PACKAGE INSERT FOR TRIPLAVAR TABLETS:

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

TRIPLAVAR (Film-coated tablets)

COMPOSITION:

TRIPLAVAR tablets: Each film-coated tablet contains 150 mg lamivudine, 300 mg zidovudine and 200 mg nevirapine.

Inactive ingredients include microcrystalline cellulose, sodium starch glycolate, corn starch, povidone, magnesium stearate, and Opadry white.

WARNING:

THE FIRST 18 WEEKS OF THERAPY WITH NEVIRAPINE, AND THEREFORE TRIPLAVAR, IS A CRITICAL PERIOD THAT REQUIRES INTENSIVE MONITORING OF PATIENTS TO IDENTIFY THE POTENTIAL APPEARANCE OF SEVERE AND LIFE-THREATENING SKIN REACTIONS (INCLUDING CASES OF STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS) OR SERIOUS HEPATITIS/HEPATIC FAILURE. THE GREATEST RISK OF HEPATIC EVENTS AND SKIN REACTIONS

OCCURS IN THE FIRST 6 WEEKS OF THERAPY. HOWEVER, THE RISK OF ANY HEPATIC EVENT CONTINUES PAST THIS PERIOD AND MONITORING SHOULD CONTINUE AT FREQUENT INTERVALS.

WOMEN (3,2-FOLD) AND PATIENTS WITH HIGHER CD4+ COUNTS (WOMEN WITH CD4+ > 250, 9,8-FOLD; MEN WITH CD4+ > 400, 6,4-FOLD) ARE AT INCREASED RISK OF HEPATIC ADVERSE EVENTS. IN ADDITION, THE DOSAGE, ESPECIALLY THE 14 DAYS LEAD-IN PERIOD, MUST BE STRICTLY ADHERED TO (SEE "DOSAGE AND DIRECTIONS FOR USE").

Cutaneous reactions:

Severe and life-threatening skin reactions, including fatal cases, have occurred in patients treated with nevirapine, as contained in TRIPLAVAR. These have included cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and hypersensitivity syndrome characterised by rash, constitutional findings and visceral involvement.

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

If a patient presents with suspected nevirapine-associated rash, liver function tests should be performed. Patients with moderate to severe

elevations [aspartate transaminase (AST) or alanine aminotransferase (ALT) > 5 x Upper Limit of Normal (ULN)] should be permanently discontinued from nevirapine, and therefore TRIPLAVAR.

If a hypersensitivity syndrome occurs, characterised by rash with constitutional symptoms, such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction, nevirapine, and therefore TRIPLAVAR, should be permanently stopped and not be reintroduced.

Hepatic reactions:

Severe or life-threatening hepatotoxicity, including fatal fulminant hepatitis, has occurred in patients treated with nevirapine, as contained in TRIPLAVAR. Serious hepatitis and hepatic failure events in nevirapine-treated patients have been reported. Increased aspartate transaminase (AST) or alanine aminotransferase (ALT) levels > 2,5 x ULN and/or co-infection with hepatitis B and/or C at the start of antiretroviral therapy is associated with greater risk of hepatic adverse events during antiretroviral therapy in nevirapine-containing regimens, such as TRIPLAVAR.

If AST or ALT > 2,5 x ULN before or during treatment, liver function tests should be monitored more frequently during regular clinic visits. Nevirapine, and therefore TRIPLAVAR, should not be administered 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 TRIPLAVAR) should be stopped immediately and not reinstated. If aspartate transaminase (AST) and alanine aminotransferase (ALT) return to baseline values, it may be possible to reintroduce nevirapine on a case by case basis, at the starting dosage regimen of 200 mg/day for 14 days followed by 400 mg/day. If liver function abnormalities rapidly recur, nevirapine should be permanently discontinued.

If clinical hepatitis occurs, characterised by anorexia, nausea, vomiting, icterus and laboratory findings [such as moderate or severe liver function test abnormalities (excluding GGT)], nevirapine, and therefore TRIPLAVAR, must be permanently stopped. TRIPLAVAR should not be readministered to patients who have required permanent discontinuation for clinical hepatitis due to nevirapine.

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 TRIPLAVAR, should be permanently discontinued. Nevirapine, and therefore TRIPLAVAR, should not be restarted in these situations.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.8 Antimicrobial (chemotherapeutic) agents. Antiviral agents.

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

Nevirapine:

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

Lamivudine and Zidovudine:

Zidovudine and lamivudine are nucleoside analogues and are both selective inhibitors of HIV-1 and HIV-2. The action of lamivudine has been shown to be synergistic with zidovudine in the inhibition of the replication of HIV in cell culture.

Both medicines are metabolised sequentially by intracellular kinases to their 5'-triphosphate (TP) forms, respectively.

Zidovudine-TP and lamivudine-TP are substrates for and competitively inhibit HIV reverse transcriptase. The main antiviral activity of these two antiretrovirals is through incorporation of their monophosphate forms into the viral DNA chain, resulting in chain termination.

Treatment with lamivudine or zidovudine has resulted in resistant strains. Treatment with lamivudine and zidovudine individually has resulted in HIV clinical isolates which show 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 zidovudine plus lamivudine delays the emergence of zidovudine resistance in antiretroviral naïve patients.

***Resistance*:**

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

Cross-resistance:

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

Pharmacokinetics:

Nevirapine:

Absorption:

Nevirapine is readily absorbed (> 90 %) after oral administration in healthy volunteers and in adults with HIV-1 infection. Following administration of nevirapine 200 mg tablets to healthy volunteers under fasting conditions, peak plasma concentrations (C_{max}) of about 2,0 to 2,5 µg/mℓ are attained at about 4 hours. Following multiple doses, nevirapine peak concentrations appear to increase linearly in the dose range of 200 to 400 mg/day. Steady state trough nevirapine concentrations of 4,5 ± 1,9 µg/mℓ (17 ± 7 µM) were attained at 400 mg/day. The absorption of nevirapine is not affected by food, antacids or

medicinal products, which are formulated with an alkaline buffering agent (e.g. didanosine).

Distribution:

Nevirapine is highly lipophilic and is essentially non-ionised at physiologic pH. Following intravenous administration to healthy adults, the apparent volume of distribution at steady state (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 are about 45 % of the concentrations in plasma; this ratio is approximately equal to the fraction not bound to plasma protein.

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 is an inducer of hepatic cytochrome P450 metabolic enzymes. This autoinduction also results in a corresponding decrease in the terminal phase half-life of nevirapine in plasma from approximately 45 hours (single dose) to approximately 25 – 30 hours following multiple dosing with 200 –

400 mg/day. Nevirapine also undergoes autoinduction resulting in 1,5- to 2-fold increase in metabolism. This effect is at its highest 14 days after initiation of therapy.

Elimination:

Approximately 91,4 ± 10,5 % of a radiolabeled dose was recovered, with urine (81,3 ± 11,1 %) representing the primary route 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, the C_{max} value of lamivudine was 1,5 (1,3 – 1,8) µg/mℓ. The median (range) lamivudine t_{max} value was 0,75 (0,50 – 2,00) hours. The extent of lamivudine absorption (AUC) and estimates of half-life following administration in combination with food were similar when compared to fasting subjects, although the rate of absorption (C_{max}, t_{max}) was slowed. Lamivudine may be taken with or without food.

Distribution:

Intravenous studies have shown the mean apparent volume of distribution to be 1,3 ℓ/kg for lamivudine.

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 due to binding site displacements are not anticipated with lamivudine.

Data show 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 after oral administration is approximately 0,12. The true extent of penetration of lamivudine or relationship with any clinical efficacy is unknown.

Metabolism:

Metabolism of lamivudine is a minor route of elimination. It is predominantly cleared by the renal route as unchanged medicine. The likelihood of metabolic drug interactions with lamivudine is therefore low due to minimal hepatic metabolism (5 – 10 %) and low plasma protein binding.

Elimination:

The observed lamivudine elimination half-life is 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, the C_{max} value of zidovudine was 1,8 (1,5 – 2,2) µg/mℓ. The median (range) zidovudine t_{max} value was 0,50 (0,25 – 2,00) hours. The extent of zidovudine absorption (AUC) and estimates of half-life following administration in combination with food were similar when compared to fasting subjects, although the rate of absorption (C_{max}, t_{max}) was slowed. Zidovudine may be taken with or without food.

Distribution:

Intravenous studies have shown the mean apparent volume of distribution to be 1,6 ℓ/kg for zidovudine.

Zidovudine plasma protein binding is 34 – 38 %. Interactions due to binding site displacements are not anticipated with zidovudine.

Data show 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 after oral administration is approximately 0,5.

Metabolism:

The 5'-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 renal excretion. Following intravenous dosing, 3'-amino-3'-deoxythymidine (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. Zidovudine renal clearance is estimated to be 0,34 ℓ/h/kg, indicating glomerular filtration and active tubular secretion by the kidneys.

Pharmacokinetics in Special Populations:

Renal/Hepatic dysfunction:

Nevirapine:

The pharmacokinetics of nevirapine have not been evaluated in patients with either renal or hepatic dysfunction.

Lamivudine:

Studies in patients with renal insufficiency have shown lamivudine elimination to be affected by renal dysfunction.

Dose reduction is therefore required for patients with a creatinine clearance < 50 mℓ/min (see **"DOSAGE AND DIRECTIONS FOR USE"**).

Zidovudine:

Patients with advanced renal failure display increased zidovudine concentrations.

Gender:

There are no significant gender differences in nevirapine clearance or plasma concentrations following either single or multiple dose administration.

Geriatrics:

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

INDICATIONS:

For treatment of HIV-1 infection:

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

CONTRA-INDICATIONS:

TRIPLAVAR is contra-indicated in the following:

- Patients with known hypersensitivity to lamivudine, zidovudine, nevirapine or any other component of the preparation.

- Zidovudine (and therefore **TRIPLAVAR**) is contra-indicated in 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).
- 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.
- The combination of zidovudine with either ribavirin or stavudine is antagonistic *in vitro*. The concomitant use of either ribavirin or stavudine with **TRIPLAVAR** should be avoided.
- Nevirapine (and therefore **TRIPLAVAR**) is contra-indicated in severe hepatic dysfunction, Child-Pugh class B or C, and in end-stage renal failure in patients not on haemodialysis.
- Nevirapine (and therefore **TRIPLAVAR**) should not be administered to 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 ULN.
- Nevirapine (and therefore **TRIPLAVAR**) should not be readministered to patients who have required permanent discontinuation for severe rash, rash accompanied by constitutional symptoms, hypersensitivity syndrome, or clinical hepatitis due to nevirapine (and therefore **TRIPLAVAR**).
- Nevirapine (and therefore **TRIPLAVAR**) should not be readministered to patients who previously had aspartate transaminase (AST) or alanine aminotransferase (ALT) > 5 x ULN during nevirapine (and therefore **TRIPLAVAR**) therapy or had rapid recurrence of liver function

abnormalities upon readministration of nevirapine (and therefore **TRIPLAVAR**) (see **"WARNINGS"**).

WARNINGS:

WARNING:

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

Patients should be instructed that the major toxicity of nevirapine is skin rashes and should be advised to promptly notify their doctor of any rash. The lead-in period should be used because it has been found to lessen the frequency of rash *(see* ***"DOSAGE AND DIRECTIONS FOR USE"****).* The majority of rashes associated with nevirapine, as contained in **TRIPLAVAR**, occur within the first 6 weeks of therapy; therefore, patients should be monitored carefully for the appearance of any rash during this

period. Patients should be instructed that dose escalation is not to occur if any rash occurs during the lead-in dosing period, until the rash has resolved.

Skin reactions:

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

Nevirapine, and therefore TRIPLAVAR, must be permanently discontinued in any patient experiencing severe rash or a rash accompanied by constitutional symptoms (such as fever, blistering, oral lesions, conjunctivitis, facial oedema, muscle or joint aches or general malaise), including Stevens-Johnson syndrome or toxic epidermal necrolysis. Nevirapine, and therefore TRIPLAVAR, must be permanently discontinued in any patient experiencing hypersensitivity syndrome characterised by rash with constitutional symptoms, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia and renal dysfunction or signs of other visceral involvement (see "Side-Effects").

Concomitant prednisone use (40 mg/day for the first 14 days of nevirapine, and therefore **TRIPLAVAR**, administration) has been shown not to decrease

the incidence of nevirapine-associated rash and may be associated with an increase in rash during the first 6 weeks of nevirapine, as in **TRIPLAVAR**, therapy.

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

Any patient experiencing severe rash or a rash accompanied by constitutional symptoms, such as fever, blistering, oral lesions, conjunctivitis, facial oedema, muscle or joint aches, or general malaise, should discontinue medication and consult a medical practitioner. In these patients nevirapine, and therefore TRIPLAVAR, must not be restarted.

If patients present with a suspected nevirapine-associated rash, liver function tests should be performed immediately. Patients with moderate to severe elevations (AST or ALT > 5 x ULN) should be permanently discontinued from nevirapine, and therefore TRIPLAVAR.

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

therefore TRIPLAVAR, should be permanently stopped and not be reintroduced.

Hepatic reactions:

Severe or life-threatening hepatotoxicity, including fatal fulminant hepatitis (transaminase elevations, with or without hyperbilirubinaemia, prolonged partial thromboplastin time or eosinophilia) has occurred in patients treated with nevirapine, as in TRIPLAVAR. Serious hepatitis and hepatic failure events in nevirapine-treated patients have been reported to occur in the first 18 weeks of therapy, but some have occurred later. The first 18 weeks of treatment is a critical period, which require close monitoring. The risk of hepatic events is greatest in the first 6 weeks of therapy. Women (3,2-fold) and patients with higher CD4+ counts (women with CD4+ > 250, 9,8-fold; men with CD4+ > 400, 6,4-fold) are at increased risk of hepatic adverse events. However, the risk continues past this period and monitoring should continue at frequent intervals throughout treatment. Patients should be informed that hepatic reactions are a major toxicity of nevirapine, and therefore TRIPLAVAR, and that occurrence of symptoms suggestive of hepatitis should lead them to contact their doctor promptly.

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

Nevirapine, and therefore **TRIPLAVAR**, is contra-indicated in patients with severe underlying liver disorders. Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events. In the case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these medicinal products. Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination therapy and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

Women have a threefold higher risk than men for rash-associated hepatic events (4,6 % vs. 1,5 %). Patients with higher CD4+ counts may also be at a higher risk for rash-associated hepatic events with nevirapine, as contained in **TRIPLAVAR**. In a retrospective review, women with CD4+ counts > 250 cells/mm^3 had a 9,8-fold higher risk of rash-associated hepatic adverse events compared to women with CD4+ counts < 250 cells/mm^3 (0,84 % vs. 0,09 %). An increased risk (6,4-fold) was observed in men with CD4+ counts > 400 cells/mm^3 compared to men with CD4+ counts < 400 cells/mm^3 (4,5 % vs. 0,7 %).

Patients should be informed that hepatic reactions are a major toxicity of nevirapine, and therefore **TRIPLAVAR**, requiring close monitoring during the first 18 weeks. However, severe liver disease can occur after 18 weeks. Therefore monitoring should continue at frequent intervals after this period depending on the patient's clinical status. They should be informed that

occurrence of symptoms suggestive of hepatitis should lead them to contact their doctor promptly.

Liver function monitoring:

All patients should have baseline liver function tests prior to nevirapine, and therefore **TRIPLAVAR**, treatment (see **"WARNINGS"** and **"CONTRA-INDICATIONS"**). If aspartate transaminase (AST) or alanine aminotransferase (ALT) are > 2,5 x ULN before or during treatment, liver tests should be monitored more frequently during more regular clinic visits. Nevirapine, and therefore **TRIPLAVAR**, should not be administered or readministered to patients with pretreatment AST > 5 x ULN.

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

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

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

***Haematological*:**

Anaemia, neutropenia and leucopenia (usually secondary to neutropenia) can be expected to occur in patients on zidovudine (and therefore **TRIPLAVAR**) and who have advanced symptomatic HIV disease. Haematological parameters should therefore be carefully monitored (see **"CONTRA-INDICATIONS"**). These haematological adverse effects are not usually observed before four to six weeks of therapy. It is generally recommended

that patients with advanced symptomatic HIV disease should undergo blood tests at least every two weeks for the first three months of therapy 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 % from baseline, more frequent monitoring may be required.

Additionally, dosage adjustment of zidovudine may be required in the following instances: severe anaemia or myelosuppression during treatment with **TRIPLAVAR**, or patients with 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 **TRIPLAVAR**, zidovudine, lamivudine, and nevirapine should be administered as separate preparations. Medical practitioners should then refer to the individual package inserts of these medicines.

Gastrointestinal:

Cases of pancreatitis have occurred less frequently in patients treated with zidovudine and lamivudine. However, it is not clear whether these cases were actually due to the medicines or to the underlying HIV disease. Should clinical signs, symptoms or laboratory abnormalities, suggestive of pancreatitis, occur, **TRIPLAVAR** therapy should be stopped immediately.

Metabolic:

Lactic acidosis, in the absence of hypoxaemia, 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 **TRIPLAVAR** 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.

Clinical features 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 causes (e.g. sepsis, uraemia, diabetic ketoacidosis, thyrotoxicosis, lymphoma).
- Lactate > 10 mmol/ℓ: STOP all therapy (80 % mortality in case studies).

Fat redistribution:

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

Patients receiving **TRIPLAVAR** 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 **TRIPLAVAR**, has not been proven to prevent the risk of transmitting HIV to others through sexual contact or blood contamination. Appropriate precautions against transmission should continue to be employed.*

INTERACTIONS:

Nevirapine:

Nevirapine has been shown to be an inducer of hepatic cytochrome P450 metabolic enzymes (CYP3A, CYP2B) and may result in lower plasma concentrations of other concomitantly administered medicines that are extensively metabolised by CYP3A or CYP2B (see **"Pharmacokinetics"**). Thus, if a patient has been stabilised on a dosage regimen for a medicine

metabolised by CYP3A or CYP2B and begins treatment with nevirapine, as in **TRIPLAVAR**, dose adjustments may be necessary.

Protease inhibitors:

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

Saquinavir: Co-administration of nevirapine and saquinavir (hard gelatin 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 levels due to this interaction may further reduce the marginal plasma levels of saquinavir which are achieved with the hard gelatin capsule formulation. The clinical significance of this interaction is not known. Co-administration did not affect the pharmacokinetics of nevirapine.

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

Indinavir: Nevirapine and indinavir (800 mg three time daily) co-administration leads to a 28 % mean decrease (p < 0,01) in indinavir AUC and no significant change in nevirapine plasma levels. A dose increase of indinavir to 1 000 mg 8 hourly should be considered when indinavir is given with nevirapine 200 mg twice daily; however, there are no data currently available to establish that the short-term or long-term antiviral activity of indinavir

1 000 mg 8 hourly 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 indicated no statistically significant changes in nelfinavir pharmacokinetic parameters after the addition of nevirapine (AUC + 4 %, C_{max} + 14 % and C_{min} – 2 %). Compared to historical controls, nevirapine levels appeared to be unchanged.

Ketoconazole:

Ketoconazole and nevirapine, and therefore **TRIPLAVAR**, should not be given concomitantly. Administration of nevirapine 200 mg twice daily with ketoconazole 400 mg four times daily resulted in a significant reduction (63 % median reduction in ketoconazole AUC and a 40 % median reduction in ketoconazole C_{max}). Ketoconazole administration resulted in a 15 – 28 % increase in the plasma levels of nevirapine compared to historical controls.

Fluconazole:

Co-administration of fluconazole and nevirapine resulted in approximately 100 % increase in nevirapine exposure compared with historical data where nevirapine was administered alone. Because of the risk of increased exposure to nevirapine, caution should be exercised if nevirapine, and therefore **TRIPLAVAR**, and fluconazole are given concomitantly and patients should be monitored closely.

Anticoagulants:

The *in vitro* interaction between nevirapine and the antithrombotic agent warfarin is complex. As a result, when giving these medicines concomitantly, plasma warfarin levels and therapeutic efficacy may change with the potential for both increases and decreases in coagulation time. The net effect of the interaction may change during the first weeks of co-administration or upon discontinuation of nevirapine. When warfarin is co-administered with **TRIPLAVAR**, prothrombin time should be more frequently monitored.

CYP isoenzyme inducers (e.g. rifampicin, rifabutin):

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

Rifabutin:

Administration of nevirapine 200 mg twice daily with rifabutin 300 mg four times daily (or 150 mg four times daily if concomitantly receiving ZDV or protease inhibitors), resulted in a significant increase 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 concentrations. High interpatient variability, however, may result in

some patients experiencing large increases in rifabutin exposure, which may place them at higher risk for toxicity. In the same study, rifabutin administration resulted in an apparent significant increase in systemic clearance of nevirapine by 9 % compared to historical controls. Care should be taken when nevirapine, and therefore **TRIPLAVAR**, and rifabutin are administered concurrently with considerations of a decrease in the dose of rifabutin. The dose of nevirapine need not be changed.

St. John's wort:

Concomitant use of nevirapine, as in **TRIPLAVAR**, and St. John's wort (*Hypericum perforatum*) or St. John's wort-containing products, is not recommended as co-administration of non-nucleoside reverse transcriptase inhibitors (NNRTIs), including nevirapine, with St. John's wort is expected to decrease NNRTI concentrations and may result in suboptimal levels of nevirapine 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 isoenzyme inhibitors (e.g. cimetidine and macrolides):

Nevirapine trough concentrations were elevated in patients who received cimetidine (+ 21 %). The results of a nevirapine-clarithromycin interaction study resulted in a significant reduction in clarithromycin AUC (- 30 %) and C_{max} (- 21 %) and C_{min} (- 46 %), but a significant increase in the AUC (58 %) and C_{max} (62 %) of the active metabolite 14-OH-clarithromycin. There was a

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

Oral contraceptives:

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

Methadone:

Based on the metabolism of methadone, the nevirapine in **TRIPLAVAR** may decrease plasma concentrations of methadone by increasing its hepatic metabolism. Narcotic withdrawal syndrome has been reported in patients treated with nevirapine (and therefore **TRIPLAVAR**) and methadone concomitantly. Methadone-maintained patients beginning nevirapine, and

therefore **TRIPLAVAR**, therapy should be monitored for evidence of withdrawal and the methadone dose should be adjusted accordingly.

Other information on interactions:

It should be noted that other compounds that are substrates of CYP3A or CYP2B6 may have decreased plasma concentrations when co-administered with nevirapine.

Zidovudine and lamivudine:

Since **TRIPLAVAR** contains zidovudine and lamivudine, any interactions attributed to these agents individually may occur with **TRIPLAVAR**. The likelihood of metabolic interactions with lamivudine is low due to limited metabolism, minimal plasma protein binding and almost complete renal clearance.

Zidovudine also displays limited protein binding, but is eliminated primarily by 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 should be exercised.

Interactions relevant to lamivudine:

The possibility of interactions with other medicines administered concurrently with **TRIPLAVAR** should be considered, particularly those medicines which are eliminated mainly 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 mechanism and were shown not to interact with lamivudine.

Prophylactic doses of co-trimoxazole have resulted in 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 renal impairment (see **"DOSAGE AND DIRECTIONS FOR USE"**).

Patients who warrant concomitant administration of co-trimoxazole, should be monitored clinically. The concomitant administration of **TRIPLAVAR** with high doses of co-trimoxazole, as used in the treatment of *Pneumocystis carinii* pneumonia (PCP) and toxoplasmosis, should be avoided. Lamivudine, on the other hand, has no effect on the pharmacokinetics of co-trimoxazole at the doses studied.

It is not recommended to co-administer lamivudine (and therefore **TRIPLAVAR**) with intravenous ganciclovir or foscarnet until further information is 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 the C_{max} (28 %) of zidovudine was observed when administered with lamivudine, the overall exposure (AUC) was not significantly altered. Zidovudine, alternatively, has no effect on the pharmacokinetics of lamivudine.

The AUC of zidovudine is decreased by 48 % $\pm$ 34 % when co-administered with rifampicin. However, the clinical significance of this is not known.

Phenytoin concentrations should be carefully monitored in patients receiving **TRIPLAVAR** and phenytoin, as phenytoin blood levels have been reported to be low in some patients receiving zidovudine, while a high level was noted 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, the available pharmacokinetic data indicate that neither the plasma levels of zidovudine nor its glucuronide metabolite is increased by paracetamol at the doses studied.

Other medicines, including, but not limited to, codeine, morphine, aspirin, indomethacin, ketoprofen, naproxen, cimetidine, clofibrate, dapsone, oxazepam, lorazepam and isoprinosine, may alter the metabolism of zidovudine by either directly inhibiting hepatic microsomal metabolism or competitive inhibition of glucuronidation. The possibilities of interaction should

therefore be considered carefully before using such medicines, especially for chronic therapy, in combination with **TRIPLAVAR**.

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 **TRIPLAVAR**).
If concomitant therapy with **TRIPLAVAR** 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 **TRIPLAVAR** should therefore be avoided. Refer to the **"Pharmacokinetics"** section for full details on the interactions between zidovudine and other antiretroviral agents.

Since some patients on **TRIPLAVAR** 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 **TRIPLAVAR** in pregnancy and lactation has not been established. Adequate contraceptive methods should be used in women of child-bearing age.

DOSAGE AND DIRECTIONS FOR USE:

Adults and children over the age of 12 years:

TRIPLAVAR 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 dose, a dose escalation (maintenance dose) of 200 mg nevirapine, as contained in TRIPLAVAR, twice a day may be carried out in the absence of severe gastrointestinal intolerance or any hypersensitivity reactions.

Recommended dose:

One **TRIPLAVAR** tablet twice daily, with or without food.

TRIPLAVAR therapy should be initiated by a medical practitioner who has experience in the management of HIV infection.

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

Patients should be advised to take **TRIPLAVAR** every day as prescribed. Patients should not alter the dose without consulting their doctor. If a dose is skipped, patients should not double the next dose but should take the next dose as soon as possible.

Monitoring of patients: Clinical chemistry, including liver function tests, should be performed prior to initiating **TRIPLAVAR** therapy and at appropriate intervals during therapy (see **"WARNINGS"**).

Dosage adjustment:

TRIPLAVAR should be discontinued if patients experience severe rash or a rash accompanied by constitutional findings (see "WARNINGS"). Patients experiencing 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").

TRIPLAVAR administration should be interrupted in patients experiencing moderate liver function test abnormalities, e.g. AST or ALT < 5 x ULN [excluding gamma-glutamyltransferase (GGT)]. If aspartate transaminase (AST) or alanine aminotransferase (ALT) return to baseline values and if the patient has no clinical signs and symptoms of hepatitis or constitutional symptoms or other findings suggestive of organ dysfunction, it may be possible to reintroduce nevirapine, based on clinical needs and judgement, on a case by case basis. Nevirapine may then be restarted at 200 mg daily increasing to 200 mg twice daily with caution, after extended observation. If moderate or severe liver function test abnormalities recur, nevirapine (and therefore **TRIPLAVAR**) should be permanently discontinued (see **"WARNINGS"**).

Patients who interrupt **TRIPLAVAR** dosing for more than 7 days should restart treatment with a lead-in treatment period using the individual medicines. The recommended dosing 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 renal impairment due to decreased clearance. Therefore, when dosage adjustment of one or both of these are necessary, it is recommended that separate preparations of lamivudine, zidovudine, and nevirapine be administered to patients with impaired renal function (creatinine clearance $\leq$ 50 mℓ/min). The separate package inserts for zidovudine,

lamivudine, and nevirapine must be consulted for full prescribing details and dosage adjustments.

Hepatic impairment: The influence of hepatic impairment on lamivudine levels is being investigated. Lamivudine clearance is predominantly renal. Based on preliminary safety data, dosage adjustment is not necessary. However, zidovudine accumulation may occur in patients with hepatic impairment due to decreased glucuronidation, based on limited data in patients with cirrhosis. Therefore, it is recommended that separate preparations of lamivudine, zidovudine, and nevirapine be administered to patients with severe hepatic impairment, as dosage adjustments of zidovudine may be necessary. 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 **TRIPLAVAR** 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 the decrease in renal function and changes in haematological parameters.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-Effects:

Nevirapine:

Blood and lymphatic system disorders:

Less frequent: Granulocytopenia, anaemia.

Immune system disorders:

Frequent: Allergic reactions.

Less frequent: Hypersensitivity (syndrome), anaphylaxis.

Nervous system disorders:

Frequent: Headache.

Gastrointestinal disorders:

Frequent: Nausea.

Less frequent: Vomiting, abdominal pain, diarrhoea.

Hepatobiliary disorders:

Frequent: Hepatitis, liver function tests abnormal.

Less frequent: Jaundice, liver failure / fulminant hepatitis.

Skin and subcutaneous tissue disorders:

Frequent: Rash.

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

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Myalgia, arthralgia.

General disorders:

Less frequent: Fatigue, fever.

Postmarketing experience has shown that the most serious adverse reactions are Stevens-Johnson syndrome, toxic epidermal necrolysis, serious hepatitis/hepatic failure and hypersensitivity syndrome, characterised by rash with constitutional symptoms, such as fever, arthralgia, myalgia and lymphadenopathy, plus visceral involvements, such as hepatitis, eosinophilia, granulocytopenia and renal dysfunction. The first 18 weeks of treatment is a critical period, which requires close monitoring (see **"WARNINGS"**).

Skin and subcutaneous tissues:

The most common clinical toxicity of nevirapine (and therefore **TRIPLAVAR**) is rash. Nevirapine-attributable rash occurred in 16 % of patients in combination regimens in Phase II/III controlled studies. Overall, 7 % of patients discontinued nevirapine due to rash.

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

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

Nevirapine (and therefore TRIPLAVAR) must be discontinued immediately in patients developing a severe rash or a rash accompanied by constitutional symptoms.

The majority of rashes of any severity occurred 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 TRIPLAVAR):

Group I: Erythema, pruritus.

Group IIA: One of the two following clinical presentations:

1. Diffuse erythematous macular or maculopapular cutaneous eruption or dry desquamation with or without pruritus *without* the presence of any additional *constitutional findings* as described in **Group III**.
2. Typical target lesions without blistering, vesicles or ulcerations in the lesions (usually referred to as erythema multiforme minor).

Group IIB: Urticaria.

Group III: One of the five following clinical presentations:

1. Extensive erythematous or maculopapular rash or moist desquamation with or without pruritus *together with* the presence of any of the following *constitutional findings*:
    - Clinically relevant increases in any one or more of the following *liver function tests*: aspartate transaminase (AST), alanine aminotransferase (ALT), alkaline phosphatase and which are *possibly related to the medicine reaction*.
    - Fever, defined as > 39 °C *possibly related to medicine reaction*.
    - Blistering and/or vesiculation of cutaneous eruptions.
    - One site of extensive mucosal lesions which are presumed to be due to medicine reaction (e.g. not due to herpes simplex, CMV).
2. Angioedema.
3. Exfoliative dermatitis: Severe widespread erythema and dry scaling of the skin with generalised superficial lymphadenopathy

and with other constitutional findings, such as fever, weight loss, hypoproteinaemia which could possibly be related to a medicine reaction.

4. Diffuse rash and serum sickness-like reactions defined as a clinical symptom complex manifested as fever, lymphadenopathy, oedema, myalgia and/or arthralgia.
5. Diffuse cutaneous eruptions, usually starting on the face and trunk or back, often with prodromal symptoms (e.g. fever, general malaise, myalgia, arthralgia) plus one or more of the following (usually referred to as Stevens-Johnson syndrome):
    - *Cutaneous bullae,* sometimes confluent, with widespread sheet-like detachment covering < 10 % of body surface (referred to as Nikolsky's sign).
    - Two or more anatomically distinct sites of mucosal erosion or ulceration not due to another cause (e.g. herpes simplex); mucosal sites include oral, laryngeal, nasal, ocular*, genital and rectal surfaces. (*Note: The diagnosis of erosive conjunctivitis requires the presence of injected conjunctivae *plus* a purulent conjunctival discharge *or* visualisation of the conjunctival erosions. The presence of only an erythematous or injected conjunctiva does *not* establish erosion of the conjunctiva.)

Group IV: Diffuse cutaneous eruptions, usually starting on the face and trunk or back, often with prodromal symptoms (e.g. fever, general malaise, myalgia, arthralgia) plus cutaneous bullae with

widespread sheet-like detachment covering > 10 % of body surface area. Note: Two or more anatomically distinct sites of mucosal erosion or ulceration not due to another cause (e.g. herpes simplex, CMV, etc.) may be observed, but are not required for inclusion of the patient in **Group IV**.

Presumed prodrome to Group III or IV:

The prodrome includes symptoms such as fever > 39 ℃ or a clinical symptom complex manifested as fever, lymphadenopathy, oedema, myalgia, and/or arthralgia and the symptoms are thought to be related to nevirapine (and therefore **TRIPLAVAR**).

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

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

   Nevirapine, and therefore **TRIPLAVAR**, may be continued for **Groups I, IIA** and **IIB**. Manage pruritus and minor accompanying symptoms with antihistamines, antipyretics and/or non-steroidal anti-inflammatory medications. If **TRIPLAVAR** is interrupted during a **Group I or IIA** reaction, nevirapine may be reintroduced once the cutaneous eruptions have cleared. The lead-in period using the individual medicines should be followed. If **Group I or IIA** cutaneous eruptions occur during the

nevirapine low dose lead-in period, dose escalation should not be attempted until the cutaneous eruptions have resolved.

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

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

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

3. **No nevirapine, and therefore TRIPLAVAR, rechallenqe of any patient with a group IIB, III or IV cutaneous eruption is allowed.**

Hepatobiliary:

The most frequently observed laboratory test abnormalities are elevations in liver function tests (LFTs), including aspartate transaminase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (GGT), total bilirubin and alkaline phosphatase. Asymptomatic elevations of GGT levels are the most frequent. Cases of jaundice have been reported. Cases of hepatitis, severe and life-threatening hepatotoxicity and fatal fulminant hepatitis have been reported in patients treated with nevirapine, as contained in **TRIPLAVAR**. The best predictor of a serious hepatic event was elevated baseline liver function tests. The first 18 weeks of treatment is a critical period, which requires close

monitoring, but such events may also occur later (see **"WARNINGS"**). The risk of hepatic events is greatest in the first 6 weeks of therapy. However, the risk continues past this period and monitoring should continue at frequent intervals throughout treatment (see **"WARNINGS"**).

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

For liver function test monitoring, refer to **"WARNINGS"**.

The following events have also been reported when nevirapine, as contained in **TRIPLAVAR**, has been used in combination with other antiretroviral agents: anaemia, pancreatitis, lipodystrophy, peripheral neuropathy and thrombocytopenia.

Since **TRIPLAVAR** contains lamivudine and zidovudine, the type and severity of adverse reactions 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 has also been reported.

Neuropsychiatric disorders:

Frequent:	Headache, insomnia.
Less frequent:	Cases of peripheral neuropathy (or paraesthesia) have been recorded, although no relationship to the dose of lamivudine has been noted.

Respiratory, thoracic and mediastinal disorders:

Frequent:	Nasal symptoms, cough.

Gastrointestinal disorders:

Frequent:	Nausea, vomiting, abdominal pain or cramps, diarrhoea.
Less frequent:	Cases of pancreatitis have been recorded, although no relationship to the dose of lamivudine has been noted. Rises in serum amylase have also been reported.

Hepatobiliary disorders:

Less frequent:	Transient rises in liver enzymes (AST, ALT) have also been reported.

Musculoskeletal, connective tissue and bone disorders:

Frequent:	Musculoskeletal pain, arthralgia.
Less frequent:	Rhabdomyolysis.

General disorders:

Frequent:	Fatigue, malaise, fever.

Skin and subcutaneous tissue disorders:

Frequent:	Rash, alopecia.

Metabolism and nutrition disorders:

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

Zidovudine:

Blood and lymphatic system disorders:

Frequent:	Pancytopenia with marrow hypoplasia and isolated thrombocytopenia. The most serious adverse reactions of zidovudine are anaemia (which may require transfusions), neutropenia and leucopenia. These occur more frequently at higher dosages of zidovudine (1200 – 1500 mg/day) and in patients with advanced HIV disease (especially when the bone

marrow reserve is poor prior to treatment), and particularly in patients with $CD4^+$ cell counts < 100/mm^3. It may be necessary to reduce the dose, i.e. use of individual medicines, or discontinue therapy (see **"DOSAGE AND DIRECTIONS FOR USE"**).

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:

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

Lactic acidosis in the absence of hypoxaemia.

The following side-effects may occur frequently and less frequently:

Neuropsychiatric disorders:

Frequent: Headache, dizziness, insomnia.

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

Special senses disorders:

Less frequent:	Taste perversion.

Respiratory, thoracic and mediastinal disorders:

Less frequent:	Cough, dyspnoea.

Gastrointestinal disorders:

Frequent:	Nausea, anorexia, 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.
Less frequent:	Sweating, urticaria, pruritus, nail and skin pigmentation.

Musculoskeletal, connective tissue and bone disorders:

Frequent:	Myalgia.

Less frequent: Myopathy.

Renal and urinary disorders:

Less frequent: Urinary frequency.

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 **TRIPLAVAR** 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 suggest caution should be exercised when nevirapine, and therefore **TRIPLAVAR**, is administered to patients with more than mild hepatic dysfunction. Nevirapine, and therefore **TRIPLAVAR**, should not be

administered to patients with severe hepatic dysfunction (AST/ALT ≥ 5 x ULN).

TRIPLAVAR 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 **TRIPLAVAR**, 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 administered (see **"DOSAGE AND DIRECTIONS FOR USE"**). The medical practitioner should refer to the individual package inserts for these medicines in these cases.

TRIPLAVAR 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 discontinued.

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

Renal impairment:

In patients with renal dysfunction who are undergoing haemodialysis, pharmacokinetic results suggest that supplementing nevirapine therapy with an additional 200 mg dose (in adults) of nevirapine following each haemodialysis treatment would help offset the effects of haemodialysis on nevirapine clearance. Otherwise patients with $CL_{CR} \geq 20$ mℓ/min do not require an adjustment in nevirapine dosing (see **"Pharmacokinetics, Renal Dysfunction"** and **"CONTRA-INDICATIONS"**). Safety in patients with end stage impairment who are not haemodialysed has not been demonstrated.
Please see **"DOSAGE AND DIRECTIONS FOR USE"** for dosage adjustments and administration in patients with hepatic and renal impairment.

Use with other medicines:

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

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

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

Information for patients:

Patients should be informed that **TRIPLAVAR** is not a cure for HIV-1 infection, and that they may continue to experience illnesses associated with advanced HIV-1 infection, including opportunistic infections. Treatment with **TRIPLAVAR** has not been shown to reduce the incidence or frequency of such illnesses, and patients should be advised to remain under the care of a doctor when using **TRIPLAVAR**.

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

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. Furthermore, 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 clinical status of the patient should be borne in mind when considering the patient's ability to drive or operate machinery.

There are no specific studies with nevirapine on the ability to drive vehicles and use machinery. However, somnolence has been reported in association with nevirapine therapy, and if this occurs during nevirapine (and therefore **TRIPLAVAR**) administration, it is advisable to refrain from such activities (see **"INTERACTIONS"**).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Nevirapine:

Overdosage with nevirapine (and therefore **TRIPLAVAR**) may manifest in any of the symptoms described under **"SIDE-EFFECTS AND SPECIAL PRECAUTIONS"**. Patients have experienced events including oedema, erythema nodosum, fatigue, fever, headache, insomnia, nausea, pulmonary infiltrates, rash, vertigo, vomiting, increase in transaminases and weight decrease. All events subsided following discontinuation of nevirapine.

There is no known antidote for nevirapine overdosage.

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

Lamivudine and zidovudine:

There is no experience of zidovudine and lamivudine (and therefore **TRIPLAVAR**) overdosage. However, 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.

Should overdosage occur, 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:

White to off-white capsule-shaped, biconvex, film-coated tablets, with central breakline on one side and plain on the other.

PRESENTATION:

White HDPE plastic container containing 30 tablets or 60 tablets.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.

KEEP OUT OF REACH OF CHILDREN.

Keep well closed.

REGISTRATION NUMBER:

To be allocated.

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

CIPLA MEDPRO (PTY) LTD

Rosen Heights

Pasita Street

Rosen Park

Bellville

7530

DATE OF PUBLICATION OF THE PACKAGE INSERT:

To be allocated.