Module 1.3.1.1: PACKAGE INSERT FOR

CIPLA NEVIRAPINE (Tablets)

AND

CIPLA NEVIRAPINE ORAL SUSPENSION (Suspension)

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

CIPLA NEVIRAPINE (Tablets)

CIPLA NEVIRAPINE ORAL SUSPENSION (Suspension)

COMPOSITION:

CIPLA NEVIRAPINE (Tablets): Each uncoated tablet contains 200 mg nevirapine.

Inactive ingredients are lactose monohydrate, magnesium stearate, corn starch, microcrystalline cellulose and sodium starch glycollate.

CIPLA NEVIRAPINE (Tablets) contains sugar: Each tablet contains 164,00 mg lactose monohydrate.

CIPLA NEVIRAPINE ORAL SUSPENSION: Each 5 mℓ contains 50 mg nevirapine (as hemihydrate).

Preservatives: Methyl paraben 0,2 % *m/v*

Propyl paraben 0,02 % *m/v*

Inactive ingredients are microcrystalline cellulose, polysorbate 80, saccharin sodium, simethicone and sorbitol.

CIPLA NEVIRAPINE ORAL SUSPENSION contains 35 mg sorbitol per 1 mℓ.

WARNING:

THE FIRST 18 WEEKS OF THERAPY WITH CIPLA NEVIRAPINE 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. However, the risk of any hepatic event continues past this period and monitoring should continue at frequent intervals.

Women (3,2 fold) and patients with higher CD4+ counts (women with CD4+ > 250, 9,8 fold; men with CD4+ > 400, 6,4 fold) at the initiation of CIPLA NEVIRAPINE treatment and patients with detectable plasma HIV-1 RNA, i.e. a concentration ≥ 50 copies/mℓ, at the initiation of treatment are at increased risk of hepatic adverse events.

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

In addition, the dosage, especially the 14 days lead-in period, must be strictly adhered to (see "DOSAGE AND DIRECTIONS FOR USE").

RESISTANT VIRUS EMERGES RAPIDLY AND UNIFORMLY WHEN CIPLA NEVIRAPINE IS ADMINISTERED AS MONOTHERAPY. THEREFORE, FOR CHRONIC TREATMENT OF HIV-1 INFECTION, CIPLA NEVIRAPINE 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:

Pharmacodynamic properties:

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

Resistance:

HIV isolates with significantly reduced susceptibility (100 – 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 NNRTIs *in vitro*, have been reported. Cross-resistance to delavirdine and efavirenz is expected after virologic failure with nevirapine. Cross-resistance between nevirapine and either HIV protease inhibitors, HIV integrase inhibitors or HIV entry inhibitors is unlikely because the enzyme targets involved are different. Similarly the potential for cross-resistance between nevirapine and NRTIs is low because the molecules have different binding sites on the reverse transcriptase.

Nevirapine must not be used as a single medicine to treat HIV or added on as a sole medicine to a failing regimen. As with all other non-nucleoside reverse transcriptase inhibitors, resistant virus emerges rapidly when nevirapine is administered as monotherapy. The choice of new antiretroviral medicines to be used in combination with nevirapine should take into consideration the potential for cross-resistance.

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

Pharmacokinetic properties:

Adults:

Absorption:

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

Effect of food and antacids:

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 highly lipophilic and is essentially non-ionised at physiologic pH. Following intravenous administration to healthy adults, the apparent volume of distribution at steady state (V_{dss}) of nevirapine was 1,21 ± 0,09 ℓ/kg, suggesting that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is found in breast milk. Nevirapine is about 60 % bound to plasma proteins in the plasma concentration range of 1 – 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.

Biotransformation and elimination:

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 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 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 – 30 hours following multiple dosing with 200 - 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.

Special populations:

Renal dysfunction:

The single-dose pharmacokinetics of nevirapine has been compared in patients 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 haemodialysis, and patients with normal renal function (CLcr > 80 mℓ/min). Renal impairment (mild, moderate and severe) resulted in no significant change in the pharmacokinetics of nevirapine. There is no information available on pharmacokinetics in patients with end-stage renal impairment who are not haemodialysed. However, patients with ESRD requiring dialysis exhibited a 43,5 % reduction in 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 haemodialysis treatment would help offset the effects of haemodialysis on nevirapine clearance. Patients with CLcr ≥ 20 mℓ/min do not require an adjustment in nevirapine dosing.

Hepatic dysfunction:

In patients with mild, moderate, or severe liver fibrosis receiving antiretroviral therapy containing nevirapine 200 mg twice daily, the multiple dose pharmacokinetic disposition of nevirapine and the five oxidative metabolites were not altered.

However, approximately 15 % of patients with hepatic fibrosis had nevirapine trough concentrations above 9 000 ng/mℓ (2-fold the usual mean trough). Patients with hepatic impairment should be monitored carefully for evidence of medicine induced toxicity.

In a single dose study, a significant increase in the AUC of nevirapine was observed in a Child-Pugh B patient with ascites, suggesting that patients with worsening hepatic function and ascites may be at risk of accumulating nevirapine in the

systemic circulation. Because nevirapine induces its own metabolism with multiple dosing, this single dose study may not reflect the impact of hepatic impairment on multiple dose pharmacokinetics (see section **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Gender:

There are no significant gender differences in nevirapine 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.

Elderly patients:

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

Paediatric patients:

Nevirapine is metabolised more rapidly in paediatric patients than in adults.

In patients aged 3 months to 16 years, clearance of nevirapine increases with increasing age in a manner consistent with increasing body surface area. Dosing of nevirapine at 150 mg/m^2 twice daily (after a two week lead in at 150 mg/m^2 daily) produced geometric mean or mean trough nevirapine concentrations between 4 – 6 µg/mℓ (as targeted from adult data).

The plasma nevirapine concentrations observed in paediatric patients less than 3 months of age were within the range observed in adults and the remainder of the paediatric population, but were more variable between patients, particularly in the second month of age.

INDICATIONS:

For treatment of HIV-1 infection:

CIPLA NEVIRAPINE is indicated for use in combination with other antiretroviral medicines for the treatment of HIV-1 infection. Resistant virus emerges rapidly and uniformly when **CIPLA NEVIRAPINE** is administered as monotherapy. Therefore, **CIPLA NEVIRAPINE** should always be administered in combination with at least two additional antiretroviral medicines.

To reduce the risk of intrapartum transmission of HIV-1 infection from mother to child in HIV-infected pregnant women who are not taking antiretroviral therapy at the time of labour:

CIPLA NEVIRAPINE is indicated as a single oral dose of 200 mg to the mother during labour preferably more than 2 hours before delivery and a single oral dose of 2 mg/kg to the infant within 48 to 72 hours after birth or before discharge, whichever is earlier, in combination with zidovudine.

CIPLA NEVIRAPINE should only be prescribed for the reduction in risk of intrapartum transmission of HIV-1 from mother to child in patients who have been tested for HIV and appropriately counselled.

Monotherapy with **CIPLA NEVIRAPINE** has been associated with the development of NNRTI resistance. In women and infants previously treated with single-dose **CIPLA NEVIRAPINE** for prevention of mother to child transmission of HIV-1, the efficacy of **CIPLA NEVIRAPINE** as part of combination therapy which the women or infants receive for their own health may be reduced.

Where other antiretroviral medicines are accessible, the single dose **CIPLA NEVIRAPINE** regimen should be combined with additional effective antiretroviral medicines (as recommended in international recognised guidelines).

CONTRAINDICATIONS:

CIPLA NEVIRAPINE is contraindicated in patients with hypersensitivity to nevirapine or any of the excipients of **CIPLA NEVIRAPINE** (see **"COMPOSITION"**).

CIPLA NEVIRAPINE is contraindicated in severe hepatic dysfunction, Child-Pugh class C, and in end-stage renal failure.

CIPLA NEVIRAPINE should not be administered to patients with pre-treatment or during treatment values of aspartate transaminase (AST) or alanine aminotransferase (ALT) > 5 X Upper Level of Normality (ULN) until baseline AST/ALT are stabilised < 5 ULN.

CIPLA NEVIRAPINE 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 **CIPLA NEVIRAPINE**.

CIPLA NEVIRAPINE should not be re-administered to patients who previously had AST or ALT > 5 x Upper Limit of Normal (ULN) during **CIPLA NEVIRAPINE** therapy or had rapid recurrence of liver function abnormalities upon re-administration of **CIPLA NEVIRAPINE** (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

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

Pregnancy and lactation: The safety of **CIPLA NEVIRAPINE** in pregnant or lactating women has not been established.

When used for the treatment of HIV-1 infection, adequate contraceptive methods should be used in women.

WARNINGS AND SPECIAL PRECAUTIONS:

CIPLA NEVIRAPINE should only be used with at least two other antiretroviral medicines.

CIPLA NEVIRAPINE should not be used as the sole active antiretroviral, as monotherapy with any antiretroviral has shown to result in viral resistance.

The first 18 weeks of therapy with CIPLA NEVIRAPINE is a critical period, 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. However, the risk of any hepatic event continues past this period and monitoring should continue at frequent intervals.

In women and infants previously treated with single-dose **CIPLA NEVIRAPINE** for prevention of mother to child transmission of HIV-1, the efficacy of **CIPLA NEVIRAPINE** as part of combination therapy which the women or infants receive for their own health may be reduced.

Skin reactions:

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

Nevirapine-attributable rash occurred in 12,5 % of patients in combination regimens in controlled studies. Severe or life-threatening skin reactions occurred with a frequency of approximately 2 %.

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.

CIPLA NEVIRAPINE must be permanently discontinued in any patient experiencing severe rash or a rash accompanied by constitutional symptoms (such as fever, blistering, oral lesions, conjunctivitis, facial oedema, muscle or joint aches or general malaise), including Stevens-Johnson syndrome or toxic epidermal necrolysis. CIPLA NEVIRAPINE must be permanently discontinued in any patient experiencing hypersensitivity syndrome 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").

Patients should be instructed that the major toxicity of CIPLA NEVIRAPINE 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 **CIPLA NEVIRAPINE** occur within the first 6 weeks of

therapy; therefore, patients should be monitored carefully for the appearance of any rash during this period.

Dose escalation should not occur if any rash occurs during the lead-in dosing period, until the rash has resolved (see **"DOSAGE AND DIRECTIONS FOR USE"**). The 200 mg once daily dosing regimen should not be continued beyond 28 days at which point an alternative regimen should be sought due to the possible risk of underexposure and resistance. Careful monitoring of paediatric patients is especially warranted, particularly in the first 18 weeks of treatment, since these patients may be less likely than adults to notice, or report, skin reactions.

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

Rhabdomyolysis has been observed in patients experiencing skin and/or liver reactions associated with **CIPLA NEVIRAPINE** use.

Concomitant prednisone use (40 mg/day for the first 14 days of **CIPLA 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 **CIPLA NEVIRAPINE** therapy.

Risk factors for developing serious cutaneous reactions include failure to follow the initial dosing of 200 mg once daily (4 mg/kg or 150 mg/m^2 once daily for paediatric

patients) 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.

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*: AST, 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 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 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 Ill 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:

CIPLA NEVIRAPINE 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 **CIPLA NEVIRAPINE** is interrupted during a **Group I or IIA** reaction, it may be reintroduced once the cutaneous eruptions have cleared. If **Group I or IIA** cutaneous eruptions occur during the **CIPLA NEVIRAPINE** 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 **CIPLA NEVIRAPINE** dose must not be escalated and if **CIPLA NEVIRAPINE** treatment is interrupted, it must not be reintroduced.

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

   CIPLA NEVIRAPINE 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.**

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 consult a medical practitioner. In these patients CIPLA NEVIRAPINE or any other nevirapine-containing formulation must not be restarted.

If patients present with a suspected CIPLA NEVIRAPINE-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 CIPLA NEVIRAPINE or any other nevirapine-containing formulation.

In patients with a hypersensitivity syndrome, characterised by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia,

granulocytopenia and renal dysfunction, CIPLA NEVIRAPINE should be permanently stopped and nevirapine should not be reintroduced.

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 CIPLA 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 is a critical period, which require close monitoring. The risk of hepatic events is greatest in the first 6 weeks of therapy.

However, the risk continues past this period and monitoring should continue at frequent intervals throughout treatment.

Rhabdomyolysis has been observed in patients experiencing skin and/or liver reactions associated with **CIPLA NEVIRAPINE** use.

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

Serious hepatotoxicity, including liver failure requiring transplantation, has been reported in HIV-uninfected individuals receiving multiple doses of **CIPLA NEVIRAPINE** in the setting of post exposure prophylaxis (PEP), an unapproved indication and therefore, is strongly discouraged.

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 (3,2 – 4,2 fold) risk of hepatic adverse events during antiretroviral therapy with **CIPLA NEVIRAPINE-**containing regimens.

Increased AST or ALT levels and/or seropositivity for hepatitis B and/or C was associated with a greater risk of hepatic adverse events. The risk of hepatic events at 1 year of **CIPLA NEVIRAPINE** treatment was less than 2 % among patients who were hepatitis B and/or C negative.

Patients with pre-treatment AST or 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.

Women (3,2 fold) and patients with higher CD4+ counts (women with CD4+ > 250, 9,8 fold; men with CD4+ > 400, 6,4 fold) at the initiation of **CIPLA NEVIRAPINE** treatment are at increased risk of hepatic adverse events.

Women have a three-fold higher risk than men for rash-associated hepatic events (5,8 % vs. 2,2 %). Patients with higher CD4+ counts may also be at a higher risk for rash-associated hepatic events with **CIPLA NEVIRAPINE**. In a retrospective review,

women with CD4+ counts > 250 cells/mm^3 had a 12 fold higher risk of rash-associated hepatic adverse events compared to women with CD4+ counts < 250 cells/mm^3 (11,0 % 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 (6,3 % vs. 1,2 %).

This increased risk for toxicity based on CD4+ count threshold has not been detected in patients with undetectable (i.e. < 50 copies/mℓ) plasma viral load.

Patients should be informed that hepatic reactions are a major toxicity of **CIPLA NEVIRAPINE** 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 discontinue **CIPLA NEVIRAPINE** and contact their doctor promptly.

Liver disease:

While nevirapine is extensively metabolised by the liver and nevirapine metabolites are extensively eliminated by the kidney, the pharmacokinetic results suggest caution should be exercised when **CIPLA NEVIRAPINE** is administered to patients with moderate hepatic dysfunction (Child-Pugh Class B). **CIPLA NEVIRAPINE** should not be administered to patients with severe hepatic dysfunction (AST/ALT > 5 X ULN), or Child-Pugh Class C (see **"CONTRAINDICATIONS"**).

CIPLA NEVIRAPINE 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.

In patients with mild liver function test 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, granulocytopenia and renal dysfunction, nevirapine should be permanently discontinued. **CIPLA NEVIRAPINE** should not be restarted in these situations.

Liver function monitoring:

All patients should have baseline liver function tests prior to **CIPLA NEVIRAPINE** treatment (see **"CONTRAINDICATIONS"**).

The most frequently observed laboratory test abnormalities are elevations in liver function tests (LFTs), including AST, ALT, γ-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 **CIPLA NEVIRAPINE**. The best predictor of a serious hepatic event was elevated baseline liver function tests.

Abnormal liver function has been reported with **CIPLA 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 **CIPLA 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. Clinical and laboratory monitoring should continue throughout **CIPLA NEVIRAPINE** treatment. Doctors and patients should be vigilant for prodromal signs or findings of hepatitis, such as anorexia, nausea, jaundice, bilirubinuria, acholic stools, hepatomegaly or liver tenderness. Patients should be instructed to seek medical attention if these occur.

If AST or ALT 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.
CIPLA NEVIRAPINE should not be administered or re-administered to patients with pre-treatment ASAT or ALAT > 5 X ULN until baseline ASAT/ALAT are stabilised at values < 5 X ULN.

If AST or ALT increase to > 5 X Upper Limit of Normality (ULN) during treatment, CIPLA NEVIRAPINE should be immediately stopped.

If AST or ALT return to baseline values, and if the patient had no clinical signs or symptoms of hepatitis, rash, constitutional symptoms or other findings suggestive of organ dysfunction, it may be possible to reintroduce CIPLA NEVIRAPINE, 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, CIPLA NEVIRAPINE should be permanently discontinued.

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

Warning on concomitant use with other medicines (for a detailed description see "INTERACTIONS"):

CIPLA NEVIRAPINE may interact with some medicines; therefore, patients should be advised to report to their medical practitioner the use of any other medicines.

CIPLA NEVIRAPINE can alter plasma exposure of other medicines, and other medicines can alter plasma exposure of **CIPLA NEVIRAPINE**.

Combining the following compounds with **CIPLA NEVIRAPINE** is not recommended: Efavirenz, rifampicin, ketoconazole, delavirdine, etravirine, rilpivirine, elvitegravir (in combination with cobicistat), atazanavir (in combination with ritonavir), boceprevir; if

not co-administered with low dose ritonavir: fosamprenavir, saquinavir, atazanavir (see **"INTERACTIONS"**).

Granulocytopenia is frequently associated with zidovudine. Therefore, patients who receive **CIPLA NEVIRAPINE** and zidovudine concomitantly and especially paediatric patients and patients who receive higher zidovudine doses or patients with poor bone marrow reserve, in particular those with advanced HIV disease, have an increased risk of granulocytopenia. In such patients haematological parameters should be carefully monitored.

The following events have also been reported when **CIPLA NEVIRAPINE** has been used in combination with other antiretroviral medicines: anaemia, pancreatitis, lipodystrophy, peripheral neuropathy and thrombocytopenia. These events are commonly associated with other antiretroviral medicines and may be expected to occur when **CIPLA NEVIRAPINE** is used in combination with other medicines. Hepatic-renal failure syndromes have been reported rarely.

Oral contraceptives and other hormonal methods of birth control, other than depo-medroxyprogesterone acetate (DMPA), should not be used as the sole method of contraception in women taking **CIPLA NEVIRAPINE**, since **CIPLA NEVIRAPINE** may lower the plasma levels of these medicines (refer to **"INTERACTIONS"**). For this reason, and to reduce the risk of HIV transmission, barrier contraception (e.g. condoms) is recommended. When postmenopausal hormone therapy is used during administration of **CIPLA NEVIRAPINE**, its therapeutic effect should be monitored.

General:

When administering **CIPLA NEVIRAPINE** as part of an antiretroviral treatment regimen, the complete product information for each therapeutic component should be consulted before initiation of treatment. **CIPLA NEVIRAPINE** has only been evaluated for safety in combination with zidovudine and didanosine in children.

In patients with renal dysfunction who are undergoing haemodialysis, pharmacokinetic results suggest that supplementing **CIPLA NEVIRAPINE** therapy with an additional 200 mg dose (in adults) of **CIPLA NEVIRAPINE** following each haemodialysis treatment would help offset the effects of haemodialysis on nevirapine clearance. Otherwise patients with Cr_{Cl} ≥ 20 mℓ/min do not require an adjustment in **CIPLA NEVIRAPINE** dosing (see **"Pharmacokinetic properties: Renal dysfunction"**). Safety in patients with end-stage renal impairment who are not haemodialysed has not been demonstrated (See **“CONTRAINDICATIONS”**).

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.

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

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 antiretroviral 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 should be informed that **CIPLA NEVIRAPINE** is not a cure for HIV-1 infection. Patients receiving **CIPLA NEVIRAPINE** and other antiretroviral medicines may continue to develop opportunistic infections and other complications of HIV infection. Treatment with **CIPLA NEVIRAPINE** has not been shown to reduce the incidence or frequency of such illnesses, and patients should therefore remain under close supervision by medical practitioners experienced in the treatment of patients with HIV-associated diseases. 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 **CIPLA NEVIRAPINE**, does not prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be employed.

The long-term effects of **CIPLA NEVIRAPINE** are unknown at this time.

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 **CIPLA NEVIRAPINE** administration, it is advisable to refrain from such activities.

Lactose:

CIPLA NEVIRAPINE (Tablets) contains sugar (lactose). **CIPLA NEVIRAPINE** (Tablets) may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **CIPLA NEVIRAPINE** (Tablets).

Sorbitol:

CIPLA NEVIRAPINE ORAL SUSPENSION contains 1,4 g of sorbitol per maximum recommended daily dose and may have a laxative effect. Patients with the rare hereditary condition of sorbitol intolerance should not take **CIPLA NEVIRAPINE ORAL SUSPENSION**.

Methyl paraben and propyl paraben:

CIPLA NEVIRAPINE ORAL SUSPENSION contains methyl paraben and propyl paraben, which may cause allergic reaction (possibly delayed).

INTERACTIONS:

CIPLA 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 metabolised by

CYP3A or CYP2B (see **"Pharmacokinetic properties"**). Thus, if a patient has been stabilised on a dosage regimen for a medicine metabolised by CYP3A or CYP2B and begins treatment with **CIPLA NEVIRAPINE**, dose adjustments may be necessary.

The absorption of **CIPLA NEVIRAPINE** is not affected by food, antacids or medicines that are formulated with an alkaline buffering agent.

Anti-infectives:

Antiretrovirals:

NRTIs:

No dosage adjustments are required when **CIPLA NEVIRAPINE** is taken in combination with zidovudine (ZDV), didanosine (ddI), zalcitabine (ddC) and stavudine, emtricitabine, abacavir, lamivudine, and tenofovir.

Granulocytopenia is frequently associated with zidovudine. Therefore, patients who receive **CIPLA NEVIRAPINE** and zidovudine concomitantly, and especially paediatric patients and patients who receive higher zidovudine doses or patients with poor bone marrow reserve, in particular those with advanced HIV disease, have an increased risk of granulocytopenia. In such patients haematological parameters should be carefully monitored.

Decreased blood phosphorus and increased blood pressure were observed in studies with co-administration of tenofovir/emtricitabine.

NNRTIs:

Efavirenz: It is not recommended to co-administer efavirenz (600 mg once daily) and **CIPLA NEVIRAPINE**, because of additive toxicity and no additional benefit in terms of improved efficacy over either NNRTI alone.

The concomitant administration of **CIPLA NEVIRAPINE** with NNRTIs (delavirdine, etravirine, rilpivirine) is not recommended.

Concomitant use of etravirine with **CIPLA NEVIRAPINE** may cause a significant decrease in the plasma concentrations of etravirine and loss of therapeutic effect of etravirine.

Protease inhibitors (PIs):

When combined with protease inhibitors and nevirapine was given 200 mg once daily for two weeks followed by 200 mg twice daily for 28 days as described below:

Atazanavir/ritonavir: It is not recommended to co-administer atazanavir/ritonavir (300/100 mg daily or 400/100 mg daily) and **CIPLA NEVIRAPINE** (see **"WARNINGS AND SPECIAL PRECAUTIONS"**). If given in combination with **CIPLA NEVIRAPINE**, atazanavir should be dosed with 400 mg, co-administered with low dose ritonavir 100 mg.

Darunavir/ritonavir: The combination of darunavir/ritonavir (400/100 mg twice daily) and **CIPLA NEVIRAPINE** can be co-administered without dose adjustments.

Fosamprenavir: It is not recommended to co-administer fosamprenavir (1 400 mg twice daily) and **CIPLA NEVIRAPINE** if fosamprenavir is not co-administered with ritonavir.

Fosamprenavir/ritonavir: Fosamprenavir/ritonavir (700/100 mg twice daily) and **CIPLA NEVIRAPINE** can be co-administered without dose adjustments.

Lopinavir/ritonavir: An increase in the dose of lopinavir/ritonavir (400/100 mg twice daily) to 533/133 mg (4 capsules) twice daily with food is recommended in combination with **CIPLA NEVIRAPINE**. Dose adjustment of **CIPLA NEVIRAPINE** is not required when co-administered with lopinavir.

For children, increase of the dose of lopinavir/ritonavir (oral solution) to 300/75 mg/m^2 twice daily with food should be considered when used in combination with **CIPLA NEVIRAPINE**, particularly for patients in whom reduced susceptibility to lopinavir/ritonavir is suspected.

Saquinavir: Co-administration of **CIPLA NEVIRAPINE** and saquinavir (600 mg three times per day) leads to a 24 % mean reduction 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. **CIPLA NEVIRAPINE** should not be given with saquinavir if not co-administered with ritonavir.

Saquinavir/ritonavir: Saquinavir/ritonavir and **CIPLA NEVIRAPINE** can be co-administered without dose adjustments.

Ritonavir: No dosage adjustments are required when **CIPLA NEVIRAPINE** is taken in combination with ritonavir (600 mg twice daily).

Indinavir: CIPLA NEVIRAPINE and indinavir (800 mg three times per day) co-administration leads to a 28 % mean decrease in indinavir AUC and no significant change in nevirapine plasma levels.

A dose increase of indinavir to 1 000 mg three times per day (q8h) should be considered when indinavir is given with **CIPLA NEVIRAPINE** 200 mg twice daily; 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 **CIPLA NEVIRAPINE** 200 mg twice daily will differ from that of indinavir 800 mg q8h with **CIPLA NEVIRAPINE** 200 mg twice daily.

Today indinavir is generally co-administered with RTV. There are limited clinical data on the interaction of **CIPLA NEVIRAPINE** with indinavir/ritonavir.

Nelfinavir: Nevirapine, and nelfinavir (750 mg three times per day) given in combination indicated no statistically significant changes in nelfinavir pharmacokinetic parameters. Compared to historical controls **CIPLA NEVIRAPINE** levels appeared to be unchanged. No dosage adjustments are required when **CIPLA NEVIRAPINE** is taken in combination with nelfinavir.

Tipranavir/ritonavir: No dosage adjustments are required when **CIPLA NEVIRAPINE** is taken in combination with tipranavir co-administered with ritonavir (500/200 mg twice daily).

Entry Inhibitors:

Enfuvirtide: Enfuvirtide and **CIPLA NEVIRAPINE** can be co-administered without dose adjustments.

Maraviroc: Maraviroc and **CIPLA NEVIRAPINE** can be co-administered without dose adjustments.

Integrase inhibitors:

Elvitegravir/cobicistat: Interaction has not been studied. Cobicistat, a cytochrome P450 3A inhibitor significantly inhibits hepatic enzymes, as well as other metabolic pathways. Therefore co-administration would likely result in altered plasma levels of cobicistat and nevirapine. Co-administration of **CIPLA NEVIRAPINE** with elvitegravir in combination with cobicistat is not recommended.

Raltegravir: Raltegravir (400 mg twice daily) and **CIPLA NEVIRAPINE** can be co-administered without dose adjustments.

Antifungals:

Ketoconazole: Ketoconazole and **CIPLA NEVIRAPINE** should not be given concomitantly. Administration of **CIPLA NEVIRAPINE** 200 mg twice daily 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}). Ketoconazole administration resulted in a 15 – 28 % increase in the plasma levels of nevirapine compared to historical controls.

Itraconazole: A dose increase for itraconazole (200 mg daily) should be considered when these two medicines are administered concomitantly.

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 **CIPLA NEVIRAPINE** and fluconazole are given concomitantly and patients should be monitored closely.

Antibiotics:

Clarithromycin: Clarithromycin (500 mg twice daily) exposure is significantly decreased, 14-OH metabolite exposure increased. Because the clarithromycin active metabolite has reduced activity against *Mycobacterium avium-intracellulare complex* overall activity against the pathogen may be altered. Alternatives to clarithromycin, such as azithromycin should be considered. Close monitoring for hepatic abnormalities is recommended.

Rifampicin: 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.

It is not recommended to co-administer rifampicin (600 mg daily) and **CIPLA NEVIRAPINE**. At present there are insufficient data to assess what dosage adjustments are required when nevirapine and rifampicin are co-administered.

Medical practitioners may consider co-administration of rifabutin instead, in patients co-infected with tuberculosis that are using a **CIPLA NEVIRAPINE**-containing regimen.

Rifabutin: Rifabutin (150 or 300 mg daily) and **CIPLA NEVIRAPINE** can be co-administered without dose adjustments. 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. Therefore, caution should be used in concomitant administration.

Antivirals for chronic hepatitis B and C:

CIPLA NEVIRAPINE may be co-administered with adefovir, entecavir, interferons (pegylated interferons alfa 2a and alfa 2b), ribavirin, or telbivudine without dose adjustments.

Boceprevir: It is not recommended to co-administer boceprevir and **CIPLA NEVIRAPINE**.

Telaprevir: Caution should be exercised when co-administering telaprevir with nevirapine. If co-administered with **CIPLA NEVIRAPINE**, an adjustment in the telaprevir dose should be considered.

Anticoagulants:

Warfarin: The in vitro interaction between nevirapine and the antithrombotic medicine warfarin is complex. As a result, when giving these medicines

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.

Herbal products:

St. John's wort: Concomitant use of **CIPLA NEVIRAPINE** and St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products is contraindicated as St. John's wort is expected to decrease nevirapine concentrations and may result in suboptimal levels and lead to loss of virologic response and possible resistance to nevirapine 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 %.

Herbal preparations containing St. John's Wort and **CIPLA NEVIRAPINE** must not be co-administered (see **"CONTRAINDICATIONS"**). If a 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 **CIPLA NEVIRAPINE** may need adjusting. The inducing effect may persist for at least 2 weeks after cessation of treatment with St. John's Wort.

Antacids:

Cimetidine: Nevirapine trough concentrations were elevated in patients who received cimetidine (+ 21 %). Cimetidine and **CIPLA NEVIRAPINE** can be co-administered without dose adjustments.

Contraceptives:

Depo-medroxyprogesterone acetate (DMPA): CIPLA NEVIRAPINE co-administration did not alter the ovulation suppression effects of DMPA 150 mg every 3 months. DMPA and **CIPLA NEVIRAPINE** can be co-administered without dose adjustments.

Oral contraceptives:

Ethinyl estradiol (EE) and norethindrone (NET): Oral hormonal contraceptives, such as ethinyl oestradiol 0,035 mg and norethindrone 1,0 mg daily, should not be used as the sole method of contraception in women taking **CIPLA NEVIRAPINE** (see **"WARNINGS AND SPECIAL PRECAUTIONS"**). Appropriate doses for hormonal contraceptives (oral or other forms of application) other than DMPA in combination with **CIPLA NEVIRAPINE** have not been established with respect to safety and efficacy.

Other means of contraception (such as barrier methods) are recommended when **CIPLA 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.

Analgesics/opioids:

Methadone: Based on the metabolism of methadone, **CIPLA NEVIRAPINE** 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 **CIPLA**

NEVIRAPINE 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 **CIPLA NEVIRAPINE**.

PREGNANCY AND LACTATION:

The safety of **CIPLA NEVIRAPINE** in pregnant or lactating women has not been established. When used for the treatment of HIV-1 infection, adequate contraceptive methods should be used in women.

Currently available data on pregnant women indicate no malformative or foeto/ neonatal toxicity. To date no other relevant epidemiological data are available. No observable teratogenicity was detected in reproductive studies performed in pregnant rats and rabbits. There are no adequate and well-controlled studies in pregnant women for the treatment of HIV-1 infection. Caution should be exercised when prescribing **CIPLA NEVIRAPINE** to pregnant women.

When used to reduce the risk of intrapartum transmission of HIV-1 infection from mother to child in HIV-infected pregnant women who are not taking antiretroviral therapy at the time of labour:

CIPLA NEVIRAPINE has been demonstrated to be safe and effective when given as part of a regimen that includes a single dose during labour.

Patients should be counselled before initiating therapy that breastfeeding is contraindicated. Patients should also be counselled on the advisability and appropriate use of alternate forms of feeding.

Evidence from a clinical study on mother to child transmission of HIV-1 using a single dose regimen confirms the results of other studies indicating that postpartum breastfeeding is associated with a significantly higher rate of HIV-1 transmission than that found in non-breastfed infants. Consequently breastfeeding is contraindicated if the benefits of the medicine in achieving HIV-1 free survival are to be maintained.

Safety and efficacy have not been established in neonates with a birth weight of < 2 500 g.

Pregnancy:

In HIV-1-infected women in labour, the half-life of **CIPLA NEVIRAPINE** after a single oral 200 mg dose is prolonged (60 – 70 hours) and oral clearance is highly variable (2,1 ± 1,5 ℓ/h). Nevirapine readily crosses the placenta such that the administration of a 200 mg dose to the mothers resulted in cord concentrations above 100 ng/mℓ and a cord blood-to-maternal blood ratio of 0,84 ± 0,19.

As hepatotoxicity is more frequent in women with CD4+ cell counts above 250 cells/mm^3 with detectable HIV-1 RNA in plasma (50 or more copies/mℓ), these conditions should be taken into consideration on therapeutic decision (see **"WARNINGS AND SPECIAL PRECAUTIONS"**). There is not enough evidence to substantiate that the absence of an increased risk for toxicity seen in pre-treated women initiating **CIPLA NEVIRAPINE** with an undetectable viral load (less than 50 copies/mℓ of HIV-1 in plasma) and CD4+ cell counts above 250 cells/mm^3 also applies to pregnant women. All the randomised studies addressing this issue specifically excluded pregnant women, and pregnant women were under-represented in cohort studies as well as in meta-analyses.

Neonates:

In neonates receiving a 2 mg/kg oral dose of **CIPLA NEVIRAPINE ORAL SUSPENSION** within 72 hours after birth, born to HIV-1-infected women administered a single 200 mg dose during labour, the geometric mean half-life of nevirapine was 47 hours. Plasma levels were maintained above 100 ng/mℓ for the first week of life.

Women of childbearing potential / Contraception in males and females:

Women of childbearing potential should not use oral contraceptives as the sole method for birth control, since nevirapine may lower the plasma concentrations of these medicines (see **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"INTERACTIONS"**).

Breastfeeding:

CIPLA NEVIRAPINE readily crosses the placenta and is found in breast milk.

It is recommended that HIV-infected mothers do not breastfeed their infants to avoid risking postnatal transmission of HIV and that mothers should discontinue breastfeeding if they are receiving **CIPLA NEVIRAPINE**.

DOSAGE AND DIRECTIONS FOR USE:

Treatment of HIV-1 Infection:

Adults:

The recommended dose for **CIPLA NEVIRAPINE** is 200 mg (1 tablet or 4 teaspoons of suspension) daily for the first 14 days **(this lead-in period should be used because it has been found to lessen the frequency of rash)**, followed by 200 mg twice daily, in combination with at least two antiretroviral medicines 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.

Paediatric patients:

CIPLA NEVIRAPINE ORAL SUSPENSION may be dosed in paediatric patients either by body surface area (BSA) or by body weight as follows:

By BSA using the Mosteller formula the recommended oral dose for paediatric patients of all ages is 150 mg/m^2 once daily for two weeks followed by 150 mg/m^2 twice daily thereafter.

Calculation of the volume of **CIPLA NEVIRAPINE ORAL SUSPENSION** 50 mg/5 mℓ required for paediatric dosing on a body surface basis of 150 mg/m^2:

BSA range (m^2)	**Volume (mℓ)**
0,08 – 0,25	2,5
0,25 – 0,42	5
0,42 – 0,58	7,5
0,58 – 0,75	10
0,75 – 0,92	12,5
0,92 – 1,08	15
1,00 – 1,25	17,5
1,25+	20

Mosteller Formula: BSA (m^2) = $\sqrt{\frac{\text{Height (cm) x Wt (kg)}}{3\,600}}$

By body weight, the recommended oral dose of **CIPLA NEVIRAPINE ORAL SUSPENSION** for paediatric patients, 2 months up to 8 years of age, is 4 mg/kg once daily for the first 14 days followed by 7 mg/kg twice daily thereafter.

For patients 8 years and older the recommended dose is 4 mg/kg once daily for two weeks followed by 4 mg/kg twice daily thereafter.

The total daily dose should not exceed 400 mg for any patient.

Calculation of the volume of **CIPLA NEVIRAPINE ORAL SUSPENSION** 50 mg/5 mℓ required for paediatric dosing after the two weeks lead-in period.

Weight Range (kg) for patients < 8 yrs. of age on a body weight basis	**Weight Range (kg) for patients ≥ 8 years of age on a body weight basis**	**Volume (mℓ)**

receiving 7 mg/kg.	**receiving 4 mg/kg.**	
1,79 – 5,36	3,13 – 9,38	2,5
5,36 – 8,93	9,38 – 15,63	5
8,93 – 12,50	15,63 – 21,88	7,5
12,50 – 16,07	21,88 – 28,12	10
16,07 – 19,64	28,12 – 34,37	12,5
19,64 – 23,21	34,37 – 40,62	15
23,21 – 26,79	40,62 – 46,88	17,5
26,79+	46,88+	20

In clinical trials with nevirapine, as in **CIPLA NEVIRAPINE ORAL SUSPENSION,** in paediatric patients less than 3 months of age, the plasma nevirapine concentrations observed were within the range observed in adults and the remainder of the paediatric population, but were more variable between patients, particularly in the second month of age.

For adults and children (> 46,88 kg or with a BSA ≥ 1,25+), who are able to swallow tablets easily, **CIPLA NEVIRAPINE** 200 mg tablets can be taken instead of **CIPLA NEVIRAPINE ORAL SUSPENSION**.

CIPLA NEVIRAPINE ORAL SUSPENSION should be shaken gently prior to administration. It is important to administer the entire measured dose of suspension by using an oral dosing syringe, dosing cup or medicine measure. An oral dosing syringe is recommended, particularly for volumes of 5 mℓ or less. If a dosing cup or medicine measure is used, it should be thoroughly rinsed with water and the rinse should also be administered to the patient.

Patients should be advised to take **CIPLA NEVIRAPINE** 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 **CIPLA NEVIRAPINE** therapy and at appropriate intervals during therapy (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Dosage Adjustment:

CIPLA NEVIRAPINE 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 (4 mg/kg/day in paediatric patients) should not have their CIPLA NEVIRAPINE dose increased until the rash has resolved (see "WARNINGS AND SPECIAL PRECAUTIONS").

CIPLA NEVIRAPINE 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 **CIPLA NEVIRAPINE**, based on clinical needs and judgement, on a case by case basis.

CIPLA NEVIRAPINE may then be restarted at 200 mg daily (4 mg/kg/day in paediatric patients) increasing to 200 mg twice daily (4 or 7 mg/kg twice daily, according to age, for paediatric patients) with caution, after extended observation. If moderate or severe liver function test abnormalities recur, **CIPLA NEVIRAPINE** should be permanently discontinued (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Patients who interrupt **CIPLA NEVIRAPINE** dosing for more than 7 days should restart the recommended dosing using 200 mg daily (4 mg/kg/day in paediatric patients) for the first 14 days (lead-in) followed by 200 mg twice daily (4 or 7 mg/kg twice daily, according to age, for paediatric patients).

For the dosage for patients with hepatic and renal dysfunction, including those undergoing haemodialysis, please refer to the section **"Pharmacokinetic properties: Adults"**.

To reduce the risk of intrapartum transmission of HIV-1 infection from mother to child in HIV-infected pregnant women who are not taking antiretroviral therapy at the time of labour:

CIPLA NEVIRAPINE is used as a single oral dose of 200 mg to the mother during labour preferably more than 2 hours before delivery followed by a single oral dose of 2 mg/kg to the infant within 48 to 72 hours after birth or before discharge, whichever is earlier, in combination with zidovudine.

SIDE-EFFECTS:

Blood and lymphatic system disorders:

Frequent: Granulocytopenia.

Less frequent: Anaemia.

Immune system disorders:

Frequent: Allergic reactions, hypersensitivity syndrome (including anaphylactic reaction, angioedema, urticaria), anaphylaxis, drug rash with eosinophilia and systemic symptoms.

Nervous system disorders:

Frequent: Headache.

Gastrointestinal disorders:

Frequent: Nausea, vomiting, abdominal pain, diarrhoea.

Hepato-biliary disorders:

Frequent: Hepatitis (including severe and life-threatening hepatotoxicity).

Less frequent: Jaundice, liver failure / fulminant hepatitis (which may be fatal).

Skin and subcutaneous tissue disorders:

Frequent: Rash.

Less frequent: Stevens-Johnson syndrome, urticaria, toxic epidermal necrolysis (which may be fatal).

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Myalgia, arthralgia.

General disorders and administration site conditions:

Less frequent: Fatigue, fever.

Investigations:

Frequent: Abnormal liver function tests (increased alanine aminotransferase; increased transaminases; increased aspartate aminotransferase; increased gamma-glutamyltransferase; increased hepatic enzymes; hypertransaminasaemia); decreased blood phosphorus; increased blood pressure.

Paediatric patients:

The most frequently reported adverse events, related to nevirapine, were similar to those observed in adults, with the exception of granulocytopenia, which was more commonly observed in children.

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdosage with **CIPLA NEVIRAPINE** may manifest in any of the symptoms described under **"SIDE-EFFECTS"**. There is no known antidote for **CIPLA NEVIRAPINE** 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 **CIPLA NEVIRAPINE** overdose is symptomatic and supportive.

IDENTIFICATION:

CIPLA NEVIRAPINE (Tablets): White, oval shaped, biconvex tablet with central break line on one side and ‘N’ debossed on the other side.

CIPLA NEVIRAPINE ORAL SUSPENSION: A white to off-white uniform suspension.

PRESENTATION:

CIPLA NEVIRAPINE (Tablets): PVC film and aluminium blister strips of 10 tablets each, packed in 60’s in a carton, or sixty (60) tablets packed in a white-coloured, high density polyethylene (HDPE) bottle containing a silica gel bag and closed with a milky-coloured screw cap, packed in a carton.

CIPLA NEVIRAPINE ORAL SUSPENSION: Cartons containing 100 mℓ or 240 mℓ oral suspension in an amber-coloured, transparent, round PET bottle with a white coloured cap.

A plastic cannula and a 2 mℓ plastic syringe fitted with a dust cap are included in the 240 mℓ pack. A transparent, polypropylene measuring cup with two rings, one each along 2,5 mℓ & 5,0 mℓ, and markings at 2,5 mℓ, 5 mℓ & 10 mℓ are also included in the pack.

A 10 mℓ translucent polypropylene syringe and plunger, with a polyethylene adaptor and cap packed in a sealed pouch is included in the 100 mℓ pack.

STORAGE INSTRUCTIONS:

Store at or below 25 °C. Protect from light.

CIPLA NEVIRAPINE (Tablets): Keep the blisters in the outer carton until required for use or store the tablets in the original plastic container until required for use.

CIPLA NEVIRAPINE ORAL SUSPENSION: Shake the bottle gently before use. Discard one month after first opening.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

CIPLA NEVIRAPINE (Tablets): 36/20.2.8/0423

CIPLA NEVIRAPINE ORAL SUSPENSION: A38/20.2.8/0339

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

CIPLA MEDPRO (PTY) LTD

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DATE OF PUBLICATION OF THE PACKAGE INSERT:

12 November 2004

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