Applicant/PHCR: **AUROBINDO PHARMA (PTY) LTD**
Product proprietary name: **BINDOPIN SUSPENSION 50 mg/5 ml**
Dosage form and strength: **SUSPENSION 50 mg/5 ml**

SCHEDULING STATUS:

S4

PROPRIETARY NAME (and dosage form):

BINDOPIN SUSPENSION 50 mg/5 ml (suspension)

COMPOSITION:

Each 5 mL of suspension contains:

Nevirapine 50 mg (as Nevirapine hemihydrate). Contains sugar: 750 mg sucrose per 5 mL.

Preservatives:

Methylparaben……0.18 % m/v

Propylparaben……..0.024 % m/v

The other ingredients are carbopol, non-crystallising sorbitol solution, polysorbate 80, propylene glycol, purified water and sodium hydroxide.

WARNING

THE FIRST 18 WEEKS OF THERAPY WITH BINDOPIN SUSPENSION 50 mg/5 ml 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).

<u>Cutaneous reactions:</u>

Severe and life threatening skin reactions, including fatal cases, have occurred in patients treated with BINDOPIN SUSPENSION 50 mg/5 ml. These have 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 BINDOPIN SUSPENSION 50 mg/5 ml and consult a doctor. In these patients BINDOPIN SUSPENSION 50 mg/5 ml must not be restarted.
If patients present with suspected BINDOPIN SUSPENSION 50 mg/5 ml-associated rash, liver function tests should be performed. Patients with moderate to severe elevations (aspartate transaminase (AST) or alanine aminotransferase (ALT) > 5 X ULN) should be permanently discontinued from BINDOPIN SUSPENSION 50 mg/5 ml.
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, BINDOPIN SUSPENSION 50 mg/5 ml should be permanently stopped and not be reintroduced.

<u>Hepatic reactions:</u>
Severe or life threatening hepatotoxicity including fatal fulminant hepatitis has occurred in patients treated with BINDOPIN SUSPENSION 50 mg/5 ml. 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 BINDOPIN SUSPENSION 50 mg/5 ml-containing regimens.

If AST or ALT > 2,5 x ULN before or during treatment, liver tests should be monitored more frequently during regular clinic visits. BINDOPIN SUSPENSION 50 mg/5 ml 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 BINDOPIN SUSPENSION 50 mg/5 ml should be stopped immediately and not reinstated. If aspartate transaminase (AST) and alanine aminotransferase (ALT) return to baseline values, it may be possible to reintroduce BINDOPIN SUSPENSION 50 mg/5 ml 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, BINDOPIN SUSPENSION 50 mg/5 ml 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)], BINDOPIN SUSPENSION 50 mg/5 ml must be permanently stopped. BINDOPIN SUSPENSION 50 mg/5 ml should not be re-administered to patients who have required permanent discontinuation for clinical hepatitis due to BINDOPIN SUSPENSION 50 mg/5 ml.

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. BINDOPIN SUSPENSION 50 mg/5 ml should not be restarted in these situations.

RESISTANT VIRUS EMERGES RAPIDLY AND UNIFORMLY WHEN BINDOPIN SUSPENSION 50 mg/5 ml IS ADMINISTERED AS MONOTHERAPY, THEREFORE, FOR CHRONIC TREATMENT OF HIV-1 INFECTION, BINDOPIN SUSPENSION 50 mg/5 ml SHOULD ALWAYS BE ADMINISTERED IN COMBINATION WITH AT LEAST TWO ADDITIONAL ANTIRETROVIRAL AGENTS.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antiviral agents.

PHARMACOLOGICAL ACTION:

Mechanism of action

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Nevirapine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The activity of nevirapine does not compete with template

or nucleoside triphosphates. HIV-2 RT and eukaryotic DNA polymerases (such as human DNA polymerases α, 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 NNRTI's *in vitro,* have been reported.

Pharmacokinetics

Adults

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

Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady state trough nevirapine concentrations of 4,5 ± 1,9 µg/mL (17 ± 7 µM) were attained at 400 mg/day. The absorption of nevirapine is not affected by food, antacids or medicinal products, which are formulated with an alkaline buffering agent (e.g. didanosine).

Nevirapine is highly lipophilic and is essentially nonionised 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.

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 %). 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 auto induction resulting in 1,5 to 2-fold increase in metabolism. This effect is at its highest after 14 days of initiation of therapy.

Pharmacokinetics in Special Populations

Renal/Hepatic Dysfunction: The pharmacokinetics of **BINDOPIN SUSPENSION 50 mg/5 ml** have not been evaluated in patients with either renal or hepatic dysfunction.

Gender: There are no significant gender differences in **BINDOPIN SUSPENSION 50 mg/5 ml** clearance or plasma concentrations following either single or multiple dose administration.

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

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

INDICATIONS:

For treatment of HIV-1 infection.

BINDOPIN SUSPENSION 50 mg/5 ml (nevirapine) is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. Resistant virus emerges rapidly and uniformly when **BINDOPIN SUSPENSION 50 mg/5 ml** is administered as monotherapy.

Therefore, **BINDOPIN SUSPENSION 50 mg/5 ml** should always be administered in combination with at least two additional antiretroviral agents.

CONTRA-INDICATIONS:

BINDOPIN SUSPENSION 50 mg/5 ml is contra-indicated in patients with hypersensitivity to the active ingredient or any of the excipients of the product.

BINDOPIN SUSPENSION 50 mg/5 ml is contra-indicated in severe hepatic dysfunction: Child-Pugh class B or C and in end-stage renal failure in patients not on haemodialysis.

BINDOPIN SUSPENSION 50 mg/5 ml should not be administered to patients with pre-treatment or during treatment with aspartate transaminase (AST) or alanine aminotransferase (ALT) > 5 x upper level of normality (ULN) until baseline AST/ALT are stabilized < 5 x ULN.

BINDOPIN SUSPENSION 50 mg/5 ml 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 **BINDOPIN SUSPENSION 50 mg/5 ml.**

BINDOPIN SUSPENSION 50 mg/5 ml should not be re-administered to patients who previously had aspartate transaminase (AST) or alanine aminotransferase (ALT) > 5 x upper limit of normal (ULN) during **BINDOPIN SUSPENSION 50 mg/5 ml** therapy or had rapid recurrence of liver function abnormalities upon re-administration of **BINDOPIN SUSPENSION 50 mg/5 ml** (See **WARNINGS AND SPECIAL PRECAUTIONS**).

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

Pregnancy and lactation: The safety of **BINDOPIN SUSPENSION 50 mg/5 ml** in pregnant or lactating women has not been established. Adequate contraceptive methods should be used in women.

WARNINGS AND SPECIAL PRECAUTIONS

The first 18 weeks of therapy with **BINDOPIN SUSPENSION 50 mg/5 ml** is a critical period, which requires intensive monitoring of patients to identify the potential appearance of severe, and life threatening skin reactions (including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis) or serious hepatitis/hepatic failure. The greatest risk of hepatic events and skin reactions occurs in the first 6 weeks of therapy. Women (3,2 fold) and patients with higher CD4 (women with CD4+ > 250, 9,8 fold; men with CD4+ > 400, 6,4 fold) counts are at increased risk of hepatic adverse events. In addition, the dosage, especially the 14 days lead-in period, must be strictly adhered to (see **DOSAGE AND DIRECTIONS FOR USE**).

Patients should be instructed that the major toxicity of BINDOPIN SUSPENSION 50 mg/5 ml is skin rashes and should be advised to promptly notify their doctor of any rash. The lead-in period should be used because it has been found to lessen the frequency of rash (see DOSAGE AND DIRECTIONS

FOR USE).

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

Skin reactions:

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

BINDOPIN SUSPENSION 50 mg/5 ml 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. BINDOPIN SUSPENSION 50 mg/5 ml 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).

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

Risk factors for developing serious cutaneous reactions include failure to follow the initial dosing of 200 mg daily during the lead-in period. A long delay between the initial symptoms and medical consultation may increase the risk of a more serious outcome of cutaneous reactions. Women are at a 3,2 fold higher risk than men of developing rash. Women with a CD4+ count of > 250 cells/mm^3 are at a 9,8 fold increased risk of developing rash.

Any patient experiencing severe rash or a rash accompanied by constitutional symptoms such as fever, blistering, oral lesions, conjunctivitis, facial oedema, muscle or joint aches, or general malaise should discontinue BINDOPIN SUSPENSION 50 mg/5 ml and consult a medical practitioner. In these patients BINDOPIN SUSPENSION 50 mg/5 ml must not be restarted.

If patients present with a suspected BINDOPIN SUSPENSION 50 mg/5 ml-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 BINDOPIN SUSPENSION 50 mg/5 ml.

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, BINDOPIN SUSPENSION 50 mg/5 ml 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 hyperbilirubinemia, prolonged partial thromboplastin time or eosinophilia) has occurred in patients treated with nevirapine. Serious hepatitis and hepatic failure events in nevirapine treated patients have been reported to occur in the first 18 weeks of therapy but some have occurred later. The first 18 weeks of treatment are a critical period, which require close monitoring. The risk of hepatic events is greatest in the first 6 weeks of therapy. Women (3,2 fold) and patients with higher CD4 (women with CD4+ > 250, 9,8 fold; men with CD4+ > 400, 6,4 fold) counts are at increased risk of hepatic adverse events. However, the risk continues past this period and monitoring should continue at frequent intervals throughout treatment. Patients should be informed that hepatic reactions are a major toxicity of **BINDOPIN SUSPENSION 50 mg/5 ml** and that occurrence of symptoms suggestive of hepatitis should lead them to contact their doctor promptly.

Increased aspartate transaminase (AST) or alanine aminotransferase (ALT) levels > 2,5 x ULN at the start of

antiretroviral therapy is associated with greater (3,2 - 4,2 fold) risk of hepatic adverse events during antiretroviral therapy in **BINDOPIN SUSPENSION 50 mg/5 ml** containing regimens.

BINDOPIN SUSPENSION 50 mg/5 ml is contraindicated in patients with severe underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events. In the case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

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

Women have a threefold higher risk than men for rash-associated hepatic events (4,6 % vs. 1,5 %). Patients with higher CD4 counts may also be at a higher risk for rash-associated hepatic events with **BINDOPIN SUSPENSION 50 mg/5 ml**. In a retrospective review, women with CD4 counts > 250 cells/mm^3 had a 9,8 fold higher risk of rash-associated hepatic adverse event compared to women with CD4 counts < 250 cells/mm^3 (0,84 % vs. 0,9 %). An increased risk (6,4 fold) was observed in men with CD4 counts > 400 cells/mm^3 compared to men with CD4 counts < 400 cells/mm^3 (4,5 % vs. 0,7 %).

Patients should be informed that hepatic reactions are a major toxicity of **BINDOPIN SUSPENSION 50 mg/5 ml** requiring close monitoring during the first 18 weeks. However, severe liver disease can occur after 18 weeks. Therefore monitoring should continue at frequent intervals after this period depending on the patient's clinical status. They should be informed that occurrence of symptoms suggestive of hepatitis should lead them to contact their doctor promptly.

Liver function monitoring

All patients should have baseline liver function tests prior to **BINDOPIN SUSPENSION 50 mg/5 ml** treatment (see **WARNINGS AND SPECIAL PRECAUTIONS** and **CONTRA-INDICATIONS**).

If aspartate transaminase (AST) or alanine aminotransferase (ALT) are > 2,5 x upper limit of normal (ULN) before or during treatment, liver tests should be monitored more frequently during more regular clinic visits. **BINDOPIN SUSPENSION 50 mg/5 ml** should not be administered or re-administered to patients with pre-treatment AST > 5 x ULN.

Abnormal liver function has been reported with nevirapine, some in the first few weeks of therapy. Asymptomatic elevations of liver enzymes are frequently described and are not necessarily a contra-indication to use nevirapine. Asymptomatic GGT elevations are not a contra-indication to continuing therapy. Monitoring of liver function tests is strongly recommended at frequent intervals, appropriate to the patient's clinical needs, especially during the first 2 to 3 months of treatment. Less frequent monitoring is needed thereafter. Doctors and patients should be vigilant for prodromal signs of findings of hepatitis such as anorexia, nausea, jaundice, bilirubinuria, acholic stools, hepatomegaly or liver tenderness. Patients should be instructed to seek medical attention if these occur.

If aspartate transaminase (AST) or alanine aminotransferase (ALT) increase to > 5 x upper limit of normality during treatment, BINDOPIN SUSPENSION 50 mg/5 ml should be immediately stopped. If aspartate transaminase (AST) or alanine aminotransferase (ALT) return to baseline values, it may be possible to reintroduce BINDOPIN SUSPENSION 50 mg/5 ml, on a case by case basis, at the starting dosage of 200 mg/day for 14 days followed by 400 mg/day. If liver function abnormalities rapidly recur, BINDOPIN SUSPENSION 50 mg/5 ml 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), **BINDOPIN SUSPENSION 50 mg/5 ml** must be permanently stopped. **BINDOPIN SUSPENSION 50 mg/5 ml** should not be re-administered to patients who have required permanent discontinuation for clinical hepatitis due to BINDOPIN SUSPENSION 50 mg/5 ml.

Patients receiving **BINDOPIN SUSPENSION 50 mg/5 ml** and other antiretroviral agents may continue to develop opportunistic infections and other complications of HIV infection. Patients should therefore remain under close supervision by medical practitioners experienced in the treatment of patients with HIV-associated diseases.

For treatment of HIV-1 infection

General: When administering **BINDOPIN SUSPENSION 50 mg/5 ml** as part of an antiretroviral treatment regimen, the complete product information for each therapeutic component should be consulted before initiation of treatment.

While nevirapine is extensively metabolised by the liver and nevirapine metabolites are extensively eliminated by the kidney, the pharmacokinetics results suggest caution should be exercised when **BINDOPIN SUSPENSION 50 mg/5 ml** is administered to patients with more than mild hepatic dysfunction. **BINDOPIN SUSPENSION 50 mg/5 ml** should not be administered to patients with severe hepatic dysfunction (AST/ALT> 5 x ULN). In patients with renal dysfunction who are undergoing haemodialysis, pharmacokinetics results suggest that supplementing **BINDOPIN SUSPENSION 50 mg/5 ml** therapy with an additional 200 mg dose of **BINDOPIN SUSPENSION 50 mg/5 ml** following each haemodialysis treatment would help offset the effects of haemodialysis on nevirapine clearance. Otherwise patients with $CL_{cr} \geq 20$ mL/min do not require an adjustment in nevirapine dosing. (See **Pharmacokinetics, *Renal/Hepatic Dysfunction* and CONTRA-INDICATIONS**). Safety in patients with end stage impairment who are not haemodialysed has not been demonstrated.

BINDOPIN SUSPENSION 50 mg/5 ml may interact with some medicines; therefore, patients should be advised to report to their medical practitioner the use of any other medications.

Oral contraceptives and other hormonal methods of birth control should not be used as the sole method of contraception in women taking **BINDOPIN SUSPENSION 50 mg/5 ml**, since nevirapine may lower plasma levels of these medications. For this reason, and to reduce the risk of HIV transmission, barrier contraception (e.g. condoms) is recommended.

Sucrose

BINDOPIN SUSPENSION 50 mg/5 ml contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take **BINDOPIN SUSPENSION 50 mg/5 ml.**

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 **BINDOPIN SUSPENSION 50 mg/5 ml** administration it is advisable to refrain from such activities.

INTERACTIONS:

Nevirapine has been shown to be an inducer of hepatic cytochrome P450 metabolic enzymes (CYP3A, CYP2B) and may result in lower plasma concentrations of other concomitantly administered medicines that are extensively metabolised by CYP3A or CYP2B (see **Pharmacokinetics**). Thus, if a patient has been stabilised on a dosage regimen for a medicine metabolised by CYP3A or CYP2B and begins treatment with **BINDOPIN SUSPENSION 50 mg/5 ml**, dose adjustment may be necessary.

Nucleoside Analogues: No dosage adjustments are required when **BINDOPIN SUSPENSION 50 mg/5 ml** is taken in combination with zidovudine (ZDV), didanosine (ddI), zalcitabine (ddc) and stavudine.

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

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

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

Indinavir: Nevirapine and indinavir (800 mg three times a day) co-administration leads to a 28 % mean decrease (p<0,01) in indinavir AUC and no significant change in nevirapine plasma levels. A dose increase of indinavir to 1000 mg (every eight hours) should be considered when indinavir is given with nevirapine 200 mg

(twice a day); however, there is no data currently available to establish that the short term or long term antiviral activity of indinavir 1000 mg (every eight hours) with nevirapine 200 mg (twice a day) will differ from that of indinavir 800 mg (every eight hours) with nevirapine 200 mg (twice a day).

Nelfinavir: Nevirapine, nelfinavir (750 mg three times a day) and stavudine (30 - 40 mg twice a day) given in combination indicated no statistically significant changes in nelfinavir pharmacokinetic parameters after the addition of nevirapine
(AUC + 4 %, C_{max} + 14 % and C_{min} - 2 %). Compared to historical controls nevirapine levels appeared to be unchanged.

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

Ketoconazole: Ketoconazole and nevirapine should not be given concomitantly. Administration of nevirapine 200 mg twice a day with ketoconazole 400 mg four times a day 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. The effects of nevirapine on itraconazole are not known. Although interaction studies have not been performed, antifungal medicinal products which are eliminated renally (e.g. fluconazole) might be substituted for ketoconazole.

Fluconazole: Co-administration of fluconazole and nevirapine resulted in approximately 100 % increase in nevirapine exposure compared with historical data where nevirapine was administered alone. Because of the risk of increased exposure to nevirapine, caution should be exercised if **BINDOPIN SUSPENSION 50 mg/5 ml** and fluconazole are given concomitantly and patients should be monitored closely. There was no clinically relevant effect of nevirapine.

Anticoagulants: The *in vitro* interaction between nevirapine and the antithrombotic agent warfarin is complex. As a result, when giving these drugs concomitantly plasma warfarin levels and therapeutic efficacy may change with the potential for both increases and decreases in coagulation time. The net effect of the

interaction may change during the first weeks of co-administration or upon discontinuation of nevirapine. When warfarin is co-administered with nevirapine prothrombin time should be more frequently monitored.

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

Rifabutin: Administration of nevirapine 200 mg twice daily with rifabutin 300 mg four times daily (or 150 mg four times daily if concomitantly receiving ZDV or protease inhibitors), resulted in a significant increase of rifabutin concentrations (29 % mean increase in rifabutin AUC and a 28 % mean increase in rifabutin C_{max}) and a significant increase (20 %) in median C_{max}. There were no significant changes in the active metabolite 25-O-desacetyl-rifabutin concentrations. High inter-patient variability however, may result in some patients experiencing large increases in rifabutin exposure, which may make them at higher risk for toxicity. In the same study, rifabutin administration resulted in an apparent significant increase in systemic clearance of nevirapine by 9 % compared to historical controls. The latter changes are not considered to be clinically important. Care should be taken when nevirapine and rifabutin are administered concurrently with considerations of a decrease in the dose of rifabutin. The dose of **BINDOPIN SUSPENSION 50 mg/5 ml** need not be changed.

St. Johns' Wort: Concomitant use of **BINDOPIN SUSPENSION 50 mg/5 ml** and St. Johns' Wort (*hypericum perforatum*) or St. Johns' Wort-containing products is not recommended as co-administration of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), including **BINDOPIN SUSPENSION 50 mg/5 ml** with St. Johns' Wort is expected to decrease NNRTI concentrations and may result in sub-optimal levels of **BINDOPIN SUSPENSION 50 mg/5 ml** and lead to loss of virologic response and possible resistance to **BINDOPIN SUSPENSION 50 mg/5 ml** or to the class of NNRTIs. The bioavailability of nevirapine is reduced by 57 ± 19 % (AUC) and the C_{max} of nevirapine is reduced by 81 ± 16 %.

CYP isoenzyme inhibitors (e.g. cimetidine and macrolides): Nevirapine trough concentrations were

elevated in patients who received cimetidine (+21 %).

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

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

Methadone: Based on the metabolism of methadone, **BINDOPIN SUSPENSION 50 mg/5 ml** 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 **BINDOPIN SUSPENSION 50 mg/5 ml** 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 **BINDOPIN SUSPENSION 50 mg/5 ml.**

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation of **BINDOPIN SUSPENSION 50 mg/5 ml** has not been demonstrated.

BINDOPIN SUSPENSION 50 mg/5 ml should not be used during pregnancy. (See **CONTRA – INDICATIONS**).

Mothers should be instructed not to breastfeed if they are receiving **BINDOPIN SUSPENSION 50 mg/5 ml**.

DOSAGE AND DIRECTIONS FOR USE:

Adults*:* The recommended dose for **BINDOPIN SUSPENSION 50 mg/5 ml** is 200 mg, i.e. 20 mL (4 medicine measures) once 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, i.e. 20 mL (4 medicine measures) twice daily, in combination with at least two antiretroviral agents to which the patient has not been previously exposed. For concomitantly administered antiretroviral therapy, the recommended dosage and monitoring should be followed.

Paediatrics: The recommended oral dose of **BINDOPIN SUSPENSION 50 mg/5 ml** for paediatric patients is as follows:

2 months up to 8 years old: 4 mg/kg once daily for two weeks followed by 7 mg/kg twice daily thereafter.

8 years and older: 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.

Adults and children (50 kg or more in weight), who are able to swallow the tablets easily; **BINDOPIN TABLETS 200 mg** can be taken instead of **BINDOPIN SUSPENSION 50 mg/5 ml.**

BINDOPIN SUSPENSION 50 mg/5 ml 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 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 rinsing should also be administered to the patient.

Patients should be advised to take **BINDOPIN SUSPENSION 50 mg/5 ml** 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 **BINDOPIN SUSPENSION 50 mg/5 ml** therapy and at appropriate intervals during therapy. (See **WARNINGS AND SPECIAL PRECAUTIONS**).

Dosage Adjustment: **BINDOPIN SUSPENSION 50 mg/5 ml 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 BINDOPIN SUSPENSION 50 mg/5 ml dose increased until the rash has resolved (See WARNINGS AND SPECIAL PRECAUTIONS).**

BINDOPIN SUSPENSION 50 mg/5 ml 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 **BINDOPIN SUSPENSION 50 mg/5 ml**, based on clinical needs and judgement, on a case by case basis. **BINDOPIN SUSPENSION 50 mg/5 ml** may then be restarted at 200 mg daily increasing to 200 mg twice daily with caution, after extended observation. If moderate or severe liver function test abnormalities recur, **BINDOPIN SUSPENSION 50 mg/5 ml** should be permanently discontinued (See **WARNINGS AND SPECIAL PRECAUTIONS**).

Patients who interrupt **BINDOPIN SUSPENSION 50 mg/5 ml** dosing for more than 7 days should restart the recommended dosing, using 200 mg/day (4 mg/kg/day in paediatric patients) for the first 14 days (lead-in) followed by 200 mg twice daily (4 mg or 7 mg/kg twice daily, according to age; for paediatric patients).

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

SIDE EFFECTS:

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

Blood and lymphatic system disorders

Rare: granulocytopenia, anaemia

Immune system disorders

Common: allergic reactions

Rare: hypersensitivity (syndrome), anaphylaxis

Nervous system disorders

Common: headache

Gastrointestinal disorders

Common: nausea

Uncommon: vomiting, abdominal pain

Rare: diarrhoea

Hepato-biliary disorders

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

Uncommon: jaundice

Rare: liver failure / fulminant hepatitis

Skin and subcutaneous tissue disorders

Common: rash (9 %)

Uncommon: Steven Johnson syndrome (0,3 %), urticaria

Rare: toxic epidermal necrolysis, angio-oedema

Musculoskeletal, connective tissue and bone disorders

Uncommon: myalgia

Rare: arthralgia

General disorders and administration site conditions

Uncommon: fatigue, fever

Post marketing experience has shown that the most serious adverse reactions are Stevens-Johnson syndrome, toxic epidermal necrolysis, serious hepatitis/hepatic failure and hypersensitivity syndrome, 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 AND SPECIAL PRECAUTIONS**).

Skin and subcutaneous tissues

The most common clinical toxicity of **BINDOPIN SUSPENSION 50 mg/5 ml** is rash. Nevirapine attributable rash occurred in 16 % of patients in combination regimens in Phase II/III controlled studies. In these clinical trials 35 % of patients treated with nevirapine experienced rash compared with 19 % of patients treated in control groups of either zidovudine + didanosine or zidovudine alone. Severe or life threatening skin reactions occurred in 6,6 % of nevirapine treated patients compared with 1,3 % of patients treated in the control groups. Overall, 7 % of patients discontinued nevirapine due to rash.

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

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

BINDOPIN SUSPENSION 50 mg/5 ml must be discontinued immediately in patients developing a severe rash or a rash accompanied by constitutional symptoms.

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

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

Group I: Erythema, pruritus.

Group IIA: One of the two following clinical presentations

1. Diffuse erythematous macular or maculopapular cutaneous eruption or dry desquamation with or without pruritus without the presence of any additional *constitutional* findings as described in **Group III.**

2. Typical target lesions without blistering, vesicles or ulcerations in the lesions (usually referred to as erythema multiforme minor).

Group IIB: Urticaria.

Group III: One of the five following clinical presentations

1. Extensive erythematous or maculopapular rash or moist desquamation with or without pruritus *together* with the presence of any of the following *constitutional findings:*

- Clinically relevant increases in any one or more of the following *liver function* tests:
  Aspartate transaminase (AST), alanine aminotransferase (ALT), alkaline phosphatase and which are *possibly related to the drug reaction.*
- Fever, defined as > 39 °C *possibly related to drug reaction.*
- Blistering and/or vesiculation of cutaneous eruptions.
- One site of extensive mucosal lesions which are presumed to be due to medicine reaction (e.g. not due to herpes simplex, CMV).

2. Angioedema

3. Exfoliative dermatitis: Severe widespread erythema and dry scaling of the skin with 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 infected conjunctivae *plus* a purulent conjunctival discharge *or* visualisation of the conjunctival erosions. The presence of only an erythematous or infected conjunctiva does *not* establish erosion of the conjunctiva).

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

Presumed prodrome to Group III or IV:

The prodrome includes symptoms such as fever > 39 °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

BINDOPIN SUSPENSION 50 mg/5 ml 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 **BINDOPIN SUSPENSION 50 mg/5 ml** 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 **BINDOPIN SUSPENSION 50 mg/5 ml** 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 **BINDOPIN SUSPENSION 50 mg/5 ml** dose must not be escalated and if **BINDOPIN SUSPENSION 50 mg/5 ml** treatment is interrupted, it must not be re-introduced.

2. Cutaneous eruption Groups III and IV

BINDOPIN SUSPENSION 50 mg/5 ml must be permanently discontinued. No re-challenge is allowed. If symptoms occur during the low dose lead-in period that are suggestive of a possible prodrome to a **Group III or IV** cutaneous eruption, dose escalation should be delayed until the possible prodrome has resolved or a non nevirapine cause is established.

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

Hepato-biliary

The most frequently observed laboratory test abnormalities are elevations in liver function tests (LFTs), including aspartate transaminase (AST), alanine aminotransferase (ALT), δ-Glutamyl transpeptidase (GGT), total bilirubin and alkaline phosphatase. Asymptomatic elevations of GGT levels are the most frequent. Cases of jaundice have been reported. Cases of hepatitis, severe and life threatening hepatotoxicity and fatal fulminant hepatitis have been reported in patients treated with nevirapine. In a large clinical trial, the risk of a serious hepatic event among 1121 patients receiving nevirapine for a median duration of greater than one year was 1,2 % (versus 0,5 % in placebo group). The best predictor of a serious hepatic event was elevated baseline liver function tests. The first 18 weeks of treatment is a critical period, which requires close monitoring, but such events may also occur later (see **WARNINGS AND SPECIAL PRECAUTIONS**). The risk of hepatic events is greatest in the first 6 weeks of therapy. However the risk continues past this period and monitoring should continue at frequent intervals throughout treatment (see **WARNINGS AND SPECIAL PRECAUTIONS**).

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

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

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Over dosage with **BINDOPIN SUSPENSION 50 mg/5 ml** may manifest in any of the symptoms described under **SIDE EFFECTS**. There is no known antidote for **BINDOPIN SUSPENSION 50 mg/5 ml** over dosage. Cases of nevirapine overdose at doses ranging from 800 to 6000 mg per day for up to 15 days have been reported. Patients have experienced events including oedema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, increase in transaminases and weight decrease. All events subsided following discontinuation of nevirapine.
Treatment of **BINDOPIN SUSPENSION 50 mg/5 ml** overdose is symptomatic and supportive.

IDENTIFICATION:

White to off-white homogenous suspension.

PRESENTATION:

240 mL solution

1. White opaque high-density polyethylene bottle, containing 240 mL of oral solution, with a plastic cap and polyethylene wad.
2. White opaque HDPE bottle, containing 240 mL of oral solution, with a polypropylene child resistant cap with an induction sealing wad.
3. White, opaque HDPE bottle, containing 240 mL of oral solution, with a polypropylene child resistant cap and polyethylene wad.

A syringe is included in the pack.

STORAGE INSTRUCTIONS

Store below 30 °C. After first opening, the suspension may be stored for a period of 2 months below 30 °C.

Do not refrigerate. Keep the bottle well closed. Shake the bottle gently before use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

43/20.2.8/0287

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

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