Nepine®

Nevirapine

FORMS AND PRESENTATION

Nepine®: Tablets: Box of 60.

COMPOSITION

Nepine®: Each tablet contains Nevirapine Anhydrous 200mg.

Excipients: microcrystalline cellulose, croscarmellose sodium, starch, povidone, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Therapeutic class: Antivirals for systemic use.

ATC code: J05AG01.

Nevirapine is a NNRTI of HIV-1. Nevirapine is a non-competitive inhibitor of the HIV-1 reverse transcriptase, but it does not have a biologically significant inhibitory effect on the HIV-2 reverse transcriptase or on eukaryotic DNA polymerases α, β, γ, or δ.

Pharmacokinetic properties

Absorption

Nevirapine is readily absorbed (> 90%) after oral administration in healthy volunteers and in adults with HIV-1 infection. Absolute bioavailability in 12 healthy adults following single-dose administration was 93 ± 9% (mean SD) for a 50 mg tablet and 91 ± 8% for an oral solution. Peak plasma Nevirapine concentrations of 2 ± 0.4 µg/ml (7.5 µM) were attained by 4 hours following a single 200 mg dose. Following multiple doses, Nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Data reported in the literature from 20 HIV infected patients suggest a steady state C_{max} of 5.74 µg/ml (5.00-7.44) and C_{min} of 3.73 µg/ml (3.20-5.08) with an AUC of 109.0 h*µg/ml (96.0-143.5) in patients taking 200 mg of Nevirapine bid. Other published data support these conclusions. Long-term efficacy appears to be most likely in patients whose Nevirapine trough levels exceed 3.5 µg/ml.

Distribution

Nevirapine is lipophilic and is essentially non-ionized at physiologic pH. Following intravenous administration to healthy adults, the volume of distribution (Vdss) of Nevirapine was 1.21 ± 0.09 l/kg, suggesting that Nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is found in breast milk. Nevirapine is about 60% bound to plasma proteins in the plasma concentration range of 1-10 µg/ml. Nevirapine concentrations in human cerebrospinal fluid (n = 6) were 45% (± 5%) of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

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 (oxidative) metabolism to several hydroxylated metabolites. In vitro studies with human liver microsomes suggest that oxidative metabolism of Nevirapine is mediated primarily by cytochrome P450 isozymes from the CYP3A family, although other isozymes may have a secondary role. In a mass balance/excretion study in eight healthy male volunteers dosed to steady state with Nevirapine 200 mg given twice daily followed by a single 50 mg dose of 14C-nevirapine, approximately 91.4 ± 10.5% of the radio-labeled dose was recovered, with urine (81.3 ± 11.1%) representing the primary route of excretion compared to feces (10.1 ± 1.5%). Greater than 80% of the radioactivity in urine was made up of glucuronide conjugates of hydroxylated metabolites. Thus cytochrome P450 metabolism, glucuronide conjugation, and urinary excretion of glucuronidated metabolites represent the primary route of Nevirapine biotransformation and elimination in humans. Only a small fraction (< 5%) of the radioactivity in urine (representing < 3% of the total dose) was made up of parent compound; therefore, renal excretion plays a minor role in elimination of the parent compound.

Nevirapine has been shown to be an inducer of hepatic cytochrome P450 metabolic enzymes. The pharmacokinetics of autoinduction is characterized by an approximately 1.5 to 2 fold increase in the apparent oral clearance of Nevirapine as treatment continues from a single dose to two-to-four weeks of dosing with 200-400 mg/day. Autoinduction also results in a corresponding decrease in the terminal phase half-life of Nevirapine in plasma from approximately 45 hours (single dose) to approximately 25-30 hours following multiple dosing with 200-400 mg/day.

INDICATIONS

Nepine® is indicated in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infected adults, adolescents, and children of any age.

Most of the experience with Nepine® is in combination with nucleoside reverse transcriptase inhibitors (NRTIs). The choice of a subsequent therapy after Nepine® should be based on clinical experience and resistance testing.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Readministration to patients who have required permanent discontinuation for severe rash, rash accompanied by constitutional symptoms, hypersensitivity reactions, or clinical hepatitis due to Nevirapine.
- Patients with severe hepatic impairment (Child-Pugh C) or pre-treatment ASAT or ALAT > 5 ULN until baseline ASAT/ALAT are stabilized < 5 ULN.
- Readministration to patients who previously had ASAT or ALAT > 5 ULN during Nevirapine therapy and had recurrence of liver function abnormalities upon readministration of Nevirapine.
- Herbal preparations containing St. John's wort *(Hypericum perforatum)* must not be used while taking Nevirapine due to the risk of decreased plasma concentrations and reduced clinical effects of Nevirapine.

PRECAUTIONS

- Nevirapine should only be used with at least two other antiretroviral agents.
- 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 Nevirapine are a critical period which requires close monitoring of patients to disclose the potential appearance of severe and life-threatening skin reactions (including cases of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN)) and serious hepatitis/hepatic failure. The greatest risk of hepatic events and skin reactions occurs in the first 6 weeks of therapy. However, the risk of any hepatic event continues past this period and monitoring should continue at frequent intervals. Female gender and higher CD4 counts (>250/mm3 in adult females and >400/mm3 in adult males) at the initiation of Nevirapine therapy are associated with a greater risk of hepatic adverse events if the patient has detectable plasma HIV-1 RNA - i.e. a concentration ≥ 50 copies/ml - at the initiation of Nevirapine. As serious and life threatening hepatotoxicity has been observed in controlled and uncontrolled studies predominantly in patients with a plasma HIV-1 viral load of 50 copies/ml or higher, Nevirapine should not be initiated in adult females with CD4 cell counts greater than 250 cells/mm3 or in adult males with CD4 cell counts greater than 400 cells/mm3, who have a detectable plasma HIV-1 RNA unless the benefit outweighs the risk.

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

The dose must be strictly adhered to, especially the 14-days lead-in period.

- Cutaneous reactions: Severe and life-threatening skin reactions, including fatal cases, have occurred in patients treated with Nevirapine mainly during the first 6 weeks of therapy. These have included cases of Stevens - Johnson syndrome, toxic epidermal necrolysis and hypersensitivity reactions characterized by rash, constitutional findings and visceral involvement. Patients should be intensively monitored during the first 18 weeks of treatment. Patients should be closely monitored if an isolated rash occurs. Nevirapine 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 edema, muscle or joint aches, or general malaise), including Stevens - Johnson syndrome, or toxic epidermal necrolysis. Nevirapine must be permanently discontinued in any patient experiencing hypersensitivity reaction (characterized by rash with constitutional symptoms, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction).

Nevirapine administration above the recommended dose might 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 Nevirapine use.

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 incidence and severity of rash during the first 6 weeks of Nevirapine therapy.

Some risk factors for developing serious cutaneous reactions have been identified; they include failure to follow the initial dosing of 200 mg daily during the lead-in period and a long delay between the initial symptoms and medical consultation. Women appear to be at higher risk than men of developing rash, whether receiving Nevirapine or non- Nevirapine containing therapy.

Patients should be instructed that a major toxicity of Nevirapine is rash. They should be advised to promptly notify their physician of any rash and avoid delay between the initial symptoms and medical consultation. The majority of rashes associated with Nevirapine occur within the first 6 weeks of initiation of therapy. Therefore, patients should be monitored carefully for the appearance of rash during this period. Patients should be instructed that dose escalation is not to occur if any rash occurs during the two-week lead-in dosing period, until the rash resolves. The 200 mg once daily dosing regimen should not be continued beyond 28 days at which point in time an alternative treatment should be sought due to the possible risk of underexposure and resistance.

Any patient experiencing severe rash or a rash accompanied by constitutional symptoms such as fever, blistering, oral lesions, conjunctivitis, facial edema, muscle or joint aches, or general malaise should discontinue the medicinal product and immediately seek medical evaluation. In these patients Nevirapine must not be restarted.

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

If a hypersensitivity reaction occurs, characterized by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction, Nevirapine must be permanently stopped and not be re-introduced.

- Hepatic reactions: Severe and life-threatening hepatoxicity, including fatal fulminant hepatitis, has occurred in patients treated with Nevirapine. The first 18 weeks of treatment is a critical period which requires close monitoring. The risk of hepatic events is greatest in the first 6 weeks of therapy. However the risk continues past this period and monitoring should continue at frequent intervals throughout treatment.

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

Increased ASAT or ALAT levels > 2.5 ULN and/or co-infection with hepatitis B and/or C at the start of antiretroviral therapy is associated with greater risk of hepatic adverse reactions during antiretroviral therapy in general, including Nevirapine containing regimens.

Female gender and higher CD4 counts at the initiation of Nevirapine therapy in treatment-naïve patients is associated with increased risk of hepatic adverse events. Women have a three fold higher risk than men for symptomatic, often rash-associated, hepatic events (5.8% versus 2.2%), and treatment-naïve patients of either gender with detectable HIV-1 RNA in plasma with higher CD4 counts at initiation of Nevirapine therapy are at higher risk for symptomatic hepatic events with Nevirapine. In a retrospective review of predominantly patients with a plasma HIV-1 viral load of 50 copies/ml or higher, women with CD4 counts >250 cells/mm3 had a 12 fold higher risk of symptomatic hepatic adverse events compared to women with CD4 counts <250 cells/mm3 (11.0% versus 0.9%). An increased risk was observed in men with detectable HIV-1 RNA in plasma and CD4 counts > 400 cells/mm3 (6.3% versus 1.2% for men with CD4 counts <400 cells/mm3). This increased risk for toxicity based on CD4 count thresholds 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 Nevirapine requiring close monitoring during the first 18 weeks. They should be informed that occurrence of symptoms suggestive of hepatitis should lead them to discontinue Nevirapine and immediately seek medical evaluation, which should include liver function tests.

- Liver monitoring: Clinical chemistry tests, which include liver function tests, should be performed prior to initiating Nevirapine therapy and at appropriate intervals during therapy.

Abnormal liver function tests have been reported with Nevirapine, some in the first few weeks of therapy.

Asymptomatic elevations of liver enzymes are frequently described and are not necessarily a contraindication to use Nevirapine. Asymptomatic GGT elevations are not a contraindication to continue therapy.

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

If ASAT or ALAT > 2.5 ULN before or during treatment, then liver tests should be monitored more frequently during regular clinic visits. Nevirapine must not be administered to patients with pre-treatment ASAT or ALAT > 5 ULN until baseline ASAT/ALAT are stabilized < 5 ULN.

Physicians and patients should be vigilant for prodromal signs or findings of hepatitis, such as anorexia, nausea, jaundice, bilirubinuria, acholic stools, hepatomegaly or liver tenderness. Patients should be instructed to seek medical attention promptly if these occur.

If ASAT or ALAT increase to > 5 ULN during treatment, Nevirapine should be immediately stopped. If ASAT and ALAT 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 Nevirapine, on a case by case basis, at the starting dose regimen of 200 mg/day for 14 days followed by 400 mg/day. In these cases, more frequent liver monitoring is required. If liver function abnormalities recur, Nevirapine should be permanently discontinued.

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

- Liver disease: The safety and efficacy of Nevirapine has not been established in patients with significant underlying liver disorders. Nevirapine is contraindicated in patients with severe hepatic impairment (Child-Pugh C). Pharmacokinetic results suggest caution should be exercised when Nevirapine is administered to patients with moderate hepatic dysfunction (Child-Pugh B). Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events. In the case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products.

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

- Other warnings: Post-Exposure-Prophylaxis: Serious hepatotoxicity, including liver failure requiring transplantation, has been reported in HIV-uninfected individuals receiving multiple doses of Nevirapine in the setting of post-exposure-prophylaxis (PEP), an unapproved use. The use of Nevirapine has not been evaluated within a specific study on PEP, especially in term of treatment duration and therefore, is strongly discouraged.

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

Combination therapy with Nevirapine has not been shown to eliminate the risk of transmission of HIV-1 to others through sexual contact or contaminated blood.

Hormonal methods of birth control other than Depo-medroxyprogesterone acetate (DMPA) should not be used as the sole method of contraception in women taking Nevirapine, since Nevirapine might lower the plasma concentrations of these medicinal products. For this reason, and to reduce the risk of HIV transmission, barrier contraception (e.g., condoms) is recommended. Additionally, when postmenopausal hormone therapy is used during administration of Nevirapine, its therapeutic effect should be monitored.

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

In clinical studies, Nevirapine has been associated with an increase in HDL- cholesterol and an overall improvement in the total to HDL-cholesterol ratio. However, in the absence of specific studies with Nevirapine on modifying the cardiovascular risk in HIV infected patients, the clinical impact of these findings is not known. The selection of antiretroviral medicinal products must be guided primarily by their antiviral efficacy.

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Osteonecrosis: Although the etiology 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.

Immune Reactivation Syndrome: In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterial infections, and *Pneumocystis jiroveci* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

The available pharmacokinetic data suggest that the concomitant use of rifampicin and Nevirapine is not recommended.

Granulocytopenia is commonly associated with zidovudine. Therefore, patients who receive Nevirapine and zidovudine concomitantly and especially pediatric 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 hematological parameters should be carefully monitored.

Ability to drive and use machines

There are no specific studies about the ability to drive vehicles and use machinery.

However, patients should be advised that they may experience adverse reactions such as fatigue during treatment with Nevirapine. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience fatigue they should avoid potentially hazardous tasks such as driving or operating machinery.

PREGNANCY AND LACTATION

Women of childbearing potential should not use oral contraceptives as the sole method for birth control; since Nevirapine might lower the plasma concentrations of these medications.

Currently available data on pregnant women indicate no malformative or feto/ 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. Caution should be exercised when prescribing Nevirapine to pregnant women. As hepatotoxicity is more frequent in women with CD4 cell counts above 250 cells/mm3 with detectable HIV-1 RNA in plasma (50 or more copies/ml), these conditions should be taken in consideration on therapeutic decision. There is not enough evidence to substantiate that the absence of an increased risk for toxicity seen in pre-treated women initiating Nevirapine with an undetectable viral load (less than 50 copies/ml of HIV-1 in plasma) and CD4 cell counts above 250 cells/mm3 also applies to pregnant women. All the randomized studies addressing this issue specifically excluded pregnant women, and pregnant women were under-represented in cohort studies as well as in meta-analysis.

Nevirapine readily crosses the placenta and is found in breast milk.

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

DRUG INTERACTIONS

Nevirapine is an inducer of CYP3A and potentially CYP2B6, with maximal induction occurring within 2-4 weeks of initiating multiple-dose therapy.

Compounds using this metabolic pathway may have decreased plasma concentrations when co-administered with Nevirapine. Careful monitoring of the therapeutic effectiveness of P450 metabolized medicinal products is recommended when taken in combination with Nevirapine.

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

Antiretrovirals

- NRTIs: Granulocytopenia is commonly associated with zidovudine. Therefore, patients who receive Nevirapine and zidovudine concomitantly and especially pediatric 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 hematological parameters should be carefully monitored.
- NNRTIs: It is not recommended to co-administer efavirenz and Nevirapine, because of additive toxicity and no benefit in terms of efficacy over either NNRTI alone.
- PIs: It is not recommended to co-administer atazanavir/ritonavir and Nevirapine.

It is not recommended to co-administer fosamprenavir and Nevirapine if fosamprenavir is not co-administered with ritonavir.

An increase in the dose of lopinavir/ritonavir to 533/133 mg (4 capsules) or 500/125 mg (5 tablets with 100/25 mg each) twice daily with food is recommended in combination with Nevirapine. Dose adjustment of Nevirapine is not required when co-administered with lopinavir.

For children, increase of the dose of lopinavir/ritonavir to 300/75 mg/m2twice daily with food should be considered when used in combination with Nevirapine, particularly for patients in whom reduced susceptibility to lopinavir/ritonavir is suspected.

Antibiotics

- Clarithromycin exposure was 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.
- No significant effect on rifabutin and Nevirapine mean PK parameters is seen. Rifabutin and Nevirapine can be co-administered without dose adjustments. However, due to the high interpatient variability some patients may experience large increases in rifabutin exposure and may be at higher risk for rifabutin toxicity. Therefore, caution should be used in concomitant administration.
- It is not recommended to co-administer rifampicin and Nevirapine. Physicians needing to treat patients co-infected with tuberculosis and using a Nevirapine containing regimen may consider co-administration of rifabutin instead.

Antifungals

- Because of the risk of increased exposure to Nevirapine, caution should be exercised if the medicinal products are given concomitantly and patients should be monitored closely.
- A dose increase for itraconazole should be considered when these two agents are administered concomitantly.
- It is not recommended to co-administer ketoconazole and Nevirapine.

Antithrombotics

Warfarin: Close monitoring of anticoagulation levels is warranted.

Contraceptives

Oral hormonal contraceptives should not be used as the sole method of contraception in women taking Nevirapine. Appropriate doses for hormonal contraceptives (oral or other forms of application) other than DMPA in combination with Nevirapine have not been established with respect to safety and efficacy.

Drug abuse

Methadone-maintained patients beginning Nevirapine therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.

Herbal products

Herbal preparations containing St. John's Wort and Nevirapine must not be co-administered. 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 Nevirapine may need adjusting. The inducing effect may persist for at least 2 weeks after cessation of treatment with St. John's Wort.

Other information:

Nevirapine metabolites: Studies using human liver microsomes indicated that the formation of Nevirapine hydroxylated metabolites was not affected by the presence of dapsone, rifabutin, rifampicin, and trimethoprim/sulfamethoxazole. Ketoconazole and erythromycin significantly inhibited the formation of Nevirapine hydroxylated metabolites.

ADVERSE EFFECTS

The most frequently reported adverse reactions related to Nevirapine therapy, across all clinical studies, were rash, allergic reactions, hepatitis, abnormal liver function tests, nausea, vomiting, diarrhea, abdominal pain, fatigue, fever, headache and myalgia.

The postmarketing experience has shown that the most serious adverse reactions are Stevens-Johnson syndrome/ toxic epidermal necrolysis, serious hepatitis/hepatic failure, and drug rash with eosinophilia and systemic symptoms, characterized by rash with constitutional symptoms such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction. The first 18 weeks of treatment is a critical period which requires close monitoring.

The following adverse reactions which may be causally related to the administration of Nevirapine have been reported.

Frequency is defined using the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

- Blood and lymphatic system disorders: Granulocytopenia (common); anemia (uncommon).
- Immune system disorders: Hypersensitivity (incl. anaphylactic reaction, angioedema, urticaria) (common); anaphylactic reaction (uncommon); drug rash with eosinophilia and systemic symptoms (rare).
- Nervous system disorders: Headache (common).
- Gastrointestinal disorders: Nausea, vomiting, abdominal pain, diarrhea (common).
- Hepatobiliary disorders: Hepatitis (including severe and life-threatening hepatotoxicity) (1.9%) (common); jaundice (uncommon); fulminant hepatitis (which may be fatal) (rare).
- Skin and subcutaneous tissue disorders: Rash (12.5%) (very common); Stevens-Johnson syndrome/ toxic epidermal necrolysis (which may be fatal) (0.2%), angioedema, urticaria (uncommon).
- Musculoskeletal and connective tissue disorders: Arthralgia, myalgia (uncommon).
- General disorders and administration site conditions: Pyrexia, fatigue (common).
- Investigations: liver function test abnormal (alanine aminotransferase increased; transaminases increased; aspartate aminotransferase increased; gamma-glutamyltransferase increased; hepatic enzyme increased; hypertransaminasemia) (common); blood phosphorus decreased; blood pressure increased (uncommon).

Description of selected adverse reactions

Patients on placebo had a higher incidence of events of granulocytopenia than patients on Nevirapine.

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

Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV-infected patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridemia, hypercholesterolemia, insulin resistance, hyperglycemia and hyperlactatemia.

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

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise.

Cases of osteonecrosis have been reported, particularly in patients with generally acknowledged risk factors, advanced HIV disease or long-term exposure to combination antiretroviral therapy (CART). The frequency of this is unknown.

Skin and subcutaneous tissues

The most common clinical toxicity of Nevirapine is rash.

Rashes are usually mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, located on the trunk, face and extremities. Hypersensitivity (anaphylactic reaction, angioedema and urticaria) have been reported. Rashes occur alone or in the context of drug rash with eosinophilia and systemic symptoms, characterized by rash with constitutional symptoms such as fever, arthralgia, myalgia and lympadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction.

Severe and life-threatening skin reactions have occurred in patients treated with Nevirapine, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Fatal cases of SJS, TEN and drug rash with eosinophilia and systemic symptoms have been reported. The majority of severe rashes occurred within the first 6 weeks of treatment and some required hospitalization, with one patient requiring surgical intervention.

Hepato-biliary

The most frequently observed laboratory test abnormalities are elevations in liver function tests (LFTs), including ALAT, ASAT, GGT, total bilirubin and alkaline phosphatase. Asymptomatic elevations of GGT levels are the most frequent. Cases of jaundice have been reported. Cases of hepatitis (severe and life-threatening hepatotoxicity, including fatal fulminant hepatitis) have been reported in patients treated with nevirapine. 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.

Pediatric population

In pediatric patients with the majority receiving combination treatment with ZDV or/and ddI, the most frequently reported adverse events related to Nevirapine were similar to those observed in adults. Granulocytopenia was more frequently observed in children. Isolated cases of Stevens-Johnson syndrome or Stevens-Johnson/ toxic epidermal necrolysis transition syndrome have been reported in this population.

DOSAGE AND ADMINISTRATION

Nepine® should be administered by physicians who are experienced in the treatment of HIV infection.

Posology

Patients 16 years and older.

The recommended dose of Nepine® is one 200 mg tablet daily for the first 14 days (this lead-in period should be used because it has been found to lessen the frequency of rash), followed by one 200 mg tablet twice daily, in combination with at least two additional antiretroviral agents.

If a dose is recognized as missed within 8 hours of when it was due, the patient should take the missed dose as soon as possible. If a dose is missed and it is more than 8 hours later, the patient should only take the next dose at the usual time.

Dose management considerations

Patients experiencing rash during the 14-day lead-in period of 200 mg/day should not have their Nepine® dose increased until the rash has resolved. The isolated rash should be closely monitored. The 200 mg once daily dosing regimen should not be continued beyond 28 days at which point in time an alternative treatment should be sought due to the possible risk of underexposure and resistance.

Patients who interrupt Nepine® dosing for more than 7 days should restart the recommended dosing regimen using the two week lead-in period.

Special populations

- Elderly: Nevirapine has not been specifically investigated in patients over the age of 65.
- Renal impairment: For patients with renal dysfunction requiring dialysis an additional 200 mg dose of Nepine® following each dialysis treatment is recommended. Patients with CLcr ≥ 20 ml/min do not require a dose adjustment.
- Hepatic impairment: Nepine® should not be used in patients with severe hepatic impairment (Child-Pugh C). No dose adjustment is necessary in patients with mild to moderate hepatic impairment.
- Pediatric population: Nepine® 200 mg tablets, following the dosing schedule described above, are suitable for larger children, particularly adolescents, below the age of 16 who weigh more than 50 kg or whose body surface area is above 1.25 m2 according to the Mosteller formula.

Method of administration

The tablets shall be taken with liquid, and should not be crushed or chewed. Nepine® may be taken with or without food.

OVERDOSAGE

There is no known antidote for Nevirapine overdose. 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 edema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, increase in transaminases and weight decrease. All of these effects subsided following discontinuation of Nevirapine.

Pediatric Population

One case of massive accidental overdose in a newborn was reported. The ingested dose was 40 times the recommended dose of 2mg/kg/day. Mild isolated neutropenia and hyperlactatemia was observed, which spontaneously disappeared within one week without any clinical complications. One year later, the child's development remained normal.

STORAGE CONDITIONS

Store below 25°C.

Keep in original pack in intact conditions.

Date of revision: April 2013

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

Manufactured by Hetero Labs Limited, India
Packed by Benta S.A.L., Lebanon

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