Professional Information

SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM):

MIVIRDO (film-coated tablets)

COMPOSITION:

Each film-coated tablet contains:

Lamivudine	150 mg
Nevirapine	200 mg
Zidovudine	300 mg

Excipients:

Colloidal silicon dioxide, FD&C Blue # 2, hydroxypropyl methyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate, titanium dioxide and triacetin.

Lactose monohydrate (sugar) 100 mg

WARNING:

THE FIRST 18 WEEKS OF TREATMENT WITH NEVIRAPINE, AND THEREFORE MIVIRDO, IS A CRITICAL PERIOD THAT NECESSITATES INTENSIVE MONITORING OF PATIENTS TO IDENTIFY THE POTENTIAL DEVELOPMENT OF SEVERE AND LIFE-THREATENING SKIN REACTIONS (INCLUDING CASES OF STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS) OR SERIOUS HEPATITIS/HEPATIC FAILURE. THE RISK OF HEPATIC EVENTS AND SKIN REACTIONS IS GREATEST DURING THE FIRST 6 WEEKS OF THERAPY. HOWEVER, THE RISK OF ANY HEPATIC EVENT CONTINUES BEYOND THIS PERIOD AND PATIENTS REQUIRE CONTINUED MONITORING AT FREQUENT INTERVALS. THE RISK OF HEPATIC ADVERSE EVENTS IS INCREASED IN WOMEN (3,2-FOLD) AND PATIENTS WITH CD+ COUNTS (WOMEN WITH CD4+ > 250, 9,8-FOLD; MEN WITH CD+ > 400, 6,4-FOLD). IT IS IMPORTANT THAT THE DOSAGE, ESPECIALLY THE 14 DAYS

LEAD-IN PERIOD, IS STRICTLY ADHERED TO (SEE "DOSAGE AND DIRECTIONS FOR USE").

Cutaneous reactions:

Severe and life-threatening skin reactions, which were fatal in some instances, have occurred in patients who received nevirapine, as contained in MIVIRDO. Such reactions 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 who develops a 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 stop taking MIVIRDO and immediately seek medical evaluation. In these patients, nevirapine, and therefore MIVIRDO, must not be reintroduced.

Liver function tests should be performed in all patients who present with suspected nevirapine-associated rash. Nevirapine, and therefore MIVIRDO, should be permanently discontinued in patients with moderate to severe elevations [aspartate transaminase (AST) or alanine aminotransferase (ALT) > 5 x Upper Limit of Normal (ULN)].

If a hypersensitivity syndrome develops, 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, and therefore MIVIRDO, should be permanently discontinued and not be reintroduced.

Hepatic reactions:

Severe or life-threatening hepatotoxicity, including fatal fulminant hepatitis, has developed in patients who received nevirapine, as contained in MIVIRDO. There have been reports of serious hepatitis and hepatic failure in nevirapine-treated patients. Increased aspartate transaminase (AST) or alanine aminotransferase (ALT) levels > 2,5 x ULN and/or hepatitis B and/or C co-infection at the onset of antiretroviral treatment is associated with a greater risk of hepatic adverse reactions during antiretroviral therapy with nevirapine-containing regimens, such as MIVIRDO. If AST or ALT > 2,5 x ULN prior to or during treatment, liver function tests require more frequent monitoring during regular clinic visits. MIVIRDO should not be prescribed to patients with pretreatment AST or ALT > 5 x ULN.

If aspartate transaminase (AST) or alanine aminotransferase (ALT) increase to > 5 x ULN during treatment, nevirapine (and therefore MIVIRDO) should be discontinued

immediately and not restarted. If aspartate transaminase (AST) and alanine aminotransferase (ALT) levels return to baseline values, it may be possible to reintroduce nevirapine on an individual basis, at the starting dosage regimen of 200 mg/day for 14 days followed by 400 mg/day. If hepatic function abnormalities rapidly recur, treatment with nevirapine should be permanently discontinued.

If clinical hepatitis develops, characterised by anorexia, nausea, vomiting, icterus and laboratory findings [such as moderate or severe liver function test abnormalities (excluding GGT)], nevirapine, and therefore MIVIRDO, must be permanently discontinued. Patients who required permanent discontinuation of treatment for clinical hepatitis due to nevirapine must never be given MIVIRDO again.

Nevirapine, and therefore MIVIRDO, should be permanently discontinued 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, and therefore MIVIRDO, should not be reintroduced in these circumstances.

PHARMACOLOGICAL CLASSIFICATION:

A.20.2.8 Antiviral agents

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

Nevirapine:

Nevirapine, a non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1, binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by disrupting the enzyme's catalytic site.

Lamivudine and zidovudine:

Zidovudine and lamivudine are nucleoside analogues that both selectively inhibit HIV-1 and HIV-2. It has been demonstrated that lamivudine and zidovudine act synergistically by inhibiting HIV replication in cell culture.

Intracellular kinases metabolise both medicines sequentially to their 5[1]-triphosphate (TP) forms.

Zidovudine-TP and lamivudine-TP are both substrates for and competitive inhibitors of HIV reverse transcriptase enzymes. The main antiviral activity of these two antiretrovirals is through incorporation of their monophosphate forms into the viral DNA chain, thus giving rise to chain termination.

Treatment with lamivudine or zidovudine has led to the development of resistant viral strains. Treatment with lamivudine and zidovudine individually has given rise to HIV clinical isolates which demonstrated reduced sensitivity *in vitro* to the nucleoside analogue to which they have been exposed. In the presence of M184V mutations, zidovudine-resistant virus isolates can become zidovudine sensitive. There is clinical evidence *in vivo* that the combination of zidovudine plus lamivudine delays the emergence of zidovudine resistance in antiretroviral naïve patients.

Resistance:

HIV isolates demonstrating significantly reduced susceptibility (100–250-fold) to nevirapine emerge *in vitro*. Time to development of nevirapine resistance *in vitro* was not modified when selection included nevirapine in combination with several other NNRTIs.

Cross-resistance:

Rapid emergence of HIV strains (such as K103N mutation), which are cross-resistant to NNRTIs *in vitro*, have been reported.

Pharmacokinetics:

Nevirapine:

Absorption:

Nevirapine is readily absorbed (> 90 %) following oral administration in healthy volunteers and in adults infected with HIV-1. Following administration of nevirapine 200 mg tablets to healthy volunteers under testing conditions, peak plasma concentrations (C_{max}) of about 2,0 to 2,5 µg/mℓ are attained at about 4 hours. After multiple doses, nevirapine peak concentrations have been shown to increase nearly 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 achieved 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).

Distribution:

Nevirapine, a highly lipophilic compound, is essentially non-ionised at physiologic pH. Subsequent to intravenous administration to healthy adults, the apparent volume of distribution at steady state (V_{dss}) of nevirapine was 1,21 ± 0,09 ℓ/kg, which indicates that nevirapine is widely distributed in humans. Nevirapine readily crosses the placenta and is excreted in breast milk.

Nevirapine is approximately 60 % bound to plasma proteins in the plasma concentration range of 1 – 10 µg/mℓ. Nevirapine concentrations in human cerebrospinal fluid are approximately 45 % of the concentrations in plasma: this ratio is more or less equal to the fraction not bound to plasma proteins.

Metabolism:

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.

Nevirapine induces hepatic cytochrome P450 metabolic enzymes. Nevirapine autoinduction results in 1,5- to 2-fold increase in metabolism. This autoinduction thus gives rise to a corresponding decrease in the terminal phase plasma half-life of nevirapine from about 45 hours (single dose) to approximately 25 – 30 hours following multiple dosing with 200 – 400 mg/day. This effect is at its highest 14 days after initiation of therapy.

Elimination:

Approximately 91,4 ± 10,5 % of a radiolabelled dose was recovered, with urine (81,3 ± 11,1 %) representing the primary role of excretion compared to faeces (10,1 ± 1,5 %).

Lamivudine:

Absorption:

Lamivudine is well absorbed from the gastrointestinal tract. The bioavailability of oral lamivudine in adults is 80 – 85 %.

Following the administration of zidovudine and lamivudine in combination lamivudine C_{max} is 1,5 (1,3 – 1,8) µg/mℓ. Lamivudine's median (range) t_{max} value is 0,75 (0,50 -2,00) hours. The extent of lamivudine absorption (AUC) and estimate of half-life after administration in combination with food are comparable to those observed in fasting subjects, although the rate of absorption (C_{max} t_{max}) is slowed. Lamivudine may be taken with or without food.

Distribution:

Intravenous studies have demonstrated that lamivudine's mean apparent volume of distribution is 1,3 ℓ/kg.

Lamivudine displays linear pharmacokinetics over the therapeutic dose range and binds to a limited extent to the major plasma protein, albumin (< 36 % serum albumin *in vitro*). Interactions with lamivudine due to binding site displacements are not anticipated.

It has been demonstrated that lamivudine penetrates the central nervous system and that it reaches the cerebrospinal fluid (CSF). The mean ratio of CSF to serum lamivudine concentration 2 – 4 hours following oral ingestion is approximately 0,12. The true extent of lamivudine penetration or relationship with any clinical efficacy remains unknown.

Metabolism:

Metabolism of lamivudine plays a minor role in its elimination. It is predominantly cleared by the renal route as unchanged compound. Metabolic substance interactions with lamivudine are therefore unlikely due to minimal hepatic metabolism (5 – 10 %) and low plasma protein binding.

Elimination:

Lamivudine has an observed elimination half-life of 5 to 7 hours. The mean systemic clearance of lamivudine is approximately 0,32 ℓ/h/kg. This is predominantly by the renal route (> 70 %) via the organic cationic transport system.

Zidovudine:

Absorption:

Zidovudine is well absorbed from the gastrointestinal tract. The bioavailability of oral zidovudine in adults is 60 – 70 %.

Following the administration of zidovudine and lamivudine in combination, zidovudine's C_{max} is 1,8 (1,6 – 2,2) µg/mℓ. Zidovudine's median (range) t_{max} value is 0,50 (0,25 – 2,00) hours. The extent of zidovudine absorption (AUC) and estimate of half-life after administration in combination with food are comparable to those observed in fasting subjects, although the rate of absorption (C_{max} t_{max}) is slowed. Zidovudine may be taken with or without food.

Distribution:

Intravenous studies have demonstrated that zidovudine has a mean apparent volume of distribution of 1,6 ℓ/kg.

Plasma protein binding of zidovudine is 34 – 38 %. Interactions due to binding site displacements are not anticipated with zidovudine.
It has been demonstrated that zidovudine penetrates the central nervous system and that it reaches the cerebrospinal fluid (CSF). The mean ratio of CSF to serum zidovudine concentration 2 – 4 hours following oral ingestion is approximately 0,5.

Metabolism:
The 5^1-glucuronide is the major metabolite of zidovudine in both plasma and urine. This metabolite accounts for approximately 50 – 80 % of the administered dose eliminated by the renal route. Subsequent to intravenous dosing, 3^1-amino-3^1-deoxylhymidine (AMT) has been identified as a metabolite of zidovudine.

Elimination:
Intravenous studies with zidovudine have shown a mean terminal plasma half-life of 1,1 hours and a mean systemic clearance of 1,6 ℓ/h/kg. The estimated renal clearance of zidovudine is 0,34 ℓ/h/kg which is indicative of both glomerular filtration and active tubular secretion by the kidneys.

Pharmacokinetics in special populations:
Renal/Hepatic dysfunction:

Nevirapine:
Renal impairment (mild, moderate and severe) does not significantly alter the pharmacokinetics of nevirapine. There is no information available on nevirapine pharmacokinetics in patients with end-stage kidney impairment who are not receiving haemodialysis.
While patients with mild hepatic dysfunction, defined as Child-Pugh Classification Score of 5 or 6, do not require nevirapine dosage adjustments, pharmacokinetics of nevirapine in patients with Child-Pugh score of 7 or with moderate to severe ascites indicate that patients with deteriorating hepatic function are at risk of accumulating nevirapine in the systemic circulation (see **"SPECIAL PRECAUTIONS"**).

Lamivudine:

Studies in patients with renal insufficiency have demonstrated that lamivudine elimination is influenced by renal dysfunction. Dose reduction is therefore necessary in patients with creatinine clearance < 50 mℓ/min (see **"DOSAGE AND DIRECTIONS FOR USE"**).

Zidovudine:

Patients with advanced renal failure display increased zidovudine concentrations.

The elderly:

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

INDICATIONS:

For treatment of HIV-1 infection:

1. **MIVIRDO** is only administered once the patient has completed the two (2) week lead-in period on the three (3) individual components; or
2. **MIVIRDO** is administered once the patient has been stabilised on the individual components at the same doses.

CONTRA-INDICATIONS:

MIVIRDO is contra-indicated in:

- Patients with known hypersensitivity to lamivudine, zidovudine, nevirapine or any other component of **MIVIRDO**.
- Patients with abnormally low neutrophil counts (< 0,75 x 10^9/ℓ), or abnormally low haemoglobin levels (< 7,5 g/dℓ or 4,65 mmol/ℓ) due to the zidovudine component.
- Children below the age of 12 years due to insufficient data, and because the dose (in a fixed dose combination) cannot be adjusted for this patient population.
- Combination with ribavirin or stavudine, since the combination of zidovudine with either ribavirin or stavudine is antagonistic *in vitro*. The concomitant use of either ribavirin or stavudine with **MIVIRDO** should be avoided.
- Patients with severe liver dysfunction, Child-Pugh class B or C, or in end-stage kidney failure not on haemodialysis due to the nevirapine component.

- Patients with pretreatment or during treatment values of aspartate transaminase (AST) or alanine aminotransferase (ALT) > 5 x ULN until baseline AST/ALT are stabilised < 5 x ULN due to the nevirapine component.
- Patients who have required permanent cessation of therapy for severe rash, rash accompanied by constitutional symptoms, hypersensitivity syndrome, or clinical hepatitis due to nevirapine.
- Patients who previously had aspartate transaminase (AST) or alanine aminotransferase (ALT) levels > 5 x ULN during nevirapine treatment or had rapid recurrence of hepatic function abnormalities upon re-administration of nevirapine (see **"WARNINGS"**).

WARNINGS:

WARNING:
The first 18 weeks of treatment with nevirapine (and therefore MIVIRDO) is a critical period and patients require intensive monitoring 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 risk of hepatic events and skin reactions is greatest during the first 6 weeks of therapy. Women (3,2-fold) and patients with higher CD4+ counts (women with CD4+ > 250, 0,8-fold; men with CD4+ > 400, 6,4-fold) have an increased risk of adverse events involving the liver. In addition, the dosage, particularly the 14 days lead-in period, must be firmly adhered to (see "DOSAGE AND DIRECTIONS FOR USE").

Skin reactions:

Patients should be informed that the major toxicity of nevirapine is skin rash. They should be advised to notify their doctor of any rash without delay. The dosing instructions during the lead-in period should be strictly followed because it has been found to lessen the frequency of rash (see **"DOSAGE AND DIRECTIONS FOR USE"**). The majority of rashes associated with nevirapine, as contained in **MIVIRDO,** develop within the first 6 weeks of

treatment; therefore, patients require careful monitoring for the appearance of any rash during this period. Patients should be educated that dose escalation is not to occur if any rash develops during the lead-in dosing period, until the rash has resolved.

Severe and life-threatening skin reactions, which were fatal in some instances, have occurred in patients who received nevirapine, as in **MIVIRDO**. Such reactions have included cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and hypersensitivity syndrome characterised by rash, constitutional findings and visceral involvement. Patients require careful monitoring during the first 18 weeks of therapy. Patients require close monitoring if an isolated rash occurs.

MIVIRDO must be permanently suspended if any patient demonstrating 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. **MIVIRDO** must be permanently suspended in any patient presenting with 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 administration of prednisone (40 mg/day for the first 14 days of nevirapine, and therefore **MIVIRDO** therapy) has been demonstrated 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, as in **MIVIRDO**, treatment.

Failure to follow the initial dosing of 200 mg daily during the lead-in period is a risk factor for developing serious cutaneous reactions.

A long hold-up between the initial symptoms and medical consultation may increase the risk of a graver outcome of cutaneous reactions. Women are at a 3,2-fold higher risk than men of experiencing rash. Women with a CD4+ count of > 250 cells/mm³ are at a 9,8-fold increased risk of experiencing rash.

Any patient developing 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 **MIVIRDO** and consult a medical practitioner. In these patients nevirapine, and therefore **MIVIRDO**, must not be reintroduced.

If patients present with a suspected nevirapine-associated rash, liver function tests should be obtained immediately. **MIVIRDO** should be permanently discontinued in patients with moderate to severe elevations (AST or ALT > 5 x ULN) of liver enzymes.

Nevirapine, and therefore **MIVIRDO**, should be permanently discontinued and not reintroduced in patients with hypersensitivity syndromes characterised by rash with constitutional symptoms, such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia and renal dysfunction.

Hepatic reactions:

Severe or life-threatening hepatotoxicity, including fatal fulminant hepatitis (transaminase elevations, with or without hyperbilirubinaemia, prolonged partial thromboplastin time or eosinophilia) has developed in patients who received nevirapine, as in **MIVIRDO**. Serious hepatitis and hepatic failure in nevirapine-treated patients have been reported to develop in the first 18 weeks of therapy, although some have occurred later. The first 18 weeks of

therapy is a critical period during which patients require close monitoring. The greatest risk of hepatic events occurs in the first 6 weeks of therapy. The risk of hepatic adverse reactions is increased in women (3,2-fold) and patients with higher CD4+ counts (women with CD4+ > 250, 9,8-fold; men with CD4+ > 400, 6,4-fold). However, the risk continues past this period and patients require continued monitoring at frequent intervals throughout treatment. Patients should be informed that liver adverse events are a major toxicity of nevirapine, and therefore **MIVIRDO**, and that they should contact their doctor promptly if they experience symptoms suggestive of hepatitis.

Increased aspartate transaminase (AST) or alanine aminotransferase (ALT) levels >2,5 x ULN at the initiation of antiretroviral therapy is associated with greater (3,2 – 4,2-fold) risk of hepatic adverse reactions during antiretroviral treatment with nevirapine-containing regimens, such as **MIVIRDO**.

One of the contra-indications to nevirapine, and therefore **MIVIRDO**, is severe underlying liver disorders. Patients with chronic hepatitis B or C infection who receive combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions. In the case of concomitant antiviral therapy for hepatitis B or C, please also refer to the relevant package inserts for these medicines. Patients with pre-existing hepatic dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination therapy and require monitoring according to standard practice, if there is evidence of deterioration in liver function in such patients, interruption or discontinuation of treatment must be considered.

The risk for rash-associated hepatic events is three times greater in women than in men (4,6 % vs 1,5 %). Patients with higher CD4+ counts may also have an increased risk for

rash-associated hepatic adverse events with nevirapine, as contained in **MIVIRDO**.

In a retrospective review, women with CD4+ counts > 250 cells/mm³ had a 9,8-fold increased risk of rash-associated hepatic adverse reactions compared to women with CD4+ counts < 250 cells/mm³ (0,84 % vs 0,09 %). An increased risk (6,4-fold) was seen in men with CD4+ counts > 400 cells/mm³ compared to men with CD4+ counts < 400 cells/mm³ (4,5 % vs 0,7 %).

Patients should be informed that liver reactions are a major toxicity of nevirapine, and therefore **MIVIRDO**, and that they require close monitoring during the first 18 weeks of treatment. However, severe liver disease can develop after 18 weeks. Depending on their clinical status, patients may therefore require continued monitoring at frequent intervals after this period. Patients should contact their doctor promptly if they experience symptoms suggestive of hepatitis.

Haematological:

Anaemia, neutropenia and leucopenia (usually secondary to neutropenia) can be expected to develop in patients taking zidovudine (and therefore **MIVIRDO**) and who have advanced symptomatic HIV disease. Haematological parameters therefore require careful monitoring (see "**CONTRA-INDICATIONS**"). These haematological adverse effects usually do not manifest before four to six weeks of therapy. It is generally recommended that patients with advanced symptomatic HIV disease have blood tests at least every two weeks for the first three months of treatment and at least monthly thereafter. Haematological adverse reactions occur infrequently in patients with early HIV disease. Blood tests may be performed less frequently (e.g. every one to three months) depending on the overall condition of the patient. When the haemoglobin level decreases by more than 25 % from baseline and the neutrophil count falls by more than 50 % of baseline, more frequent monitoring may be necessary.

Additionally, it may be necessary to adjust zidovudine dosage in the following instances: severe anaemia or myelosuppression during treatment with **MIVIRDO**, pre-existing bone marrow compromise, e.g. haemoglobin < 9 g/dℓ (5,59 mmol/ℓ) or neutrophil count < 1,0 x 10^9/ℓ (see "**DOSAGE AND DIRECTIONS FOR USE**"). As dosage adjustment is not possible with a fixed dose combination such as **MIVIRDO**, zidovudine, lamivudine, and nevirapine should be administered as separate preparations. Medical practitioners should then refer to the individual package inserts of these medicines.

Gastrointestinal:

Pancreatitis was reported less frequently in patients treated with zidovudine and lamivudine. However, it is uncertain whether these cases were due to the medicines or to the underlying HIV disease. If clinical signs, symptoms or laboratory abnormalities suggestive of pancreatitis occur, **MIVIRDO** therapy should be discontinued immediately.

Metabolic:

Lactic acidosis, in the absence of hypoxemia, including fatal cases, and severe hepatomegaly with steatosis have been reported in patients treated with zidovudine. It is not known whether there is a causal relationship with zidovudine, but these events have been reported in HIV-positive patients without AIDS. In the setting of rapidly elevating aminotransferase levels, progressive hepatomegaly or metabolic/lactic acidosis of unknown aetiology, treatment with **MIVIRDO** should be suspended.

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of lamivudine alone or in combination in the treatment of HIV infection.

INTERACTIONS:

Nevirapine:

It has been shown that nevirapine is an inducer of hepatic cytochrome P450 metabolic enzymes (CYP3A, CYP2B). Administration of nevirapine may result in lower plasma levels 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 treatment with nevirapine, as in **MIVIRDO**, is initiated, dose adjustments may be required.

Protease inhibitors: In the following studies, 200 mg nevirapine was administered one 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 daily) leads to a 24 % mean reduction ($p = 0,041$) in saquinavir AUC and no significant change in nevirapine plasma levels. The reduction in saquinavir concentrations due to this interaction may further reduce the marginal plasma levels of saquinavir which are obtained with the hard gelatin capsule formulation. It is not known whether this interaction is clinically significant. Concomitant administration did not alter the pharmacokinetics of nevirapine.

Ritonavir: No dosage adjustments are necessary when nevirapine is given in combination with ritonavir.

Indinavir: Nevirapine and indinavir (800 mg three times daily) co-administration leads to a 28 % mean decrease ($p < 0,01$) in indinavir AUC and no significant change in nevirapine plasma concentrations. An indinavir dose increase to 1000 mg 8 hourly should be

considered when indinavir is administered with nevirapine 200 mg twice daily; however, there are no data currently on hand to ascertain that the short-term or long-term antiviral activity of indinavir 1000 mg 8 hourly in combination with nevirapine 200 mg twice daily will differ from that of indinavir 800 mg 8 hourly with nevirapine 200 mg twice daily.

Nelfinavir: Nevirapine, nelfinavir (750 mg three times daily) and stavudine (30 – 40 mg twice daily) given in combination do not produce 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, nelfinavir concentrations appear to be unchanged.

Ketoconazole:

Ketoconazole and nevirapine, and therefore **MIVIRDO**, should not be administered concomitantly. Co-administration of nevirapine 200 mg twice daily with ketoconazole 400 mg four times daily causes a significant reduction in ketoconazole parameters (63 % median reduction in ketoconazole AUC and a 40 % median reduction in ketoconazole C_{max}). Ketoconazole administration produces a 15 – 28 % increase in nevirapine plasma concentrations compared to historical controls.

Fluconazole:

Concurrent administration of fluconazole and nevirapine produces approximately 100 % increase in nevirapine exposure compared with historical data where nevirapine was given alone. Due to the risk of increased exposure to nevirapine, caution is required in nevirapine, and therefore **MIVIRDO**, and fluconazole are administered concomitantly and patients require close monitoring.

Anticoagulants:

There is a complex interaction between nevirapine and the anti-thrombotic agent warfarin *in vivo.* Consequently, when these medicines are given concomitantly, plasma warfarin concentrations 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 concomitant administration or cessation of therapy with nevirapine.

Prothrombin time INR requires more frequent monitoring when warfarin is co-administered with **MIVIRDO**.

CYP iso-enzymes inducers (e.g. rifampicin, rifabutin):

Nevirapine given in combination with rifampicin did not result in significant changes in rifampicin C_{max} and AUC. In contrast, rifampicin produced a significant reduction in nevirapine AUC (- 58 %), C_{max} (- 50 %) and C_{min} (- 68 %) compared to historical data. At present there are insufficient data to consider what dosage adjustments are necessary when nevirapine, as in **MIVIRDO**, and rifampicin are given concurrently.

Rifabutin:

Administration of nevirapine 200 mg twice daily with rifabutin 300 mg four times daily (or 150 mg four times daily if concomitantly taking ZDV or protease inhibitors), caused a significant increase in 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 levels. High interpatient variability, however, may cause some patients to experience large increase in rifabutin exposure, which may increase their risk for toxicity. In the same study, rifabutin administration produced an apparent significant increase in systemic clearance of nevirapine by 9 % compared to historical controls. Care is required when nevirapine, and therefore **MIVIRDO**, and rifabutin are co-administered with considerations of a decrease in the rifabutin dose. The dose of nevirapine need not be adjusted.

St. John's Wort:

Concurrent use of nevirapine, as in **MIVIRDO**, and St. John's Wort (*Hypericum perforatum*) or St. John's Wort-containing products, is not recommended as concomitant use of non-nucleoside reverse transcriptase inhibitors (NNRTIs), including nevirapine, with St. John's Wort is expected to decrease NNRTI levels. This may produce suboptimal nevirapine concentrations 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 %.

CYP iso-enzymes inhibitors (e.g. cimetidine and macrolides):

Nevirapine trough concentrations were raised in patients who received cimetidine (+ 21 %). The results of a nevirapine-clarithromycin interaction study demonstrated a significant reduction in clarithromycin AUC (- 30 %) and C_{max} (- 21 %) and C_{min} (- 45 %). However, there was no significant increase in the AUC (58 %) and C_{max} (62 %) of the active metabolite 14-OH-clarithromycin. A significant increase in the nevirapine C_{min} (28 %) and a non-significant increase in nevirapine AUC (26 %) and C_{max} (24 %) were also shown. Test results would indicate that no dose adjustment is required for either clarithromycin or nevirapine when the two medical products are given together. Close monitoring of liver abnormalities and activity against *Mycobacterium avium*-intracellular complex (MAC) is nevertheless recommended. It is further recommended that alternate therapy to clarithromycin be considered when treating a patient with *Mycobacterium avium*-intracelluler complex (MAC), as the active metabolite is not effective in this instance.

Oral contraceptives:

Alternate means of contraception (such as barrier methods) are recommended when nevirapine, as in **MIVIRDO**, is given to women of child-bearing potential, as oestrogen levels

are significantly decreased when used in combination with nevirapine. For other therapeutic indications requiring hormonal regulation, the therapeutic effect in patients who also take **MIVIRDO** should be monitored.

Methadone:

Based on the metabolism of methadone, the nevirapine in **MIVIRDO** may reduce plasma levels of methadone by increasing its hepatic metabolism. There have been reports of narcotic withdrawal symptoms in patients treated with nevirapine (and therefore **MIVIRDO**) and methadone concomitantly. Methadone-maintained patients starting therapy with **MIVIRDO** require monitoring for evidence of withdrawal and the methadone dose should be adjusted accordingly.

Other information on interactions:

It should be noted that the plasma levels of other compounds that are substrates of CYP3A or CYP2B5 may be reduced when co-administered with nevirapine, and therefore **MIVIRDO**.

Lamivudine and zidovudine:

Since **MIVIRDO** contains zidovudine and lamivudine, any interactions attributed to these agents individually may occur with **MIVIRDO**.

Metabolic interactions with lamivudine are unlikely due to its limited metabolism, minimal plasma protein binding and almost complete renal clearance.

Zidovudine also displays limited protein binding, but is eliminated primarily through hepatic conjugation to an inactive glucuronidated metabolite.

The interactions listed below are by no means complete, but are representative of the classes of medicine where caution is required.

Interactions relevant to lamivudine:

The possibility of interactions with other medicines co-administered with **MIVIRDO** should be considered, particularly those medicines which are mainly eliminated by active renal secretion, especially via the cationic transport system (e.g. trimethoprim). Other nucleoside analogues (e.g. zidovudine, didanosine and zalcitabine) and various other medicines (e.g. ranitidine, cimetidine) are only partly eliminated by this means and were shown not to interact with lamivudine.

Prophylactic doses of co-trimoxazole have caused a 40 % increase in lamivudine exposure, due to the trimethoprim component. There is no interaction with the sulphamethoxazole component. However, no dosage adjustment of lamivudine is necessary unless the patient has impaired renal function (see "**DOSAGE AND DIRECTIONS FOR USE**").

Patients who require concomitant administration of co-trimoxazole should be monitored clinically. The concomitant administration of **MIVIRDO** with high doses of co-trimoxazole, as used in the treatment of *Pneumocystis jerovii (carinii)* pneumonia (PCP) and toxoplasmosis, should be avoided. Lamivudine, on the other hand, does not affect the pharmacokinetics of co-trimoxazole at the doses studied.

Concomitant administration of lamivudine (and therefore **MIVIRDO**) with intravenous ganciclovir or foscarnet is not recommended until further information becomes available.
As lamivudine metabolism does not involve CYP3A, interactions with medicines metabolised by this system (e.g. protease inhibitors) are unlikely.

Interactions relevant to zidovudine:

Although a modest increase in zidovudine C_{max} (28 %) was noted following co-administration with lamivudine, overall exposure (AUC) did not change significantly. Zidovudine, alternatively, does not affect the pharmacokinetics of lamivudine.

Zidovudine AUC decreases by 48 % ± 34 % when co-administered with rifampicin. However, it is not known whether this is clinically significant.

Phenytoin concentrations should be carefully monitored in patients also receiving **MIVIRDO**, as phenytoin blood levels were reportedly low in some patients receiving zidovudine, while a high level was observed in a single patient.

The concomitant use of paracetamol with zidovudine in a placebo-controlled trial was associated with an increased incidence of neutropenia, especially following chronic therapy. However, available pharmacokinetic data suggest that paracetamol at the doses evaluated does not cause an increase in the plasma levels of either zidovudine or its glucuronide metabolite.

Other medicines, including, but not limited to, codeine, morphine, aspirin, indomethacin, ketoprofen, naproxen, cimetidine, clofibrate, dapsone, oxazepam, lorazepam and isoprinosine, may modify the metabolism of zidovudine by either direct inhibition of hepatic microsomal metabolism or competitive inhibition of glucuronidation. The possibilities of such interactions should therefore be considered carefully before using such medicines, especially for chronic therapy, in combination with **MIVIRDO**.

Concurrent treatment, particularly acute therapy, with potentially nephrotoxic or myelosuppressive medicines (e.g. systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, ganciclovir, interferon, flucytosine, vincristine, vinblastine and doxorubicin) may also increase the risk of adverse events with zidovudine (and therefore **MIVIRDO**).

If concurrent therapy with **MIVIRDO** and any of these medicines is unavoidable, then renal function and haematological parameters should be monitored with extra care, and, if required, the dosage of one or more of the agents should be reduced.

The combination of zidovudine with either stavudine or ribavirin is antagonistic *in vitro*. The concomitant use of these medicines with **MIVIRDO** should therefore be avoided (see **"CONTRA-INDICATIONS**").

Since some patients taking **MIVIRDO** may still develop opportunistic infections, the concomitant use of prophylactic antimicrobial therapy may be necessary. Such prophylactic medicines include co-trimoxazole, aerosolised pentamidine, pyrimethamine and acyclovir. Although the data from clinical trials are limited there is no indication of a significantly increased risk of adverse reactions to zidovudine with these medicines.
According to limited data, probenecid increases the mean AUC and half-life of zidovudine by decreasing glucuronidation. Probenecid also reduces renal excretion of the glucuronide metabolite (and possibly zidovudine itself).

PREGNANCY AND LACTATION:

The safety of **MIVIRDO** in pregnancy and lactation has not been established. Adequate contraceptive methods should be employed in women of child-bearing age.

DOSAGE AND DIRECTIONS FOR USE:

Adults and children over the age of 12 years:

MIVIRDO should only be administered to patients who are stabilised on the individual components at the same doses or who have completed an initial two (2) week lead-in period on the three individual components at the following doses:

- Lamivudine 300 mg daily, administered as either 300 mg once daily or 150 mg twice daily.
- Zidovudine 300 mg twice daily.
- Nevirapine 200 mg once daily.

Following this lead-in dosing period, a dose escalation (maintenance dose) of 200 mg nevirapine, as contained in **MIVIRDO**, twice a day may be carried out in the absence of severe gastrointestinal intolerance or any hypersensitivity reactions.

Recommended dose:

One **MIVIRDO** tablet twice daily with or without food.

A medical practitioner experienced in the management of HIV infection should initiate **MIVIRDO** therapy.

In situations where discontinuation of therapy with one of the active ingredients of **MIVIRDO** or dose reduction is required, separate preparations of lamivudine, zidovudine, and nevirapine, which are available in tablets/capsules and oral solution, should be used.

Patients should be instructed to take **MIVIRDO** every day as prescribed. Patients should not change 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 obtained before initiation of **MIVIRDO** therapy and at appropriate intervals during treatment (see "**WARNINGS**" and **Special Precautions**).

Dosage adjustment:

MIVIRDO should be discontinued if patients develop severe rash or a rash accompanied by constitutional findings (see "**WARNINGS**"). Patients who develop a rash during the 14-day

nevirapine lead-in period of 200 mg/day should not have their nevirapine dose increased until the rash has resolved (see "**WARNINGS**").

Treatment with **MIVIRDO** should be interrupted in patients demonstrating moderate liver function test abnormalities, e.g. AST or ALT < x ULN [excluding gamma-glutamyltransferase (GGT)]. If aspartate transaminase (AST) or alanine aminotransferase (ALT) levels return to baseline values and if the patient shows no clinical signs and symptoms of hepatitis or constitutional symptoms or other findings suggestive of organ dysfunction, it may be possible to reintroduce nevirapine, based on clinical needs and judgement, on an individual basis. Nevirapine may then be restarted at 200 mg daily increasing cautiously to 200 mg twice daily, after comprehensive observation. If the patient develops recurrence of moderate or severe liver function test abnormalities, nevirapine (and therefore **MIVIRDO**) should be permanently discontinued (see "**WARNINGS**").

Patients who interrupt **MIVIRDO** treatment for more than 7 days should restart treatment according to the lead-in dosing regimen using the individual medicines. The recommended dose of nevirapine is 200 mg daily for the first 14 days (lead-in) followed by 200 mg twice daily.

Renal Impairment:

The concentrations of lamivudine and zidovudine are increased in patients with impaired renal function due to decreased clearance. Therefore, as dosage adjustment of one or both of these may be required, it is recommended that separate preparations of lamivudine, zidovudine, and nevirapine be administered to patients with renal impairment (creatinine clearance ≤ 50 mℓ/min). The separate package inserts for zidovudine, lamivudine, and nevirapine must be consulted for full prescribing details and dosage adjustment.

Hepatic impairment:

The effect of liver impairment on lamivudine levels is under investigation. Lamivudine clearance is predominantly renal. However, it appears from limited data in patients with cirrhosis that zidovudine accumulation may occur in patients with impaired liver function due to decreased glucuronidation. It is therefore recommended that, since dosage adjustments of zidovudine may be necessary, separate preparations of lamivudine, zidovudine, and nevirapine are prescribed for patients with severe hepatic impairment. The package insert for zidovudine must be consulted for full prescribing details and dosage adjustments.

Dosage adjustments in patients with haematological adverse reactions:

It may be necessary to adjust the dosage of zidovudine if the haemoglobin level falls below 9 g/dℓ or 5,59 mmol/ℓ or the neutrophil count drops below 1,0 x 10^9/ℓ (see "**CONTRA-INDICATIONS**"). Patients with poor bone marrow reserve prior to treatment, particularly patients with advanced HIV disease, are more prone to these haematological effects. Separate preparations of zidovudine, lamivudine, and nevirapine should be used, as **MIVIRDO** dosage cannot be adjusted. Medical practitioners should refer to the individual package inserts of these medicines for full prescribing details.

Dosage in the elderly:

Special care is advised in the elderly due to age-associated changes, such as decrease in renal function and changes in haematological parameters.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

MIVIRDO can cause side-effects.

Nevirapine:

Blood and lymphatic disorders:

Less frequent: Granulocytopenia, anaemia.

Immune system disorders:

Frequent: Allergic reactions.

Less frequent: Hypersensitivity (syndrome), anaphylaxis, angioedema.

Nervous system disorders:

Frequent: Headache.

Gastrointestinal disorders:

Frequent: Nausea.

Less frequent: Vomiting, abdominal pain, diarrhoea.

Hepatobiliary disorders:

Frequent: Hepatitis, abnormal liver function tests.

Less frequent: Jaundice, liver failure/fulminant hepatitis.

Skin and subcutaneous tissue disorders:

Frequent: Rash.

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

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Myalgia, arthralgia.

General disorders:

Less frequent: Fatigue, fever.

Post marketing experience has revealed that the most serious adverse events 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 involvement, such as hepatitis, eosinophilla, granulocytopenia and kidney dysfunction. The first 18 weeks of treatment is a critical period, during which patients require close monitoring (see "**WARNINGS**").

Skin and subcutaneous tissues:

Rash is the most common clinical toxicity following nevirapine administration with 16 % of patients in combination regimens in Phase II/III controlled studies developing nevirapine-attributable rash. Overall 7 % of patients stopped nevirapine therapy due to rash.

Rashes are mostly mild to moderate, maculopapular erythematous cutaneous eruptions, with or without pruritus, occurring on the trunk, face and extremities. There have been reports of allergic reactions (anaphylaxis, angioedema and urticaria). Severe and life-threatening skin reactions have been reported in patients who received nevirapine (and therefore **MIVIRDO**), and these have included Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). There have been reports of fatal cases of SJS, TEN and hypersensitivity syndromes.

Rashes may develop in isolation 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.

Treatment with nevirapine (and therefore **MIVIRDO**) must be discontinued immediately in patients who experience a severe rash or a rash accompanied by constitutional symptoms. Most rashes of any severity develop within the first 6 weeks of treatment and some patients may require hospitalisation.

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

Group I: Erythema, pruritus.

Group IIA: One of the following clinical manifestations:

1. Diffuse erythematous macular or maculopapular cutaneous eruption or dry desquamation with or without pruritus without any additional constitutional findings as described in Group III being present.
2. Typical target lesions with the absence of 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 manifestations:

1. Extensive erythematous or maculopapular rash or moist desquamation with or without pruritus in combination with 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 medicine reaction.
    - Fever, defined as > 39 °C possibly related to the medicine reaction.
    - Blistering and/or vesiculation of cutaneous eruptions.

- One site of extensive mucosal lesions which are presumed to be due to a 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 reaction to a medicine.
4. Diffuse rash and serum sickness-like reactions defined as a clinical symptom complex presenting with fever, lymphadenopathy, oedema, myalgia and/or arthralgia.
5. Diffuse cutaneous eruptions, usually beginning on the face and trunk or back, often with prodromal symptoms (e.g. fever, general malaise, myalgia, arthralgia) with one or more of the following (usually referred to as Stevens-Johnson syndrome) in addition:
   - *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 attributable 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 beginning 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 necessary 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 presenting as fever, lymphadenopathy, oedema, myalgia, and/or arthralgia and the symptoms are considered to be related to nevirapine (and therefore **MIVIRDO**).

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

1. **Cutaneous eruption Groups I, IIA and IIB:**

   Treatment with nevirapine, and therefore **MIVIRDO**, may be continued for **Groups I, IIA and IIB.** Antihistamines, antipyretics and/or non-steroidal anti-inflammatory agents can be used to manage pruritus and minor accompanying symptoms. If **MIVIRDO** is suspended during a **Group I** or **IIA** reaction, nevirapine may be introduced once the cutaneous eruptions have cleared. The lead-in dosing regimen using the individual medicines should be followed. If **Group I or IIA** cutaneous eruptions develop during the nevirapine low dose lead-in period, dose escalation should not be undertaken until the cutaneous eruptions have resolved.

   If **Group IIB** cutaneous eruption develops during the low dose lead-in period, the nevirapine dose must not be escalated and if nevirapine treatment is suspended, it must not be reintroduced.

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

Treatment with nevirapine, and therefore **MIVIRDO,** must be permanently discontinued. No rechallenge is allowed. If symptoms develop during the low dose lead-in period that are indicative of a possible prodrome to a **Group III or IV** cutaneous eruption, dose escalation should be postponed until the possible prodrome has resolved or a non-nevirapine cause is established.

3. It is not allowed to rechallenge any patients who have experienced a **Group IIB, III or IV** cutaneous eruption with nevirapine, and therefore **MIVIRDO**.

Hepatobiliary:

The laboratory test abnormalities most frequently observed include elevations in liver function tests (LFTs), including aspartate transaminase (AST), alanine aminotransferase (ALT), y-glutamyl transpeptidase (GGT), total bilirubin and alkaline phosphatase. Of these, asymptomatic elevations of GGT levels are the most frequent. There have been reports of jaundice. Cases of hepatitis, severe and life-threatening hepatotoxicity and fatal fulminant hepatitis have reported in patients who received nevirapine, as contained in **MIVIRDO**.

The best predictor of a serious liver adverse event was elevated baseline liver function tests. The first 18 weeks of therapy is a critical period, during which patients require close monitoring, but such events may also develop later (see "**WARNINGS**"). The risk of developing a hepatic event is greatest during the first 6 weeks of therapy. However, the risk continues beyond this period and patients should be monitored at frequent intervals throughout treatment (see "**WARNINGS**").

Clinical hepatitis may occur in isolation or in association with rash and/or additional constitutional symptoms.

For monitoring of liver function tests, refer to **Special Precautions**.

The following events have further been reported when nevirapine, as contained in **MIVIRDO**, was administered in combination with other antiretroviral agents: anaemia, pancreatitis, lipodystrophy, peripheral neuropathy and thrombocytopenia.

Since **MIVIRDO** contains lamivudine and zidovudine, the type and severity of adverse events associated with the separate compounds may be expected.

Lamivudine:

Blood and lymphatic system disorders:

Less frequent: Anaemia and neutropenia (both occasionally severe) have occurred when used in combination with zidovudine.

Thrombocytopenia and pure red cell aplasia.

Metabolism and nutrition disorders:

Frequent: Hyperlactataemia.

Less frequent: Lactic acidosis, lipodystrophy (redistribution/accumulation of body fat).

Nervous system disorders:

Frequent: Headache, insomnia.

Less frequent: Paraesthesia, cases of peripheral neuropathy.

Respiratory, thoracic and mediastinal disorders:

Frequent: Nasal symptoms, cough.

Gastrointestinal disorders:

Frequent: Nausea, vomiting, abdominal pain or cramps, diarrhoea.

Less frequent: Pancreatitis, rises in serum amylase.

Hepatobiliary disorders:

Less frequent: Transient rises in liver enzymes (AST, ALT).

Skin and subcutaneous tissue disorders:

Frequent: Rash, alopecia.

Musculoskeletal, connective tissue and bond disorders:

Frequent: Musculoskeletal pain, arthralgia.

Less frequent: Rhabdomyolysis

General disorders:

Frequent: Fatigue, malaise, fever.

Zidovudine:

Blood and lymphatic system disorders:

Frequent: Pancytopenia with marrow hypoplasia and thrombocytopenia.

The most serious adverse reactions of zidovudine are anaemia (which may require transfusions), neutropenia and leucopenia.

It may be necessary to reduce the dose, i.e. use of individual medicines, or discontinue therapy (see "**DOSAGE AND DIRECTIONS FOR USE**").

Less frequent: Pure red cell aplasia, aplastic anaemia.

Factors that may increase the incidence of neutropenia are patients whose neutrophil counts, haemoglobin levels and serum vitamin B_{12} levels are low at the initiation of therapy, and patients taking concomitant paracetamol (see "**INTERACTIONS**").

Metabolism and nutrition disorders:

Frequent: Hyperlactataemia.

Less frequent: Lactic acidosis (see "**WARNINGS**"), anorexia, lipodystrophy (see "**WARNINGS**").

The following side-effects have been reported and frequencies are unknown:

Lactic acidosis in the absence of hypoxaemia.

Neuropsychiatric disorders:

Frequent: Headache, dizziness, insomnia.

Less frequent: Loss of mental acuity, somnolence, anxiety, depression, convulsions, paraesthesia.

Disorders of the special senses:

Less frequent: Taste perversion.

Cardiac disorders:

Less frequent: Cardiomyopathy.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Cough, dyspnoea.

Gastrointestinal disorders:

Frequent: Nausea, vomiting, dyspepsia, diarrhoea, abdominal pain. Anorexia and vomiting were more common in zidovudine-treated patients with early HIV disease.

Less frequent: Flatulence, oral mucosa pigmentation, pancreatitis.

Hepatobiliary disorders:

Less frequent: Liver disorders, such as severe hepatomegaly with steatosis, raised blood levels of liver enzymes and bilirubin.

Skin and subcutaneous tissue disorders:

Frequent: Rash, pruritus.

Less frequent: Sweating, urticaria, nail and skin pigmentation.

Musculoskeletal, connective tissue and bone disorders:

Frequent: Myalgia.

Less frequent: Myopathy.

Renal and urinary disorders:

Less frequent: Urinary frequency.

Reproductive system and breast disorders:

Less frequent: Gynaecomastia.

General disorders:

Frequent: Fever, malaise, asthenia.

Less frequent: Influenza-like syndrome, chills, generalised pain, chest pain.

Should any of these side-effects be sufficiently severe, a reduction or suspension of zidovudine therapy may assist in the evaluation and management of these events. In this situation **MIVIRDO** should therefore be discontinued and zidovudine, lamivudine, and nevirapine should be administered as separate preparations in appropriate dosages (see "**SPECIAL PRECAUTIONS**").

SPECIAL PRECAUTIONS:

Hepatic Impairment:

While nevirapine is extensively metabolised by the liver and nevirapine metabolites are extensively eliminated by the kidneys, pharmacokinetic results further indicate that caution is required when nevirapine, and therefore **MIVIRDO**, is given to patients with more than mild hepatic dysfunction. Nevirapine, and therefore **MIVIRDO**, should not be given to patients with severe liver dysfunction (AST/ALT ≥ 5 x ULN).

MIVIRDO should be administered with caution to any patient with hepatomegaly, hepatitis, or other known risk factors for liver disease (particularly obese women). Should these patients receive **MIVIRDO**, they should be monitored closely while on therapy.

In cases where dosage adjustment is necessary, it is recommended that separate preparations of zidovudine, lamivudine, and nevirapine should be used (see "**DOSAGE AND DIRECTIONS FOR USE**"). The medical practitioner should refer to the individual package inserts for these medicines in those cases.

MIVIRDO should be used with caution in patients with advanced liver cirrhosis as a result of chronic hepatitis B infection, as there is a low risk of rebound hepatitis if lamivudine is stopped.

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

Liver function monitoring:

Baseline liver function tests should be obtained in all patients prior to **MIVIRDO** treatment (see "**WARNINGS**" and "**CONTRA-INDICATIONS**"). If aspartate transaminase (AST) or alanine aminotransferase (ALT) levels are > 2,5 x ULN prior to or during treatment, liver function tests should be monitored more frequently during more regular clinic visits. Nevirapine, and therefore **MIVIRDO**, should not be given or re-administered to patients with pretreatment AST values > 5 x ULN.

There have been reports of abnormal liver function with nevirapine, as contained in **MIVIRDO**; some during the first few weeks of therapy. While asymptomatic elevations of liver enzymes are frequently described, such elevations are not necessarily contra-indications to nevirapine, and therefore **MIVIRDO**, administration. Asymptomatic GGT elevations are not contra-indications to continuation of treatment. It is strongly recommended that liver function tests are monitored at frequent intervals, appropriate to the patient's clinical needs, particularly during the last 2 to 3 months of therapy. Less frequent monitoring is required thereafter.

Doctors and patients should be vigilantly on the look-out 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 they experience any of these.

If aspartate transaminase (AST) or alanine aminotransferase (ALT) levels rise to > 5 x ULN during therapy, MIVIRDO should be discontinued immediately. If levels of aspartate transaminase (AST) or alanine aminotransferase (ALT) return to baseline values, it may be possible to reintroduce nevirapine, on an individual basis, at the starting dosage regimen of 200 mg/day for 14 days followed by 400 mg/day. If liver function abnormalities rapidly recur, nevirapine, and therefore **MIVIRDO**, should be permanently suspended.

If clinical hepatitis develops, characterised by anorexia, nausea, vomiting, icterus and laboratory findings, such as moderate or severe liver function test abnormalities (excluding GGT), nevirapine, and therefore **MIVIRDO**, must be permanently discontinued. Nevirapine, and therefore **MIVIRDO**, should not be re-administered to patients who had to permanently suspend treatment as a result of clinical hepatitis due to nevirapine.

Renal Impairment:

In patients with kidney dysfunction who are receiving haemodialysis, pharmacokinetic results indicate that supplementing nevirapine therapy with an additional 200 mg dose (in adults) of nevirapine after each haemodialysis treatment would help offset the effects of haemodialysis on nevirapine clearance. Otherwise no dosage adjustment is necessary in patients with CL_{CR} ≥ 20 mℓ/min (see "**Pharmacokinetics**, **Renal Dysfunction**" and "**CONTRA-INDICATIONS**"). Safety in patients with end stage renal impairment who are not haemodialysed has not been established.

Please see "**DOSAGE AND DIRECTIONS FOR USE**" for dosage adjustments and administration in patients with hepatic and renal impairment.

Lactic acidosis:

Clinical features of lactic acidosis are non-specific and include nausea, vomiting, abdominal pain, dyspnoea, fatigue and weight loss. Suspicious biochemical features include mild raised transaminases, raised lactate dehydrogenase (LDH) and/or creatine kinase. In patients with suspicious symptoms or biochemistry, measure the venous lactate level (normal < 2 mmol/ℓ) and respond as follows:

- Lactate 2-5 mmol/ℓ monitor regularly, and be alert for clinical signs.
- Lactate 5 -10 mmol/ℓ without symptoms; monitor closely.
- Lactate 5 -10 mmol/ℓ with symptoms: STOP all therapy. Exclude other cause (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, lymphoma).
- Lactate >10 mmol/ℓ: STOP all therapy (80 % mortality in case studies).

Immune reconstitution syndrome:

Immune reconstitution syndrome has been reported during the initial phase of treatment with combination antiretroviral therapy in HIV infected patients with severe immune deficiency.

Osteonecrosis:

There have been reports of osteonecrosis, particularly in patients with advanced HIV disease or long-term exposure to combination antiretroviral therapy.

Fat redistribution:

Fat redistribution or accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and blood glucose concentrations have occurred. The aetiology of the lipodystrophy syndrome is multi-factorial, with e.g. HIV disease, older age and duration of antiretroviral therapy all playing vital, possibly synergistic roles.

Patients taking **MIVIRDO** 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.

Patients should be advised that currently prescribed antiretroviral therapy, including **MIVIRDO**, has not been proven to prevent the risk of transmitting HIV to others through sexual contact or blood contamination. Patients need to continue to employ appropriate precautions against transmission.

Use with other medicines:

Since **MIVIRDO** may interact with some medicines, patients should be instructed to report to their medical practitioner the use of any other medicines.

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

Patients should be cautioned about the simultaneous use of self-administered medicines (see "**INTERACTIONS**").

Information for patients:

Patients should be informed that **MIVIRDO** does not cure HIV-1 infection, and that they may continue to develop illnesses associated with advanced HIV-1 infection, including opportunistic infections. **MIVIRDO** therapy has not been demonstrated to reduce the incidence or frequency of such illnesses, and patients should be instructed to remain under the care of a doctor when taking **MIVIRDO**.

Patients should be informed that the long-term effects of **MIVIRDO** are unknown at this time. They should also be informed that **MIVIRDO** therapy has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination.

Lactose intolerance:

MIVIRDO contains lactose monohydrate. Consequently, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take **MIVIRDO**.

Ability to drive and use machines:

The effect of zidovudine or lamivudine on driving performance or the ability to operate machinery has not been studied. Based on the pharmacology of these medicines, a detrimental effect on such activities cannot be predicted. Nevertheless, the side-effect profiles of zidovudine and lamivudine and the official status of the patient should be taken into account when considering the patient's ability to drive or operate machinery.

No specific studies with nevirapine on the ability to drive vehicles and use machinery have been performed. However, there have been reports of somnolence in association with nevirapine treatment, and if this occurs during **MIVIRDO** administration, it is advisable to refrain from such activities (see "**INTERACTIONS**").

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Nevirapine:

Overdosage with nevirapine may manifest in any of the symptoms described under "**SIDE-EFFECTS AND SPECIAL PRECAUTIONS**". Patients have developed oedema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, increases in transaminases and weight decrease.

There is no known antidote for nevirapine overdosage.

Treatment of nevirapine (and therefore **MIVIRDO**) overdose is symptomatic and supportive.

Lamivudine and zidovudine:

There are limited data available on the sequlae of ingestion of acute overdoses of zidovudine and lamivudine in humans. No specific signs or symptoms are attributed to such overdosage.

In the event of overdosage, the patient should be carefully monitored for evidence of toxicity (see "**SIDE-EFFECTS AND SPECIAL PRECAUTIONS**"), and the necessary supportive treatment should be applied. Continuous haemodialysis could be used in the treatment of overdosage, since lamivudine is dialysable, although this has not been investigated. Haemodialysis and peritoneal dialysis enhance the elimination of the glucuronide metabolite of zidovudine, but appear to have a limited effect on elimination of zidovudine itself. Medical practitioners should refer to the individual package inserts of lamivudine and zidovudine for further details.

IDENTIFICATION:

MIVIRDO tablets 150 mg/200 mg/300 mg are blue coloured, capsule shaped, biconvex, film-coated tablets, debossed with "M" and "104" on one side and plain on other side.

PRESENTATION:

MIVIRDO is packed in high density propylene (HDPE) bottle pack comprising of white opaque wide mouth HDPE bottle with a white opaque polypropylene (PP) screw closure in 60's and 100's pack* in a cardboard carton.

*Not all packs may be marketed

STORAGE INSTRUCTIONS:

Store at or below 30 ˚C. Store in the original container. The bottle must be tightly closed.

Do not remove from the carton until required for use.

KEEP OUT OF REACH AND SIGHT OF CHILDREN.

REGISTRATION NUMBER:

45/20.2.8/0388

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

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

Gauteng, 1601

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

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