NEVIRAPINE VIATRIS

1. Product Name

Nevirapine Viatris 200 mg tablet, uncoated.

2. Qualitative and Quantitative Composition

Each tablet contains 200 mg of nevirapine.

Excipient with known effect: lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Nevirapine Viatris 200 mg tablets are white to off-white, oval shaped, biconvex uncoated tablets, debossed with “NE 200” with a single bisect separating the “NE” and “200” on one side and debossed with “M” with a single bisect separating the “M” on the other side.

The tablet can be divided into equal doses.

4. Clinical Particulars

4.1 Therapeutic indications

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

Resistant virus emerges rapidly and uniformly when nevirapine is administered as monotherapy. Therefore, Nevirapine Viatris should always be administered in combination with at least two additional antiretroviral agents.

4.2 Dose and method of administration

Dose

Adults 16 years and older

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

Patients should be advised of the need to take Nevirapine Viatris 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.

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. It is strongly recommended to monitor liver function every two to three weeks in the first three months of treatment and then monthly during the next three months.

Dosage adjustment

Nevirapine Viatris must be discontinued if patients experience severe rash or a rash accompanied by constitutional findings (see section 4.4). Patients experiencing rash during the 14-day lead-in period of 200 mg/day should not have their nevirapine dose increased until the rash has resolved (see section 4.4). The 200 mg once daily dosing regimen should not be continued beyond 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 the liver function test elevations have returned to baseline. Nevirapine may then be restarted at half the previous dose level. Nevirapine Viatris should be permanently discontinued if moderate or severe liver function test abnormalities recur (see sections 4.4 and 4.8).

If clinical hepatitis occurs, characterised by anorexia, vomiting, icterus AND laboratory findings such as moderate or severe liver function test abnormalities (excluding GGT), Nevirapine Viatris must be permanently stopped. Nevirapine Viatris should not be re-administered 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 one 200 mg tablet per day for the first 14 days (lead-in). This is followed by one 200 mg tablet twice daily.

Method of administration

Nevirapine Viatris can be taken with or without food.

4.3 Contraindications

Nevirapine Viatris is contraindicated in patients with clinically significant hypersensitivity to the active ingredient or any of the excipients of the product (see section 6.1).

Nevirapine Viatris should not be administered to patients with severe hepatic dysfunction (Child-Pugh C) or pre-treatment ASAT or ALAT > 5X Upper Limit of Normality (ULN) until baseline ASAT/ALAT are stabilised < 5X ULN.

Nevirapine Viatris should not be re-administered to patients who have required permanent discontinuation for severe rash, rash accompanied by constitutional symptoms, hypersensitivity reactions, or clinical hepatitis due to nevirapine.

Nevirapine Viatris should not be re-administered in patients who previously had ASAT or ALAT > 5X Upper Limit of Normality (ULN) during nevirapine therapy and had rapid recurrence of liver function abnormalities upon re-administration of nevirapine (see section 4.4).

The use of Nevirapine Viatris tablets is contraindicated in patients with rare hereditary conditions such as galactose intolerance. The tablets contain lactose (see section 4.4).

Herbal preparations containing St John's wort (hypericum perforatum) must not be used while taking Nevirapine Viatris due to the risk of decreased plasma concentrations and reduced clinical effects of nevirapine (see section 4.5).

4.4 Special warnings and precautions for use

The first 18 weeks of therapy with nevirapine are a critical period, which require close monitoring of patients to disclose the potential appearance of severe and life-threatening skin reactions (including cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)), 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 and higher CD4 counts (> 250/mm^3 in adult females and > 400/mm^3 in adult males) at the initiation of nevirapine therapy are associated with a greater risk of hepatic adverse events if the patient has detectable plasma HIV-1 RNA - i.e. a concentration ≥ 50 copies/mL - at the initiation of nevirapine.

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 cells/mm³ or in adult males with CD4+ cell counts greater than 400 cells/mm³ 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 Viatris and seek medical evaluation immediately. Nevirapine Viatris 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).

Skin reactions

Severe and life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine. These have included cases of SJS, TEN, and hypersensitivity syndrome characterised by rash, constitutional findings and visceral involvement. The best results in managing SJS or TEN come from early diagnosis and immediate discontinuation of any suspected drug. Early withdrawal is associated with a better prognosis. Therefore, patients should be carefully monitored during the first 18 weeks of treatment. Patients should be closely monitored if an isolated rash occurs. Nevirapine Viatris 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, muscle or joint aches, or general malaise), including SJS or TEN. Nevirapine Viatris must be permanently discontinued if any patient is experiencing hypersensitivity reactions, characterised by rash with constitutional symptoms, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopaenia, and renal dysfunction or signs of other visceral involvement (see sections 4.4 and 4.8).

Patients should be advised that the major toxicity of nevirapine is rash. The lead-in period should be used as it has been found to lessen the frequency of rash. The majority of rashes associated with nevirapine occur within the first six weeks of therapy therefore patients should be monitored carefully for the appearance of rash during this period. Patients should be instructed that the dose escalation is not to occur if any rash occurs during this lead-in period until the rash has resolved. The 200 mg once daily dosing regimen should not be continued beyond 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 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, muscle or joint aches, or general malaise should discontinue medication and immediately seek medical evaluation. In these patients Nevirapine Viatris 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 (ASAT or ALAT >5 X ULN) should be permanently discontinued from Nevirapine Viatris.

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, granulocytopaenia, and renal dysfunction, Nevirapine Viatris should be permanently stopped and not be re-introduced.

Hepatic reactions

Severe and life-threatening hepatotoxicity, including fatal fulminant hepatitis, has occurred in patients treated with nevirapine. 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. Patients should be informed that hepatic reactions are a major toxicity of nevirapine. Patients with signs or symptoms of hepatitis must be advised to discontinue Nevirapine Viatris and immediately seek medical evaluation, which should include liver function tests.

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

Increased ASAT or ALAT levels > 2.5 X 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 naive patients are associated with increased risk of hepatic adverse events.

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/mm³ had a 12-fold higher risk of symptomatic hepatic adverse events compared to women with CD4 counts < 250 cells/mm³ (11.0% versus 0.9%). An increased risk was observed in men with detectable HIV-1 RNA in plasma and CD4 counts > 400 cells/mm³ (6.3% versus 1.2 % for men with CD4 counts < 400 cells/mm³). 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.

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 continuing therapy.

Monitoring of hepatic 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.

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

If ASAT or ALAT increase to > 5X ULN during treatment, Nevirapine Viatris should be immediately stopped. If ASAT and ALAT return to baseline values and if the patient had no clinical signs or 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 Viatris should be restarted with heightened clinical and laboratory vigilance at the starting dosage regimen of 200 mg/day for 14 days followed by 400 mg/day. 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 re-administered to patients who have required permanent discontinuation for clinical hepatitis due to nevirapine.

Other warnings

The following events have been reported when nevirapine has been used in combination with other anti-retroviral agents: pancreatitis, peripheral neuropathy and thrombocytopaenia. These events are commonly associated with other anti-retroviral 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 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 associated with HIV diseases. The long-term effects of nevirapine are unknown at this time. Nevirapine therapy has not been shown to reduce the risk of horizontal transmission of HIV-1 to others.

Although the utility of nevirapine for the prevention of mother to child HIV-1 transmission has been demonstrated for women who were not receiving other antiretrovirals, extended treatment of the mother with combination antiretroviral agents prior to delivery is recommended, when feasible, to minimise HIV-1 transmission to the infant.

Nevirapine is extensively metabolised by the liver and nevirapine metabolites are extensively eliminated 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 Viatris should not be administered to patients with severe hepatic dysfunction (Child-Pugh Class C). In adult 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 CLcr ≥ 20 mL/min do not require an adjustment in nevirapine dosing (see section 5.2).

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 levels of these

medications (see section 4.5). Therefore, when postmenopausal hormone therapy is used during administration of nevirapine, its therapeutic effect should be monitored.

Nevirapine Viatris tablets contain 928 mg of lactose per maximum recommended daily dose. Patients with rare hereditary conditions of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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.

Warning on concomitant use with other drugs

(For detailed description see section 4.5)

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.

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

Information for patients

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.

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. Any patient experiencing severe rash, or a rash accompanied by constitutional symptoms such as fever, blistering, oral lesions, conjunctivitis, swelling, muscle or joint aches, or general malaise should discontinue medication and consult a physician.

Patients should be informed that liver function test abnormalities are common in patients with HIV infection. Liver function test abnormalities have occurred in patients treated with nevirapine. Some of these patients developed severe or life-threatening hepatotoxicity including fatal fulminant hepatitis.

Patients should be informed to take Nevirapine Viatris every day as prescribed. Patients should not alter the dose without consulting their doctor. If a dose is missed, patients should take the next dose as soon as possible. However, if a dose is skipped, the patient should not double the next dose.

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.

4.5 Interaction with other medicines and other forms of interaction

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). Thus, if a patient has been stabilized on a dosage regimen for a drug metabolised by CYP3A or CYP2B and begins on nevirapine, dosage adjustments may be necessary.

The absorption of nevirapine is not affected by food, antacids or medicinal products which are formulated with an alkaline buffering agent.

The majority of the interaction data is presented as percent changes (geometric mean) with a 95% prediction interval (95% PI).

Drugs by therapeutic areas	Interaction	Recommendations concerning co-administration
ANTI-INFECTIVES		
Antiretrovirals		
NRTIs		
Didanosine 100-150 mg BID (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	Didanosine AUC ↔ Didanosine C_{max} ↔ Didanosine C_{min} §	No dosage adjustments are required when nevirapine is taken in combination with didanosine.
Emtricitabine	Emtricitabine is not an inhibitor of human CYP 450 enzymes.	No dosage adjustments are required when nevirapine is taken in combination with emtricitabine.
Abacavir	In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms.	No dosage adjustments are required when nevirapine is taken in combination with abacavir.
Lamivudine 150 mg BID (NVP 200 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, (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	Stavudine AUC ↔ Stavudine C_{max} ↔ Stavudine C_{min} § Nevirapine: compared to historical controls, levels appeared to be unchanged.	No dosage adjustments are required when nevirapine is taken in combination with stavudine.

Drugs by therapeutic areas	Interaction	Recommendations concerning co-administration
Tenofovir 300 mg QD (NVP 200 mg BID)	Tenofovir levels remain unchanged. Tenofovir does not have an effect on NVP levels.	No dosage adjustments are required when nevirapine is taken in combination with tenofovir.
Zalcitabine 0.125-0.25 mg TID (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	Zalcitabine AUC ↔ Zalcitabine C_{max} ↔ Zalcitabine C_{min} §	No dosage adjustments are required when nevirapine is taken in combination with zalcitabine.
Zidovudine 100-200 mg TID (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	Zidovudine AUC ↓24 (↓69 to ↑83) Zidovudine C_{max} ↓26 (↓84 to ↑254) 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.
NNRTIs		
Efavirenz 600 mg QD (NVP 200 mg QD x 14 days; 400 mg QD x 14 days)	Efavirenz AUC ↓28 (↓34 to ↓14)[a] Efavirenz C_{max} ↓12 (↓23 to ↑1) [a] Efavirenz C_{min} ↓32 (↓35 to ↓19) [a]	This co-administration is not recommended since the co-administration of efavirenz and nevirapine could lead to a higher risk for side effects (see section 4.4). 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 section 5.3).
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 section 4.4).
Rilpivirine	Interaction has not been studied.	The concomitant administration of nevirapine with NNRTIs is not recommended (see section 4.4).
PIs		
Atazanavir/ritonavir 300/100 mg QD 400/100 mg QD (NVP 200 mg BID)	<u>Atazanavir 300/100mg</u>: Atazanavir AUC ↓42 (↓52 to ↓29)[a] Atazanavir C_{max} ↓28 (↓40 to ↓14)[a] Atazanavir C_{min} ↓72 (↓80 to ↓60)[a] <u>Atazanavir 400/100mg:</u> Atazanavir AUC ↓19 (↓35 to↑2)[a] Atazanavir C_{max} ↔ Atazanavir C_{min} ↓59 (↓73 to ↓40)[a] (compared to 300/100 mg without NVP) Nevirapine AUC ↑25 (↑17 to ↑34)[a] Nevirapine C_{max} ↑17 (↑9 to↑25)[a] Nevirapine C_{min} ↑32 (↑22 to ↑43)[a]	If given in combination with nevirapine, atazanavir should be dosed with 400 mg co-administered with low dose ritonavir 100 mg.

Drugs by therapeutic areas	Interaction	Recommendations concerning co-administration
Darunavir/ritonavir 400/100 mg BID (NVP 200 mg BID)	Darunavir AUC ↔ Darunavir C_{min}↔ Nevirapine AUC ↑27 Nevirapine C_{min} ↑47	Darunavir/ritonavir increases the plasma concentrations of nevirapine as a result of CYP3A4 inhibition. Since this difference is not considered to be clinically relevant, the combination of darunavir co-administered with 100 mg ritonavir and nevirapine can be used without dose adjustments.
Fosamprenavir 1400 mg BID (NVP 200 mg BID)	Amprenavir AUC ↓33 (↓45 to ↓20)[a] Amprenavir C_{max} ↓25 (↓37 to ↓11)[a] Amprenavir C_{min} ↓35 (↓51 to ↓15)[a] Nevirapine AUC ↑29 (↑19 to ↑40)[a] Nevirapine C_{max} ↑25 (↑14 to ↑37)[a] Nevirapine C_{min} ↑34 (↑21 to ↑49)[a]	Nevirapine should not be given with fosamprenavir if not co-administered with ritonavir (see section 4.4).
Fosamprenavir/ ritonavir 700/100 mg BID (NVP 200 mg BID)	Amprenavir AUC not significantly altered Amprenavir C_{max} not significantly altered Amprenavir C_{min} ↓19 (↓32 to ↓5)[a] Nevirapine AUC ↑14 (↑5 to ↑24)[a] Nevirapine C_{max} ↑13 (↑3 to ↑24)[a] Nevirapine C_{min} ↑22 (↑10 to ↑35)[a]	No dosing adjustments are required when nevirapine is co-administered with 700/100 mg of fosamprenavir/ritonavir b.i.d.
Indinavir 800 mg q8h (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	Indinavir AUC ↓31 (↓64 to ↑30) Indinavir C_{max} ↓15 (↓53 to ↑55) Indinavir C_{min} ↓44 (↓77 to ↑39) 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 RTV. There are limited clinical data on the interaction of nevirapine with indinavir/ritonavir.
Lopinavir/ritonavir 400/100 mg BID (NVP 200 mg BID)	<u>In HIV positive adults</u>: Lopinavir AUC ↓27 Lopinavir C_{max} ↓19 Lopinavir C_{min} ↓46	Although the clinical relevance of this observation has not been fully established, an increase in the dose of lopinavir/ritonavir to 533/133 mg (4 capsules) twice daily with food is recommended in combination with nevirapine.

Drugs by therapeutic areas	Interaction	Recommendations concerning co-administration
Lopinavir/ritonavir 300/75 mg/m^2 BID (NVP 7 mg/kg or 4 mg/kg QD x 2 weeks; BID x 1 week)	Paediatric patients: Results from a pharmacokinetic study were consistent with the findings in adults: Lopinavir AUC ↓22 (↓44 to ↑9)[a] Lopinavir C_{max} ↓14 (↓36 to ↑16)[a] Lopinavir C_{min} ↓55 (↓75 to ↓18)[a]	For children, increase of the dose of lopinavir/ritonavir to 300/75 mg/m^2 twice daily with food should be considered when used in combination with nevirapine, particularly for patients in whom reduced susceptibility to lopinavir/ritonavir is suspected.
Nelfinavir 750 mg TID (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	Nelfinavir: no clinically relevant changes in pharmacokinetic parameters after the addition of nevirapine. Total exposure of nelfinavir plus the AG1402 metabolite: AUC ↓20 (↓72 to ↑128) C_{max} ↓12 (↓61 to ↑100) C_{min} ↓35 (↓90 to ↑316) 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 (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	The co-administration leads to no clinically relevant change in ritonavir or nevirapine plasma levels. Ritonavir AUC↔ Ritonavir C_{max} ↔ Ritonavir C_{min} ↔	No dosage adjustments are required when nevirapine is taken in combination with ritonavir.
Saquinavir 600 mg TID (NVP 200 mg QD x 14 days; 200 mg BID x 21 days)	Saquinavir AUC ↓38 (↓47 to ↓11)[a] Saquinavir C_{max} ↓32 (↓44 to ↓6)[a] Saquinavir C_{min} §	Nevirapine should not be given with saquinavir if not co-administered with ritonavir (see section 4.4).
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 (NVP 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 clinical non-significant 20% decrease of TPV C_{min}. No significant interaction is expected between nevirapine and tipranavir co-administered with low dose ritonavir.	No dosage adjustments are required when nevirapine is taken in combination with tipranavir co-administered with ritonavir.

Drugs by therapeutic areas	Interaction	Recommendations concerning co-administration
Early Inhibitors		
Enfuvirtide	No clinically significant pharmacokinetic interactions are expected between enfuvirtide and concomitantly given medicinal products metabolised by CYP450 enzymes.	Due to the metabolic pathway of enfuvirtide no interaction is expected. Therefore no dose adjustment is recommended when co-administering enfuvirtide with nevirapine.
Maraviroc 300 mg Single Dose (Nevirapine 200 mg BID)	Maraviroc AUC ↔ Maraviroc C_{max} ↑ 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	No clinical data available.	Due to the metabolic pathway of raltegravir no interaction is expected. Therefore 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 coadministration 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 section 4.4).
Antivirals for Hepatitis B and C		
Interferons (pegylated interferons alfa 2a and alfa 2b)	Interferons have no known effect on CYP 3A4 or 2B6. No clinically relevant drug-drug interaction is expected.	Interferons and nevirapine may be co-administered without dose adjustments.
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	Telbivudine is not a substrate, inducer or inhibitor of the cytochrome P450 (CYP450) enzyme system. 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.

Drugs by therapeutic areas	Interaction	Recommendations concerning co-administration
Adefovir	Results of *in vitro* studies showed a weak antagonism of nevirapine by adefovir (see section 5.3), this has not been confirmed in clinical trials and reduced efficacy is not expected. Adefovir did not influence any of the common CYP isoforms known to be involved in human drug metabolism and is excreted renally. No clinically relevant drug-drug interaction is expected.	Adefovir and nevirapine may be co-administered without dose adjustments.
Ribavirin	Results of *in vitro* studies showed a weak antagonism of nevirapine by ribavirin (see section 5.3), this has not been confirmed in clinical trials and reduced efficacy is not expected. Ribavirin does not inhibit cytochrome P450 enzymes, and there is no evidence from toxicity studies that ribavirin induces liver enzymes. No clinically relevant drug-drug interaction is expected.	Ribavirin and nevirapine may be co-administered without dose adjustments.
Antibiotics		
Clarithromycin 500 mg BID (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	Clarithromycin AUC ↓31 (↓57 to ↑9) Clarithromycin C_{min} ↓56 (↓92 to ↑126) Metabolite 14-OH clarithromycin AUC ↑42 (↓41 to ↑242) Metabolite 14-OH clarithromycin C_{max} ↑47 (↓39 to ↑255) Nevirapine AUC ↑26 Nevirapine C_{max} ↑24 Nevirapine C_{min} ↑28 compared to historical controls.	No dose adjustment is recommended for either clarithromycin or nevirapine when the two medicinal products are co-administered. Close monitoring of hepatic abnormalities is nevertheless recommended. However, alternative therapy to clarithromycin should be considered when treating a patient for mycobacterium avium-intracellulare complex, as the active metabolite is not effective in this instance.
Rifabutin 150 or 300 mg QD (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	Rifabutin AUC ↑17 (↓53 to ↑191) Rifabutin C_{max} ↑28 (↓44 to ↑195) Metabolite 25-O-desacetylrifabutin AUC ↑24% (↓83 to ↑787) Metabolite 25-O-desacetylrifabutin C_{max} ↑29% (↓67 to ↑400). 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.

Drugs by therapeutic areas	Interaction	Recommendations concerning co-administration
Rifampicin 600 mg QD (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	Rifampicin C_{max} and AUC: no significant change. Nevirapine AUC ↓58 Nevirapine C_{max} ↓50 Nevirapine C_{min} ↓68 compared to historical data.	Nevirapine and rifampicin should not be used in combination. Limited clinical data exist with a dose adjustment for nevirapine when co-administered with rifampicin (see section 4.4). Physicians needing to treat patients co-infected with tuberculosis and using a nevirapine containing regimen may consider use of rifabutin instead.
Antifungals		
Fluconazole 200 mg QD (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	Fluconazole AUC ↔ Fluconazole C_{max} ↔ Fluconazole C_{min} ↔ 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 (NVP 200 mg QD)	Itraconazole AUC ↓61 Itraconazole C_{max} ↓38 Itraconazole C_{min} ↓87 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 (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	Ketoconazole AUC ↓72 (↓95 to ↑101) Ketoconazole C_{max} ↓44 (↓86 to ↑158) Nevirapine plasma levels: ↑15-28% compared to historical controls.	Ketoconazole and nevirapine should not be given concomitantly (see section 4.4).
ANTACIDS		
Cimetidine	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.	The net effect of the interaction may change during the first weeks of co-administration or upon discontinuation of nevirapine, and close monitoring of anticoagulation levels is therefore warranted.

Drugs by therapeutic areas	Interaction	Recommendations concerning co-administration
CONTRACEPTIVES		
Depo-medroxy-progesterone acetate (DMPA) 150 mg every 3 months (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	DMPA AUC ↔ DMPA C_{max} ↔ DMPA C_{min} ↔ Nevirapine AUC ↑20 Nevirapine C_{max} ↑20	No dose adjustment is necessary when DMPA and nevirapine are co-administered. Nevirapine co-administration did not alter the ovulation suppression effects of DMPA.
Ethinyl estradiol (EE) 0.035 mg and	EE AUC ↓20 (↓57 to ↑52) EE C_{max} ↔ EE C_{min} §	Oral hormonal contraceptives should not be used as the sole method of contraception in women taking nevirapine (see section 4.4). 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 (single dose) (NVP 200 mg QD x 14 days; 200 mg BID x 14 days)	NET AUC ↓19 (↓50 to ↑30) NET C_{max} ↓16 (↓49 to ↑37) NET C_{min} §	
ANALGESICS/OPIOIDS		
Methadone Individual Patient Dosing (NVP 200 mg QD x 14 days; 200 mg BID ≥ 7 days)	Methadone AUC ↓65 (↓82 to ↓32) Methadone C_{max} ↓50 (↓67 to ↓25)	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 section 4.3).

NVP = Nevirapine
§ = C_{min} below detectable level of the assay
↑ = Increase, ↓ = Decrease, ↔ = No Effect
[a] data presented as geometric mean with a 90% prediction interval (90% PI).

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, rifabutin, rifampicin and

trimethoprim/sulfamethoxazole. Ketoconazole and erythromycin significantly inhibited the formation of nevirapine hydroxylated metabolites. Clinical studies have not been performed.

4.6 Fertility, pregnancy and lactation

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.

No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits. In rats, a significant decrease in foetal body weight occurred at maternally toxic doses providing systemic exposure approximately 50% higher, based on AUC, than that seen at the recommended human clinical dose. The maternal and development no-observable-effect level dosages in rats and rabbits produced systemic exposures approximately equivalent to or approximately 50% higher, respectively, than those seen at the recommended daily human dose, based on AUC.

There have been no adequate and well controlled studies of nevirapine in pregnant women.

The US Antiretroviral Pregnancy Registry, which has been surveying pregnancy outcomes since January 1989, suggests that there is no signal apparent for birth defects related to nevirapine. 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.

Nevirapine for the prevention of mother to child transmission of HIV-1 has been demonstrated to be safe and effective when given as part of a regimen that includes a single 200 mg oral dose to mothers during labour followed by a single 2 mg/kg dose to the infant within 72 hours after birth.

Pregnant women

In HIV-1-infected women in labour, the half-life of nevirapine after a single oral 200 mg dose is prolonged (60-70 hours) and oral clearance is highly variable (2.1±1.5l/h), consistent with the physiological stresses of labour (studies PACTG 250 [n=17] and HIVNET 006 [n=21]). Nevirapine readily crosses the placenta such that the administration of a 200 mg dose to the mothers resulted in cord concentrations above 100 ng/mL and a cord blood-to-maternal blood ratio of 0.84±0.19 (n=36; range 0.37-1.22).

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). There is not enough evidence to substantiate that the absence of an increased risk for toxicity seen in pre-treated women initiating nevirapine with an undetectable viral load (less than 50 copies/mL of HIV-1 in plasma) and CD4+ cell counts above 250 cells/mm^3 also applies to pregnant women. All the randomised studies addressing this issue specifically excluded pregnant women, and pregnant women were under-represented in cohort studies as well as in meta-analyses.

Neonates

In neonates receiving a 2 mg/kg oral dose of nevirapine suspension within 72 hours after birth, born to HIV-1-infected women administered a single 200 mg dose during labour, the geometric mean half-life of nevirapine was 47 hours (n=36). Plasma levels were maintained above 100 ng/mL for the first week of life (studies PACTG 250 and HIVNET 006).

Breast-feeding

It is recommended that HIV-infected mothers do not breast-feed their infants to avoid risking postnatal transmission of HIV. Results from 2 pharmacokinetic studies (ACTG 250 and HIVNET 006) have shown that nevirapine readily crosses the placenta and is found in breast milk. In study ACTG 250, breast milk samples collected in 3 of 10 HIV-1-infected pregnant women after administration of a single oral dose of 100 mg or 200 mg nevirapine (at a median of 5.8 hours before delivery), demonstrated a median ratio of the concentration of nevirapine in breast milk to that in maternal serum of 76% (54-104%). Results from study HIVNET 006 (n=20) indicate a median breast milk to maternal plasma concentration of 60.5% (25-122%), after a single oral 200 mg nevirapine dose.

Consistent with the recommendation that HIV-infected mothers do not breast-feed their infants to avoid risking postnatal transmission of HIV, mothers should discontinue breast-feeding if they are receiving nevirapine.

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 provided with the recommended clinical dose of nevirapine.

No human data on fertility are available.

4.7 Effects on ability to drive and use machines

There are no specific studies about the ability to drive vehicles and use machinery during treatment with Nevirapine Viatris. 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 Undesirable effects

Summary of the safety profile

Adults

Apart from rash and abnormal Liver Function Tests (LFT), the most frequent adverse events related to nevirapine therapy across all clinical trials were nausea, fatigue, fever, headache, vomiting, diarrhoea, abdominal pain and myalgia. In very rare instances 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 post-marketing experience has shown that the most serious adverse events are SJS, TEN, serious hepatitis/hepatic failure and hypersensitivity syndrome, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopaenia, and renal dysfunction. The first 18 weeks of treatment is a critical period which requires close monitoring (see section 4.4).

Skin and subcutaneous tissue

The most common clinical toxicity of nevirapine is rash. Severe or life-threatening skin reactions occur with a frequency of approximately 2% (see table 1). These include Stevens-Johnson syndrome (SJS) and, rarely, toxic epidermal necrolysis (TEN) which occur almost exclusively within the first six weeks of therapy. Based on a denominator of 2861 nevirapine-treated clinical trial patients, the overall incidence of SJS was 0.3% (9/2861).

Rashes occur alone or in the context of a hypersensitivity syndrome characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy plus visceral

involvement, such as hepatitis, eosinophilia, granulocytopenia and renal dysfunction. Fatal cases of SJS, TEN and hypersensitivity syndrome have been reported.

Table 1: Risk of Rash (%) in Adult Placebo Controlled Trials [1,2] through 52 weeks of treatment [3] - Regardless of Causality

	Nevirapine	Placebo
	n=1374 %	n=1331 %
Rash events of all grades[4]	24.0	14.9
Grade 3 or 4[4]	1.7	0.2

[1] Trial 1090: Background therapy included 3TC for all patients and combinations of NRTIs and PIs
[2] Trials 1037, 1038 and 1046: Background therapy included AZT and AZT + ddI; Nevirapine monotherapy was administered in some patients
[3] % based on Kaplan-Meier probability estimates
[4] NCI grading system

Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. Allergic reactions (including anaphylaxis, angio-oedema and urticaria) have been reported. The majority of rashes of any severity occur within the first 6 weeks of treatment.

In Trial 1100.1486 (VERxVE) antiretroviral-naive patients received a lead-in dose of nevirapine immediate-release 200 mg once daily for 14 days (n=1068) and then were randomised to receive either nevirapine immediate-release 200 mg twice daily or nevirapine prolonged-release 400 mg once daily. All patients received tenofovir + emtricitabine as background therapy. Safety data included all the patient visits up to the point in time when the last patient completed 144 weeks in the trial. This also includes safety data for patient visits in the post-week 144 open label extension (which patients in either treatment group who completed the 144 week blinded phase could enter). Severe or life-threatening rash considered related to nevirapine treatment occurred in 1.1% of patients during the lead-in phase with nevirapine immediate-release. Severe rash occurred in 1.4% and 0.2% of the nevirapine immediate-release and nevirapine prolonged-release groups respectively during the randomised phase. No life-threatening (Grade 4) rash events considered related to nevirapine were reported during the randomised phase of this study. Six cases of Stevens-Johnson Syndrome were reported in the trial, all but one occurred within the first 30 days of nevirapine treatment.

In Study 1100.1526 (TRANxITION) patients on nevirapine immediate-release 200 mg twice daily treatment for at least 18 weeks were randomised to either receive nevirapine prolonged-release 400 mg once daily (n=295) or remain on their nevirapine immediate-release treatment (n=148). In this study, no Grade 3 or 4 rash was observed in either treatment group.

Hepatobiliary

The most frequently observed laboratory test abnormalities are elevations in liver function tests including ALAT, ASAT, GGT, total bilirubin and alkaline phosphatase. Asymptomatic elevations of GGT levels are most frequent. Cases of jaundice have been reported. Cases of hepatitis, severe and life-threatening hepatotoxicity, and fulminant hepatitis have been reported in patients treated with nevirapine. In clinical trials, the risk of clinical hepatic events with nevirapine at 1 year was approximately 2-fold that of placebo.

In Trial 1100.1486 (VERxVE) treatment-naive patients received a lead-in dose of nevirapine 200 mg immediate-release once daily for 14 days and then were randomised to receive either nevirapine immediate-release 200 mg twice daily or nevirapine prolonged-release 400 mg once daily. All patients received tenofovir + emtricitabine as background therapy. Patients were enrolled with CD4+ counts <250 cells/mm^3 for women and <400 cells/mm^3 for men. Data on potential symptoms of hepatic events were prospectively collected in this trial. The safety data include all patient visits

up to the time of the last patient's completion of study week 144. The incidence of symptomatic hepatic events during the nevirapine immediate-release lead-in phase was 0.5%. After the lead-in period the incidence of symptomatic hepatic events was 2.4% in the nevirapine immediate-release group and 1.6% in the nevirapine prolonged-release group. Overall, there was a comparable incidence of symptomatic hepatic events among men and women enrolled in VERxVE.

In Study 1100.1526 (TRANxITION) no Grade 3 or 4 clinical hepatic events were observed in either treatment group.

Increased ASAT or ALAT levels and/or seropositivity for hepatitis B and/or C was associated with a greater risk of hepatic adverse events for both nevirapine and control groups. The risk of hepatic events at 1 year of nevirapine treatment was less than 2% among patients who were hepatitis B and/or C negative. 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).

Clinical hepatitis may be isolated or associated with rash and/or additional constitutional symptoms.

For liver function test monitoring see section 4.4.

Paediatric patients

Safety has been assessed in 361 HIV-1-infected paediatric patients between the ages of 3 days to 19 years. The majority of these patients received nevirapine in combination with AZT or ddI, or AZT + ddI in two studies. In an open-label trial BI 882 (ACTG 180) 37 patients were followed for a mean duration of 33.9 months (range: 6.8 months to 5.3 years, including long-term follow-up trial BI 892). In ACTG 245, a double-blind placebo controlled study, 305 patients with a mean age 7 years (range: 10 months to 19 years) received combination treatment with nevirapine for at least 48 weeks at a dose of 120 mg/m² once daily for two weeks followed by 120 mg/m² twice daily thereafter. The most frequently reported adverse events related to nevirapine were similar to those observed in adults, with the exception of granulocytopaenia which was more commonly observed in children. Two nevirapine treated patients in these studies experienced SJS or Stevens-Johnson/toxic epidermal necrolysis transition syndrome. Both patients recovered after nevirapine treatment was discontinued.

In post-marketing surveillance, anaemia has been more commonly observed in children.

Prevention of vertical transmission

The safety of nevirapine when administered as a single 200 mg dose (two doses in one study) to HIV-infected pregnant women at the onset of labour, and a single 2 mg/kg dose (6 mg in one study) of nevirapine suspension administered to the infant within the first 72 hours of life, has been assessed in over 950 mother-infant pairs in randomized, controlled clinical trials. Infant follow-up ranged from 6 weeks to 18 months after receipt of a single dose. Similar low rates of adverse events were observed in the nevirapine and control groups in these studies. No mothers or infants experienced serious rash or hepatic events that were considered to be related to nevirapine.

Summary of adverse reactions

In summary the list of side effects which can be expected with nevirapine treatment includes:

<u>Blood and lymphatic system disorders</u>
Granulocytopenia, anaemia

<u>Immune system disorders</u>
Drug reaction with eosinophilia and systemic symptoms, anaphylactic reaction, hypersensitivity (including anaphylactic reaction, angioedema, urticaria)

Nervous system disorders
Headache

Gastrointestinal disorders
Diarrhoea, abdominal pain, nausea, vomiting

Hepatobiliary disorders
Hepatitis (including severe and life threatening hepatotoxicity), hepatitis fulminant (which may be fatal), jaundice

Skin and subcutaneous tissue disorders
Rash, Stevens-Johnson Syndrome/toxic epidermal necrolysis (which may be fatal), angioedema, urticaria

Musculoskeletal and connective tissue disorders
Arthralgia, myalgia

General disorders and administration site conditions
Pyrexia, fatigue

Investigations
Liver function test abnormal (alanine aminotransferase increased; transaminases increased; aspartate aminotransferase increased; gamma-glutamyltransferase increased; hepatic enzyme increased; hypertransaminasaemia), blood phosphorus decreased, blood pressure increased.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

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

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, non-nucleoside reverse transcriptase inhibitors, 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, β, 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, which in the general population would be

considered to be associated with a lower cardiovascular risk. 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.

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. In recent studies using human cord blood lymphocytes and human embryonic kidney 293 cells, EC50 values (50% inhibitory concentration) ranged from 14-302 nM against laboratory and clinical isolates of HIV-1.

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 (median EC50 value of 63 nM). Nevirapine had no antiviral activity *in vitro* against isolates from group O HIV-1 and 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. Nevirapine exhibited additive to synergistic anti-HIV-1 activity in combination with the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir and tipranavir, and the NRTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir and zidovudine. The anti-HIV-1 activity of nevirapine was antagonized 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-1 RT gene Y181C and/or V106A 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 and 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/mm³ 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 IC50, 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.

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.

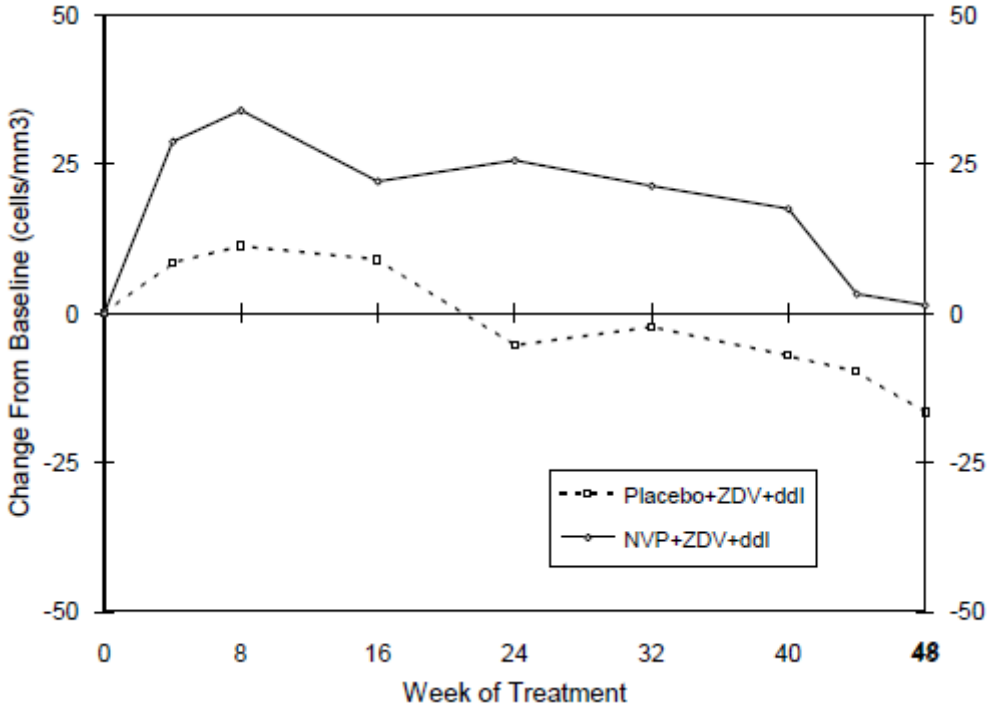
Nevirapine must not be used as a single agent to treat HIV or added on as a sole agent to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors, resistant virus emerges rapidly when nevirapine is administered as monotherapy. The choice of new antiretroviral agents to be 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 efficacy and safety

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/mm³ (mean 153 cells/mm³) 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.

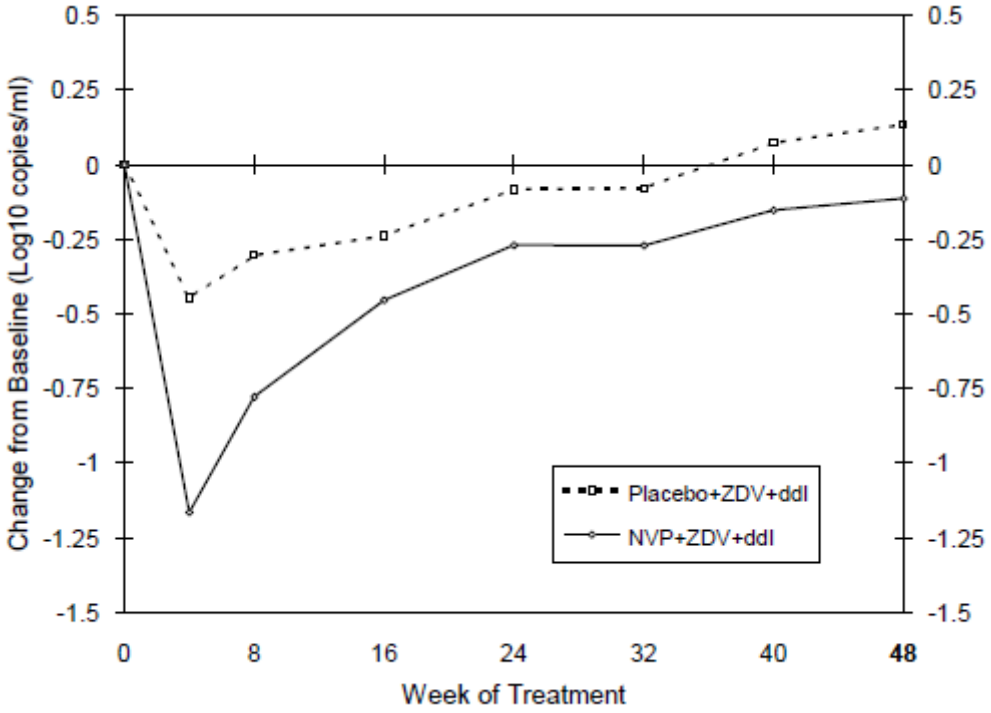
Figure 1: Mean Change from Baseline for CD4+ Cell Count (absolute number of CD4+ cells/mm³), Trial ACTG 241.



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

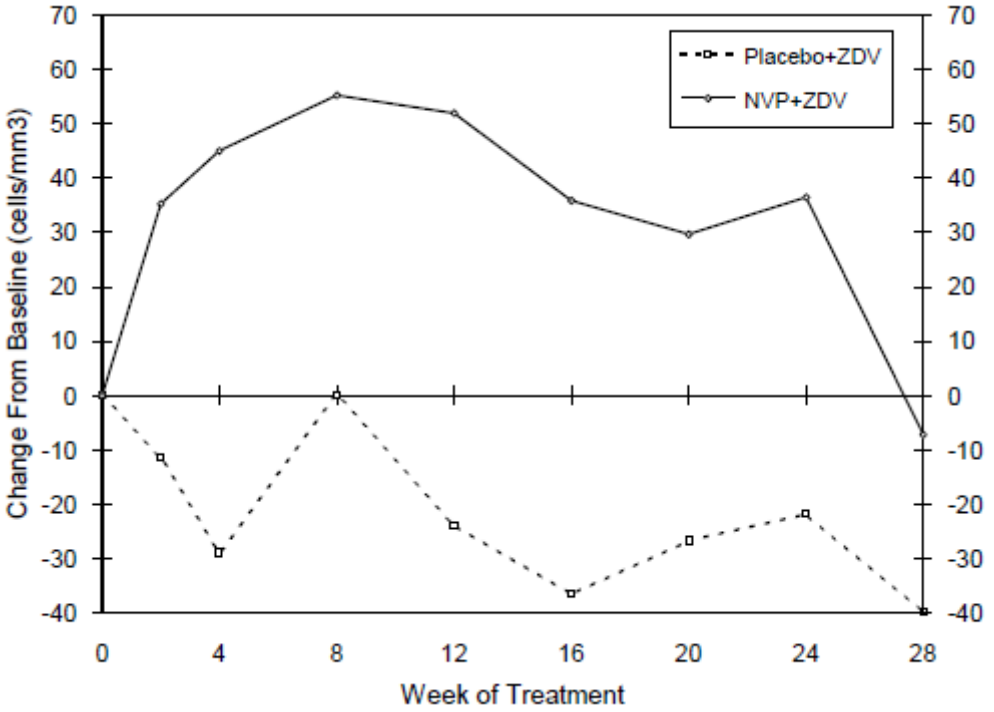


	Number of patients with HIV-1 RNA data at each timepoint			
	Baseline	Week 16	Week 32	Weeks 40-48
NVP+AZT+ddI	95	84	75	74
Placebo+AZT +ddI (ZDV=AZT)	93	82	75	75

*the clinical significance of changes in serum viral RNA measurements during treatment with nevirapine has not been established.

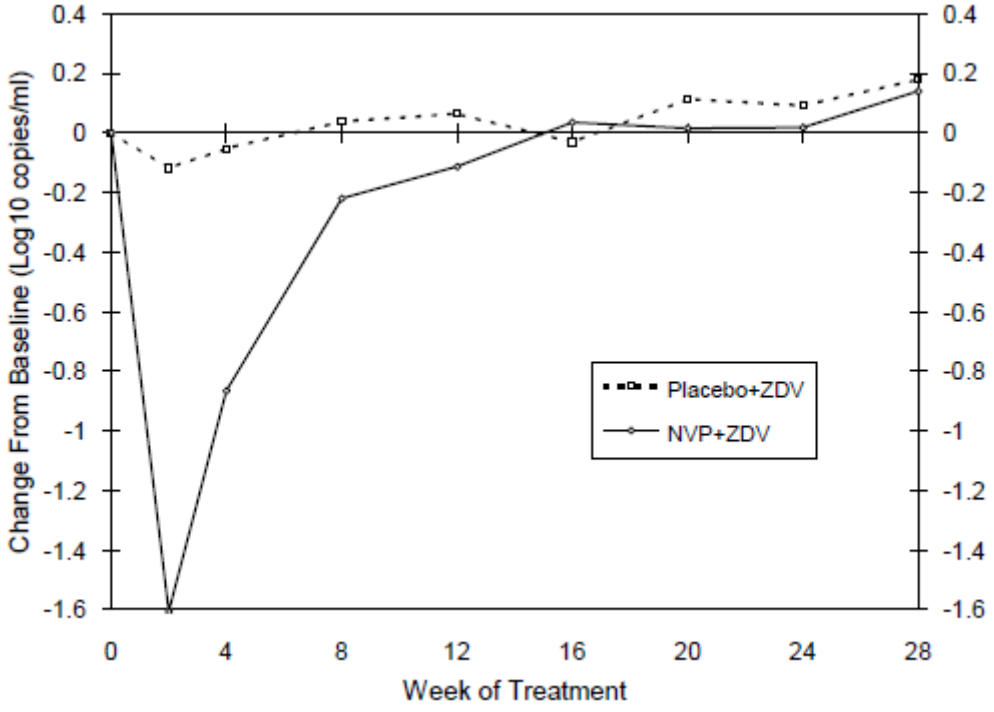
Trial BI 1037 compared treatment with nevirapine + AZT versus AZT in 60 HIV-1-infected patients (median age 33 years, 70% Caucasian, 93% male) with CD4+ cell counts between 200 and 500 cells/mm³ (mean 373 cells/mm³) and a mean baseline plasma HIV-1 RNA concentration of 4.24 log_{10} copies/ml (17,378 copies/mL), who had received between 3 and 24 months of prior AZT therapy (median 35 weeks). Treatment doses were nevirapine 200 mg daily for 2 weeks, followed by 200 mg twice daily, or placebo; AZT, 500-600 mg/day. Mean changes in CD4+ cell counts are shown in Figure 3. Mean HIV-1 RNA concentration changes from baseline are shown in Figure 4. The improvement was statistically significant at weeks 2, 4 and 8.

Figure 3: Mean Change from Baseline for CD4+ Cell Count (absolute number of CD4+ cells/mm³), Trial BI 1037



	Number of patients with CD4 cell counts at each timepoint			
	Baseline	Week 8	Week 16	Weeks 20-28
NVP+AZT	30	28	26	26
Placebo+AZT (ZDV=AZT)	30	30	28	29

Figure 4: Median Change from Baseline in HIV-1 RNA Concentrations (Log_{10} copies/mL), Trial BI 1037

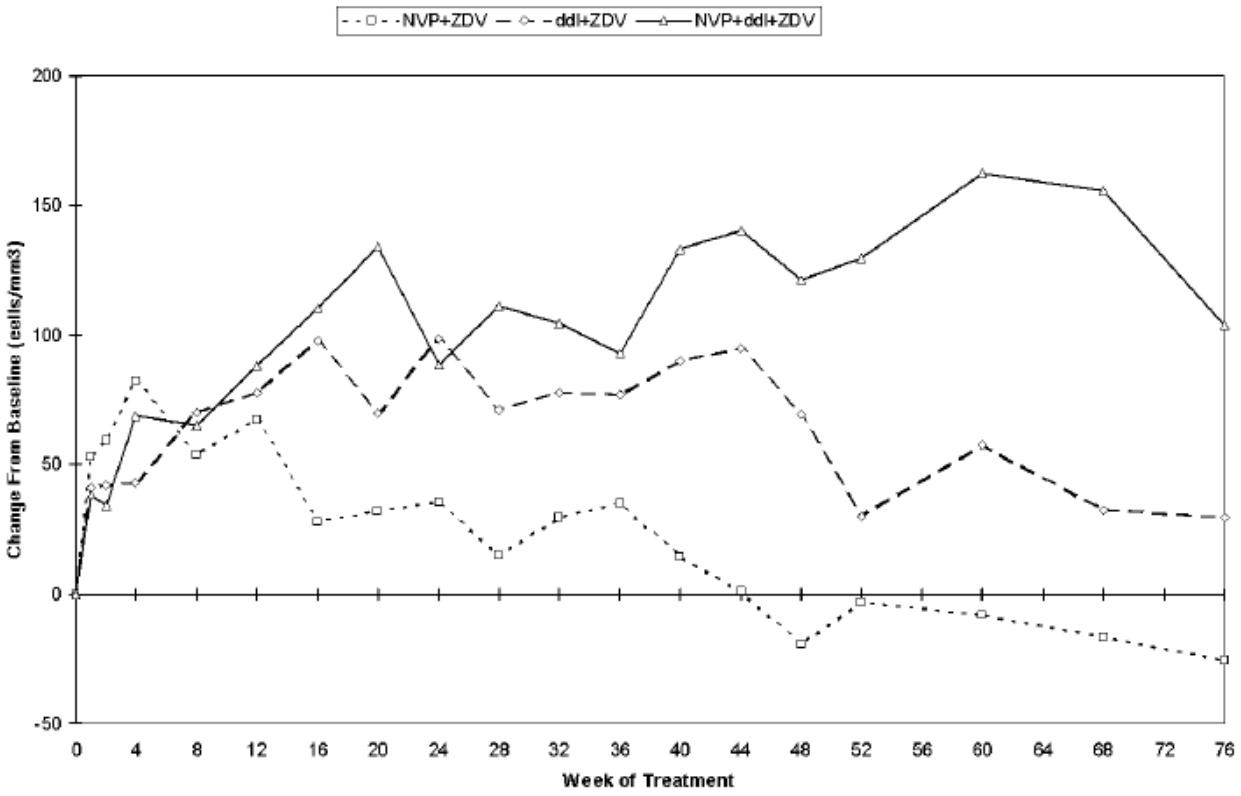


	Number of patients with HIV-1 RNA data at each timepoint			
	Baseline	Week 8	Week 16	Weeks 20-28
NVP+AZT	30	27	26	26
Placebo+AZT (ZDV=AZT)	30	29	28	29

Patients without a history of prior antiretroviral therapy

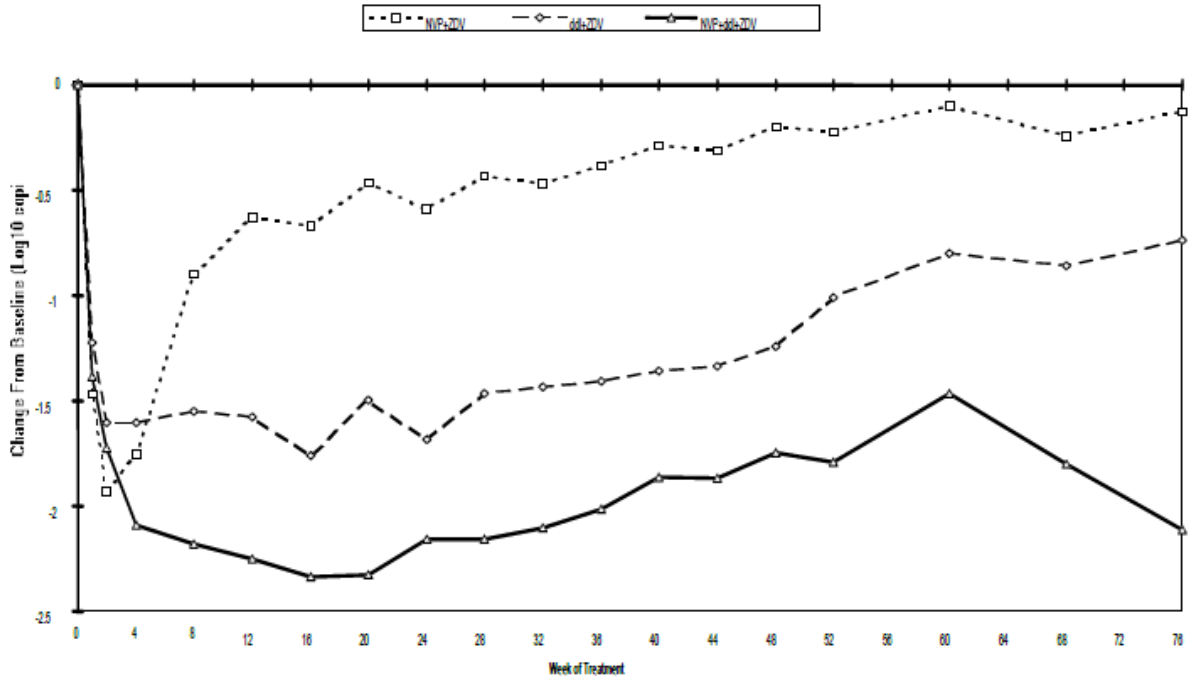
BI Trial 1046 compared treatment with nevirapine + AZT + ddI versus nevirapine + AZT versus AZT + ddI in 151 HIV-1-infected patients (median age 37 years, 94% Caucasian, 93% male) with CD4+ cell counts of 200-600 cells/mm³ (mean 375 cells/mm³) and a mean baseline plasma HIV-1 RNA concentration of 4.41 $\log_{10}$ 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%); the clinical significance of this finding is unknown.

Figure 5: Mean Change from Baseline for CD4+ Cell Count (absolute number of CD4+ cells/mm³), 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 (ZDV=AZT)	47	35	27	26	15

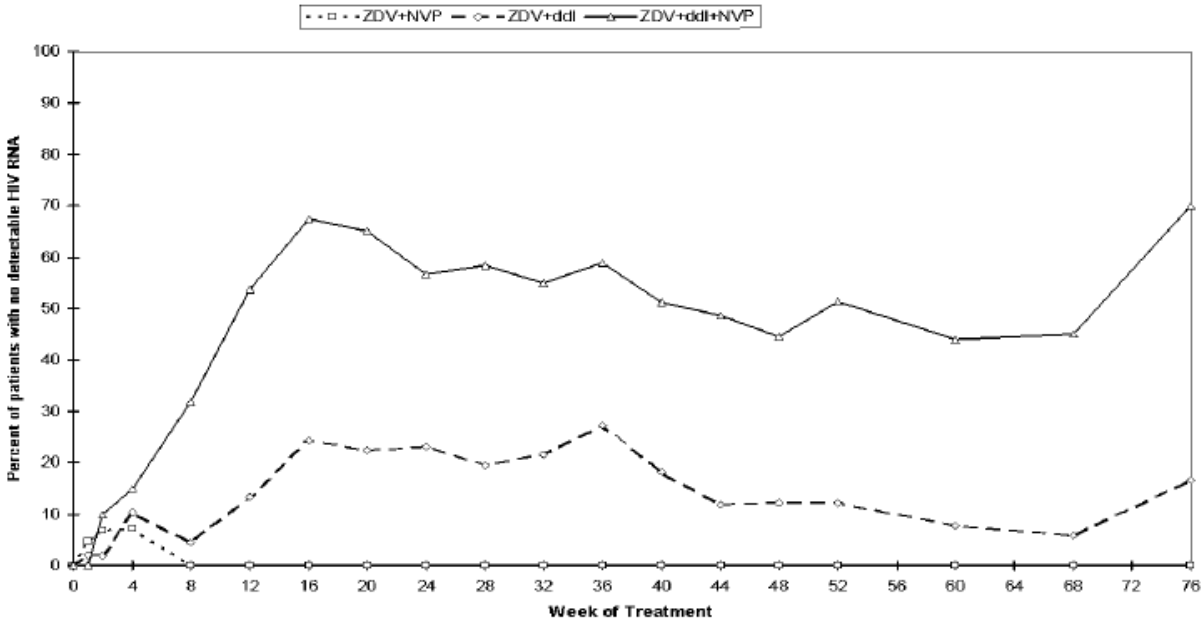
Figure 6: Mean Change from Baseline in HIV-1 RNA* Concentrations (Log_{10} copies/mL), Trial BI 1046



	Number of patients with HIV-1 RNA data at each timepoint				
	Baseline	Week 16	Week 32	Week 52	Week 76
NVP+AZT+ddI	51	40	40	37	10
Placebo+AZT+ddI	51	37	37	33	6
NVP+AZT+Placebo (ZDV=AZT)	46	35	26	25	6

* the clinical significance of changes in serum viral RNA measurements during treatment with nevirapine has not been established.

Figure 7: 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+AZT+ddI	51	40	40	37	10
Placebo+AZT+ddI	51	37	37	33	6
NVP+AZT+Placebo (ZDV=AZT)	46	35	26	25	6

* the clinical significance of viral RNA measurements during treatment with nevirapine has not been established.

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 a 11298 HIV-1- infected patients (mean age 37 years, 51% Caucasian, 87% male) with CD4 + cell counts ≤ 50 cells/mm³ (mean 25 cells/mm³). Eighty-four per cent (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) suggest switching ddI with ddC dosing last. The median time to HIV progression event or death nevirapine + AZT + ddI treatment group as compared to the AZT + ddI group (82 weeks versus 62 weeks). Mortality was similar for the two groups, throughout the trial. The median time to HIV progression event or death was shorter for AZT + ddC (53 weeks) and alternating AZT and ddI (57 weeks) group.

5.2 Pharmacokinetic properties

Absorption and bioavailability in adults

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 mcg/mL (7.5 mcM) 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 mcg/mL (17 ± 7 mcM), (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. ddI).

Distribution

Nevirapine is highly lipophilic and is essentially nonionized at physiologic pH. Animal studies have shown that nevirapine is widely distributed to nearly all tissues and readily crosses the blood-brain barrier. Following intravenous administration in healthy adults, the apparent volume of distribution (Vdss) of nevirapine was 1.21 ± 0.09 l/kg, suggesting that nevirapine is also widely distributed in humans. Nevirapine readily crosses the placenta and is found in breast milk (see section 4.6). Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 mcg/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

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.

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.

Elimination

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.

Special populations

Gender

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.

Age and race

Nevirapine pharmacokinetics in HIV-1 infected adults do not appear to change with age (range 18-68 years) or race (Black, Hispanic, or Caucasian). This information is derived from an evaluation of pooled data derived from several clinical trials.

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 nevirapine AUC 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

A steady state study comparing 46 patients with mild (n=17: Ishak Score 1-2), moderate (n=20; Ishak Score 3-4), or severe (n=9; Ishak Score 5-6, Child-Pugh A in 8 pts., for 1 Child-Pugh score not applicable) liver fibrosis as a measure of hepatic impairment was conducted.

The patients studied were receiving antiretroviral therapy containing nevirapine 200 mg twice-daily for at least 6 weeks prior to pharmacokinetic sampling, with a median duration of therapy of 3.4 years. In this study, the multiple dose pharmacokinetic disposition of nevirapine and the five oxidative metabolites were not altered.

However, approximately 15% of these patients with hepatic fibrosis had nevirapine trough concentrations above 9.000 ng/mL (2-fold the usual mean trough). Patients with hepatic impairment should be monitored carefully for evidence of drug induced toxicity.

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).

5.3 Preclinical safety data

Genotoxicity

In genetic toxicology assays, nevirapine showed no evidence of mutagenic or clastogenic activity in a battery of *in vitro* and *in vivo* assays including microbial assays for gene mutation (Ames: Salmonella strains and E.coli), mammalian cell gene mutation assays (CHO/HGPRT), cytogenic assays using Chinese hamster ovary cell line and a mouse bone marrow micronucleus assay following oral administration. In reproductive toxicology studies, evidence of impaired fertility was seen in female rats at doses providing systemic exposure, based on AUC, approximately equivalent to that provided with recommended clinical dose of nevirapine.

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

Nevirapine Viatris tablet also contains

- colloidal silicon dioxide
- lactose monohydrate
- magnesium stearate
- microcrystalline cellulose
- povidone
- sodium starch glycolate.

Contains sugars as lactose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Keep out of reach of children.

Store at or below 25°C. Store in the original container.

6.5 Nature and contents of container

PVC/Alu blister pack, 60 tablets.

HDPE bottle, 60 tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

21 October 2010

10. Date of Revision of the Text

24 July 2023

Summary table of changes

Section	Summary of new information
4.4, 4.5, 5.1	Removed information relating to delavirdine, boceprevir and telaprevir.
4.6	Updated information relating to pregnancy.
5.1, 5.3	Relocated *In Vitro* HIV Susceptibility, Resistance and Cross-resistance from section 5.3 to 5.1.
4.4, 4.5, 4.8, 5.1, 5.2, 5.3	Editorial changes.
6.1	Included allergen statement.