed by 150 mg/m^2 twice daily thereafter. The total daily dose should not exceed 400 mg for any patient.

Mosteller Formula: $\text{BSA } (m^2) = \sqrt{\frac{\text{Height (cm) x Wt (kg)}}{3600}}$

Table 1 Calculation of the Volume of VIRAMUNE Oral Suspension (50 mg per 5 mL) Required for Pediatric Dosing Based on Body Surface and a Dose of 150 mg/m^2

BSA range (m^2)	Volume (mL)
0.06 – 0.12	1.25
0.12 – 0.25	2.5
0.25 – 0.42	5
0.42 – 0.58	7.5
0.58 – 0.75	10
0.75 – 0.92	12.5
0.92 – 1.08	15
1.08 – 1.25	17.5
1.25+	20

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.

2.3 Monitoring of Patients

Intensive clinical and laboratory monitoring, including liver enzyme 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 enzyme 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 and Precautions (5)]*. In some cases, hepatic injury has progressed despite discontinuation of treatment.

2.4 Dosage Adjustment

Patients with Rash

Discontinue VIRAMUNE if a patient experiences severe rash or any rash accompanied by constitutional findings *[see Boxed Warning and Warnings and Precautions (5.2)]*. **Do not increase VIRAMUNE dose if a patient experiences mild to moderate rash without constitutional symptoms during the 14-day lead-in period of 200 mg/day (150 mg/m^2/day in pediatric patients) until the rash has resolved** *[see Warnings and Precautions (5.2)]*. **The total duration of the once daily lead-in dosing period should not exceed 28 days at which point an alternative regimen should be sought.**

Patients with Hepatic Events

If a clinical (symptomatic) hepatic event occurs, permanently discontinue VIRAMUNE. Do not restart VIRAMUNE after recovery *[see Warnings and Precautions (5.1)]*.

Patients with Dose Interruption

For patients who interrupt VIRAMUNE dosing for more than 7 days, restart the recommended dosing, using one 200 mg tablet daily (150 mg/m^2/day in pediatric patients) for the first 14 days (lead-in) followed by one 200 mg tablet twice daily (150 mg/m^2 twice daily for pediatric patients).

Patients with Renal Impairment

Patients with CrCL greater than or equal to 20 mL per min do not require an adjustment in VIRAMUNE dosing. The pharmacokinetics of nevirapine have not been evaluated in patients with CrCL less than 20 mL per min. An additional 200 mg dose of VIRAMUNE following each dialysis treatment is indicated in patients requiring dialysis. Nevirapine metabolites may accumulate in patients receiving dialysis; however, the clinical significance of this accumulation is not known *[see Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 200 mg, white, oval, biconvex, tablets embossed with 54 193 on one side
Oral suspension: 50 mg per 5 mL, white to off-white oral suspension

4 CONTRAINDICATIONS

4.1 Hepatic Impairment

VIRAMUNE is contraindicated in patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.7)]*.

4.2 Post-Exposure Prophylaxis

VIRAMUNE is contraindicated for use as part of occupational and non-occupational post-exposure prophylaxis (PEP) regimens *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

The most serious adverse reactions associated with VIRAMUNE 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, include monitoring of liver enzyme 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 *[see Dosage and Administration (2.1)]*.

5.1 Hepatotoxicity and Hepatic Impairment

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%) of subjects who received VIRAMUNE and 1% of subjects 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, subjects 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 subjects 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 enzyme tests.

Transaminases should be checked immediately if a patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity reaction. Transaminases should also be checked 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 transaminases are initially normal or alternative diagnoses are possible *[see Boxed Warning and Dosage and Administration (2.3)]*.

If clinical hepatitis or transaminase elevations combined with rash or other systemic symptoms occur, permanently discontinue VIRAMUNE. 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 $CD4^+$ cell counts. In general, during the first 6 weeks of treatment, women have a 3-fold higher risk than men for symptomatic, often rash-associated, hepatic events (6% versus 2%), and patients with higher $CD4^+$ cell counts at initiation of VIRAMUNE therapy are at higher risk for symptomatic hepatic events with VIRAMUNE. In a retrospective review, women with $CD4^+$ cell counts greater than 250 cells/mm^3 had a 12-fold higher risk of symptomatic hepatic adverse events compared to women with $CD4^+$ cell counts less than 250 cells/mm^3 (11% versus 1%). An increased risk was observed in men with $CD4^+$ cell counts greater than 400 cells/mm^3 (6% versus 1% for men with $CD4^+$ cell counts less than 400 cells/mm^3). However, all patients, regardless of gender, $CD4^+$ cell count, or antiretroviral treatment history, should be monitored for hepatotoxicity since symptomatic hepatic adverse events have been reported at all $CD4^+$ cell counts. Co-infection with hepatitis B or C and/or increased transaminase elevations 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-1 uninfected individuals receiving multiple doses of VIRAMUNE in the setting of post-exposure prophylaxis (PEP), an unapproved use. Use of VIRAMUNE for occupational and non-occupational PEP is contraindicated *[see Contraindications (4.2)]*.

Increased nevirapine trough concentrations have been observed in some patients with hepatic fibrosis or cirrhosis. Therefore, carefully monitor patients with either hepatic fibrosis or cirrhosis for evidence of drug-induced toxicity. Do not administer nevirapine to patients with moderate or severe (Child-Pugh Class B or C, respectively) hepatic impairment *[see Contraindications (4.1), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)]*.

5.2 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 2% of VIRAMUNE recipients compared to less than 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 Boxed Warning]*. 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, measure transaminases immediately. Permanently discontinue VIRAMUNE in patients with rash-associated transaminase elevations *[see Warnings and Precautions (5.1)]*.

Therapy with VIRAMUNE must be initiated with a 14-day lead-in period of 200 mg per day (150 mg/m^2 per day in pediatric patients), which has been shown to reduce the frequency of rash. Discontinue VIRAMUNE if a patient experiences severe rash or any rash accompanied by constitutional findings. Do not increase VIRAMUNE dose to a patient experiencing a mild to moderate rash without constitutional symptoms during the 14-day lead-in period of 200 mg per day (150 mg/m^2/day in pediatric patients) until the rash has resolved. The total duration of the once-daily lead-in dosing period must not exceed 28 days at which point an alternative regimen should be sought *[see Dosage and Administration (2.4)]*. Patients must 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 per 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.

5.3 Resistance

VIRAMUNE must not be used as a single agent to treat HIV-1 or added on as a sole agent to a failing regimen. 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 *[see Microbiology (12.4)]*.

5.4 Drug Interactions

See Table 4 for listings of established and potential drug interactions *[see Drug Interactions (7)]*.

Concomitant use of St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products and VIRAMUNE is not recommended. Co-administration of St. John's wort with non-nucleoside reverse transcriptase inhibitors (NNRTIs), including VIRAMUNE, 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. Co-administration of VIRAMUNE and efavirenz is not recommended as this combination has been associated with an increase in adverse reactions and no improvement in efficacy.

5.5 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 indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

5.6 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.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience in Adult Patients

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most serious adverse reactions associated with VIRAMUNE 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 Boxed Warning and Warnings and Precautions (5.1, 5.2)]*.

Hepatic Reaction

In controlled clinical trials, symptomatic hepatic events regardless of severity occurred in 4% (range 0% to 11%) of subjects who received VIRAMUNE and 1% of subjects in control groups. Female gender and higher $CD4^+$ cell counts (greater than 250 cells/mm^3 in women and greater than 400 cells/mm^3 in men) place patients at increased risk of these events *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Asymptomatic transaminase elevations (AST or ALT greater than 5X ULN) were observed in 6% (range 0% to 9%) of subjects who received VIRAMUNE and 6% of subjects in control groups. Co-infection with hepatitis B or C and/or increased transaminase elevations 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.

Liver enzyme abnormalities (AST, ALT, GGT) were observed more frequently in subjects receiving VIRAMUNE than in controls (see Table 3).

Skin Reaction

The most common clinical toxicity of VIRAMUNE is rash, which can be severe or life-threatening *[see Boxed Warning and Warnings and Precautions (5.2)]*. 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 (Trials 1037, 1038, 1046, and 1090), Grade 1 and 2 rashes were reported in 13% of subjects receiving VIRAMUNE compared to 6% receiving placebo during the first 6 weeks of therapy. Grade 3 and 4 rashes were reported in 2% of VIRAMUNE recipients compared to less than 1% of subjects receiving placebo. Women tend to be at higher risk for development of VIRAMUNE-associated rash *[see Boxed Warning and Warnings and Precautions (5.2)]*.

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

Table 2 Percentage of Subjects with Moderate or Severe Drug-Related Events in Adult Placebo-Controlled Trials

	Trial 1090[1]		Trials 1037, 1038, 1046[2]	
	VIRAMUNE	Placebo	VIRAMUNE	Placebo
	(n=1121)	(n=1128)	(n=253)	(n=203)
Median exposure (weeks)	58	52	28	28
Any adverse event	15%	11%	32%	13%
Rash	5	2	7	2
Nausea	1	1	9	4
Granulocytopenia	2	3	<1	0
Headache	1	<1	4	1
Fatigue	<1	<1	5	4
Diarrhea	<1	1	2	1
Abdominal pain	<1	<1	2	0
Myalgia	<1	0	1	2

[1] Background therapy included 3TC for all subjects and combinations of NRTIs and PIs. Subjects had $CD4^+$ cell counts less than 200 cells/mm^3.
[2] Background therapy included ZDV and ZDV+ddI; VIRAMUNE monotherapy was administered in some subjects. Subjects had $CD4^+$ cell count greater than or equal to 200 cells/mm^3.

Laboratory Abnormalities
Liver enzyme test abnormalities (AST, ALT) were observed more frequently in subjects receiving VIRAMUNE than in controls (Table 3). Asymptomatic elevations in GGT occur frequently but are not a contraindication to continue VIRAMUNE therapy in the absence of elevations in other liver enzyme tests. Other laboratory abnormalities (bilirubin, anemia, neutropenia, thrombocytopenia) were observed with similar frequencies in clinical trials comparing VIRAMUNE and control regimens (see Table 3).

Table 3 Percentage of Adult Subjects with Laboratory Abnormalities

	Trial 1090[1]		Trials 1037, 1038, 1046[2]	
	VIRAMUNE	Placebo	VIRAMUNE	Placebo
Laboratory Abnormality	**(n=1121)**	**(n=1128)**	**(n=253)**	**(n=203)**
Blood Chemistry				
SGPT (ALT) >250 U/L	5	4	14	4
SGOT (AST) >250 U/L	4	3	8	2
Bilirubin >2.5 mg/dL	2	2	2	2
Hematology				
Hemoglobin <8.0 g/dL	3	4	0	0
Platelets <50,000/mm^3	1	1	<1	2
Neutrophils <750/mm^3	13	14	4	1

[1] Background therapy included 3TC for all subjects and combinations of NRTIs and PIs. Subjects had $CD4^+$ cell counts less than 200 cells/mm^3.
[2] Background therapy included ZDV and ZDV+ddI; VIRAMUNE monotherapy was administered in some subjects. Subjects had $CD4^+$ cell count greater than or equal to 200 cells/mm^3.

6.2 Clinical Trial Experience in Pediatric Patients
Adverse events were assessed in BI Trial 1100.1032 (ACTG 245), a double-blind, placebo-controlled trial of VIRAMUNE (n=305) in which pediatric subjects received combination treatment with VIRAMUNE. In this trial two subjects were reported to experience Stevens-Johnson syndrome or Stevens-Johnson/toxic epidermal necrolysis transition syndrome. Safety was also assessed in trial BI 1100.882 (ACTG 180), an open-label trial of VIRAMUNE (n=37) in which subjects 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 subjects in trial BI 1100.892). The most frequently reported adverse events related to VIRAMUNE in pediatric subjects were similar to those observed in adults, with the exception of granulocytopenia, which was more commonly observed in children receiving both zidovudine and VIRAMUNE. Cases of allergic reaction, including one case of anaphylaxis, were also reported.

The safety of VIRAMUNE was also examined in BI Trial 1100.1368, an open-label, randomized clinical trial performed in South Africa in which 123 HIV-1 infected treatment-naïve subjects between 3 months and 16 years of age received combination treatment with VIRAMUNE oral suspension, lamivudine and zidovudine for 48 weeks *[see Use In Specific Populations (8.4) and Clinical Pharmacology (12.3)]*. Rash (all causality) was reported in 21% of the subjects, 4 (3%) of whom discontinued drug due to rash. All 4 subjects experienced the rash early in the course of therapy (less than 4 weeks) and resolved upon nevirapine discontinuation. Other clinically important adverse events (all causality) include neutropenia (9%), anemia (7%), and hepatotoxicity (2%) *[see Use in Specific Populations (8.4) and Clinical Studies (14.2)]*.

Safety information on use of VIRAMUNE in combination therapy in pediatric subjects 2 weeks to less than 3 months of age was assessed in 36 subjects from the BI 1100.1222 (PACTG 356) trial. No unexpected safety findings were observed although granulocytopenia was reported more frequently in this age group compared to the older pediatric age groups and adults.