PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

VIROPON 200 mg TABLETS

COMPOSITION:

Each uncoated tablet contains nevirapine 200 mg.

Excipients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone K-30, sodium starch glycollate.

Contains sugar: Lactose monohydrate 340 mg (see **"WARNINGS and SPECIAL PRECAUTIONS"**.)

WARNING:

THE FIRST 18 WEEKS OF THERAPY WITH VIROPON 200 mg TABLETS IS A CRITICAL PERIOD THAT REQUIRES INTENSIVE MONITORING OF PATIENTS TO IDENTIFY THE POTENTIAL APPEARANCE OF SEVERE AND LIFE-THREATENING SKIN REACTIONS (INCLUDING CASES OF STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS) OR SERIOUS HEPATITIS/HEPATIC FAILURE. THE GREATEST RISK OF HEPATIC EVENTS AND SKIN REACTIONS OCCURS IN THE FIRST 6 WEEKS OF THERAPY. WOMEN (3,2 FOLD) AND PATIENTS WITH HIGHER CD4+ (WOMEN WITH CD4+ > 250, 9,8 FOLD; MEN WITH CD4+ > 400, 6,4 FOLD) COUNTS ARE AT INCREASED RISK OF HEPATIC ADVERSE EVENTS. IN ADDITION, THE DOSAGE, ESPECIALLY THE 14 DAYS LEAD-IN PERIOD, MUST BE STRICTLY ADHERED TO (SEE "DOSAGE AND DIRECTIONS FOR USE")

Cutaneous reactions:

Severe and life threatening skin reactions, including fatal cases, have occurred in patients treated with VIROPON 200 mg TABLETS. These have included cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and hypersensitivity syndrome characterized by rash, constitutional findings and visceral involvement.

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 consult a doctor. In these patients VIROPON 200 mg TABLETS must not be restarted.

If patients present with suspected VIROPON 200 mg TABLETS-associated rash, liver function tests should be performed. Patients with moderate to severe elevations (aspartate transaminase (AST) or alanine aminotransferase (ALT > 5 X ULN) should be permanently discontinued from VIROPON 200 mg TABLETS.

If a hypersensitivity syndrome occurs, characterized by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction, VIROPON 200 mg TABLETS should be permanently stopped and not be reintroduced.

Hepatic reactions:

Severe or life threatening hepatotoxicity including fatal fulminant hepatitis has occurred in patients treated with nevirapine. Serious hepatitis and hepatic failure events in nevirapine treated patients have been reported. Increased aspartate transaminase (AST) or alanine aminotransferase (ALT 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 VIROPON 200 mg TABLETS-containing regimens.

If AST or ALT > 2,5 x ULN before or during treatment, liver tests should be monitored more frequently during regular clinic visits. VIROPON 200 mg TABLETS should not be administered to patients with pre-treatment AST or ALT > 5 x ULN.

If aspartate transaminase (AST) or alanine aminotransferase (ALT) increase to > 5 x Upper Limit of Normality (ULN) during treatment VIROPON 200 mg TABLETS should be stopped immediately and not reinstated. If aspartate transaminase (AST) and alanine aminotransferase (ALT) return to baseline values, it may be possible to reintroduce VIROPON 200 mg TABLETS on a case by case basis, at the starting dosage regimen of 200 mg/day for 14 days followed by 400 mg/day. If liver function abnormalities rapidly recur, VIROPON 200 mg TABLETS should be permanently discontinued.

If clinical hepatitis occurs, characterized by anorexia, nausea, vomiting, icterus and laboratory findings [such as moderate or severe liver function test abnormalities (excluding GGT)], VIROPON 200 mg TABLETS must be permanently stopped. VIROPON 200 mg TABLETS should not be re-administered to patients who have required permanent discontinuation for clinical hepatitis due to VIROPON 200 mg TABLETS.

In patients with mild liver function test abnormalities, accompanied by signs of hypersensitivity syndrome characterized 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 discontinued.

VIROPON 200 mg TABLETS should not be restarted in these situations.

RESISTANT VIRUS EMERGES RAPIDLY AND UNIFORMLY WHEN VIROPON 200 mg TABLETS IS ADMINISTERED AS MONOTHERAPY, THEREFORE, FOR CHRONIC TREATMENT OF HIV-1 INFECTION, VIROPON 200 mg TABLETS SHOULD ALWAYS BE ADMINISTERED IN COMBINATION WITH AT LEAST TWO ADDITIONAL ANTIRETROVIRAL AGENTS.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antimicrobial (chemotherapeutic) agents. Antiviral agents.

PHARMACOLOGICAL ACTION:

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.

Resistance: HIV isolates with significantly reduced susceptibility (100 to 250 fold) to nevirapine emerge *in vitro*. Time to emergence of nevirapine resistance *in vitro* was not altered when selection included nevirapine in combination with several other NNRTIs.

Cross-resistance: Rapid emergence of HIV strains, which are cross resistant to NNRTI's *in vitro*, have been reported.

Pharmacokinetic properties:

Adults:

Nevirapine is readily absorbed (> 90 %) after oral administration in healthy volunteers and in adults with HIV-1 infection. **Following administration of nevirapine 200 mg tablets to healthy volunteers under fasting conditions, peak plasma concentrations (C_{max}) of about 2,0 to 2,5 µg/ml are attained at about 4 hours.**

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 µg/ml (17± 7 µm) were attained at 400 mg/day. The absorption of nevirapine is not affected by food, antacids or medicinal products, which are formulated with an alkaline buffering agent (e.g. didanosine).

Nevirapine is highly lipophilic and is essentially non-ionized at physiologic pH. Following intravenous administration to healthy adults, the apparent volume of distribution at steady state (Vdss) 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. Nevirapine is about 60 % bound to plasma proteins in the plasma concentration range of 1 to 10 µg/ml. Nevirapine concentrations in human cerebrospinal fluid are about 45 % of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

In vivo studies in humans and *in vitro* studies with human liver microsomes have shown that nevirapine is extensively biotransformed via cytochrome P450 isozymes from the CYP3A family, although other isozymes may have a secondary role. Approximately 91,4 ± 10,5 % of a radiolabeled dose was recovered, with urine (81,3 ± 11, 1 %) representing the primary route of excretion compared to faeces (10,1 ± 1,5 %). Nevirapine is an inducer of hepatic cytochrome P450 metabolic enzymes. This 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 to 30 hours following multiple dosing with 200 to 400 mg/day.

Nevirapine also undergoes autoinduction resulting in 1,5 to 2-fold increase in metabolism. This effect is at its highest after 14 days of initiation of therapy.

Pharmacokinetics in Special Populations:

Renal/Hepatic Dysfunction: The pharmacokinetics of **VIROPON 200 mg TABLETS** have not been evaluated in patients with either renal or hepatic dysfunction.

Gender: There are no significant gender differences in **VIROPON 200 mg TABLETS** clearance or plasma concentrations following either single or multiple dose administration.

Race: Pooled data from several clinical trials revealed no marked difference in nevirapine steady-state trough concentrations with long-term nevirapine treatment at 400 mg/day.

Geriatrics: Nevirapine pharmacokinetics in HIV-1 infected adults do not appear to change with age (range 18 to 68 years).

INDICATIONS:

For treatment of HIV-1 infection:

VIROPON 200 mg TABLETS (nevirapine) is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. Resistant virus emerges rapidly and uniformly when **VIROPON 200 mg TABLETS** is administered as monotherapy. Therefore, **VIROPON 200 mg TABLETS** should always be administered in combination with at least two additional antiretroviral agents.

CONTRAINDICATIONS:

VIROPON 200 mg TABLETS is contraindicated in patients with hypersensitivity to the active ingredient or any of the excipients of the product.

VIROPON 200 mg TABLETS is contraindicated in severe hepatic dysfunction: Child-Pugh class B or C and in end-stage renal failure in patients not on haemodialysis.

VIROPON 200 mg TABLETS should not be administered to patients with pre-treatment or during treatment with aspartate transaminase (AST) or alanine aminotransferase (ALT) > 5 X Upper Level of Normality (ULN) until baseline AST/ALT are stabilized < 5 ULN.

VIROPON 200 mg TABLETS should not be re-administered to patients who have required permanent discontinuation for severe rash, rash accompanied by constitutional symptoms; hypersensitivity syndrome, or clinical hepatitis due to **VIROPON 200 mg TABLETS.**

VIROPON 200 mg TABLETS should not be re-administered to patients who previously had aspartate transaminase (AST) or alanine aminotransferase (ALT) > 5 x Upper Limit of Normality (ULN) during **VIROPON 200 mg TABLETS** therapy or had rapid recurrence of liver function abnormalities upon re-administration of **VIROPON 200 mg TABLETS** (See **"WARNINGS and SPECIAL PRECAUTIONS"**).

Patients with pre-treatment aspartate transaminase (AST) or alanine aminotransferase (ALT) of 2 to 3 x Upper Limit of Normal (ULN) should be observed frequently during the early treatment period for development of either clinical or laboratory evidence of liver function deterioration.

Human reproduction: The safety of **VIROPON 200 mg TABLETS** in pregnant or lactating women has not been established. Adequate contraceptive methods should be used in women.

WARNINGS and SPECIAL PRECAUTIONS:

The first 18 weeks of therapy with **VIROPON 200 mg TABLETS** is a critical period, which requires intensive monitoring of patients to identify the potential appearance of severe, and life threatening skin reactions (including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis) or serious hepatitis/hepatic failure. The greatest risk of hepatic events and skin reactions occurs in the first 6 weeks of therapy. Women (3,2 fold) and patients with higher CD4 (women with CD4+ > 250, 9,8 fold; men with CD4+ > 400, 6,4 fold) counts are at increased risk of hepatic adverse events. In addition, the dosage, especially the 14 days lead-in period, must be strictly adhered to (see **"DOSAGE AND DIRECTIONS FOR USE"**).

Patients should be instructed that the major toxicity of VIROPON 200 mg TABLETS is skin rashes and should be advised to promptly notify their doctor of any rash. The lead-in period should be used because it has been found to lessen the frequency of rash (see "DOSAGE AND DIRECTIONS FOR USE").

The majority of rashes associated with nevirapine occur within the first 6 weeks of therapy; therefore, patients should be monitored carefully for the appearance of any rash during this period. Patients should be instructed that dose escalation is not to occur if any rash occurs during the lead-in dosing period, until the rash has resolved.

Skin reactions:

Severe and life threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine. These have included cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and hypersensitivity syndrome characterized 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.

VIROPON 200 mg TABLETS 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 Stevens-Johnson syndrome or toxic epidermal necrolysis. VIROPON 200 mg TABLETS must be permanently discontinued in any patient experiencing hypersensitivity syndrome characterized by rash with constitutional symptoms, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia and renal dysfunction or signs of other visceral involvement (see "SIDE EFFECTS").

Concomitant prednisone use (40 mg/day for the first 14 days of nevirapine administration) has been shown not 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 are at a 3,2 fold higher risk than men of developing rash. Women with a CD4+ count of > 250 cells/mm^3 are at a 9,8 fold increased risk of developing rash.

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 consult a medical practitioner. In these patients VIROPON 200 mg TABLETS must not be restarted.

If patients present with a suspected VIROPON 200 mg TABLETS-associated rash, liver function tests should be performed immediately. Patients with moderate to severe elevations (AST or ALT > 5 x ULN) should be permanently discontinued from VIROPON 200 mg TABLETS.

In patients with a hypersensitivity syndrome, characterized by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia and renal dysfunction, VIROPON 200 mg TABLETS should be permanently stopped and not be reintroduced.

Hepatic reactions:

Severe or life threatening hepatotoxicity, including fatal fulminant hepatitis (transaminase elevations, with or without hyperbilirubinemia, prolonged partial thromboplastin time or eosinophilia) has occurred in patients treated with nevirapine. Serious hepatitis and hepatic failure events in nevirapine treated patients have been reported to occur in the first 18 weeks of therapy but some have occurred later. The first 18 weeks of treatment are a critical period, which require close monitoring. The risk of hepatic events is greatest in the first 6 weeks of therapy. Women (3,2 fold) and patients with higher CD4 (women with CD4+ > 250, 9,8 fold; men with CD4+ > 400, 6,4 fold) counts are at increased risk of hepatic adverse events. 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 VIROPON 200 mg TABLETS and that occurrence of symptoms suggestive of hepatitis should lead them to contact their doctor promptly.

Increased aspartate transaminase (AST) or alanine aminotransferase (ALT) levels > 2,5 x ULN at the start of antiretroviral therapy is associated with greater (3,2 to 4,2 fold) risk of hepatic adverse events during antiretroviral therapy in **VIROPON 200 mg TABLETS** containing regimens.

VIROPON 200 mg TABLETS is contraindicated in patients with severe underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events. In the case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during combination therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Women have a threefold higher risk than men for rash-associated hepatic events (4,6 % vs. 1,5 %). Patients with higher CD4 counts may also be at a higher risk for rash-associated hepatic events with **VIROPON 200 mg TABLETS**. In a retrospective review, women with CD4 counts > 250 cells/mm^3 had a 9,8 fold higher risk of rash-associated hepatic adverse event compared to women with CD4 counts < 250 cells/mm^3 (0,84 % vs. 0,9 %). An increased risk (6,4 fold) was observed in men with CD4 counts > 400 cells/mm^3 compared to men with CD4 counts < 400 cells/mm^3 (4,5 % vs. 0,7 %).

Patients should be informed that hepatic reactions are a major toxicity of **VIROPON 200 mg TABLETS** requiring close monitoring during the first 18 weeks. However, severe liver disease can occur after 18 weeks. Therefore monitoring should continue at frequent intervals after this period depending on the patient's clinical status. They should be informed that occurrence of symptoms suggestive of hepatitis should lead them to contact their doctor promptly.

Liver function monitoring:

All patients should have baseline liver function tests prior to **VIROPON 200 mg TABLETS** treatment (see **"WARNINGS and SPECIAL PRECAUTIONS"** and **"CONTRAINDICATIONS"**).

If aspartate transaminase (AST) or alanine aminotransferase (ALT) are > 2,5 x Upper Limit of Normal (ULN) before or during treatment, liver tests should be monitored more frequently during more regular clinic visits**. VIROPON 200 mg TABLETS** should not be administered or re-administered to patients with pre-treatment AST > 5 x ULN.

Abnormal liver function has 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 liver function tests is strongly recommended at frequent intervals, appropriate to the patient's clinical needs, especially during the first 2 to 3 months of treatment. Less frequent monitoring is needed thereafter. Doctors and patients should be vigilant for prodromal signs of 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 aspartate transaminase (AST) or alanine aminotransferase (ALT) increase to > 5 x Upper Limit of Normality during treatment, VIROPON 200 mg TABLETS should be immediately stopped. If aspartate transaminase (AST) or alanine aminotransferase (ALT) return to baseline values, it may be possible to reintroduce VIROPON 200 mg TABLETS, on a case by case basis, at the starting dosage of 200 mg/day for 14 days followed by 400 mg/day. If liver function abnormalities rapidly recur, VIROPON 200 mg TABLETS should be permanently discontinued.

If clinical hepatitis occurs, characterized by anorexia, nausea, vomiting, icterus and laboratory findings such as moderate or severe liver function test abnormalities (excluding GGT), VIROPON 200 mg TABLETS must be permanently stopped. VIROPON 200 mg TABLETS should not be re-administered to patients who have required permanent discontinuation for clinical hepatitis due to VIROPON 200 mg TABLETS.

Patients receiving **VIROPON 200 mg TABLETS** and other antiretroviral agents may continue to develop opportunistic infections and other complications of HIV infection. Patients should therefore remain under close supervision by medical practitioners experienced in the treatment of patients with HIV-associated diseases.

General: When administering **VIROPON 200 mg TABLETS** as part of an antiretroviral treatment regimen, the complete product information for each therapeutic component should be consulted before initiation of treatment.

While nevirapine is extensively metabolized by the liver and nevirapine metabolites are extensively eliminated by the kidney, the pharmacokinetics results suggest caution should be exercised when **VIROPON 200 mg TABLETS** is administered to patients with more than mild hepatic dysfunction. **VIROPON 200 mg TABLETS** should not be administered to patients with severe hepatic dysfunction (AST/ALT > 5 x ULN). In patients with renal dysfunction who are undergoing haemodialysis, pharmacokinetics results suggest that supplementing **VIROPON 200 mg TABLETS** therapy with an additional 200 mg dose of **VIROPON 200 mg TABLETS** following each haemodialysis treatment would help offset the effects of haemodialysis on nevirapine clearance. Otherwise patients with CLcr ≥ 20 ml/min do not require an adjustment in nevirapine dosing. (See **"Pharmacokinetic properties"**, **"Renal Dysfunction"** and **"CONTRAINDICATIONS"**). Safety in patients with end stage impairment who are not haemodialysed has not been demonstrated.

Information for patients*:* Patients should be informed that **VIROPON 200 mg TABLETS** 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 **VIROPON 200 mg TABLETS** 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 doctor when using **VIROPON 200 mg TABLETS**.

Patients should be informed that the long term effects of **VIROPON 200 mg TABLETS** are unknown at this time.

VIROPON 200 mg TABLETS may interact with some medicines; therefore, patients should be advised to report to their medical practitioner the use of any other medications.

Oral contraceptives and other hormonal methods of birth control should not be used as the sole method of contraception in women taking **VIROPON 200 mg TABLETS**, since nevirapine may lower plasma levels of these medications. For this reason, and to reduce the risk of HIV transmission, barrier contraception (e.g. condoms) is recommended.

Lipodystrophy and metabolic abnormalities

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis.

Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination Anti-Retroviral Therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections

Patients receiving **VIROPON 200 mg TABLETS** should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

The risk of HIV transmission to others

Patients should be advised that current antiretroviral therapy, including **VIROPON 200 mg TABLETS**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

Effects on ability to drive and use machines:

There are no specific studies about the ability to drive vehicles and use machinery. However, somnolence has been reported in association with nevirapine therapy and if this occurs during **VIROPON 200 mg TABLETS** administration it is advisable to refrain from such activities.

VIROPON 200 mg TABLETS contain lactose.

Patients with the rare hereditary conditions of galactose intolerance e.g. galatosaemia, Lapp lactase deficiency, or glucose-galactose malabsorption should not take **VIROPON 200 mg TABLETS.**

Lactose may have an effect on the glycaemic control of patients with diabetes mellitus.

INTERACTIONS:

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 medicines that are extensively metabolized by CYP3A or CYP2B (see **"Pharmacokinetic properties"**). Thus, if a patient has been stabilized on a dosage regimen for a medicine metabolized by CYP3A or CYP2B and begins treatment with **VIROPON 200 mg TABLETS**, dose adjustment may be necessary.

Nucleoside Analogues: No dosage adjustments are required when **VIROPON 200 mg TABLETS** is taken in combination with zidovudine (ZDV), didanosine (ddl), zalcitabine (ddc) and stavudine (d4T).

Protease inhibitors: In the following studies, nevirapine was given 200 mg once daily for two weeks followed by 200 mg twice daily for 28 days.

Saquinavir: Co-administration of nevirapine and saquinavir (hard gelatin capsules, 600 mg tid) leads to a 24 % mean reduction (p=0,041) in saquinavir AUC and no significant change in nevirapine plasma levels. The reduction in saquinavir levels due to this interaction may further reduce the marginal plasma levels of saquinavir which are achieved with the hard gelatin capsule formulation. The clinical significance of this interaction is not known.

Co-administration did not affect the pharmacokinetics of nevirapine.

Ritonavir: No dosage adjustments are required when nevirapine is taken in combination with ritonavir.

Indinavir: Nevirapine and indinavir (800 mg tid) co-administration leads to a 28 % mean decrease (p < 0,01) in indinavir AUC and no significant change in nevirapine plasma levels. A dose increase of indinavir to 1 000 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 1 000 mg q8h with nevirapine 200 mg bid will differ from that of indinavir 800 mg q8h with nevirapine 200 mg bid.

Nelfinavir: Nevirapine, nelfinavir (750 mg tid) and stavudine (30 to 40 mg bid) given in combination indicated no statistically significant changes in nelfinavir pharmacokinetic parameters after the addition of nevirapine (AUC +4 %, C_{max} +14 % and C_{min} – 2 %).

Compared to historical controls nevirapine levels appeared to be unchanged.

There were no increased safety concerns noted when nevirapine was administered in combination with any of the protease inhibitors.

Ketoconazole: Ketoconazole and nevirapine should not be given concomitantly. Administration of nevirapine 200 mg bid with ketoconazole 400 mg qid resulted in a significant reduction (63 % median reduction in ketoconazole AUC and a 40 % median reduction in ketoconazole C_{max}). In the same study, ketoconazole administration resulted in a 15 to 28 % increase in the plasma levels of nevirapine compared to historical controls. The effects of nevirapine on itraconazole are not known. Although interaction studies have not been performed, antifungal medicinal products which are eliminated renally (e.g. fluconazole) might be substituted for ketoconazole.

Fluconazole: Co-administration of fluconazole and nevirapine resulted in approximately 100 % increase in nevirapine exposure compared with historical data where nevirapine was administered alone. Because of the risk of increased exposure to nevirapine, caution should be exercised if **VIROPON 200 mg TABLETS** and fluconazole are given concomitantly and patients should be monitored closely. There was no clinically relevant effect of nevirapine.

Anticoagulants: The *in vitro* interaction between nevirapine and the antithrombotic agent warfarin is complex. As a result, when giving these drugs concomitantly plasma warfarin levels and therapeutic efficacy may change with the potential for both increases and decreases in coagulation time. The net effect of the interaction may change during the first weeks of co-administration or upon discontinuation of nevirapine. When warfarin is co-administered with nevirapine prothrombin time should be more frequently monitored.

CYP isoenzyme inducers (e.g. rifampicin, rifabutin): Nevirapine in combination with rifampicin resulted in no significant change in rifampicin C_{max} and AUC. In contrast, rifampicin produced a significant lowering of nevirapine AUC (–58 %), C_{max} (–50 %) and C_{min} (–68 %) compared to historical data. At present there are insufficient data to assess what dosage adjustments are required when nevirapine and rifampicin are co-administered.

Rifabutin: Administration of nevirapine 200 mg twice daily with rifabutin 300 mg four times daily (or 150 mg four times daily if concomitantly receiving ZDV or protease inhibitors), resulted in a significant increase of rifabutin concentrations (29 % mean increase in rifabutin AUC and a 28 % mean increase in rifabutin C_{max}) and a significant increase (20 %) in median C_{max}. There were no significant changes in the active metabolite 25-O-desacetyl-rifabutin concentrations. High inter-patient variability however, may result in some patients experiencing large increases in rifabutin exposure, which may make them at higher risk for toxicity. In the same study, rifabutin administration resulted in an apparent significant increase in systemic clearance of nevirapine by 9 % compared to historical controls. The latter changes are not considered to be clinically important. Care should be taken when nevirapine and rifabutin are administered concurrently with considerations of a decrease in the dose of rifabutin. The dose of **VIROPON 200 mg TABLETS** need not be changed.

St. Johns' Wort: Concomitant use of **VIROPON 200 mg TABLETS** and St. Johns' Wort (*hypericum perforatum*) or St. Johns' Wort containing products is not recommended as co-administration of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), including **VIROPON 200 mg TABLETS** with St. Johns' Wort is expected to decrease NNRTI concentrations and may result in sub optimal levels of **VIROPON 200 mg TABLETS** and lead to loss of virologic response and possible resistance to **VIROPON 200 mg TABLETS** or to the class of NNRTIs. The bioavailability of nevirapine is reduced by 57 ± 19 % (AUC) and the C_{max} of nevirapine is reduced by 81 ± 16 %.

CYP isoenzyme inhibitors (e.g. cimetidine and macrolides): Nevirapine trough concentrations were elevated in patients who received cimetidine (+21 %).

The results of a nevirapine-clarithromycin interaction study resulted in a significant reduction in clarithromycin AUC (30 %) and C_{max} (–21 %) and C_{min} (–46 %) but a significant increase in the AUC (58 %) and C_{max} (62 %) of the active metabolite 14-OH clarithromycin. There was a significant increase in the nevirapine C_{min} (28 %) and a non-significant increase in nevirapine AUC (26 %) and C_{max} (24 %). Test results would suggest that no dose adjustment is necessary for either clarithromycin or nevirapine when the two medicinal products are co-administered. Close monitoring of hepatic abnormalities and activity against *Mycobacterium avium*-intracellular complex (MAC) is nevertheless recommended and alternate therapy to clarithromycin should be considered when treating a patient for *Mycobacterium avium*-intracellular complex (MAC), as the active metabolite is not effective in this instance.

Oral contraceptives: Other means of contraception (such as barrier methods) are recommended, when nevirapine is administered to women of childbearing potential, as oestrogen levels are significantly decreased when used with nevirapine. For other therapeutic uses requiring hormonal regulation, the therapeutic effect in patients being treated with nevirapine should be monitored.

Methadone: Based on the metabolism of methadone, **VIROPON 200 mg TABLETS** may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Narcotic withdrawal syndrome has been reported in patients treated with nevirapine and methadone concomitantly. Methadone-maintained patients beginning **VIROPON 200 mg TABLETS** therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

Other information on interactions:

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/sulphamethoxazole. Ketoconazole and 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 or CYP2B6 may have decreased plasma concentrations when co-administered with **VIROPON 200 mg TABLETS.**

HUMAN REPRODUCTION:

See **"CONTRAINDICATIONS".**

DOSAGE AND DIRECTIONS FOR USE:

Adults: The recommended dose for **VIROPON 200 mg TABLETS** 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 antiretroviral agents to which the patient has not been previously exposed. For concomitantly administered antiretroviral therapy, the recommended dosage and monitoring should be followed.

The total daily dose should not exceed 400 mg.

Patients should be advised to take **VIROPON 200 mg TABLETS** every day as prescribed.

Patients should not alter the dose without consulting their doctor. If a dose is skipped, patients should not double the next dose but should take the next dose as soon as possible.

Monitoring of patients: Clinical chemistry, including liver function tests, should be performed prior to initiating **VIROPON 200 mg TABLETS** therapy and at appropriate intervals during therapy. (See **"WARNINGS and SPECIAL PRECAUTIONS"**).

Dosage Adjustment: VIROPON 200 mg TABLETS should be discontinued if patients experience severe rash or a rash accompanied by constitutional findings (See "WARNINGS and SPECIAL PRECAUTIONS"). Patients experiencing rash during the 14-day lead-in period of 200 mg/day should not have their VIROPON 200 mg TABLETS dose increased until the rash has resolved (See "WARNINGS and SPECIAL PRECAUTIONS").

VIROPON 200 mg TABLETS administration should be interrupted in patients experiencing moderate liver function test abnormalities, e.g. AST or ALT < 5 X ULN [excluding gamma glutamyl transferase (GGT)]. If aspartate transaminase (AST) or alanine aminotransferase (ALT) return to baseline values and if the patient has no clinical signs and symptoms of hepatitis or constitutional symptoms or other findings suggestive of organ dysfunction, it may be possible to reintroduce **VIROPON 200 mg TABLETS**, based on clinical needs and judgement, on a case by case basis. **VIROPON 200 mg TABLETS** may then be restarted at 200 mg daily increasing to 200 mg twice daily with caution, after extended observation. If moderate or severe liver function test abnormalities recur, **VIROPON 200 mg TABLETS** should be permanently discontinued (See **"WARNINGS and SPECIAL PRECAUTIONS"**).

Patients who interrupt **VIROPON 200 mg TABLETS** dosing for more than 7 days should restart the recommended dosing using one 200 mg tablet daily for the first 14 days (lead-in) followed by one 200 mg tablet twice daily.

For the dosage for patients with hepatic dysfunction including those undergoing haemodialysis, please refer to the section **"Pharmacokinetic Properties"**.

SIDE EFFECTS:

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:

Rare: granulocytopenia, anaemia

Immune system disorders:

Common: allergic reactions

Rare: hypersensitivity (syndrome), anaphylaxis

Nervous system disorders:

Common: headache

Gastrointestinal disorders:

Common: nausea

Uncommon*:* vomiting, abdominal pain

Rare: diarrhoea

Hepato-biliary disorders:

Common: hepatitis (1,2 %), liver function tests abnormal

Uncommon: jaundice

Rare: liver failure/fulminant hepatitis

Skin and subcutaneous tissue disorders:

Common: rash (9 %)

Uncommon: Stevens-Johnson syndrome (0,3 %), urticaria

Rare*:* toxic epidermal necrolysis, angioedema

Musculoskeletal, connective tissue and bone disorders:

Uncommon: myalgia

Rare: arthralgia

General disorders and administration site conditions:

Uncommon: fatigue, fever

Post marketing experience has shown that the most serious adverse reactions are Stevens-Johnson syndrome, toxic epidermal necrolysis, serious hepatitis/hepatic failure and hypersensitivity syndrome, characterized by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvements, such as hepatitis, eosinophilia, granulocytopenia and renal dysfunction. The first 18 weeks of treatment is a critical period, which requires close monitoring (See **"WARNINGS and SPECIAL PRECAUTIONS"**).

Skin and subcutaneous tissues:

The most common clinical toxicity of **VIROPON 200 mg TABLETS** is rash. Nevirapine attributable rash occurred in 16 % of patients in combination regimens in **Phase II/III** controlled studies. In these clinical trials 35 % of patients treated with nevirapine experienced rash compared with 19 % of patients treated in control groups of either zidovudine + didanosine or zidovudine alone. Severe or life threatening skin reactions occurred in 6,6 % of nevirapine treated patients compared with 1,3 % of patients treated in the control groups. Overall, 7 % of patients discontinued nevirapine due to rash.

Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. Allergic reactions (anaphylaxis, angioedema and urticaria) have been reported. Severe and life threatening skin reactions have occurred in patients treated with nevirapine, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Fatal cases of SJS, TEN and hypersensitivity syndrome have been reported.

Rashes may occur alone or in the context of hypersensitivity syndrome characterized by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia and renal dysfunction.

VIROPON 200 mg TABLETS must be discontinued immediately in patients developing a severe rash or a rash accompanied by constitutional symptoms.

The majority of rashes of any severity occur within the first 6 weeks of treatment and some patients required hospitalization.

Functional groupings of cutaneous eruptions (rashes) presumed to be related to nevirapine:

Group I: Erythema, pruritus

Group IIA: One of the two following clinical presentations.

1. Diffuse erythematous macular or maculopapular cutaneous eruption or dry desquamation with or without pruritus without the presence of any additional constitutional findings as described in **Group III.**
2. Typical target lesions without blistering, vesicles or ulcerations in the lesions (usually referred to as erythema multiforme minor).

Group IIB: Urticaria.

Group III: One of the five following clinical presentations

1. Extensive erythematous or maculopapular rash or moist desquamation with or without pruritus together with the presence of any of the following constitutional findings:
   - Clinically relevant increases in any one or more of the following liver function tests:
     Aspartate transaminase (AST), alanine aminotransferase (ALT), alkaline phosphatase and which are possibly related to the drug reaction.
   - Fever, defined as > 39 °C possibly related to drug reaction.
   - Blistering and/or vesiculation of cutaneous eruptions.
   - One site of extensive mucosal lesions which are presumed to be due to medicine reaction (e.g. not due to herpes simplex, CMV).
2. Angioedema
3. Exfoliative dermatitis: Severe widespread erythema and dry scaling of the skin with generalized superficial lymphadenopathy and with other constitutional findings such as fever, weight loss, hypoproteinaemia which could possibly be related to a medicine reaction.
4. Diffuse rash and serum sickness-like reactions defined as a clinical symptom complex manifested as fever, lymphadenopathy, oedema, myalgia and/or arthralgia.
5. Diffuse cutaneous eruptions, usually starting on the face and trunk or back, often with prodromal symptoms (e.g. fever, general malaise, myalgia, arthralgia) plus one or more of the following (usually referred to as Stevens-Johnson syndrome):
   - Cutaneous bullae sometimes confluent, with widespread sheet like detachment covering < 10 % of body surface (referred to as Nikolsky's Sign).
   - Two or more anatomically distinct sites of mucosal erosion or ulceration not due to another cause (e.g. herpes simplex); mucosal sites include oral, laryngeal, nasal ocular*, genital and rectal surfaces. (*Note: The diagnosis of erosive conjunctivitis requires the presence of injected conjunctivae plus a purulent conjunctival discharge or visualization of the conjunctival erosions. The presence of only an erythematous or injected conjunctiva does not establish erosion of the conjunctiva).

Group IV: Diffuse cutaneous eruptions, usually starting on the face and trunk or back, often with prodromal symptoms (e.g. fever, general malaise, myalgia, arthralgia) plus cutaneous bullae with widespread sheet like detachment covering > 10 % of body surface area. Note: Two or more anatomically distinct sites of mucosal erosion or ulceration not due to another cause (e.g. herpes simplex, CMV etc.) may be observed, but are not required for inclusion of the patient in **Group IV**.

Presumed prodrome to Group III or IV:

The prodrome includes symptoms such as fever > 39 % or a clinical symptom complex manifested as fever, lymphadenopathy, oedema, myalgia, and/or arthralgia and the symptoms are thought to be related to nevirapine.

The following management algorithms are suggested based on the grouping of the cutaneous eruptions. The management regimens outlined below are based on the information that is currently available from nevirapine studies.

1. Cutaneous eruption Group I, IIA and IIB:

VIROPON 200 mg TABLETS may be continued for **Groups I, IIA and IIB.** Manage pruritus and minor accompanying symptoms with antihistamines, antipyretics and/or non-steroidal anti-inflammatory medications. If **VIROPON 200 mg TABLETS** is interrupted during a **Group I or IIA** reaction, it may be re-introduced once the cutaneous eruptions have cleared. If **Group I or IIA** cutaneous eruptions occur during the **VIROPON 200 mg TABLETS** low dose lead-in period, dose escalation should not be attempted until the cutaneous eruptions have resolved.

If **Group IIB** cutaneous eruption occurs during the low dose lead-in period, the **VIROPON 200 mg TABLETS** dose must not be escalated and if **VIROPON 200 mg TABLETS** treatment is interrupted, it must not be re-introduced.

2. Cutaneous eruption Group III and IV:

VIROPON 200 mg TABLETS must be permanently discontinued. No re-challenge is allowed. If symptoms occur during the low dose lead-in period that are suggestive of a possible prodrome to a **Group III or IV** cutaneous eruption, dose escalation should be delayed until the possible prodrome has resolved or a non nevirapine cause is established.

3. No nevirapine re-challenge of any patient with a group IIB, III or IV cutaneous eruption is allowed.

Hepato-biliary:

The most frequently observed laboratory test abnormalities are elevations in liver function tests (LFTs), including aspartate transaminase (AST), alanine aminotransferase (ALT), d-Glutamyl transpeptidase (GGT), total bilirubin and alkaline phosphatase. Asymptomatic elevations of GGT levels are the most frequent. Cases of jaundice have been reported. Cases of hepatitis, severe and life threatening hepatotoxicity and fatal fulminant hepatitis have been reported in patients treated with nevirapine. In a large clinical trial, the risk of a serious hepatic event among 1 121 patients receiving nevirapine for a median duration of greater than one year was 1,2 % (versus 0,5 % in placebo group). 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, but such events may also occur later (see **"WARNINGS and SPECIAL PRECAUTIONS"**). 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 **"WARNINGS and SPECIAL PRECAUTIONS"**).

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

For liver function test monitoring refer to **"WARNINGS and SPECIAL PRECAUTIONS"**.

The following events have also been reported when nevirapine has been used in combination with other antiretroviral agents; anaemia, pancreatitis, lipodystrophy, 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdosage with **VIROPON 200 mg TABLETS** may manifest in any of the symptoms described under **"SIDE EFFECTS" and "WARNINGS and SPECIAL PRECAUTIONS"**. There is no known antidote for **VIROPON 200 mg TABLETS** overdosage. Cases of nevirapine overdose at doses ranging from 800 to 6 000 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.

Treatment of **VIROPON 200 mg TABLETS** overdose is symptomatic and supportive.

IDENTIFICATION:

White to off-white, oval shaped, biconvex tablets, one side debossed with "C" and "35", with a single bisect separating "C" and "35". The other side has a single bisect.

PRESENTATION:

1. 60 tablets are packed in white round 140 ml HDPE containers with a screw type polypropylene closure with an induction sealing wad. The void in the container is filled with absorbent cotton.
2. 60 tablets are packed in white round 100 ml HDPE containers with stock ribbed polypropylene closure with induction sealing wad. The void in the container is filled with absorbent cotton.

The HDPE container will be further packed in a pre-printed carton with a package leaflet.

Not all packs or pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS:

Store at or below 30 °C in the original package. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

A40/20.2.8/0382

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Novagen Pharma (Pty) Ltd
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South Africa

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION:

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Date of latest revision of the text as approved by Council: 2 February 2015
Date of notification with regard to amended Reg. 9 and 10: 2 February 2015

P1519105

DETACH BEFORE DISPENSING

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM

VIROPON 200 mg TABLETS (Nevirapine)

Read all of this leaflet carefully before you start taking VIROPON 200 mg TABLETS.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- **VIROPON 200 mg TABLETS** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

1. WHAT VIROPON 200 mg TABLETS CONTAINS

- The active substance is nevirapine. Each uncoated tablet contains nevirapine 200 mg.
- The other ingredients are: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate.

Contains sugar: Lactose monohydrate 340 mg

Important information about some of the ingredients of VIROPON 200 mg TABLETS.

VIROPON 200 mg TABLETS contain lactose. Patients with the rare hereditary conditions of lactose or galactose intolerance should not take **VIROPON 200 mg TABLETS.**

Lactose may have an effect on the control of your blood sugar if you have diabetes mellitus.

2. WHAT VIROPON 200 mg TABLETS IS USED FOR

Nevirapine tablets belong to a group of medicines called antiretrovirals. They are used in combination with other antiretroviral agents to delay the progression of Human Immunodeficiency Virus (HIV) in both adults and children with HIV infection and those who have gone on to develop the symptoms of AIDS. It is important to realise that nevirapine tablets are not a cure for HIV infection and that you may continue to develop infection or other illnesses associated with HIV infection. It is also important to realise that nevirapine tablets have not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

3. BEFORE YOU TAKE VIROPON 200 mg TABLETS

If you are taking other medicines on a regular basis, including complementary or traditional medicines, the use of VIROPON 200 mg TABLETS with these medicines may cause undesirable interactions. Please consult your doctor, pharmacist or other healthcare professional, for advice.

Do not take VIROPON 200 mg TABLETS

- If you are hypersensitive (allergic) to nevirapine or any of the other ingredients of nevirapine tablets.
- If you previously experienced hepatitis, severe skin rash, or liver injury while on nevirapine tablet treatment.
- If you are currently taking rifampicin (used to treat tuberculosis).
- If you are taking products containing *Hypericum perforatum* (St John's Wort) as this may stop nevirapine tablets from working properly.

If the answer is "YES" to any of these questions, and if you have not already discussed them with your doctor, go back to him BEFORE starting treatment.

Take special care with VIROPON 200 mg TABLETS

- **Patients taking VIROPON 200 mg TABLETS may develop severe liver disease or severe skin reactions that can cause death.** Your doctor will want to check you during the first 18 weeks of therapy. The greatest risk of liver disease and skin reactions occurs in the first 6 weeks of therapy. These reactions can also occur later.
- If you develop a severe rash or a rash with any of the following symptoms stop using **VIROPON 200 mg TABLETS** and call your doctor right away: fever, muscle or joint aches, blisters, mouth sores, conjunctivitis (red or inflamed eyes), swelling of your face, general ill feeling.
- Women and patients with higher CD4 counts (blood counts) seem to have a greater chance of developing liver damage, often accompanied by a rash, while taking nevirapine.
- Patients with higher liver function tests and patients with hepatitis B or C have a greater chance of developing liver damage while taking nevirapine.
- If you develop any of the following symptoms of liver problems call your doctor right away: anorexia (lack of appetite), nausea (queasiness, feeling that one is about to vomit), yellowing of your skin or whites of your eyes, dark urine, pale stools, pain, ache, or sensitivity to touch on your right side below your ribs.
- If you have evidence of lipodystrophy you should have a thorough cardiovascular risk assessment.
- If you experience joint aches and pain, joint stiffness or difficulty in movement.
- If you have been told by your doctor that you have an intolerance to some sugars.
- If you have diabetes mellitus (high blood sugar).

Taking VIROPON 200 mg TABLETS with food or drink:

VIROPON 200 mg TABLETS can be taken before or after meals. The absorption of nevirapine is not affected by food.

Pregnancy: The safety of nevirapine in human pregnancy has not been established.

If you are pregnant or breast feeding your baby while taking VIROPON 200 mg TABLETS, please consult your doctor, pharmacist or other healthcare professional for advice.

Breastfeeding: You should discontinue breastfeeding if you are taking nevirapine tablets. Some health experts recommend that you discontinue breastfeeding if you have HIV infection in order to lower the chances of passing the infection on to your baby.

Driving and using machinery:

If somnolence (sleepiness) occurs while taking **VIROPON 200 mg TABLETS**, then it is advisable not to drive or use machinery.

Taking other medicines with VIROPON 200 mg TABLETS:

Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines).

When you are taking **VIROPON 200 mg TABLETS**, it is especially important that your healthcare professional knows if you are taking any of the following:

- Cimetidine
- Clarithromycin
- Fluconazole
- Ketoconazole – Ketoconazole and nevirapine should not be given together.
- Warfarin – Your doctor will want to monitor your blood levels more frequently when you are taking **VIROPON 200 mg TABLETS** at the same time as warfarin.
- Methadone
- Rifampicin
- Rifabutin
- Oral contraceptives (birth control) – Nevirapine may decrease the amount of these medicines in the body and cause them to be less effective. Talk with your doctor about other types of birth control (e.g. condoms) that you can use.
- St. John's Wort or St. John's Wort containing products – These medicines may decrease the amount of nevirapine in the body.

4. HOW TO TAKE VIROPON 200 mg TABLETS

Do not share medicines prescribed for you with any other person.

Always take VIROPON 200 mg TABLETS exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure. If you have the impression that the effect of VIROPON 200 mg TABLETS is too strong or too weak, talk to your doctor or pharmacist.

Nevirapine tablets should only be taken by mouth. The normal dosage is one 200 mg tablet for the first 14 days of treatment (this "lead in" period has been shown to lower the incidence of skin rash) followed by one 200 mg tablet twice daily. Nevirapine tablets will always be taken in combination with other HIV anti-retrovirals, for which you should follow the instructions within the supplied package leaflet.

It is essential to follow strictly the once a day dosage during the 14 day "lead-in" period before rising to the twice daily dosage.

You should continue to take nevirapine tablets for as long as instructed by your doctor. As explained in *"Take special care with nevirapine tablets",* above, your doctor will monitor you by liver tests or for undesirable effects such as rash. Depending on the outcome he or she may decide to interrupt or stop your nevirapine tablets treatment. He or she might then decide to restart you on a lower dose. If you stop taking nevirapine tablets for more than 7 days your doctor will instruct you to start the 14 day "lead-in" period (described above) once again before returning to the twice daily dose.

Do not exceed the dose prescribed by your doctor.

If you take more VIROPON 200 mg TABLETS than you should:

There is at present little information on the effects of nevirapine tablets overdose.

In the event of overdosage, consult your doctor or pharmacist. If neither is available, seek help at the nearest hospital or poison control centre.

If you forget to take VIROPON 200 mg TABLETS:

Do not take a double dose to make up for forgotten individual doses.

5. POSSIBILE SIDE EFFECTS

VIROPON 200 mg TABLETS can have side effects.

The major side effects of nevirapine tablets are severe and life threatening cutaneous reactions and serious hepatic injuries. These reactions occur mainly in the first 8 weeks of treatment with nevirapine tablets. This is therefore an important period which requires a close surveillance. When rash does occur it is normally mild to moderate. However, in about 7 % of patients a rash, which appears as a blistering skin reaction, can be severe or life-threatening and fatalities have been recorded. Most of the cases of both severe rash and mild/moderate rash occur in the first eight weeks of treatment. If you ever do observe any rash symptoms please inform your doctor immediately. If the symptoms are severe you must stop treatment and visit your doctor immediately.

Hypersensitivity (allergic) reactions can occur. Such reactions may appear in the form of rash accompanied by other side effects such as fever, blistering, mouth sores, eye inflammation, facial swelling, general swelling, muscle or joint aches, a reduction in white blood cells (granulocytopaenia), general feelings of illness or severe problems with liver or kidneys.

If you experience rash and any of the other side effects of a hypersensitivity reaction, please be sure to tell your doctor immediately as such reactions can be potentially life-threatening.

Abnormal liver functioning has been reported with the use of nevirapine tablets, including some cases of hepatitis, which have resulted in recorded fatalities. If you experience clinical symptoms suggesting an injury of the liver, such as loss of appetite, nausea, vomiting, jaundice, you should inform your doctor.

Other side effects which can occur are fever, nausea, headache, sleepiness, vomiting, diarrhoea, stomach pain, muscle pain and any of these side effects can occur together with the rash side effect (hypersensitivity reaction). Joint pain has been reported as a stand-alone event in rare instances in patients receiving nevirapine containing regimens.

In addition, a reduction in white blood cells (granulocytopaenia) can occur, which is more common in children. In very rare instances a reduction in red blood cells or white blood cells (neutropenia) may be related to nevirapine therapy. As with rash symptoms, please inform your doctor of any side effects. If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Not all side effects reported for VIROPON 200 mg TABLETS are included in this leaflet. Should your general health worsen while taking VIROPON 200 mg TABLETS, please consult your doctor, pharmacist or other healthcare professional for advice.

6. STORING AND DISPOSING OF VIROPON 200 mg TABLETS

Store at or below 30 °C in the original package. Protect from light.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

7. PRESENTATION OF VIROPON 200 mg TABLETS

1. 60 tablets are packed in white round 140 ml HDPE containers with a screw type polypropylene closure with an induction sealing wad. The void in the container is filled with absorbent cotton.
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9. REGISTRATION NUMBER

A40/20.2.8/0382

10. NAME, BUSINESS ADDRESS AND TELEPHONE NUMBER OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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11. DATE OF PUBLICATION OF THE PATIENT INFORMATION LEAFLET

Date of registration: 11 August 2006
Date of latest revision of the text as approved by Council: 2 February 2015
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