AUSTRALIAN PRODUCT INFORMATION

NEVIRAPINE VIATRIS

(nevirapine) tablet

1 NAME OF THE MEDICINE

Nevirapine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each NEVIRAPINE VIATRIS tablet contains 200 mg of nevirapine as the active ingredient.

Excipients with known effect: sugars as lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

NEVIRAPINE VIATRIS 200 mg tablets are white to off-white, oval shaped, biconvex uncoated tablets, debossed with "NE" scoreline "200" on one side and "M" scoreline on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NEVIRAPINE VIATRIS in combination with antiretroviral agents is indicated for the treatment of HIV-1 infection in adults.

Resistant virus emerges rapidly when nevirapine is administered as monotherapy or in dual combination therapy with an antiretroviral agent. Therefore, nevirapine should always be administered in combination with at least two additional antiretroviral agents.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults 16 Years and Older

The recommended dose is NEVIRAPINE VIATRIS 200 mg 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 200 mg twice daily, in combination with at least two additional antiretroviral agents. For concomitantly administered antiretroviral therapy, the manufacturer's recommended dosage and monitoring should be followed.

NEVIRAPINE VIATRIS can be taken with or without food.

Dosage Management Considerations

Patients should be advised of the need to take nevirapine every day as prescribed. If a dose is missed the patient should not double the next dose but should take the next dose as soon as possible.

Clinical chemistry tests, which include liver function tests, should be performed prior to initiating nevirapine therapy and at appropriate intervals during therapy.

Nevirapine administration should be discontinued if patients who experience severe rash or a rash accompanied by constitutional symptoms. Patients experiencing rash during the 14-day lead-in period should not have their nevirapine dose increased until the rash has resolved (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE: INFORMATION FOR PATIENTS). The 200 mg once daily dosing regimen should not be continued beyond 4 weeks (28 days) at which point an alternative antiretroviral regimen should be sought.

Nevirapine administration should be interrupted in patients experiencing moderate or severe liver function test abnormalities (excluding GGT) until liver function tests have returned to baseline. Nevirapine may then be restarted using the two-week lead-in period. Nevirapine should be permanently discontinued if moderate or severe liver function test abnormalities recur.

If clinical hepatitis occurs, characterised by anorexia, vomiting, icterus AND laboratory findings such as moderate or severe liver function test abnormalities (excluding GGT), nevirapine must be permanently stopped. Nevirapine should not be readministered to patients who have required permanent discontinuation for clinical hepatitis due to nevirapine.

Patients who interrupt nevirapine dosing for more than 7 days should restart the recommended dosing, using the recommended lead-in dose for the first 14 days followed by the recommended twice daily dose.

4.3 CONTRAINDICATIONS

NEVIRAPINE VIATRIS is contraindicated in patients with clinically significant hypersensitivity to the active ingredient or any of the excipients.

NEVIRAPINE VIATRIS should not be administered to patients with severe hepatic dysfunction (Child-Pugh C) or pre-treatment AST or ALT > 5x Upper Limit of Normality (ULN) until baseline AST/ALT are stabilised (< 5x ULN).

NEVIRAPINE VIATRIS should not be readministered to:

- patients who have required permanent discontinuation for severe rash, rash accompanied by constitutional symptoms, hypersensitivity reactions, or clinical hepatitis due to nevirapine;

- patients who previously had AST or ALT > 5x ULN during nevirapine therapy and had recurrence of liver function abnormalities upon re-administration of nevirapine (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

NEVIRAPINE VIATRIS tablets contain 928 mg lactose monohydrate per maximum recommended daily dose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Herbal preparations containing St John's Wort (*Hypericum perforatum*) must not be used while taking nevirapine due to the risk of decreased plasma concentrations and reduced clinical effects of nevirapine (see also Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

On the basis of pharmacodynamic data, nevirapine should only be used with at least two other antiretroviral agents.

The first 18 weeks of therapy with nevirapine are a critical period which requires close monitoring of patients to disclose the potential appearance of severe and life-threatening skin reactions (including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis) and serious hepatitis/hepatic failure. The greatest risk of hepatic events and skin reactions occurs in the first 6 weeks of therapy. However, the risk of any hepatic event continues past this period and monitoring should continue at frequent intervals. Female gender, higher CD4+ counts (> 250/mm^3 and > 400/mm^3 if adult male); hepatitis C virus [HCV-Ab] co-infection and detectable plasma HIV-1 RNA levels in treatment experienced patients at the initiation of nevirapine therapy are associated with a greater risk of hepatic adverse events and rash-associated, hepatic events.

However, hepatotoxicity associated with nevirapine use can occur in both genders, all CD4+ cell counts and at any time during treatment.

As serious and life-threatening hepatotoxicity has been observed in controlled and uncontrolled studies predominantly in patients with a plasma HIV-1 viral load of 50 copies/mL or higher, nevirapine should not be initiated in adult females with CD4+ cell counts greater than 250 cell/mm^3 or in adult males with CD4+ cell counts greater than 400 cells/mm^3 who have a detectable plasmatic HIV-1 RNA unless the benefit outweighs the risk.

In some cases, hepatic injury has progressed despite discontinuation of treatment. Patients developing signs or symptoms of hepatitis, severe skin reaction or hypersensitivity reactions must discontinue nevirapine and seek medical evaluation immediately. Nevirapine should not be restarted following severe hepatic, skin or hypersensitivity reactions.

The dosage must be strictly adhered to, especially the 14-days lead-in period (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Cutaneous Reactions

Severe and life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine mainly during the first 6 weeks of therapy. These have included cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and hypersensitivity reactions characterised by rash, constitutional findings and visceral involvement. Patients should be carefully monitored during the first 18 weeks of treatment. Patients should be closely monitored if an isolated rash occurs.

Nevirapine must be permanently discontinued in any patient experiencing severe rash or a rash accompanied by constitutional symptoms (such as fever, blistering, oral lesions, conjunctivitis, facial oedema/swelling, muscle or joint aches, or general malaise), including SJS or TEN. Nevirapine must be permanently discontinued in any patient experiencing hypersensitivity reactions characterised by rash with constitutional symptoms, plus visceral involvement (such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction or signs of visceral involvement) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE: INFORMATION FOR PATIENTS and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Patients should be instructed that the major toxicity of nevirapine is rash. The lead-in period should be used because it has been found to lessen the frequency of rash (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). The majority of rashes associated with nevirapine occur within the first 6 weeks of initiation of therapy, therefore, patients should be monitored carefully for the appearance of rash during this period.

Patients should be instructed that dose escalation to twice-daily dosing is not to occur if any rash occurs during the two-week lead-in dosing period, until the rash has resolved. The 200 mg once daily dosing regimen should not be continued beyond 4 weeks (28 days) at which point an alternative antiretroviral regimen should be sought.

In rare instances, rhabdomyolysis has been observed in patients experiencing skin and/or liver reactions associated with nevirapine use.

Concomitant prednisone use (40 mg/day for the first 14 days of nevirapine administration) has not been shown to decrease the incidence of nevirapine-associated rash and may be associated with an increase in rash during the first 6 weeks of nevirapine therapy.

Risk factors for developing serious cutaneous reactions include failure to follow the initial dosing of 200 mg daily during the lead-in period. A long delay between the initial symptoms and medical consultation may increase the risk of a more serious outcome of cutaneous reactions. Women appear to be at higher risk than men of developing rash, whether receiving nevirapine or non-nevirapine containing therapy.

Any patient experiencing severe rash or a rash accompanied by constitutional symptoms such as fever, blistering, oral lesions, conjunctivitis, facial oedema/swelling, muscle or joint aches, or general malaise should discontinue medication and immediately seek medical evaluation. In these patients nevirapine must not be restarted.

If patients present with a suspected nevirapine-associated rash, liver function tests should be performed. Patients with moderate to severe elevations (AST or ALT > 5x ULN) should be permanently discontinued from nevirapine.

If a hypersensitivity reaction occurs, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction, nevirapine should be permanently stopped and not be re-introduced.

Hepatic Reactions

Severe or life-threatening hepatotoxicity, including fatal fulminant hepatitis, has occurred in patients treated with nevirapine. The first 18 weeks of treatment are a critical period which requires close monitoring. The risk of hepatic events is greatest in the first 6 weeks of therapy. However, the risk continues past this period and monitoring should continue at frequent intervals throughout treatment. Patients should be informed that hepatic reactions are a major toxicity of nevirapine. Patients with signs or symptoms suggestive of hepatitis must be advised to immediately seek medical evaluation, which should include liver function tests (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE: INFORMATION FOR PATIENTS).

In rare instances, rhabdomyolysis has been observed in patients experiencing skin and/or liver reactions associated with nevirapine use.

Increased AST or ALT levels > 2.5x ULN and/or co-infection with hepatitis B and/or C at the start of antiretroviral therapy is associated with greater risk of hepatic adverse events during antiretroviral therapy in general, including nevirapine-containing regimens.

Female gender and higher CD4+ counts at the initiation of nevirapine therapy in treatment naïve patients are associated with increased risk of hepatic adverse events. Women have a three-fold higher risk than men for symptomatic, often rash-associated, hepatic events (5.8% vs. 2.2%). In a retrospective review of predominantly patients with a plasma HIV-1 viral load of 50 copies/mL or higher, women with CD4+ counts > 250 cells/mm^3 had a 12-fold higher risk of symptomatic hepatic adverse events compared to women with CD4+ counts < 250 cells/mm^3 (11.0% vs. 0.9%). An increased risk was observed in men with detectable HIV-1 RNA in plasma and CD4+ counts > 400 cells/mm^3 (6.3% vs. up to 2.3% for men with CD4+ counts < 400 cells/mm^3). This increased risk for toxicity based on CD4+ count threshold has not been detected in patients with undetectable (i.e. < 50 copies/mL) plasma viral load.

All patients, regardless of gender, CD4+ cell counts, or antiretroviral treatment history, should be monitored for hepatotoxicity since symptomatic hepatic adverse events have been reported at all CD4+ cell counts.

Liver Monitoring

Abnormal liver function tests have been reported with nevirapine, some in the first few weeks of therapy. Asymptomatic elevations of liver enzymes are frequently described and are not necessarily a contraindication to use nevirapine. Asymptomatic GGT elevations are not a contraindication to continue therapy.

Monitoring of liver function tests is strongly recommended at frequent intervals, appropriate to the patient's clinical needs, especially during the first 18 weeks of treatment. Clinical and laboratory monitoring should continue throughout nevirapine treatment. Physicians and patients should be vigilant for prodromal signs or findings of hepatitis, such as anorexia, nausea, jaundice, bilirubinuria, acholic stools, hepatomegaly or liver tenderness. Patients should be instructed to seek medical attention if these occur.

If AST or ALT values > 2.5x ULN before or during treatment, then liver tests should be monitored more frequently during regular clinic visits. Nevirapine should not be administered to patients with pre-treatment AST or ALT > 5x ULN until baseline AST/ALT are stabilised at values < 5x ULN.

If AST or ALT increase to > 5x ULN, nevirapine should be immediately stopped. If AST or ALT return to baseline values and if the patient had no clinical signs/symptoms of hepatitis or constitutional symptoms or other findings suggestive of organ dysfunction, it may be possible to reintroduce

nevirapine, based on clinical needs and judgment, on a case by case basis. Nevirapine should be restarted with heightened clinical and laboratory vigilance at the starting dosage regimen of one 200 mg tablet daily for 14 days followed by one 200 mg tablet twice daily. If liver function abnormalities rapidly recur, nevirapine should be permanently discontinued.

If clinical hepatitis occurs, characterised by anorexia, nausea, vomiting, icterus AND laboratory findings such as moderate or severe liver function test abnormalities (excluding GGT), nevirapine must be permanently stopped. Nevirapine should not be readministered to patients who have required permanent discontinuation for clinical hepatitis due to nevirapine.

Other

The following events have also been reported when nevirapine has been used in combination with other antiretroviral agents: anaemia, pancreatitis, peripheral neuropathy and thrombocytopenia. These events are commonly associated with other antiretroviral agents and may be expected to occur when nevirapine is used in combination with other agents; however, it is unlikely that these events are due to nevirapine treatment.

Patients receiving nevirapine or any of 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. The long-term effects of nevirapine are unknown at this time. Nevirapine therapy has not been shown to reduce the risk of transmission of HIV-1 to others.

Nevirapine is extensively metabolised by the liver and nevirapine metabolites are eliminated largely by the kidney. Pharmacokinetic results suggest caution should be exercised when nevirapine is administered to patients with moderate hepatic dysfunction (Child-Pugh Class B). Nevirapine should not be administered to patients with severe hepatic dysfunction (Child-Pugh Class C) (see Section 4.3 CONTRAINDICATIONS).

In patients with renal dysfunction who are undergoing dialysis, pharmacokinetic results suggest that supplementing nevirapine therapy with an additional 200 mg dose of nevirapine following each dialysis treatment would help offset the effects of dialysis on nevirapine clearance. Otherwise patients with $CL_{cr} \geq 20$ mL/min do not require an adjustment in nevirapine dosing (see Section 5.2 PHARMACOKINETIC PROPERTIES: PHARMACOKINETICS IN SPECIAL POPULATIONS).

Hormonal methods of birth control other than DMPA should not be used as the sole method of contraception in women taking nevirapine. Nevirapine may lower the plasma concentrations of these medications (see also Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). Therefore, when postmenopausal hormone therapy is used during administration of nevirapine, its therapeutic effect should be monitored.

Nevirapine may be taken with other additional antiretroviral agents. Please also refer to the manufacturers' prescribing information of the antiretroviral agents for contraindications, warnings, side effects and potential drug interactions.

Combination antiretroviral therapy has been associated with the redistribution of body fat (lipodystrophy) in HIV infected patients. The long-term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors (PIs) and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age, and with drug related factors such as longer duration of antiretroviral treatment and associated metabolic disturbances. Clinical examination should include evaluation for physical signs of fat redistribution. Consideration should be given to the measurement of fasting serum lipids and blood glucose. Lipid disorders should be managed as clinically appropriate.

Immune Reactivation Syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause

serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of combination antiretroviral therapy. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and Pneumocystis pneumonia. Autoimmune disorders (such as Graves' disease) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment. Any inflammatory symptoms should be evaluated, and treatment instituted when necessary.

Information for Patients

Patients should be instructed that the major toxicity of nevirapine is rash and should be advised to promptly notify their physician of any rash. The majority of rashes associated with nevirapine occur within the first 6 weeks of initiation of therapy. Therefore, patients should be monitored carefully for the appearance of rash during this period. Patients should be instructed that dose escalation is not to occur if any rash occurs during the two-week lead-in dosing period, until the rash resolves. The 200 mg once daily dosing regimen should not be continued beyond 4 weeks (28 days) at which point an alternative regimen should be sought.

Patients should be informed that liver function test abnormalities are common in patients with HIV infection. Abnormal liver function tests and cases of clinical hepatitis have been reported with nevirapine. **Patients should be instructed to consult their physicians immediately should symptoms of hepatitis occur.**

Patients should be informed that nevirapine is not a cure for HIV-1 infection, and that they may continue to experience illnesses associated with advanced HIV-1 infection, including opportunistic infections. Treatment with nevirapine has not been shown to reduce the incidence or frequency of such illnesses, and patients should be advised to remain under the care of a physician when using nevirapine.

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

Nevirapine may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other medications.

Patients should be instructed that oral contraceptives and other hormonal methods of birth control should not be used as a method of contraception in women taking nevirapine.

Patients should be informed to take nevirapine 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.

Use in the Elderly

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric Use

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Warning on concomitant use with other medicines (for detailed description see table listed below).

Nevirapine can alter plasma exposure of other drugs, and other drugs can alter plasma exposure of nevirapine.

Combining the following compounds with nevirapine is not recommended: Efavirenz, rifampicin, ketoconazole, etravirine, rilpivirine, elvitegravir (in combination with cobicistat); if not co-administered with low dose ritonavir: fosamprenavir, saquinavir, atazanavir.

Nevirapine has been shown to be an inducer of hepatic cytochrome P450 metabolic enzymes (CYP3A, CYP2B) and may result in lower plasma concentrations of other concomitantly administered drugs that are extensively metabolised by CYP3A or CYP2B (see Section 5.2 PHARMACOKINETIC PROPERTIES). Thus, if a patient has been stabilised on a dosage regimen for a drug metabolised by CYP3A or CYP2B and begins treatment with nevirapine, dose adjustments may be necessary.

The absorption of nevirapine is not affected by food or antacids.

The interaction data is presented as geometric mean value with 90% confidence interval (90% CI) whenever these data were available.

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
ANTI-INFECTIVES		
Antiretrovirals		
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Didanosine 100-150 mg BID	Didanosine AUC ↔ Didanosine C_{min} § Didanosine C_{max} ↔	No dosage adjustments are required when nevirapine is taken in combination with didanosine.
Emtricitabine	In vitro, emtricitabine was not an inhibitor of human CYP 1A2, 2A6, 2B6, 2C9, 2C19, 2D6 or 3A4 enzymes.	No dosage adjustments are required when nevirapine is taken in combination with emtricitabine.
Abacavir	In vitro, abacavir did not inhibit CYP 3A4, 2C9 or 2D6.	No dosage adjustments are required when nevirapine is taken in combination with abacavir.
Lamivudine 150 mg BID	No changes to lamivudine apparent clearance and volume of distribution, suggesting no induction effect of nevirapine on lamivudine clearance.	No dosage adjustments are required when nevirapine is taken in combination with lamivudine.
Stavudine 30/40 mg BID	Stavudine AUC ↔ Stavudine C_{min} § Stavudine C_{max} ↔ Nevirapine: compared to historical controls, levels appeared to be unchanged.	No dosage adjustments are required when nevirapine is taken in combination with stavudine.
Tenofovir 300 mg QD	Tenofovir plasma levels remain unchanged. Tenofovir does not have an effect on nevirapine levels.	No dosage adjustments are required when nevirapine is taken in combination with tenofovir.
Zalcitabine 0.125-0.25 mg TID	Zalcitabine AUC ↔ Zalcitabine C_{min} § Zalcitabine C_{max} ↔	No dosage adjustments are required when nevirapine is taken in combination with zalcitabine.

Zidovudine 100-200 mg TID	Zidovudine AUC ↓28 (↓40 to ↓4) Zidovudine C_{max} ↓30 (↓51 to ↑4) Paired data suggest that zidovudine had no effect on the pharmacokinetics of nevirapine.	No dosage adjustments are required when nevirapine is taken in combination with zidovudine.
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz 600 mg QD	Efavirenz AUC ↓28 (↓34 to ↓14) Efavirenz C_{min} ↓32 (↓35 to ↓19) Efavirenz C_{max} ↓12 (↓23 to ↑1)	This co-administration is not recommended since the co-administration of efavirenz and nevirapine could lead to a higher risk for side effects (see also *Warning on concomitant use with other medicines*). Moreover, this co-administration does not improve efficacy over either NNRTI alone. Nevirapine in combination with efavirenz exhibited a strong antagonistic anti-HIV-1 activity *in vitro* (see also Section 5.1 PHARMACODYNAMIC PROPERTIES: MICROBIOLOGY).
Etravirine	Concomitant use of etravirine with nevirapine may cause a significant decrease in the plasma concentrations of etravirine and loss of therapeutic effect of etravirine.	The concomitant administration of nevirapine with NNRTIs is not recommended (see also *Warning on concomitant use with other medicines*).
Rilpivirine	Interaction has not been studied.	The concomitant administration of nevirapine with NNRTIs is not recommended (see also *Warning on concomitant use with other medicines*).
Protease Inhibitors (PIs)		
Atazanavir/ritonavir 300/100 mg QD 400/100mg QD	Atazanavir/r 300/100mg: Atazanavir/r AUC ↓42 (↓52 to ↓29) Atazanavir/r C_{min} ↓72 (↓80 to ↓60) Atazanavir/r C_{max} ↓28 (↓40 to ↓14) Atazanavir/r 400/100mg: Atazanavir/r AUC ↓19 (↓35 to ↑2) Atazanavir/r C_{min} ↓59 (↓73 to ↓40) Atazanavir/r C_{max} ↔ (compared to 300/100mg without nevirapine) Nevirapine AUC ↑25 (↑17 to ↑34) Nevirapine C_{min} ↑32 (↑22 to ↑43) Nevirapine C_{max} ↑17 (↑9 to ↑25)	If given in combination with nevirapine, atazanavir should be dosed with 400mg co-administered with low dose ritonavir 100mg.
Darunavir/ritonavir 400/100 mg BID	Darunavir AUC ↑24 (↓3 to ↑57) Darunavir C_{min} ↔ Darunavir C_{max} ↑40 (↑14 to ↑73) Nevirapine AUC ↑27 (↑12 to ↑44) Nevirapine C_{min} ↑47 (↑20 to ↑82) Nevirapine C_{max} ↑18 (↑2 to ↑37)	Darunavir/ritonavir increases the plasma concentrations of nevirapine as a result of CYP3A4 inhibition. Darunavir co-administered with 100 mg ritonavir and nevirapine can be used without dose adjustments.

Fosamprenavir 1400 mg BID	Amprenavir AUC ↓33 (↓45 to ↓20) Amprenavir C_{min} ↓35 (↓51 to ↓15) Amprenavir C_{max} ↓25 (↓37 to ↓11) Nevirapine AUC ↑29 (↑19 to ↑40) Nevirapine C_{min} ↑34 (↑21 to ↑49) Nevirapine C_{max} ↑25 (↑14 to ↑37)	Nevirapine should not be given with fosamprenavir if not co-administered with ritonavir. (see also *Warning on concomitant use with other medicines*).
Fosamprenavir/ritonavir 700/100 mg BID	Amprenavir AUC ↓11 (↓23 to ↑3) Amprenavir C_{min} ↓19 (↓31 to ↓4) Amprenavir C_{max} ↔ Nevirapine AUC ↑14 (↑5 to ↑24) Nevirapine C_{min} ↑22 (↑10 to ↑35) Nevirapine C_{max} ↑13 (↑3 to ↑24)	No dosing adjustments are required when nevirapine is co-administered with 700/100 mg of fosamprenavir/ritonavir BID.
Indinavir 800 mg Q8H	Indinavir AUC ↓31 (↓39 to ↓22) Indinavir C_{min} ↓44 (↓53 to ↓33) Indinavir C_{max} ↓15 (↓24 to ↓4) No clinically relevant change in nevirapine plasma levels was found.	No definitive clinical conclusions have been reached regarding the potential impact of co-administration of nevirapine and indinavir. A dose increase of indinavir to 1000 mg Q8H should be considered when indinavir is given with nevirapine 200 mg BID; however, there are no data currently available to establish that the short term or long term antiviral activity of indinavir 1000 mg Q8H with nevirapine 200 mg BID will differ from that of indinavir 800 mg Q8H with nevirapine 200 mg BID. Today indinavir is generally co-administered with ritonavir. There are limited clinical data on the interaction of nevirapine with indinavir/ritonavir.
Lopinavir/ritonavir (capsules) 400/100 mg BID	In HIV positive adults: Lopinavir AUC ↓27 Lopinavir C_{min} ↓46 Lopinavir C_{max} ↓19	An increase in the dose of lopinavir/ritonavir to 533/133 mg (4 capsules) twice daily with food is recommended in combination with nevirapine.
Nelfinavir 750 mg TID	Nelfinavir: AUC ↔ C_{max} ↔ Total exposure of nelfinavir plus the AG1402 metabolite: AUC ↓20 (↓72 to ↑128) C_{min} ↓35 (↓90 to ↑316) C_{max} ↓12 (↓61 to ↑100) Nevirapine: compared to historical controls, levels appeared to be unchanged.	No dosage adjustments are required when nevirapine is taken in combination with nelfinavir.
Ritonavir 600 mg BID	Nevirapine AUC ↔ Nevirapine C_{max} ↔ Ritonavir AUC ↔ Ritonavir C_{min} ↔ Ritonavir C_{max} ↔	No dosage adjustments are required when nevirapine is taken in combination with ritonavir.
Saquinavir 600 mg TID	Saquinavir AUC ↓38 (↓47 to ↓11) Saquinavir C_{min} § Saquinavir C_{max} ↓32 (↓44 to ↓6)	Nevirapine should not be given with saquinavir if not co-administered with ritonavir. (see also *Warning on concomitant use with other medicines*).

Saquinavir/ritonavir	The limited data available with saquinavir soft gel capsule boosted with ritonavir do not suggest any clinically relevant interaction between saquinavir boosted with ritonavir and nevirapine	No dosage adjustments are required when nevirapine is taken in combination with saquinavir co-administered with ritonavir.
Tipranavir/ritonavir 500/200 mg BID	No specific drug-drug interaction study has been performed. The limited data available from a phase IIa study in HIV-infected patients have shown a clinically non-significant 20% decrease of tipranavir C_{min}.	No dosage adjustments are required when nevirapine is taken in combination with tipranavir co-administered with ritonavir.
Entry Inhibitors		
Enfuvirtide	Due to the metabolic pathway of enfuvirtide no clinically significant pharmacokinetic interactions are expected between enfuvirtide and nevirapine.	No dosage adjustment is recommended when co-administering enfuvirtide with nevirapine.
Maraviroc 300 mg QD	Maraviroc AUC ↔ Maraviroc C_{min} § Maraviroc C_{max} ↑54 compared to historical controls Nevirapine concentrations not measured, no effect is expected.	Comparison to exposure in historical controls suggests that maraviroc 300 mg twice daily and nevirapine can be co-administered without dose adjustment.
Integrase Inhibitors		
Raltegravir 400 mg BID	No clinical data available.	Due to the metabolic pathway of raltegravir no interaction is expected. No dose adjustment is recommended when co-administering raltegravir with nevirapine.
Elvitegravir/cobicistat	Interaction has not been studied. Cobicistat, a cytochrome P450 3A inhibitor significantly inhibits hepatic enzymes, as well as other metabolic pathways. Therefore, co-administration would likely result in altered plasma levels of cobicistat and nevirapine	Co-administration of nevirapine with elvitegravir in combination with cobicistat is not recommended (see also *Warning on concomitant use with other medicines*).
Antivirals for Hepatitis B and C		
Entecavir	Entecavir is not a substrate, inducer or an inhibitor of cytochrome P450 (CYP450) enzymes. Due to the metabolic pathway of entecavir, no clinically relevant drug-drug interaction is expected.	Entecavir and nevirapine may be co-administered without dose adjustments.
Telbivudine	*In vitro*, telbivudine was not a substrate or inhibitor of the cytochrome P450 (CYP450) enzyme system (CYP1A2, 2C9, 2C19, 2D6, 2E1 or 3A4). Telbivudine did not induce CYP450 enzymes in animal. Due to the metabolic pathway of telbivudine, no clinically relevant drug-drug interaction is expected.	Telbivudine and nevirapine may be co-administered without dose adjustments.
Adefovir	Results of an in vitro study showed an additive or no interaction effect of nevirapine with adefovir (see also Section 5 PHARMACOLOGICAL PROPERTIES), this has not been confirmed in clinical trials and	Adefovir and nevirapine may be co-administered without dose adjustments.

	reduced efficacy is not expected. Adefovir did not inhibit and is not a substrate of common CYP isoforms, such as CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4.	
Antibiotics		
Clarithromycin 500 mg BID	Clarithromycin AUC ↓31 (↓38 to ↓24) Clarithromycin C_{min} ↓56 (↓70 to ↓36) Clarithromycin C_{max} ↓23 (↓31 to ↓14) Metabolite 14-OH clarithromycin AUC ↑42 (↑16 to ↑73) Metabolite 14-OH clarithromycin C_{max} ↑47 (↑21 to ↑80) Nevirapine AUC ↑26 Nevirapine C_{min} ↑28 Nevirapine C_{max} ↑24 compared to historical controls	Clarithromycin exposure was significantly decreased, 14-OH metabolite exposure increased. Because the clarithromycin active metabolite has reduced activity against *Mycobacterium aviumintracellulare complex* overall activity against the pathogen may be altered. Alternatives to clarithromycin, such as azithromycin should be considered. Close monitoring for hepatic abnormalities is recommended.
Rifabutin 150 or 300 mg QD	Rifabutin AUC ↑17 (↓2 to ↑40) Rifabutin C_{max} ↑28 (↑9 to ↑51) Metabolite 25-O-desacetylrifabutin AUC ↑24 (↓16 to ↑84) Metabolite 25-O-desacetylrifabutin C_{max} ↑29 (↓2 to ↑68) A clinically not relevant increase in the apparent clearance of nevirapine (by 9%) compared to historical pharmacokinetic data was reported.	No dose adjustment is recommended when rifabutin and nevirapine are co-administered. Due to the high intersubject variability 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.
Rifampicin 600 mg QD	Rifampicin AUC ↔ Rifampicin C_{max} ↔ Nevirapine AUC ↓58 Nevirapine C_{min} ↓68 Nevirapine C_{max} ↓50 compared to historical controls	It is not recommended to co-administer rifampicin and nevirapine. Physicians needing to treat patients co- infected with tuberculosis and using a nevirapine containing regimen may consider co-administration of rifabutin instead.
Antifungals		
Fluconazole 200 mg QD	Fluconazole AUC ↔ Fluconazole C_{min} ↔ Fluconazole C_{max} ↔ Nevirapine exposure: ↑100% compared with historical data where nevirapine was administered alone.	Because of the risk of increased exposure to nevirapine, caution should be exercised if the medicinal products are given concomitantly and patients should be monitored closely.
Itraconazole 200 mg QD	Itraconazole AUC ↓61 Itraconazole C_{min} ↓87 Itraconazole C_{max} ↓38 There was no significant difference in nevirapine pharmacokinetic parameters.	A dose adjustment for itraconazole should be considered when these two agents are administered concomitantly.

Ketoconazole 400 mg QD	Ketoconazole AUC ↓72 (↓80 to ↓60) Ketoconazole C_{min} § Ketoconazole C_{max} ↓44 (↓58 to ↓27) Nevirapine plasma levels: ↑15-28% compared to historical controls.	Ketoconazole and nevirapine should not be given concomitantly (see also *Warning on concomitant use with other medicines*).
ANTACIDS		
Cimetidine	Cimetidine: no significant effect on cimetidine PK parameters is seen. Nevirapine C_{min} ↑7	The limited data suggest no dose adjustment when Cimetidine is co-administered with nevirapine.
ANTITHROMBOTICS		
Warfarin	The interaction between nevirapine and the antithrombotic agent warfarin is complex, with the potential for both increases and decreases in coagulation time when used concomitantly.	Close monitoring of anticoagulation levels is warranted.
CONTRACEPTIVES		
Depot-medroxy progesterone acetate (DMPA) 150 mg every 3 months	DMPA AUC ↔ DMPA C_{min} ↔ DMPA C_{max} ↔ Nevirapine AUC ↑20 Nevirapine C_{max} ↑20	Nevirapine co-administration did not alter the ovulation suppression effects of DMPA. No dose adjustment is necessary when DMPA and nevirapine are co-administered.
Ethinyl estradiol (EE) 0.035 mg	EE AUC ↓20 (↓33 to ↓3) EE C_{min} § EE C_{max} ↔	Oral hormonal contraceptives should not be used as the sole method of contraception in women taking nevirapine (see also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE: INFORMATION FOR PATIENTS). Appropriate doses for hormonal contraceptives (oral or other forms of application) other than DMPA in combination with nevirapine have not been established with respect to safety and efficacy.
Norethindrone (NET) 1.0 mg QD	NET AUC ↓19 (↓30 to ↓7) NET C_{min} § NET C_{max} ↓16 (↓27 to ↓3)	
ANALGESICS/OPIOIDS		
Methadone Individual Patient Dosing	Methadone AUC ↓60 (↓69 to ↓49) Methadone C_{min} § Methadone C_{max} ↓42 (↓50 to ↓33)	Narcotic withdrawal syndrome has been reported in patients treated with nevirapine and methadone concomitantly. Methadone-maintained patients beginning nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
HERBAL PRODUCTS		
St John's Wort	Serum levels of nevirapine can be reduced by concomitant use of the herbal preparation St John's Wort (*Hypericum perforatum*). This is due to induction of drug metabolism enzymes and/or transport proteins by St John's Wort.	Herbal preparations containing St John's Wort should not be combined with nevirapine. If patient is already taking St John's Wort check nevirapine and if possible viral levels and stop St John's Wort. Nevirapine levels may increase on stopping St John's Wort. The dose of nevirapine may need adjusting. The inducing effect may persist for at least 2 weeks after cessation of treatment with St John's Wort (see also Section 4.3 CONTRAINDICATIONS).

§ = C_{min} below detectable level of the assay
↑ = Increase, ↓ = Decrease, ↔ = No Effect

Other Information

In vitro studies using human liver microsomes indicated that the formation of nevirapine hydroxylated metabolites was not affected by the presence of dapsone and trimethoprim/sulphamethoxazole. Erythromycin significantly inhibited the formation of nevirapine hydroxylated metabolites. Clinical studies have not been performed.

It should be noted that other compounds that are substrates of CYP3A and CYP2B6 might have decreased plasma concentrations when co-administered with nevirapine. The following drugs have been reported as substrates for the CYP3A isoenzyme system and might theoretically interact with nevirapine: some calcium channel blocking drugs including diltiazem and verapamil; some antiarrhythmic drugs (including disopyramide, lidocaine (lignocaine)); ciclosporin; some imidazole antifungal agents including itraconazole; some anticonvulsant drugs (including carbamazepine); some antidepressant drugs (including fluoxetine, fluvoxamine and nefazodone); some antihistamines (loratadine); gestodene; grapefruit juice. These potential interactions have not been investigated, however the results from studies of other CYP3A inducing drugs have demonstrated a negligible effect on nevirapine.

Table 1 Potential drug interactions

Examples of drugs in which plasma concentrations may be decreased by co-administration with nevirapine	
Drug Class	**Examples of Drugs**
Antiarrhythmics	Amiodarone, disopyramide, lidocaine (lignocaine)
Anticonvulsants	Carbamazepine, clonazepam, ethosuximide
Antifungals	Itraconazole
Calcium channel blockers	Diltiazem, nifedipine, verapamil
Cancer chemotherapy	Cyclophosphamide monohydrate
Ergot alkaloids	Ergotamine
Immunosuppressants	Ciclosporin, 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

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 observed following a human clinical dose of 400 mg/day.

No human data on fertility are available.

Use in Pregnancy

Pregnancy Category: B3

Data from the Antiretroviral Pregnancy Registry (1171 first trimester and 1529 second/third trimester exposures to nevirapine as of June 2021) on pregnant women indicate no increased malformative or foeto/neonatal toxicity.

The use of nevirapine during pregnancy, if deemed necessary, may be considered.

There was no evidence for teratogenicity in reproductive studies performed in rats and rabbits treated with oral doses up to 50 and 300 mg/kg/day nevirapine. In rats a significant decrease in fetal body weight occurred at maternally toxic doses providing systemic exposure approximately 50% higher, based on AUC, than that seen at the recommended clinical dose. Maternal toxicity and observable effects on fetal development were not observed in the rat with a systemic exposure equivalent to that seen at the recommended human dose or in the rabbit with a systemic exposure approximately 50% higher than that seen at the recommended human dose.

There have been no adequate and well controlled studies of nevirapine in pregnant women, nor are there reports of infants born to women who conceived while receiving nevirapine chronic dosing in clinical trials. Nevirapine readily crosses the placenta. Nevirapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The US 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. While the Registry population exposed and monitored to date is not sufficient to detect an increase in the risk of relatively rare defects, for nevirapine sufficient numbers of first trimester exposures have been monitored to detect at least a 1.5-fold increase in risk of overall birth defects. These findings should provide some assurance in counselling patients.

Caution should be exercised when prescribing nevirapine to pregnant women. As hepatotoxicity is more frequent in women with CD4+ cell counts above 250 cells/mm^3 with detectable HIV-1 RNA in plasma (50 or more copies/mL), these conditions should be taken in consideration on therapeutic decision (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Severe hepatic events, including fatalities, have been reported in pregnant women receiving chronic nevirapine therapy as part of combination treatment of HIV-1 infection. Regardless of pregnancy status, women with CD4+ cell counts greater than 250 cells/mm^3 should not initiate nevirapine unless the benefit outweighs the risk.

Women of childbearing potential should not use oral contraceptives as the sole method for birth control, since nevirapine might lower the plasma concentrations of these medications (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Use in Lactation

Nevirapine is excreted in the breast milk.

It is generally recommended that HIV-1 infected women should not breastfeed infants regardless of the use of antiretroviral agents, to avoid post-natal transmission of HIV-1.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no specific studies about the ability to drive vehicles and use machinery. However, patients should be advised that they may experience undesirable effects such as fatigue during treatment with nevirapine. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience fatigue, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most frequently reported adverse events related to nevirapine therapy were rash, fever, nausea, headache, fatigue, somnolence, vomiting, diarrhoea, abdominal pain and myalgia. Cases of anaemia and neutropenia may be associated with nevirapine therapy. Arthralgia has been reported as a stand-alone event in rare instances in patients receiving nevirapine containing regimens.

The following adverse events which may be causally related to the administration of nevirapine have been reported. The frequencies estimated are based on pooled clinical trial data for events considered related to nevirapine treatment.

Frequency classes: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

Blood and lymphatic system disorders
Common: granulocytopenia
Uncommon: anaemia
Immune system disorders
Common: hypersensitivity (including anaphylactic reaction, angioedema, urticaria)
Uncommon: drug reaction with eosinophilia and systemic symptoms, anaphylactic reaction
Nervous system disorders
Common: headache
Gastrointestinal disorders
Common: nausea, vomiting, abdominal pain, diarrhoea
Hepatobiliary disorders
Common: hepatitis (1.2 %) (including severe and life-threatening hepatotoxicity), liver function tests abnormal
Uncommon: jaundice
Rare: liver failure/fulminant hepatitis (which may be fatal)
Skin and subcutaneous tissue disorders
Very common: rash
Uncommon: Stevens-Johnson syndrome (0.3 %), urticaria, toxic epidermal necrolysis (which may be fatal), angiooedema
Musculoskeletal and connective tissue disorders
Common: myalgia
Uncommon: arthralgia
General disorders and administration site conditions
Common: fatigue, pyrexia
Uncommon: fever
Investigations
Common: liver function test abnormal (alanine aminotransferase increased; transaminases increased; aspartate aminotransferase increased; gamma-glutamyltransferase increased; hepatic enzyme increased; hypertransaminasaemia).
Uncommon: blood phosphorus decreased, blood pressure increased

Skin and Subcutaneous Tissues

The most common clinical toxicity of nevirapine is rash, with nevirapine-attributable rash occurring in 9% of patients in combination regimens in controlled studies (Trials 1100.1037, 1100.1038, 1100.1046, 1100.1090). In these clinical trials, 24% of patients treated with nevirapine-containing regimen experienced rash compared with 15% of patients treated in control groups. Severe or life-threatening rash occurred in 1.7% of nevirapine-treated patients compared with 0.2% of patients treated in the control groups.

Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. Allergic reactions (anaphylaxis, angiooedema and urticaria) have been reported. Rashes occur alone or in the context of hypersensitivity reactions, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia and renal dysfunction.

Severe and life-threatening skin reactions including Stevens-Johnson syndrome (SJS) and uncommonly toxic epidermal necrolysis (TEN) have occurred in patients treated with nevirapine. Fatal cases of SJS, TEN and hypersensitivity reactions have been reported. The majority of severe rashes occurred within the first 6 weeks of treatment.

Hepatobiliary

The most frequently observed laboratory test abnormalities are elevations in liver function tests (LFTs) including ALT, AST, GGT, total bilirubin and alkaline phosphatase. Asymptomatic elevations of GGT levels are more frequent in nevirapine recipients than in controls. Cases of jaundice have been reported. Cases of hepatitis, severe and life-threatening hepatotoxicity, and fatal fulminant hepatitis have occurred in patients treated with nevirapine. In a large clinical trial (Trial 1100. 1090), the risk of a serious hepatic event among

1121 patients receiving nevirapine for a median duration of greater than one year was 1.2% (versus 0.6% in placebo group).

Increased AST or ALT levels and/or seropositivity for hepatitis B and/or C were associated with a greater risk of hepatic adverse events for both nevirapine and control groups. The best predictor of a serious hepatic event was elevated baseline liver function tests.

The first 18 weeks of treatment is a critical period which requires close monitoring. The risk of hepatic events is greatest in the first 6 weeks of therapy. However, the risk continues past this period and monitoring should continue at frequent intervals throughout treatment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Clinical hepatitis may be isolated or associated with rash and/or additional constitutional symptoms.

Post-marketing Surveillance

The post-marketing experience has shown that the most serious adverse reactions are Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatitis/hepatic failure and hypersensitivity reactions, (characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction).

The following events have been reported with the use of nevirapine in clinical practice:

Body as a Whole:	fever, somnolence, drug withdrawal, redistribution/accumulation of body fat
Gastrointestinal:	vomiting
Liver and Biliary:	jaundice, fulminant and cholestatic hepatitis, hepatic necrosis, hepatic failure
Haematology:	anaemia, eosinophilia, neutropenia
Musculoskeletal:	arthralgia
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 oedema, muscle or joint aches, general malaise, fatigue or significant hepatic abnormalities plus one or more of the following: hepatitis, eosinophilia, granulocytopenia, lymphadenopathy and/or renal dysfunction have been reported with the use of nevirapine.

Monitoring of Patients

Clinical chemistry tests, which include liver function tests, should be performed prior to initiating nevirapine therapy and at appropriate intervals during therapy.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no known antidote for nevirapine overdosage. Cases of nevirapine overdose at doses ranging from 800 to 6000 mg per day for up to 15 days have been reported. Patients have experienced events including oedema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, increase in transaminases and weight decrease. All events subsided following discontinuation of nevirapine.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Non-nucleoside reverse transcriptase inhibitor, ATC code: J05AG01.

Mechanism of Action

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Nevirapine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The activity of nevirapine does not compete with template or nucleoside triphosphates. HIV-2 RT and eukaryotic DNA polymerases (such as human DNA polymerases α, ß, γ, or δ) are not inhibited by nevirapine.

In clinical studies, nevirapine has been associated with an increase in HDL-cholesterol and an overall improvement in the total to HDL-cholesterol ratio. However, in the absence of specific studies with nevirapine on modifying the cardiovascular risk in HIV infected patients, the clinical impact of these findings is not known. The selection of antiretroviral drugs must be guided primarily by their antiviral efficacy.

Microbiology

In Vitro HIV Susceptibility

The *in vitro* antiviral activity of nevirapine has been measured in a variety of cell lines including peripheral blood mononuclear cells, monocyte derived macrophages, and lymphoblastoid cell lines. Nevirapine exhibited antiviral activity *in vitro* against group M HIV-1 isolates from clades A, B, C, D, F, G, and H, and circulating recombinant forms (CRF), CRF01_AE, CRF02_AG and CRF12_BF in assays with human embryonic kidney 293 cells (median IC_{50} value of 63 nM; range, 14-302 nM). Nevirapine had no significant antiviral activity *in vitro* against isolates from group O HIV-1 and no activity against HIV-2.

Nevirapine in combination with efavirenz exhibited a strong antagonistic anti-HIV-1 activity *in vitro* and was additive to antagonistic with the protease inhibitor ritonavir or the fusion inhibitor enfuvirtide in C8166 cells. Nevirapine exhibited predominantly additive anti-HIV-1 activity in combination with the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir and tipranavir, and additive to synergistic anti-HIV-1 activity with the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir and zidovudine. The anti-HIV-1 activity of nevirapine was antagonised by the anti-HBV drug adefovir and by the anti-HCV drug ribavirin *in vitro*.

Resistance

HIV isolates with reduced susceptibility (100-250-fold) to nevirapine emerge *in vitro*. Genotypic analysis showed mutations in the HIV RT gene at amino acid positions 181 and/or 106 depending upon the virus strain and cell line employed. Time to emergence of nevirapine resistance *in vitro* was not altered when selection included nevirapine in combination with several other NNRTIs.

Phenotypic and genotypic changes in HIV-1 isolates from patients treated with either nevirapine (n = 24) or nevirapine+AZT (n = 14) were monitored in Phase I/II trials over 1 to ≥ 12 weeks. After 1 week of nevirapine monotherapy, isolates from 3/3 patients had decreased susceptibility to nevirapine *in vitro*; one or more of the RT mutations at amino acid positions 103, 106, 108, 181, 188 and 190 were detected in some patients as early as 2 weeks after therapy initiation. By week eight of nevirapine monotherapy, 100% of the patients tested (n = 24) had HIV isolates with a > 100-fold decrease in susceptibility to nevirapine *in vitro* compared to baseline and had one or more of the nevirapine-associated RT resistance mutations; 19 of 24 patients (80%) had isolates with a position 181 mutation regardless of dose. Nevirapine+AZT combination therapy did not alter the emergence rate of nevirapine-resistant virus or the magnitude of nevirapine resistance *in vitro*; however, a different RT mutation pattern, predominantly distributed amongst amino acid positions 103, 106, 188, and 190, was observed. In patients (6 of 14) whose baseline isolates possessed a wild type RT gene, nevirapine+AZT combination therapy did not appear to delay emergence of AZT-resistant RT mutations. The development of genotypic and phenotypic resistance to nevirapine / ddI / AZT as a function of virologic response to therapy in a group of drug-naive individuals receiving various combinations of these agents was

examined in a double blind controlled randomised trial (INCAS study). In this study, antiretroviral naive subjects with CD4+ cells counts of 200-600/mm^3 were treated with either nevirapine+ AZT (n = 46), AZT + ddI (n = 51) or nevirapine+ AZT + ddI (n = 51) and followed for 52 weeks or longer on therapy. Virologic evaluations were performed at baseline, six months and 12 months. The phenotypic resistance test performed required a minimum of 1000 copies/mL HIV RNA in order to be able to amplify the virus. Of the three study groups, 16, 19 and 28 patients respectively had evaluable baseline isolates and subsequently remained in the study for at least 24 weeks. At baseline, there were five cases of phenotypic resistance to nevirapine; the IC_{50} values were 5 to 6.5-fold increased in three and >100 fold in two. At 24 weeks, all available isolates recoverable from patients receiving nevirapine were resistant to this agent, while 18/21 (86%) patients carried such isolates at 30-60 weeks. In 16 subjects, viral suppression was below the limits of detection (< 20 copies/mL = 14, < 400 copies/mL = 2). Assuming that suppression below < 20 copies/mL implies nevirapine susceptibility of the virus, 45% (17/38) of patients had virus measured or imputed to be susceptible to nevirapine. All 11 subjects receiving nevirapine+ AZT who were tested for phenotypic resistance were resistant to nevirapine by six months. Over the entire period of observation, one case of ddI (5%) resistance was seen. AZT (19%) resistance emerged as more frequent after 30-60 weeks, especially in patients receiving double combination therapy. Based on the increase in IC_{50}, AZT resistance appeared lower in the nevirapine+ AZT + ddI group than the other treatment groups.

With respect to nevirapine resistance, all isolates that were sequenced carried at least one mutation associated with resistance, the most common single changes being K103N and Y181C. In summary, the use of highly active drug therapies is associated with a delay in the development of antiretroviral drug resistance. The genotypic correlates of phenotypic nevirapine resistance were identified in 12 plasma isolates from 11 triple therapy patients. Treatment-emergent, nevirapine resistance-associated mutations were:

Mutation	Frequency
K101E	2
K103N	8
V106A	2
Y181C	5
G190A	6

Combinations of mutations were observed in nine of the 12 patients. These data from INCAS illustrate that the use of highly active drug therapies is associated with a delay in the development of antiretroviral drug resistance.

Genotypic analysis was performed on isolates from 86 antiretroviral naïve patients who discontinued the clinical study after experiencing virologic failure (rebound, partial response) or due to an adverse event or who had transient increase in viral load during the course of the study. The analysis of these samples of patients receiving nevirapine in combination with tenofovir and emtricitabine showed that isolates from 50 patients contained resistance mutations expected with a nevirapine-based regimen. Of these 50 patients, 28 developed resistance to efavirenz and 39 developed resistance to etravirine (the most frequently emergent resistance mutations being Y181C).

The observed mutations at failure were those expected with a nevirapine-based regimen. Two new substitutions on codons previously associated with nevirapine resistance were observed: one patient with Y181I and one patient with Y188N; resistance to nevirapine was confirmed by phenotype.

The clinical relevance of phenotypic and genotypic changes associated with nevirapine therapy has not been established.

Cross-Resistance

Rapid emergence of HIV strains which are cross-resistant to NNRTIs has been observed *in vitro*. Data on cross-resistance between the NNRTI nevirapine and nucleoside analogue RT inhibitors are very limited. In four patients, AZT-resistant isolates tested *in vitro* retained susceptibility to nevirapine and in six patients,

nevirapine-resistant isolates were susceptible to AZT and ddI. Cross-resistance between nevirapine and HIV protease inhibitors is unlikely because the enzyme targets involved are different.

Cross-resistance to efavirenz is expected after virologic failure with nevirapine. Depending on resistance testing results, an etravirine-containing regimen may be used subsequently.

Nevirapine 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.

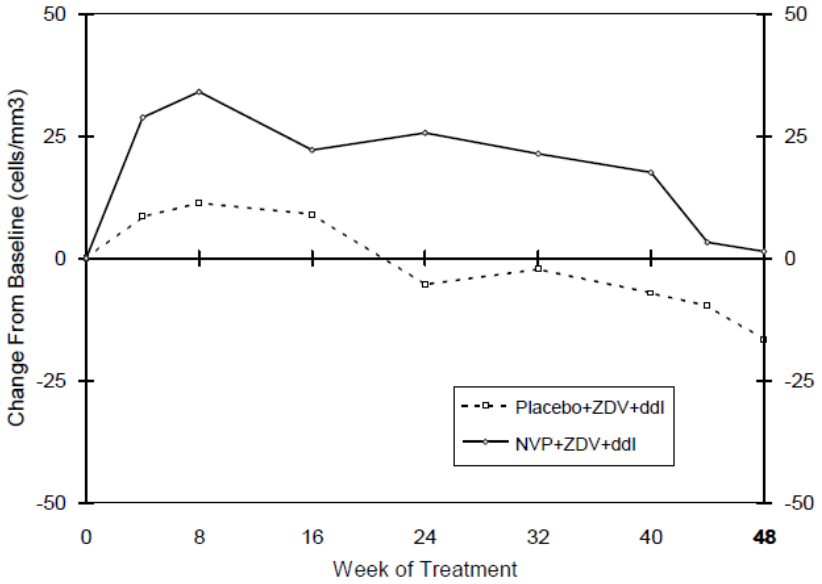
When discontinuing an antiretroviral regimen containing nevirapine, the long half-life of nevirapine should be taken into account; if antiretrovirals with shorter half-lives than nevirapine are stopped concurrently, low plasma concentrations of nevirapine alone may persist for a week or longer and virus resistance may subsequently develop.

Clinical Trials

Patients with a Prior History of Nucleoside Therapy

ACTG 241 compared treatment with Nevirapine + AZT + ddI versus AZT + ddI in 398 HIV-1-infected patients (median age 38 years, 74% Caucasian, 80% male) with CD4+ cell counts ≤ 350 cells/mm^3 (mean 153 cells/mm^3) and a mean baseline plasma HIV-1 RNA concentration of 4.59 $\log_{10}$ copies/mL (38,905 copies/mL), who had received at least 6 months of nucleoside therapy prior to enrolment (median 115 weeks). Treatment doses were nevirapine, 200 mg daily for two weeks, followed by 200 mg twice daily, or placebo; AZT, 200 mg three times daily; ddI, 200 mg twice daily. A significant benefit of triple therapy with nevirapine compared to double therapy was observed throughout a 48-week treatment period in terms of CD4+ cell count (Figure 1), % CD4+, quantitative PBMC microculture and plasma viral DNA (Figure 2). Favourable responses to triple therapy with nevirapine were seen at all CD4+ count levels.

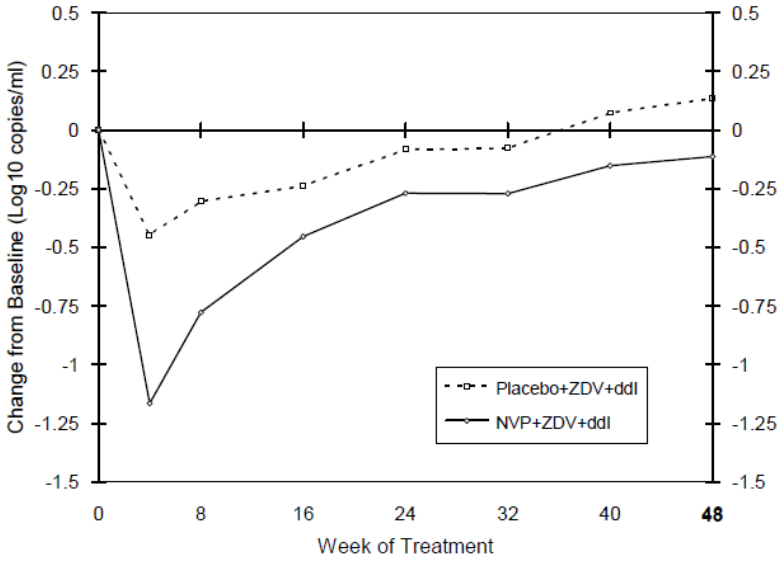
Figure 1: Mean Change from Baseline for CD4+ Cell Count (absolute number of CD4+ cells/mm^3), Trial ACTG 241



Number of patients with CD4 cell counts at each timepoint

	Baseline	Week 16	Week 32	40-48 Weeks
NVP+AZT+ddI	196	177	157	161
Placebo+AZT+ddI (ZDV=AZT)	196	176	160	167

Figure 2: Mean Change from Baseline in HIV-1 RNA Concentrations (Log_{10} copies/mL), Virology Sub-study of Trial ACTG 241



Number of patients with HIV-1 RNA data at each timepoint

	Baseline	Week 16	Week 32	40-48 Weeks
NVP+AZT+ddI	95	84	75	74
Placebo+AZT+ddI (ZDV=AZT)	93	82	75	75

Clinical Endpoint Trial:

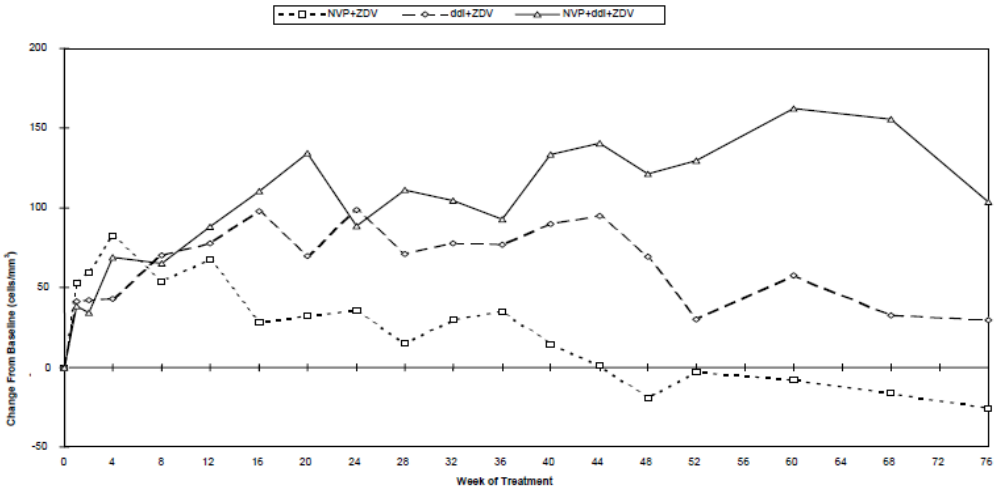
ACTG 193a was a placebo-controlled trial which compared treatment with nevirapine + AZT + ddI versus AZT + ddI, as well as studying AZT + ddC and AZT alternating with ddI monthly, in 1298 HIV-1-infected patients (mean age 37 years, 51% Caucasian, 87% male) with CD4+ cell counts < 50 cells/mm^3 (mean 25 cells/mm^3). Eighty-four percent (84%) of patients had received nucleoside therapy prior to enrolment (median 15 months). Treatment doses were nevirapine 200 mg daily for two weeks, followed by 200 mg twice daily, or placebo; AZT 200 mg three times daily; ddC 0.75 mg three times daily; ddI 200 mg twice daily (or 125 mg twice daily for patients weighing less than 60 kg). The median time to HIV progression event or death was significantly delayed in the nevirapine + AZT + ddI treatment group as compared to the AZT + ddI group (82 weeks versus 62 weeks, p = 0.013). Mortality was similar for the two groups throughout the trial (112 versus 114, respectively, p = 0.126). Patients with prior nucleoside experience had a median time to HIV progression event or death of 79 weeks for the nevirapine + AZT +ddI treatment group as compared to 54 weeks in the AZT + ddI treatment group (p = 0.004). The results for patients who were nucleoside naive were not statistically significant (p = 0.333). The median time to HIV progression event or death was shorter for AZT + ddC (53 weeks) and alternating AZT and ddI (57 weeks) groups.

Patients who are Antiretroviral Naive

BI Trial 1046 compared treatment with nevirapine + AZT + ddI versus nevirapine + AZT versus AZT + ddI in 151 HIV-1-infected patients (median age 37 years, 94% Caucasian, 93% male) with CD4+ cell counts of 200-600 cells/mm^3 (mean 375 cells/mm^3) and a mean baseline plasma HIV-1 RNA concentration of 4.41 log_{10} copies/mL (25,704 copies/mL). Treatment doses were nevirapine, 200 mg daily for two weeks, followed by 200 mg twice daily, or placebo; AZT, 200 mg three times daily; ddI, 125 or 200 mg twice daily. Changes in CD4+ cell counts at 52 weeks: mean levels of CD4+ cell counts in those randomised to nevirapine + AZT + ddI and AZT + ddI remained significantly above baseline; the nevirapine + AZT + ddI group was significantly improved compared to the AZT + ddI group. Changes in HIV-1 viral RNA at 52 weeks: there was a significantly better response in the nevirapine + AZT + ddI group than the AZT + ddI group as measured by mean changes in plasma viral RNA. The proportion of patients whose HIV-1 RNA was decreased to below the limit of detection (20 copies/mL) for every timepoint from 40 to 52 weeks was significantly greater in the

nevirapine + AZT + ddI group (18/40 or 45%), when compared to the AZT + ddI group (2/36 or 6%) or the nevirapine + AZT group (0/28 or 0%) (Figures 3 - 5). The clinical significance of this finding is unknown.

Figure 3: Mean Change from Baseline for CD4+ Cell Count (absolute number of CD4+ cells/mm^3), Trial BI 1046

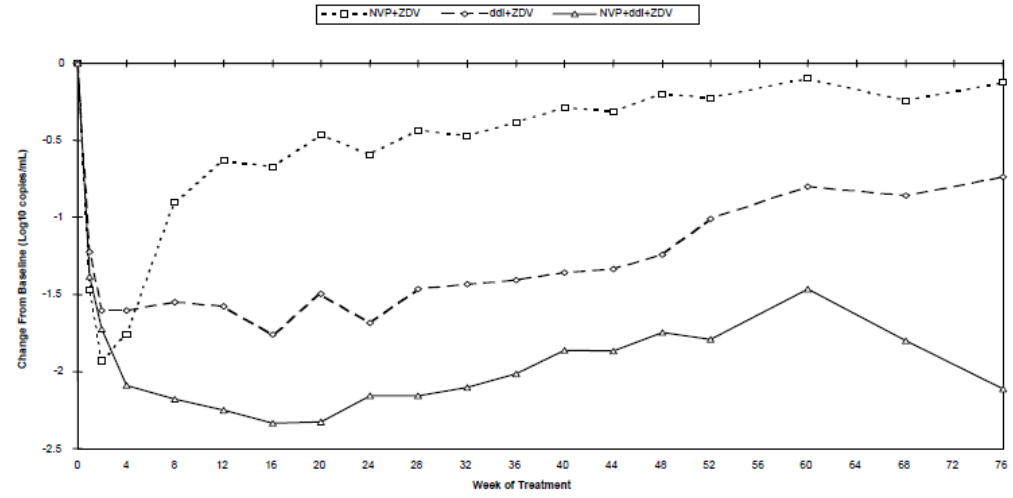


Number of patients with CD4 cell counts at each timepoint

	Baseline	Week 16	Week 32	Week 52	Week 76
NVP+AZT+ddI	51	41	40	38	15
Placebo+AZT+ddI	52	38	35	33	12
NVP+AZT+Placebo	47	35	27	26	15

(ZDV=AZT)

Figure 4: Mean Change from Baseline in HIV-1 RNA Concentrations (Log_{10} copies/mL), Trial BI 1046

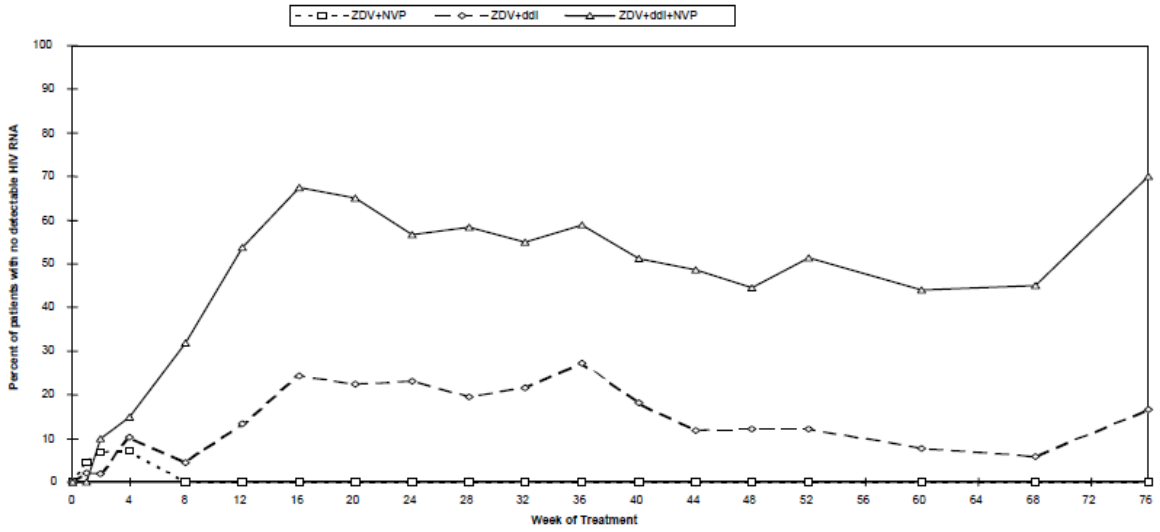


Number of patients with HIV-1 RNA data at each timepoint

	Baseline	Week 16	Week 32	Week 52	Week 76
NVP+ZDV+ddI	51	40	40	37	10
Placebo+ZDV+ddI	51	37	37	33	6
NVP+ZDV+Placebo	46	35	26	25	6

(ZDV=AZT)

Figure 5: Percent of Patients with HIV RNA Below the Limit of Detection, Trial BI 1046



Number of patients with HIV-1 RNA data at each timepoint

	Baseline	Week 16	Week 32	Week 52	Week 76
NVP+ZDV+ddI	51	40	40	37	10
Placebo+ZDV+ddI	51	37	37	33	6
NVP+ZDV+Placebo	46	35	26	25	6

(ZDV=AZT)

5.2 PHARMACOKINETIC PROPERTIES

Absorption and Bioavailability

Nevirapine is readily absorbed (>90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in 12 healthy adults following single-dose administration was 93±9% (mean ± SD) for a 50 mg tablet and 91 ± 8% for an oral solution. Peak plasma nevirapine concentrations of 2 ± 0.4 microgram/mL (7.5 μM) were attained by 4 hours following a single 200 mg dose. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady state trough nevirapine concentrations of 4.5 ± 1.9 microgram/mL (17 ± 7 μM), (n = 242) were attained at 400 mg/day.

The absorption of nevirapine is not affected by food, antacids or medicinal products that are formulated with an alkaline buffering agent (e.g. didanosine).

Distribution

Nevirapine is highly lipophilic and is essentially non-ionised at physiologic pH. Following intravenous administration in healthy adults, the apparent volume of distribution (V_{dss}) of nevirapine was 1.21 ± 0.09 L/kg, suggesting that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is found in breast milk (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION: USE IN PREGNANCY). Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 microgram/mL. Nevirapine concentrations in human cerebrospinal fluid (n = 6) were 45% (± 5%) of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

Metabolism/Excretion

In vivo studies in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 (oxidative) metabolism to several hydroxylated metabolites. *In vitro* studies with human liver microsomes suggest that oxidative metabolism of nevirapine is mediated primarily by cytochrome P450 isoenzymes from the CYP3A family, although other isoenzymes may have a secondary role. In a mass balance/excretion study in eight healthy male volunteers dosed to steady state with nevirapine 200 mg twice daily followed by a single 50 mg dose of ^{14}C-nevirapine, approximately 91.4% ±

10.5% of the radiolabelled dose was recovered, with urine (81.3% ± 11.1%) representing the primary route of excretion compared to faeces (10.1% ± 1.5%). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus, cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of nevirapine biotransformation and elimination in humans. Only a small fraction (< 5%) of the radioactivity in urine (representing <3% of the total dose) was made up of parent compound; therefore, renal excretion of nevirapine plays a minor role in elimination of the parent compound.

Nevirapine has been shown to be an inducer of hepatic cytochrome P450 metabolic enzymes. The pharmacokinetics of autoinduction are characterised by an approximately 1.5-to 2-fold increase in the apparent oral clearance of nevirapine as treatment continues from a single dose to two-to-four weeks of dosing with 200-400 mg/day. Autoinduction also results in a corresponding decrease in the terminal phase half-life of nevirapine in plasma from approximately 45 hours (single dose) to approximately 25-30 hours following multiple dosing with 200-400 mg/day.

Adults

Nevirapine pharmacokinetics in HIV-1 infected adults do not appear to change with age (range 19-68 years).

Pharmacokinetics in Special Populations

Renal Dysfunction

The single-dose pharmacokinetics of nevirapine have been compared in 23 subjects with either mild (50 ≤ CLcr < 80 mL/min), moderate (30 ≤ CLcr < 50 mL/min) or severe renal dysfunction (CLcr < 30 mL/min), renal impairment or end-stage renal disease (ESRD) requiring dialysis, and 8 subjects with normal renal function (CLcr > 80 mL/min). Renal impairment (mild, moderate and severe) resulted in no significant change in the pharmacokinetics of nevirapine. However, subjects with ESRD requiring dialysis exhibited a 43.5% reduction in nevirapine AUC (94.9 ± 28.8 microg.h/mL versus 168.1 ± 38.1 microg.h/mL) and reduction in nevirapine half-life (28.2 ± 8.5 h versus 66.3 ± 19.9 h) compared to normal volunteers over a one-week exposure period. There was also accumulation of nevirapine hydroxy-metabolites in plasma. The results suggest that supplementing nevirapine therapy with an additional 200 mg dose of nevirapine following each dialysis treatment would help offset the effects of dialysis on nevirapine clearance. Otherwise patients with CLcr ≥ 20 mL/min do not require an adjustment in nevirapine dosing.

Hepatic Impairment

Patients with hepatic impairment should be monitored carefully for evidence of drug induced toxicity. Patients with hepatic impairment associated with ascites may be at risk of accumulating nevirapine with resultant increase in AUC.

A steady state study was conducted comparing 46 adult patients with liver fibrosis. Three groups were studied: Mild fibrosis n = 17 participants with Ishak Score 1 - 2; Moderate fibrosis, n = 20 participants with Ishak Score 3 - 4; Cirrhosis, n = 9 participants with Ishak Score 5 - 6 and Child Pugh A. The patients studied received antiretroviral therapy including nevirapine 200 mg twice-daily for at least 6 weeks prior to pharmacokinetic sampling. The median duration of therapy was 3.4 years.

Results of the pharmacokinetic analyses are summarised in Table 2. Approximately 15% of the patients with hepatic fibrosis had nevirapine trough concentrations above 9.0 micrograms/mL with no correlation between grade of fibrosis and higher plasma concentration.

In this study, the multiple dose pharmacokinetic disposition of nevirapine and the five oxidative metabolites were not altered compared to the established pharmacokinetics in patients.

Table 2 Geometric means and 95% confidence intervals for nevirapine pharmacokinetic parameters

Parameter	Population	Mild fibrosis § Gmean / CI	Moderate fibrosis Gmean / CI	Cirrhosis Gmean / CI
C_{minSS} (ng/mL)	n=46	4583 [3351, 6268]	6021 [4786, 7574]	5854 [4337, 7901]
$AUC_{SS(t)}$ (h•µg/mL)	n=46	55.0 [40,75]	72.3 [57, 91]	70.2 [52, 95]
C_{maxSS} (ng/mL)	intensive only (n=33)	7117 [5146, 9844]	7087 [5679, 8846]	7262 [5163, 10215]

§ without patients 131 and 301
population: all = troughs on all patients, intensive = additional samples drawn at 1, 2, and 4 hours

In a 200 mg nevirapine single dose pharmacokinetic study of HIV-negative patients with mild and moderate hepatic impairment (Child-Pugh A, n = 6; Child-Pugh B, n = 4), a significant increase in the AUC of nevirapine was observed in one Child-Pugh B patient with ascites suggesting that patients with worsening hepatic function and ascites may be at risk of accumulating nevirapine in the systemic circulation. Because nevirapine induces its own metabolism with multiple dosing, this single dose study may not reflect the impact of hepatic impairment on multiple dose pharmacokinetics (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Gender and Ethnic Background

In the multinational 2NN study, a population pharmacokinetic substudy of 1077 patients was performed that included 391 females. Female patients showed a 13.8% lower clearance of nevirapine than did male patients. This difference is not considered clinically relevant. Since neither body weight nor Body Mass Index (BMI) had influence on the clearance of nevirapine, the effect of gender cannot be explained by body size.

Nevirapine pharmacokinetics in HIV-1 infected adults do not appear to change with race (Black, Hispanic or Caucasian). This information is derived from an evaluation of pooled data derived from several clinical trials.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

In genetic toxicity assays, nevirapine showed no evidence of mutagenic activity (Salmonella strains, E. coli and Chinese hamster ovary cells) or clastogenic activity (Chinese hamster ovary cell *in vitro* and a mouse bone marrow micronucleus assay).

Carcinogenicity

In carcinogenicity studies, nevirapine was administered in the diet for two years to mice and rats at respective doses of 50, 375 and 750 mg/kg/day and 3.5, 17.5 and 35 mg/kg/day. In mice, the two higher doses were associated with increased incidences of hepatocellular adenomas and carcinomas; adenomas were also increased in low dose males. In rats, an increased incidence of hepatocellular adenomas was observed at all doses in males and at the high dose in females. Nevirapine strongly induces liver enzyme activities in mice and rats, and liver tumour induction in these species probably involves a nongenotoxic mechanism. Plasma nevirapine levels were lower than clinical levels at all doses in both species, due to more rapid drug clearance.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, povidone, sodium starch glycollate A, colloidal anhydrous silica and magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C in original container.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: HDPE bottle with PP closure

Pack sizes: 60 or 100 tablets

Some pack sizes may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

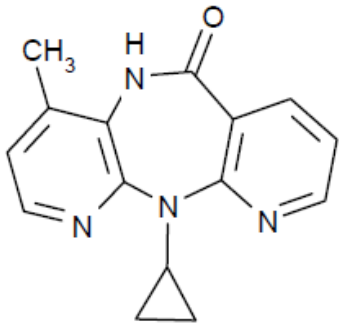
AUST R 167307 – NEVIRAPINE VIATRIS nevirapine 200 mg tablet bottle

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Chemical name: 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one

Molecular formula: $C_{15}H_{14}N_4O$

Molecular weight: 266.3

Nevirapine is a non-nucleoside reverse transcriptase inhibitor with activity against HIV-1. Nevirapine is a white to off-white crystalline powder.

CAS Number

129618-40-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

17/04/2012

10 DATE OF REVISION

04/07/2023

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
4.3	Revision to lactose warning statement
4.5, 5.1	Removal of information relating to delavirdine, boceprevir and telaprevir
4.6	Update to pregnancy information
5.1	Addition of pharmacotherapeutic group and ATC code information

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