SCHEDULING STATUS:

Schedule 4

PROPRIETARY NAME AND DOSAGE FORM:

NEVIRAPINE MYLAN 200 mg (Tablets)

WARNING:

THE FIRST 18 WEEKS OF THERAPY WITH NEVIRAPINE MYLAN 200 mg 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 who were treated with NEVIRAPINE MYLAN 200 mg. These included cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and hypersensitivity syndrome characterised 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 NEVIRAPINE MYLAN 200 mg must not be restarted.

If patients present with suspected NEVIRAPINE MYLAN 200 mg-associated rash, liver function tests should be performed. Patients with moderate to severe elevations of aspartate transaminase (AST) or alanine aminotransferase (ALT) > 5 x Upper Limit of Normality (ULN) should be permanently discontinued from NEVIRAPINE MYLAN 200 mg.

If a hypersensitivity syndrome occurs, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction, NEVIRAPINE MYLAN 200 mg 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 NEVIRAPINE MYLAN 200 mg - containing regiments. If AST or ALT > 2,5 x ULN before or during treatment, liver tests should be monitored more frequently during regular clinic visits. NEVIRAPINE MYLAN 200 mg 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 NEVIRAPINE MYLAN 200 mg should be stopped immediately and not reinstated.

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 MYLAN 200 mg must be permanently stopped. NEVIRAPINE MYLAN 200 mg should not be re-administered to patients who have required permanent discontinuation for clinical hepatitis due to NEVIRAPINE MYLAN 200 mg.

In patients with mild liver function abnormalities, accompanied by signs of 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, nevirapine should be permanently discontinued. NEVIRAPINE MYLAN 200 mg should not be restarted in these situations.

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

COMPOSITION:

Each **NEVIRAPINE MYLAN 200 mg** tablet contains nevirapine USP 200 mg

List of Excipients: microcrystalline cellulose, povidone (K 30), sodium starch glycolate, colloidal anhydrous silica, magnesium stearate

Contains 464 mg of lactose monohydrate (sugar)

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antimicrobial (Chemotherapeutic) Agents. Antiviral Agents

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Mechanism of action:

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of the human immunodeficiency virus (HIV-1). Nevirapine binds directly to reverse transcriptase 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 reverse transcriptase and eukaryotic DNA polymerases (such as human DNA polymerases α, β, γ, or δ) are not inhibited by nevirapine.

Resistance:

HIV isolates with reduced susceptibility (100 to 250-fold) to nevirapine emerge *in vitro*. Phenotypic and genotypic changes occur in HIV isolates from patients treated with nevirapine or nevirapine + zidovudine over one to 12 weeks. By week 8 of nevirapine monotherapy, 100 % of the patients tested had HIV isolates with a > 100-fold decrease in susceptibility to nevirapine, regardless of dose.

Nevirapine + zidovudine combination therapy did not alter the emergence rate of nevirapine-resistant virus.

The use of highly active medicine therapies is associated with a delay in the development of antiretroviral medicine 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 NRTIs are very limited.

Cross-resistance between nevirapine and human immunodeficiency virus protease inhibitors is unlikely because the enzyme targets involved are different.

Cross-resistance among the currently registered NNRTIs is broad. Some genotypic resistance data indicate that in most patients failing NNRTI, viral strains express cross-resistance to the other NNRTIs. The currently available data do not support sequential use of NNRTIs.

Pharmacokinetic properties:

Adults:

Absorption:

Nevirapine is readily absorbed (> 90 %) after oral administration in healthy volunteers and in adults with HIV-1 infection.

Peak plasma nevirapine concentrations of 2 ± 0,4 µg/ml (7,5 µM) were attained by 4 hours following a single 200 mg dose. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day.

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

Distribution:

Nevirapine is lipophilic and is essentially nonionised at physiologic pH. Following intravenous administration to healthy adults, the volume of distribution (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 - 10 µg/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/Elimination:

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 isozymes from the CYP3A family, although other isozymes may have a secondary role. In a mass balance/excretion study in eight healthy male volunteers dosed to steady state with nevirapine 200 mg given 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 plays a minor role in elimination of the parent compound.

Nevirapine has been shown to be an inducer of hepatic cytochrome P450 metabolic enzymes. The pharmacokinetics of auto induction 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. Auto induction 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.

Renal dysfunction:

The single-dose pharmacokinetics of nevirapine have been compared in 23 subjects with either mild (50 ≤ CLcr < 80 ml/min), moderate (30 ≤ CLcr < 50 ml/min) or severe renal dysfunction (CLcr < 30 ml/min), renal impairment or end-stage renal disease (ESRD) requiring dialysis, and 8 subjects with normal renal function (CLcr > 80 ml/min). Renal impairment (mild, moderate and severe) resulted in no significant change in the pharmacokinetics of nevirapine. However, subjects with ESRD requiring dialysis exhibited a 43,5 % reduction in [N] 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 dysfunction:

The single-dose pharmacokinetics of nevirapine have been compared in 10 subjects with hepatic dysfunction and 8 subjects with normal hepatic function. Overall, the results suggest that patients with mild to moderate hepatic dysfunction, defined as Child-Pugh Classification Score ≤ 7, do not require an adjustment in nevirapine dosing. However, the pharmacokinetics of nevirapine in one subject with a Child-Pugh score of 8 and moderate to severe ascites suggests that patients with worsening hepatic function may be at risk of accumulating nevirapine in the systemic circulation.

Gender:

Although a slightly higher weight adjusted volume of distribution of nevirapine was found in female subjects compared to males, no significant gender differences in nevirapine plasma concentrations following single or multiple dose administrations were seen. Nevirapine pharmacokinetics in HIV-1 infected adults does not appear to change with age (range 19 - 68 years).

Nevirapine has not been specifically investigated in patients over the age of 65.

Paediatric patients:

Nevirapine clearance adjusted for body weight reaches maximum values by age 1 to 2 years and then decreases with increasing age. Nevirapine apparent clearance adjusted for body weight is approximately two-fold greater in children

younger than 8 years compared to adults. Nevirapine half-life after dosing to steady state is 25,9 ± 9,6 hours. With long-term medicine administration, the mean values for nevirapine terminal half-life changes with age as follows: 2 months to 1 year (32 hours), 1 to 4 years (21 hours), 4 to 8 years (18 hours), greater than 8 years (28 hours).

INDICATIONS:

NEVIRAPINE MYLAN 200 mg is indicated as part of combination therapy for the antiviral treatment of HIV-1 infected patients.

CONTRA-INDICATIONS:

Hypersensitivity to **NEVIRAPINE MYLAN 200 mg** or to any of the excipients in the tablets.

NEVIRAPINE MYLAN 200 mg 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 MYLAN 200 mg**.

NEVIRAPINE MYLAN 200 mg should not be used in patients with severe hepatic impairment or pre-treatment ASAT or ALAT > 5 ULN until baseline ASAT/ALAT are stabilised < 5 ULN.

NEVIRAPINE MYLAN 200 mg should not be re-administered in patients who previously had ASAT or ALAT > 5 ULN during **NEVIRAPINE MYLAN 200 mg** therapy and had recurrence of liver function abnormalities upon re-administration.

Herbal preparations containing St John's Wort *(Hypericum perforatum*) must not be used while taking **NEVIRAPINE MYLAN 200 mg** due to the risk of decreased plasma concentrations and reduced clinical effects of **NEVIRAPINE MYLAN 200 mg** (see **INTERACTIONS).**

The available pharmacokinetic data suggest that the concomitant use of rifampicin and **NEVIRAPINE MYLAN 200 mg** is not recommended (see **INTERACTIONS).**

WARNINGS:

The first 18 weeks of therapy with NEVIRAPINE MYLAN 200 mg 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 occur in the first 6 weeks of therapy. Women (3,2 risk ratio) and patients with higher CD4 counts (women with CD4 counts >250 cells/mm^3, 9,8 risk ratio; men with CD4 counts >400 cells/mm^3, 6,4 risk ratio) 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).

Lactose intolerance:

The formulation contains 464 mg lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, should not take **NEVIRAPINE MYLAN 200 mg.**

Cutaneous reactions:

Severe and life-threatening skin reactions, including fatal cases, have occurred in patients treated with **NEVIRAPINE MYLAN 200 mg** mainly during the first 6 weeks of therapy. These have included cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity reactions characterised by rash, constitutional findings and visceral involvement. Patients should be intensively monitored during the first 18 weeks of treatment. Patients should be closely

monitored if an isolated rash occurs. **NEVIRAPINE MYLAN 200 mg** 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. **NEVIRAPINE MYLAN 200 mg** must be permanently discontinued in any patient experiencing hypersensitivity reaction (characterised 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**).

NEVIRAPINE MYLAN 200 mg administration above the recommended dose might increase the frequency and seriousness of skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

Concomitant prednisone use (40 mg/day for the first 14 days of **NEVIRAPINE MYLAN 200 mg** administration) has been shown not to decrease the incidence of **NEVIRAPINE MYLAN 200 mg** -associated rash, and may be associated with an increase in incidence and severity of rash during the first 6 weeks of **NEVIRAPINE MYLAN 200 mg** therapy.

Some risk factors for developing serious cutaneous reactions have been identified; they include failure to follow the initial dosing of 200 mg daily during

the lead-in period and a long delay between the initial symptoms and medical consultation. Women appear to be at higher risk than men of developing rash.

Patients should be instructed that a major toxicity of **NEVIRAPINE MYLAN 200 mg** is rash. They should be advised to promptly notify their doctor of any rash and avoid delay between the initial symptoms and medical consultation**.** The majority of rashes associated with **NEVIRAPINE MYLAN 200 mg** 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, facial oedema, muscle or joint aches, or general malaise should discontinue medication and immediately seek medical evaluation. In these patients **NEVIRAPINE MYLAN 200 mg** must not be restarted.

If patients present with a suspected **NEVIRAPINE MYLAN 200 mg** associated rash, liver function tests should be performed. Patients with moderate to severe elevations (ASAT or ALAT > 5 ULN) should be permanently discontinued from **NEVIRAPINE MYLAN 200 mg**.

If a hypersensitivity reaction occurs, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction, **NEVIRAPINE MYLAN 200 mg** should be permanently stopped and not be re-introduced.

Hepatic reactions:

Severe or life-threatening hepatotoxicity, including fatal fulminant hepatitis (transaminase elevations, with or without hyperbilirubinaemia, prolonged partial thromboplastin time or eosinophilia) has occurred in patients treated with NEVIRAPINE MYLAN 200 mg. Serious hepatitis and hepatic failure events in NEVIRAPINE MYLAN 200 mg 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 risk ratio) and patients with higher CD4 counts (women with CD4 counts > 250 cells/mm^3, 9,8 risk ratio; men with CD4 counts > 400 cells/mm^3, 6,4 risk ratio) 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 NEVIRAPINE MYLAN 200 mg and that occurrence of symptoms suggestive of hepatitis should lead them to contact their doctor promptly.

Increased ASAT or ALAT levels ≥ 2,5 ULN and/or co-infection with hepatitis B and/or C at the start of antiretroviral therapy is associated with greater risk of severe and potentially fatal hepatic adverse reactions during antiretroviral therapy in general, including nevirapine-containing regimens.

Female gender and patients with higher CD4 counts are at increased risk of hepatic adverse events.

Women have a three fold higher risk than men for symptomatic, often rash-associated, hepatic events (5,8 % versus 2,2 %), and patients with higher CD4 counts at initiation of **NEVIRAPINE MYLAN 200 mg** therapy are at higher risk for symptomatic hepatic events with **NEVIRAPINE MYLAN 200 mg.** In a retrospective review, women with CD4 counts > 250 cells/mm^3 had a 12 fold higher risk of symptomatic hepatic adverse events compared to women with CD4 counts < 250 cells/mm^3 (11,0 % versus 0,9 %). An increased risk was observed in men with CD4 counts > 400 cells/mm^3 (6,3 % versus 1,2 % for men with CD4 counts < 400 cells/mm^3).

Patients should be informed that hepatic reactions are a major toxicity of **NEVIRAPINE MYLAN 200 mg** requiring close monitoring during the first 18 weeks. They should be informed that occurrence of symptoms suggestive of hepatitis should lead them to discontinue **NEVIRAPINE MYLAN 200 mg** and immediately seek medical evaluation, which should include liver function tests.

Liver monitoring:

All patients should have baseline liver function tests prior to treatment.

Abnormal liver function tests have been reported with **NEVIRAPINE MYLAN 200 mg**, some in the first few weeks of therapy.

Asymptomatic elevations of liver enzymes are frequently described and are not necessarily a contra-indication to use **NEVIRAPINE MYLAN 200 mg**. Asymptomatic GGT elevations are not a contra-indication to continue therapy.

Monitoring of hepatic tests should be done every two weeks during the first 2 months of treatment, at the 3rd month and then regularly thereafter. Liver test monitoring should be performed if the patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity.

If ASAT or ALAT ≥ 2,5 ULN before or during treatment, then liver tests should be monitored more frequently during regular clinic visits. **NEVIRAPINE MYLAN 200 mg** should not be administered to patients with pre-treatment ASAT or ALAT > 5 ULN until baseline ASAT/ALAT are stabilised < 5 ULN.

Medical practitioners 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 promptly if these occur.

If ASAT or ALAT increase to > 5 ULN during treatment, **NEVIRAPINE MYLAN 200 mg** should be immediately stopped.

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 MYLAN 200 mg** must be permanently stopped. **NEVIRAPINE MYLAN 200 mg** should not be re-administered to patients who have required permanent discontinuation for clinical hepatitis due to **NEVIRAPINE MYLAN 200 mg**.

Liver disease:

The safety and efficacy of **NEVIRAPINE MYLAN 200 mg** has not been established in patients with significant underlying liver disorders. **NEVIRAPINE MYLAN 200 mg** is contra-indicated in patients with severe hepatic impairment. 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 antiretroviral 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.

NEVIRAPINE MYLAN 200 mg may interact with some medicinal products; therefore, patients should be advised to report to their doctor the use of any other medications.

Pharmacokinetic results suggest caution should be exercised when **NEVIRAPINE MYLAN 200 mg** is administered to patients with moderate hepatic dysfunction and should not be administered in patients with severe hepatic dysfunction. Overall, the results suggest that patients with mild to moderate hepatic dysfunction, defined as Child-Pugh Classification Score ≤7, do not require an adjustment in **NEVIRAPINE MYLAN 200 mg** dosing. In patients with renal dysfunction, who are undergoing dialysis, pharmacokinetic results suggest that supplementing **NEVIRAPINE MYLAN 200 mg** therapy with an additional 200 mg dose of **NEVIRAPINE MYLAN 200 mg** following each dialysis treatment would help offset the effects of dialysis on **NEVIRAPINE MYLAN 200 mg** clearance. Otherwise patients with CLcr ≥30 ml/min do not require an adjustment in **NEVIRAPINE MYLAN 200 mg** dosing.

INTERACTIONS:

Interaction with other finished pharmaceutical products (FPPs) and other forms of interaction:

Nucleoside reverse transcriptase inhibitors (NRTI):

No dosage adjustments are required when **NEVIRAPINE MYLAN 200 mg** is taken in combination with zidovudine, didanosine, or zalcitabine. When the zidovudine data were pooled from two studies (n = 33) in which HIV-1 infected patients received nevirapine 400 mg/day either alone or in combination with 200 - 300 mg/day didanosine or 0,375 to 0,75 mg/day zalcitabine on a background of zidovudine therapy, nevirapine produced a non-significant decline of 13 % in zidovudine area under the curve (AUC) and a non-significant increase of 5,8 % in zidovudine C_{max}. In a subset of patients (n = 6) who were administered nevirapine 400 mg/day and didanosine on a background of zidovudine therapy, nevirapine produced a significant decline of 32 % in zidovudine AUC and a non-significant decline of 27 % in zidovudine C_{max}. Paired data suggest that zidovudine had no effect on the pharmacokinetics of nevirapine. In one crossover study, nevirapine had no effect on the steady-state pharmacokinetics of either didanosine (n = 18) or zalcitabine (n = 6).

Results from a 36 day study in HIV infected patients (n = 25) administered nevirapine, nelfinavir (750 mg three times daily) and stavudine (30-40 mg twice daily) showed no statistically significant changes in the AUC or C_{max} of stavudine. Furthermore, a population pharmacokinetic study of 90 patients assigned to receive lamivudine with nevirapine or placebo revealed no changes to lamivudine apparent clearance and volume of distribution, suggesting no induction effect of nevirapine on lamivudine clearance.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs):

Results from a clinical trial (n=14) showed that steady-state pharmacokinetic parameters of nevirapine were not affected by co-administration of efavirenz. However, plasma levels of efavirenz were significantly reduced in the presence of nevirapine. The AUC of efavirenz decreased by 22 % and the C_{min} by 36 %.

***Protease inhibitors (PIs)*:**

Nevirapine is a mild to moderate inducer of the hepatic enzyme CYP3A; therefore, it is possible that co-administration with PIs (also metabolised by CYP3A) may result in an alteration in the plasma concentration of either agent.

Saquinavir:

Results from a clinical trial (n = 31) with HIV infected patients administered nevirapine and saquinavir (hard gelatin capsules; 600 mg three times daily) indicated that their co-administration leads to a mean reduction of 24 % (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.

Another study (n = 20) evaluated once daily dosing of saquinavir soft gel capsule (sgc) with a 100 mg dose of ritonavir. All patients concomitantly received nevirapine. The study showed that the combination of saquinavir sgc and 100 mg of ritonavir had no measurable effect on the pharmacokinetic parameters of

nevirapine, compared to historical controls. The effect of nevirapine on the pharmacokinetics of saquinavir sgc in the presence of 100 mg of ritonavir, was modest and clinically insignificant.

Indinavir:

Results from a clinical trial (n = 25) with HIV infected patients administered nevirapine and indinavir (800 mg 8-hourly) indicated that their co-administration leads to a 28 % mean decrease ($p < 0,01$) in indinavir AUC and no significant change in nevirapine plasma levels. 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 8-hourly should be considered when indinavir is given with nevirapine 200 mg twice daily.; however, there are no data available to establish that the short-term or long-term antiviral activity of indinavir 1000 mg 8 hourly with nevirapine 200 mg twice daily will differ from that of indinavir 800 mg 8-hourly with nevirapine 200 mg twice daily.

Ritonavir:

Results from a clinical trial (n = 25) with HIV infected patients administered nevirapine and ritonavir (600 mg twice daily [using a gradual dose escalation regimen]) indicated that their co-administration leads to no significant change in ritonavir or nevirapine plasma levels.

Nelfinavir:

Results from a 36 day study in HIV infected patients (n = 25) administered nevirapine, nelfinavir (750 mg three times daily) and stavudine (30 - 40 mg twice daily) showed 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 with the co-administration of nevirapine with any of these PIs when used in combination.

Lopinavir/ritonavir:

In HIV positive adults, nevirapine used in combination with lopinavir/ritonavir 400/100 mg (3 capsules) twice daily has been reported to result in a decline in the lopinavir AUC of 27 % compared with historical data. 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.

Results from a pharmacokinetic study in paediatric patients were consistent with the findings in adults.

Ketoconazole:

In one study, administration of nevirapine 200 mg twice daily with ketoconazole 400 mg once daily 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 - 28 % increase in the plasma levels of nevirapine compared to historical controls. Ketoconazole and **NEVIRAPINE MYLAN 200 mg** (nevirapine) should not be given concomitantly. The effects of **NEVIRAPINE MYLAN 200 mg** on itraconazole are not known.

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 the medicinal products are given concomitantly and patients should be monitored closely. There was no clinically relevant effect of nevirapine on fluconazole.

***Oral Contraceptives*:**

As oral contraceptives should not be used as the sole method of contraception in HIV infected patients, other means of contraception (such as barrier methods) are recommended in patients being treated with **NEVIRAPINE MYLAN 200 mg**. Furthermore a pharmacokinetic interaction has been identified. Nevirapine 200 mg twice daily was co-administered with a single dose of an oral contraceptive containing ethinyl estradiol (EE) 0,035 mg and norethindrone (NET) 1,0 mg. Compared to plasma concentrations observed prior to nevirapine administration, the median AUC for 17α-EE was significantly decreased by 29 % after 28 days of

nevirapine dosing. There was a significant reduction in EE mean resident time and half-life. There was a significant reduction (18 %) in median AUC for NET, without changes in mean resident time or half-life. The magnitude of the effect suggests that the dose of the oral contraceptive should be adjusted to allow adequate treatment for indications other than contraception (e.g., endometriosis), if used with **NEVIRAPINE MYLAN 200 mg**.

***Other medicinal products metabolised by CYP3A*:**

Methadone:

Nevirapine is an inducer of CYP3A and potentially CYP2B6, with maximal induction occurring within 2 - 4 weeks of initiating multiple-dose therapy. Based on the known metabolism of methadone, nevirapine may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Narcotic withdrawal syndrome has been reported in patients treated with **NEVIRAPINE MYLAN 200 mg** and methadone concomitantly. Methadone-maintained patients beginning **NEVIRAPINE MYLAN 200 mg** therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

Other compounds that are substrates of *CYP3A and CYP2B6* may have decreased plasma concentrations when co-administered with **NEVIRAPINE MYLAN 200 mg**. Therefore, careful monitoring of the therapeutic effectiveness of P450 metabolised medicinal products is recommended when taken in combination with **NEVIRAPINE MYLAN 200 mg**.

***CYP isoenzyme inhibitors*:**

Clarithromycin:

The results of a nevirapine-clarithromycin interaction study (n = 18) resulted in a significant reduction in clarithromycin AUC (30 %) and C_{max} (- 21 %) 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 %). These results would suggest that no dose adjustment is necessary for either clarithromycin and **NEVIRAPINE MYLAN 200 mg** when the two medicinal products are co-administered. Close monitoring of hepatic abnormalities and activity against *Myobacterium avium*-intracellular complex (MAC) is nevertheless recommended.

Monitoring of steady-state nevirapine trough plasma concentrations in patients who received long-term nevirapine treatment revealed that nevirapine trough concentrations were elevated in patients who received cimetidine (+ 7 %, n = 13).

CYP isoenzyme inducers:

Rifampicin:

An open-label study (n = 14) to determine the effects of nevirapine on the steady state pharmacokinetics of 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.

The available pharmacokinetic data suggest that the concomitant use of rifampicin and **NEVIRAPINE MYLAN 200 mg** is not recommended. Therefore, these medicinal products should not be used in combination. Medical practitioners needing to treat patients co-infected with tuberculosis and using a **NEVIRAPINE MYLAN 200 mg** (nevirapine)-containing regimen may consider use of rifabutin instead (see **CONTRA-INDICATIONS**). Rifabutin and **NEVIRAPINE MYLAN 200 mg** can be administered concurrently without dose adjustments (see below). Alternatively medical practitioners may consider switching to a triple NRTI combination for a variable period of time, depending on the tuberculosis treatment regimen.

In a pharmacokinetic study the concomitant administration of nevirapine with rifabutin resulted in a non-significant 12 % (median) increase in the steady-state AUC, a non-significant 3 % decrease in C_{minss} and a significant 20 % increase in the C_{maxss}. Non-significant changes were found on 25-O-desacetyl-rifabutin (rifabutin active metabolite) AUC, C_{minss} or $C_{maxss.}$ A statistically significant increase in the apparent clearance of nevirapine (9 %) compared to historical pharmacokinetic data was reported. This study suggests that there is no clinically relevant interaction between **NEVIRAPINE MYLAN 200 mg** and rifabutin. Therefore, the two medicines can be administered concurrently without dose

adjustments provided that a careful monitoring of the adverse reactions is performed.

***Warfarin*:**

The interaction between **NEVIRAPINE MYLAN 200 mg** 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 MYLAN 200 mg**, and frequent close monitoring of anticoagulation levels is therefore warranted.

Hypericum perforatum:

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 medicine metabolism enzymes and/or transport proteins by St John's Wort. Herbal preparations containing St John's Wort should therefore 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 **CONTRA-INDICATIONS**).

Other information:

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.

PREGNANCY AND LACTATION:

Pregnancy:

There are no adequate and well-controlled studies in pregnant women. Therefore, **NEVIRAPINE MYLAN 200 mg** should not be used during pregnancy.

Lactation:

Results from a pharmacokinetic study have shown that nevirapine readily crosses the placenta and is found in breast milk.

It is recommended that HIV-infected mothers do not breast-feed their infants to avoid risking postnatal transmission of HIV and that mothers should discontinue breast-feeding if they are receiving **NEVIRAPINE MYLAN 200 mg**.

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

Additionally, when oral contraceptives are used for hormonal regulation during administration of **NEVIRAPINE MYLAN 200 mg** the therapeutic effect should be monitored.

DOSAGE AND DIRECTIONS FOR USE:

NEVIRAPINE MYLAN 200 mg should be administered by medical practitioners who are experienced in the treatment of HIV infection.

Patients over the age of 16 years:

The recommended dose of **NEVIRAPINE MYLAN 200 mg** 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 to which the patient has not been previously exposed. Resistant virus emerges rapidly and uniformly when **NEVIRAPINE MYLAN 200 mg** is administered as monotherapy; therefore **NEVIRAPINE MYLAN 200 mg** should always be administered in combination therapy. For concomitantly administered antiretroviral therapy, the recommended dosage and monitoring should be followed.

Paediatric (adolescent) patients:

NEVIRAPINE MYLAN 200 mg tablets, following the dosing schedule described above, are suitable for larger children, particularly adolescents, below the age of 16 who weigh 50 kg or more. An oral suspension dosage form, which can be

dosed according to body weight, is available for children in this age group weighing less than 50 kg.

Dose management considerations:

Clinical chemistry tests, which include liver function tests, should be performed prior to initiating **NEVIRAPINE MYLAN 200 mg** therapy and at appropriate intervals during therapy.

Patients experiencing rash during the 14-day lead-in period of 200 mg/day should not have their **NEVIRAPINE MYLAN 200 mg** dose increased until the rash has resolved. The isolated rash should be closely monitored.

Patients who interrupt **NEVIRAPINE MYLAN 200 mg** dosing for more than 7 days should restart the recommended lead-indosing, using one 200 mg tablet daily for the first 14 days followed by one 200 mg tablet twice daily.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

The most frequently reported adverse events related to **NEVIRAPINE MYLAN 200 mg** therapy, are rash, nausea, fatigue, fever, headache, vomiting, diarrhoea, abdominal pain and myalgia.

The post marketing experience has shown that the most serious adverse reactions are Stevens-Johnson syndrome and toxic epidermal necrolysis and

serious hepatitis/hepatic failure and hypersensitivity reactions, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction. The first 18 weeks of treatment is a critical period which requires close monitoring.

The following adverse events which may be causally related to the administration of **NEVIRAPINE MYLAN 200 mg** have been reported.

Blood and lymphatic system disorders:

Less frequent: Granulocytopenia, anaemia

Immune system disorders:

Frequent: Allergic reactions

Less frequent: Hypersensitivity (syndrome), anaphylaxis, angio-oedema, immune reconstitution syndrome

Metabolism and nutrition disorders:

Less frequent: Lipodystrophy and other metabolic disorders

Nervous system disorders:

Frequent: Headache

Gastrointestinal disorders:

Frequent: Nausea

Less frequent: Vomiting, abdominal pain, diarrhoea

Hepato-biliary disorders:

Frequent: Hepatitis, abnormal liver function tests

Less frequent: Jaundice, liver failure / fulminant hepatitis

Skin and subcutaneous tissue disorders:

Frequent: Rash

Less frequent: Stevens-Johnson syndrome, urticaria, toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Myalgia, arthralgia

General disorders and administration site conditions:

Less frequent: 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, characterised 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**).

Special Precautions:

Fat redistribution:

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

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients including the loss of peripheral

and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

The following events have also been reported when **NEVIRAPINE MYLAN 200 mg** has been used in combination with other anti-retroviral agents: pancreatitis, peripheral neuropathy and thrombocytopaenia. These events are commonly associated with other antiretroviral agents and may be expected to occur when **NEVIRAPINE MYLAN 200 mg** is used in combination with other agents; however it is unlikely that these events are due to **NEVIRAPINE MYLAN 200 mg** treatment. Hepatic-renal failure syndromes have been rarely reported.

Immune reactivation syndrome:

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), 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 carinii

(jerovici) pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Combination therapy with **NEVIRAPINE MYLAN 200 mg** is not a curative treatment of patients infected with HIV-1; patients may continue to experience illnesses associated with advanced HIV-1 infection, including opportunistic infections.

Skin and subcutaneous tissues:

The most common clinical toxicity of **NEVIRAPINE MYLAN 200 mg** is 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. Rashes occur alone or in the context of hypersensitivity reactions, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lympadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction.

Severe and life-threatening skin reactions have occurred in patients treated with **NEVIRAPINE MYLAN 200 mg**, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Fatal cases of SJS, TEN and hypersensitivity

reactions have been reported. The majority of severe rashes occurred within the first 6 weeks of treatment and some required hospitalisation.

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

Group I: Erythema, pruritus

Group II: 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) (SGOT), alanine aminotransferase (ALT) (SGPT), alkaline phosphatase

and which are possibly related to the medicine reaction.

- Fever, defined as > 39 °C possibly related to medicine 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 generalised 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 visualisation 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 of 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 °C, 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 Groups I, IIA and IIB:**

   NEVIRAPINE MYLAN 200 mg may be continued for **Groups I, IIA and IIB**. Manage pruritus and minor accompanying symptoms with antihistamines, antipyretics and/or nonsteroidal anti-inflammatory medications.

   If **NEVIRAPINE MYLAN 200 mg** 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 **NEVIRAPINE MYLAN 200 mg** 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 **NEVIRAPINE MYLAN 200 mg** dose must not be escalated, and if **NEVIRAPINE MYLAN 200 mg** treatment is interrupted, it must not be re-introduced.

2. **Cutaneous eruption Groups III and IV:**

   NEVIRAPINE MYLAN 200 mg must be permanently discontinued. No rechallenge 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 rechallenge 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 ALAT, ASAT, 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 hepatoxicity, including fatal fulminant hepatitis) have been reported in patients treated with **NEVIRAPINE MYLAN 200 mg**.

The best predictor of a serious hepatic event is elevated baseline liver function tests. The first 18 weeks of treatment is a critical period which requires close monitoring.

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 zidovudine or didanosine, or zidovudine + didanosine in two studies. 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 Stevens-Johnson syndrome or Stevens-Johnson/toxic epidermal necrolysis transition syndrome. Both patients recovered after nevirapine treatment was discontinued.

The long-term effects of **NEVIRAPINE MYLAN 200 mg** are unknown at this time. Combination therapy with **NEVIRAPINE MYLAN 200 mg** has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or contaminated blood.

Effects on ability to drive and use machines:

No studies on the effects on the ability to drive and use machines have been performed.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no known antidote for **NEVIRAPINE MYLAN 200 mg** overdosage. Cases of **NEVIRAPINE MYLAN 200 mg** overdose at doses ranging from 800 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.

Treatment is symptomatic and supportive.

IDENTIFICATION:

White to off-white, biconvex uncoated tablet, debossed with “M107” on one side and scored on both sides.

PRESENTATION:

Blister pack of 10 tablets comprises of clear transparent PVC film with backing of aluminium foil coated with heat seal lacquer.

60 **NEVIRAPINE MYLAN 200 mg** tablets packed in a white HDPE bottle with a white opaque polypropylene (PP) screw closure with induction sealing liner and with absorbent cotton.

STORAGE INSTRUCTIONS:

Store at or below 30 °C in the original container protected from moisture. Do not use if seal over bottle opening is broken or missing. Do not remove blisters from the carton until required for use. Keep the container tightly closed.

KEEP OUT OF REACH AND SIGHT OF CHILDREN.

REGISTRATION NUMBER:

NEVIRAPINE MYLAN 200 mg: 46/20.2.8/0005

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

Viatris Healthcare (Pty) Ltd

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