1. Name of the medicinal product

Tenofovir Disoproxil Fumarate Tablets 300 mg

2. Qualitative and quantitative composition

Each film-coated tablet contains Tenofovir Disoproxil Fumarate 300 mg equivalent to 245 mg of Tenofovir Disoproxil

Each tablet contains 153.330 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. Pharmaceutical Form

Film coated tablets

Tenofovir Disoproxil Fumarate Tablets 300 mg is White circular film coated convex tablets engraved TDF on one side and plain on the other side.

4. Clinical Particulars

4.1 Therapeutic indications

Tenofovir Disoproxil Fumarate 300 mg Film coated tablets is indicated for the treatment of HIV-1 infection.

4.2 Posology and method of administration

Posology

Adults: The recommended dose of Tenofovir Disoproxil Fumarate for the treatment of HIV is 245 mg once daily taken orally with food

Special populations

Elderly: No data are available on which to make a dose recommendation for patients over the age of 65 years.

Renal impairment: Tenofovir is eliminated by renal excretion and the exposure to Tenofovir increases in patients with renal dysfunction. In patients with renal impairment Tenofovir Disoproxil fumarate should only be used if the potential benefits of treatment are considered to outweigh the potential risks. Dose interval adjustments are recommended for patients with creatinine clearance < 50 ml/min.

Mild renal impairment (creatinine clearance 50-80 ml/min): Limited data from clinical studies support once daily dosing of Tenofovir Disoproxil fumarate in patients with mild renal impairment.

Moderate renal impairment (creatinine clearance 30-49 ml/min): Administration of 245 mg Tenofovir Disoproxil (as fumarate) every 48 hours is recommended based on modelling of single-dose pharmacokinetic data in HIV negative and non-HBV infected subjects with varying degrees of renal impairment, including end-stage renal disease requiring haemodialysis, but has not been confirmed in clinical studies. Therefore, clinical response to treatment and renal function should be closely monitored in these patients

Severe renal impairment (creatinine clearance < 30 ml/min) and haemodialysis patients: Adequate dose adjustments cannot be applied due to lack of alternative tablet strengths; therefore use in this group of patients is not recommended. If no alternative treatment is available, prolonged dose intervals may be used as follows:
Severe renal impairment: 245 mg Tenofovir Disoproxil (as fumarate) may be administered every 72-96 hours (dosing twice a week).
Haemodialysis patients: 245 mg Tenofovir Disoproxil (as fumarate) may be administered every 7 days following completion of a haemodialysis session.

Hepatic impairment: No dose adjustment is required in patients with hepatic impairment.

Paediatric population: Tenofovir Disoproxil Fumarate tablets 300 mg is not recommended for use in children.

Method of administration

Tenofovir Disoproxil Fumarate tablets should be taken once daily, orally with food.

4.3 Contraindications

Tenofovir Disoproxil Fumarate is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the products.

4.4 Special warnings and precautions for use

Lactic Acidosis/Severe Hepatomegaly with Steatosis

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. Particular caution should be exercised when administering nucleoside analogs to any patient with known risk factors for liver disease; however, cases have also been reported in patients with no known risk factors. Treatment with tenofovir disoproxil fumarate should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).

Patients Coinfected with HIV and Hepatitis B Virus

It is recommended that all patients with HIV be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy. Tenofovir disoproxil fumarate is not approved for the treatment of chronic HBV infection and the safety and efficacy of Tenofovir disoproxil fumarate have not been established in patients coinfected with HBV and HIV.

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HBV and HIV and have discontinued tenofovir disoproxil fumarate. Hepatic function should be

monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV and HBV and discontinue tenofovir disoproxil fumarate. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Renal Impairment

Tenofovir is principally eliminated by the kidney. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported in association with the use of tenofovir disoproxil fumarate.

It is recommended that creatinine clearance be calculated in all patients prior to initiating therapy and as clinically appropriate during therapy with tenofovir disoproxil fumarate. Routine monitoring of calculated creatinine clearance and serum phosphorus should be performed in patients at risk for renal impairment.

Dosing interval adjustment of tenofovir disoproxil fumarate and close monitoring of renal function are recommended in all patients with creatinine clearance <50 mL/min. No safety or efficacy data are available in patients with renal dysfunction who received tenofovir disoproxil fumarate using these dosing guidelines, and so the potential benefit of tenofovir disoproxil fumarate therapy should be assessed against the potential risk of renal toxicity.

Tenofovir disoproxil fumarate should be avoided with concurrent or recent use of a nephrotoxic agent.

Bone Effects

In Study 903 through 144 weeks, decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients receiving tenofovir disoproxil fumarate + lamivudine + efavirenz (-2.2% ± 3.9) compared with patients receiving stavudine + lamivudine + efavirenz (-1.0% ± 4.6). Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the tenofovir disoproxil fumarate group vs. -2.4% ± 4.5 in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was

sustained through Week 144. Twenty-eight percent of tenofovir disoproxil fumarate-treated patients vs. 21% of the stavudine treated patients lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 patients in the tenofovir disoproxil fumarate group and 6 patients in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N-telopeptide) in the tenofovir disoproxil fumarate group relative to the stavudine group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in the tenofovir disoproxil fumarate group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within the normal range. The effects of tenofovir disoproxil fumarate -associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown.

Cases of osteomalacia (associated with proximal renal tubulopathy) have been reported in association with the use of tenofovir disoproxil fumarate.

Bone monitoring should be considered for HIV infected patients who have a history of pathologic bone fracture or are at risk for osteopenia. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including tenofovir disoproxil fumarate. During the initial phase of

combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium infection, cytomegalovirus, Pneumocystis jirovecii pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

Animal Toxicology

Tenofovir and tenofovir disoproxil fumarate administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6 fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2 to 20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

Tenofovir disoproxil fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus

assay, tenofovir disoproxil fumarate was negative when administered to male mice.

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

Other

Tenofovir disoproxil fumarate tablets should not be used in combination with the fixed-dose combination products TRUVADA or ATRIPLA since it is a component of these products.

Precautions:

When administered with tenofovir disoproxil fumarate, C_{max} and AUC of didanosine (Videx, Videx EC) administered as either the buffered or enteric-coated formulation increased significantly. The mechanism of this interaction is unknown. Higher didanosine concentrations could potentiate didanosine-associated adverse events, including pancreatitis and neuropathy. Suppression of CD4 cell counts has been observed in patients receiving tenofovir DF with didanosine at a dose of 400 mg daily. In adults weighing >60 kg, the didanosine dose should be reduced to 250 mg when it is coadministered with tenofovir disoproxil fumarate tablets. Data are not available to recommend a dose adjustment of didanosine for patients weighing <60 kg. When coadministered, tenofovir disoproxil fumarate and didanosine EC may be taken under fasted conditions or with a light meal (<400 kcal, 20% fat). Coadministration of didanosine buffered tablet formulation with tenofovir disoproxil fumarate tablets should be under fasted conditions.

Coadministration of tenofovir disoproxil fumarate and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse events. Didanosine should be discontinued in patients who develop didanosine-associated adverse events.

Since tenofovir is primarily eliminated by the kidneys, coadministration of tenofovir disoproxil fumarate with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of tenofovir and/or increase the concentrations of other renally eliminated drugs. Some examples include, but are not limited to adefovir dipivoxil, cidofovir, acyclovir, valacyclovir, ganciclovir, and valganciclovir.

Higher tenofovir concentrations could potentiate tenofovir disoproxil fumarate -associated adverse events, including renal disorders.

Atazanavir and lopinavir/ritonavir have been shown to increase tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving atazanavir and lopinavir/ritonavir and tenofovir disoproxil fumarate should be monitored for tenofovir disoproxil fumarate associated adverse events. tenofovir disoproxil fumarate should be discontinued in patients who develop tenofovir disoproxil fumarate-associated adverse events.

Tenofovir disoproxil fumarate decreases the AUC and C_{min} of atazanavir. When coadministered with tenofovir disoproxil fumarate**, it is recommended that atazanavir 300 mg is given with ritonavir 100 mg. Atazanavir without ritonavir should not be coadministered with** tenofovir disoproxil fumarate**.**

4.5 Interaction with other medicinal products and other forms of interaction

At concentrations substantially higher (~300-fold) than those observed in vivo, tenofovir did not inhibit in vitro drug metabolism mediated by any of the following human CYP450 isoforms: CYP3A4, CYP2D6, CYP2C9, or CYP2E1. However, a small (6%) but statistically significant reduction in metabolism of CYP1A substrate was observed. Based on the results of in vitro experiments and the known elimination pathway of tenofovir, the potential for CYP450 mediated interactions involving tenofovir with other medicinal products is low.

Tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. Coadministration of tenofovir disoproxil fumarate with drugs that are eliminated by active tubular secretion may increase serum concentrations of either tenofovir or the coadministered drug, due to competition for this elimination pathway. Drugs that decrease renal function may also increase serum concentrations of tenofovir.

Tenofovir disoproxil fumarate has been evaluated in healthy volunteers in combination with abacavir, adefovir dipivoxil, atazanavir, didanosine, efavirenz, emtricitabine, indinavir, lamivudine, lopinavir/ritonavir, methadone, nelfinavir, oral contraceptives, ribavirin, and saquinavir/ritonavir.
When administered with multiple doses of tenofovir disoproxil fumarate tablets, the C_{max} and AUC of didanosine 400 mg increased significantly. The mechanism of this interaction is unknown.

When didanosine 250 mg enteric-coated capsules were administered with tenofovir disoproxil fumarate, systemic exposures to didanosine were similar to those seen with the 400 mg enteric-coated capsules alone under fasted conditions.

Drug Interactions: Changes in Pharmacokinetic Parameters for Tenofovir[1] in the Presence of the Coadministered Drug

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters[2] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	⇔	⇔	NC
Adefovir dipivoxil	10 once	22	⇔	⇔	NC
Atazanavir[3]	400 once daily × 14 days	33	↑ 14 (↑ 8 to ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Didanosine (enteric-coated)	400 once	25	⇔	⇔	⇔
Didanosine (buffered)	250 or 400 once daily × 7 days	14	⇔	⇔	⇔
Efavirenz	600 once daily × 14 days	29	⇔	⇔	⇔
Emtricitabine	200 once daily × 7 days	17	⇔	⇔	⇔
Indinavir	800 three times daily × 7 days	13	↑ 14 (↓ 3 to ↑ 33)	⇔	⇔
Lamivudine	150 twice daily × 7 days	15	⇔	⇔	⇔
Lopinavir/ Ritonavir	400/100 twice daily × 14 days	24	⇔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Nelfinavir	1250 twice daily × 14 days	29	⇔	⇔	⇔
Saquinavir/ Ritonavir	1000/100 twice daily × 14 days	35	⇔	⇔	↑ 23 (↑ 16 to ↑ 30)

1. Patients received Tenofovir disoproxil fumarate Tablets 300 mg once daily.
2. Increase = ↑; Decrease = ↓; No Effect = ⇔; NC = Not Calculated
3. Reyataz Prescribing Information

Following multiple dosing to HIV-negative subjects receiving either chronic methadone maintenance therapy or oral contraceptives, or single doses of ribavirin, steady state tenofovir pharmacokinetics were similar to those observed in previous studies, indicating lack of clinically significant drug interactions between these agents and tenofovir disoproxil fumarate.

Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of tenofovir disoproxil fumarate

Coadministered Drug	Dose of Coadministered Drug (mg)	N	% Change of Tenofovir Pharmacokinetic Parameters[1] (90% CI)		
			C_{max}	AUC	C_{min}
Abacavir	300 once	8	↑12 (↓1 to ↑ 26)	⇔	NA
Adefovir dipivoxil	10 once	22	⇔	⇔	NA
Atazanavir[2]	400 once daily × 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to↓ 19)	↓ 40 (↓ 48 to ↓ 32)
Atazanavir[2]	Atazanavir/ Ritonavir 300/100 once daily × 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25[3] (↓ 42 to ↓ 3)	↓ 23[3] (↓ 46 to ↑ 10)
Efavirenz	600 once daily × 14 days	30	⇔	⇔	⇔
Emtricitabine	200 once daily × 7 days	17	⇔	⇔	↑ 20 (↑ 12 to ↑ 29)
Indinavir	800 three times daily × 7 days	12	↑ 11 (↓ 30 to ↑ 12)	⇔	⇔
Lamivudine	150 twice daily × 7 days	15	↓ 24 (↓ 34 to ↓ 12)	⇔	⇔
Lopinavir Ritonavir	Lopinavir/ Ritonavir 400/100 twice daily × 14 days	24	⇔ ⇔	⇔ ⇔	⇔ ⇔
Methadone[4]	40–110 once daily × 14 days[5]	13	⇔	⇔	⇔
Nelfinavir M8 metabolite	1250 twice daily × 14 days	29	⇔ ⇔	⇔ ⇔	⇔ ⇔
Oral Contraceptives[6]	Ethinyl Estradiol/ Norgestimate (Ortho-Tricyclen) once daily × 7 days	20	⇔	⇔	⇔
Ribavirin	600 once	22	⇔	⇔	NA
Saquinavir Ritonavir	Saquinavir/Ritonavir 1000/100 twice daily × 14 days	32	↑ 22 (↑ 6 to ↑ 41) ⇔	↑ 29[7] (↑ 12 to ↑ 48) ⇔	↑ 47[7] (↑ 23 to ↑ 76) ↑ 23 (↑ 3 to ↑ 46)

1. Increase = ↑; Decrease = ↓; No Effect = ⇔; NA = Not Applicable

2. Reyataz Prescribing Information

3. In HIV-infected patients, addition of tenofovir DF to atazanavir 300 mg plus ritonavir 100 mg,

resulted in AUC and C_{min} values of atazanavir that were 2.3- and 4-fold higher than the respective values observed for atazanavir 400 mg when given alone.

4. R-(active), S- and total methadone exposures were equivalent when dosed alone or with tenofovir disoproxil fumarate.

5. Individual subjects were maintained on their stable methadone dose. No pharmacodynamic alterations

(opiate toxicity or withdrawal signs or symptoms) were reported.

6. Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite) exposures were

equivalent when dosed alone or with tenofovir disoproxil fumarate.

7. Increases in AUC and C_{min} are not expected to be clinically relevant; hence no dose adjustments are

required when tenofovir DF and ritonavir-boosted saquinavir are coadministered.

Didanosine[1] Dose (mg)/Method of Administration[2]	**Tenofovir disoproxil fumarate Method of Administration 2**	**N**	**% Difference (90% CI) vs. Didanosine 400 mg Alone, Fasted[3]**	
			C_{max}	**AUC**
Buffered tablets				
400 once daily[4] × 7 days	Fasted 1 hour after didanosine	14	↑ 28 (↑ 11 to ↑ 48)	↑ 44 (↑ 31 to ↑ 59)
Enteric coated capsules				
400 once, fasted	With food, 2 hours after didanosine	26	↑ 48 (↑ 25 to ↑ 76)	↑ 48 (↑ 31 to ↑ 67)
400 once, with food	Simultaneously with didanosine	26	↑ 64 (↑ 41 to ↑ 89)	↑ 60 (↑ 44 to ↑ 79)
250 once, fasted	Simultaneously with didanosine	28	↓ 10 (↓ 22 to ↑ 3)	⇔
250 once, fasted	Simultaneously with didanosine	28	⇔	↑ 14 (0 to ↑ 31)
250 once, with food	Simultaneously with didanosine	28	↓ 29 (↓ 39 to ↓ 18)	↓ 11 (↓ 23 to ↑ 2)

Drug Interactions: Pharmacokinetic Parameters for Didanosine in the Presence of Tenofovir disoproxil fumarate

1. See PRECAUTIONS regarding use of didanosine with Tenofovir disoproxil fumarate.
2. Administration with food was with a light meal (~373 kcal, 20% fat).
3. Increase = ↑; Decrease = ↓; No Effect = ⇔

4.6 Pregnancy and lactation

Pregnancy

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to tenofovir. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, tenofovir disoproxil fumarate should be used during pregnancy only if clearly needed.

Antiretroviral Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to tenofovir disoproxil fumarate, an Antiretroviral Pregnancy Registry has been established. Healthcare providers are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers:

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV. Studies in rats have demonstrated that tenofovir is secreted in milk. It is not known whether tenofovir is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving tenofovir disoproxil fumarate.

Fertility

No human data on the effect of Tenofovir Disoproxil Fumarate tablets (300 mg) are available.

There were no effects on fertility, mating performance or early embryonic development when tenofovir disoproxil fumarate was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be informed that dizziness has been reported during treatment with tenofovir disoproxil fumarate.

4.8 Undesirable effects

Clinical Trials: More than 12,000 patients have been treated with tenofovir disoproxil fumarate tablets alone or in combination with other antiretroviral medicinal products for periods of 28 days to 215 weeks in phase I–III clinical trials and expanded access studies. A total of 1,544 patients have received tenofovir disoproxil fumarate tablets 300 mg once daily in phase I–III clinical trials; over 11,000 patients have received tenofovir disoproxil fumarate tablets in expanded access studies.

Treatment-Naïve Patients

Study 903 - Treatment-Emergent Adverse Events: The most common adverse reactions seen in a double-blind comparative controlled study in which 600 treatment-naïve patients received tenofovir disoproxil fumarate (N=299) or stavudine (N=301) in combination with lamivudine and efavirenz for 144 weeks (Study 903) were mild to moderate gastrointestinal events and dizziness.

Mild adverse events (Grade 1) were common with a similar incidence in both arms, and included dizziness, diarrhea, and nausea. Selected treatment-emergent moderate to severe adverse events are summarized in following table

Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in ≥5% in Any Treatment Group in Study 903 (0–144 Weeks)

	Tenofovir Disoproxil Fumarate + 3TC + EFV N=299	**d4T + 3TC + EFV N=301**
Body as a Whole		
Headache	14%	17%
Pain	13%	12%
Fever	8%	7%
Abdominal pain	7%	12%
Back pain	9%	8%
Asthenia	6%	7%
Digestive System		
Diarrhea	11%	13%
Nausea	8%	9%
Dyspepsia	4%	5%
Vomiting	5%	9%
Metabolic Disorders		
Lipodystrophy[1]	1%	8%
Musculoskeletal		
Arthralgia	5%	7%
Myalgia	3%	5%
Nervous System		
Depression	11%	10%
Insomnia	5%	8%
Dizziness	3%	6%
Peripheral neuropathy[2]	1%	5%
Anxiety	6%	6%
Respiratory		
Pneumonia	5%	5%
Skin and Appendages		
Rash event[3]	18%	12%

1. Lipodystrophy represents a variety of investigator-described adverse events not a protocol-defined syndrome.

2. Peripheral neuropathy includes peripheral neuritis and neuropathy.

3. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

Laboratory Abnormalities: With the exception of fasting cholesterol and fasting triglyceride elevations that were more common in the stavudine group (40% and 9%) compared with tenofovir disoproxil fumarate (19% and 1%) respectively, laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir disoproxil fumarate and stavudine treatment arms. a summary of grade 3 and 4 laboratory abnormalities is provided in following table.

Grade 3/4 Laboratory Abnormalities Reported in =1% of Tenofovir Disoproxil Fumarate Treated Patients in Study 903 (0–144 Weeks)

	Tenofovir Disoproxil Fumarate + 3TC + EFV	**d4T + 3TC + EFV**
	N=299	**N=301**
Any ≥ Grade 3 Laboratory Abnormality	36%	42%
Fasting Cholesterol (>240 mg/dL)	19%	40%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	12%	12%
Serum Amylase (>175 U/L)	9%	8%
AST (M: >180 U/L) (F: >170 U/L)	5%	7%
ALT (M: >215 U/L) (F: >170 U/L)	4%	5%
Hematuria (>100 RBC/HPF)	7%	7%
Neutrophils (<750/mm^3)	3%	1%
Fasting Triglycerides (>750 mg/dL)	1%	9%

Study 934 - Treatment Emergent Adverse Events: In Study 934, 511 antiretroviral-naïve patients received either tenofovir disoproxil fumarate + EMTRIVA administered in combination with efavirenz (N=257) or zidovudine/lamivudine administered in combination with efavirenz

(N=254). Adverse events observed in this study were generally consistent with those seen in previous studies in treatment-experienced or treatment-naïve patients (Table below).

Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in =3% in Any Treatment Group in Study 934 (0–48 Weeks)

	Tenofovir Disoproxil Fumarate + FTC + EFV	**AZT/3TC + EFV**
	N=257	**N=254**
Gastrointestinal Disorder		
Diarrhea	7%	4%
Nausea	8%	6%
Vomiting	1%	4%
General Disorders and Administration Site Condition		
Fatigue	7%	6%
Infections and Infestations		
Sinusitis	4%	2%
Upper respiratory tract infections	3%	3%
Nasopharyngitis	3%	1%
Nervous System Disorders		
Somnolence	3%	2%
Headache	5%	4%
Dizziness	8%	7%
Psychiatric Disorders		
Depression	4%	7%
Insomnia	4%	5%
Abnormal dreams	4%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	5%	4%

Laboratory Abnormalities: Laboratory abnormalities observed in this study were generally consistent with those seen in previous studies (Table below).

Significant Laboratory Abnormalities Reported in =1% of Patients in Any Treatment

Group in Study 934 (0–48 Weeks)

	Tenofovir Disoproxil Fumarate + 3TC + EFV	**d4T + 3TC + EFV**
	N=257	**N=254**
Any ≥ Grade 3 Laboratory Abnormality	25%	22%
Fasting Cholesterol (>240 mg/dL)	15%	17%
Creatine Kinase (M: >990 U/L) (F: >845 U/L)	7%	6%
Serum Amylase (>175 U/L)	7%	3%
Alkaline Phosphatase (>550 U/L)	1%	0%
AST (M: >180 U/L) (F: >170 U/L)	3%	2%
ALT (M: >215 U/L) (F: >170 U/L)	2%	2%
Hemoglobin (<8.0 mg/dL)	0%	3%
Hyperglycemia (>250 g/dL)	1%	1%
Hematuria (>75 RBC/HPF)	2%	2%
Neutrophils (<750/mm^3)	3%	4%
Fasting Triglycerides (>750 mg/dL)	4%	2%

Treatment-Experienced Patients

Treatment-Emergent Adverse Events: The adverse reactions seen in treatment experienced patients were generally consistent with those seen in treatment naïve

patients including mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting, and flatulence. Less than 1% of patients discontinued participation in the clinical studies due to gastrointestinal adverse events (Study 907).

A summary of moderate to severe, treatment-emergent adverse events that occurred during the first 48 weeks of Study 907 is provided in Table below.

Selected Treatment-Emergent Adverse Events (Grades 2–4) Reported in =3% in Any Treatment Group in Study 907 (0–48 Weeks)

	Tenofovir disoproxil fumarate (N=368) (Week 0–24)	**Placebo (N=182) (Week 0–24)**	**Tenofovir disoproxil fumarate (N=368) (Week 0–48)**	**Placebo Crossover to Tenofovir disoproxil fumarate (N=170) (Week 24–48)**
Body as a Whole				
Asthenia	7 %	6 %	11 %	1 %
Pain	7 %	7 %	12 %	4 %
Headache	5 %	5 %	8 %	2 %
Abdominal pain	4 %	3 %	7 %	6 %
Back pain	3 %	3 %	4 %	2 %
Chest pain	3 %	1 %	3 %	2 %
Fever	2 %	2 %	4 %	2 %
Digestive System				
Diarrhea	11 %	10 %	16 %	11 %
Nausea	8 %	5 %	11 %	7 %
Vomiting	4 %	1 %	7 %	5 %
Anorexia	3 %	2 %	4 %	1 %
Dyspepsia	3 %	2 %	4 %	2 %
Flatulence	3 %	1 %	4 %	1 %
Respiratory				
Pneumonia	2 %	0 %	3 %	2 %
Nervous System				
Depression	4 %	3 %	8 %	4 %
Insomnia	3 %	2 %	4 %	4 %
Peripheral neuropathy1	3 %	3 %	5 %	2 %
Dizziness	1 %	3 %	3 %	1 %
Skin and Appendage				
Rash event2	5 %	4 %	7 %	1 %
Sweating	3 %	2 %	3 %	1 %
Musculoskeletal				
Myalgia	3 %	3 %	4 %	1 %
Metabolic				
Weight loss	2 %	1 %	4 %	2 %

1. Peripheral neuropathy includes peripheral neuritis and neuropathy.

2. Rash event includes rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, and pustular rash.

Laboratory Abnormalities: Laboratory abnormalities observed in this study occurred with similar frequency in the tenofovir disoproxil fumarate and placebo-treated groups. A summary of Grade 3 and 4 laboratory abnormalities is provided in Table below.

Grade 3/4 Laboratory Abnormalities Reported in =1% of Tenofovir Disoproxil Fumarate Treated Patients in Study 907 (0–48 Weeks)

	Tenofovir disoproxil fumarate (N=368) (Week 0–24)	**Placebo (N=182) (Week 0–24)**	**Tenofovir disoproxil fumarate (N=368) (Week 0–48)**	**Placebo Crossover to tenofovir disoproxil fumarate (N=170) (Week 24–48)**
	%	**%**	**%**	**%**
Any ≥ Grade 3 Laboratory Abnormality	25 %	38 %	35 %	34 %
Triglycerides (>750 mg/dL)	8 %	13 %	11 %	9 %
Creatine Kinase (M: >990U/L) (F: >845 U/L)	7 %	14 %	12 %	12 %
Serum Amylase (>175 U/L)	6 %	7 %	7 %	6 %
Urine Glucose (≥3+)	3 %	3 %	3 %	2 %
AST (M: >180 U/L) (F: >170 U/L)	3 %	3 %	4 %	5 %
ALT (M: >215 U/L) (F: >170 U/L)	2 %	2 %	4 %	5 %
Serum Glucose (>250 U/L)	2 %	4 %	3 %	3 %
Neutrophils (<750/mm3)	1 %	1 %	2 %	1 %

Post Marketing Experience: The following events have been identified during post-approval use of tenofovir disoproxil fumarate. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting or potential causal connection to tenofovir disoproxil fumarate.

Immune system disorders

Allergic reaction

Metabolism and nutrition disorders

Hypophosphatemia, Lactic acidosis

Respiratory, thoracic, and mediastinal disorders

Dyspnea

Gastrointestinal disorders

Abdominal pain, Increased amylase, Pancreatitis

Hepatobiliary disorders

Increased liver enzymes, Hepatitis

Skin and subcutaneous tissue disorders

Rash

Musculoskeletal and connective tissue disorders

Myopathy, Osteomalacia (both associated with proximal renal tubulopathy)

Renal and urinary disorders

Renal insufficiency, Renal failure, Acute renal failure, Fanconi syndrome, Proximal tubulopathy, Proteinuria, Increased creatinine, Acute tubular necrosis, Nephrogenic diabetes insipidus, Polyuria, Interstitial nephritis (including acute cases).

General disorders and administration site conditions

Asthenia

4.9 Overdose

Limited clinical experience at doses higher than the therapeutic dose of tenofovir disoproxil fumarate tablets 300 mg is available. In Study 901, 600 mg tenofovir disoproxil fumarate was administered to 8 patients orally for 28 days. No severe adverse reactions were reported. The effects of higher doses are not known.

If overdose occurs the patient must be monitored for evidence of toxicity, and standard supportive treatment applied as necessary.

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of tenofovir disoproxil fumarate, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamic properties

Mechanism of Action: Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonate diester analog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate.

Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Antiviral Activity: The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes. The EC_{50} (50% effective concentration) values for tenofovir were in the range of 0.04 mcM to 8.5 mcM.

In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G, and O (EC_{50} values ranged from 0.5 mcM to 2.2 mcM) and strain specific activity against HIV-2 (EC_{50} values ranged from 1.6 mcM to 4.9 mcM).

Resistance: HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R mutation in reverse transcriptase and showed a 2–4 fold reduction in susceptibility to tenofovir.

In Study 903 of treatment-naïve patients (tenofovir disoproxil fumarate + lamivudine + efavirenz versus stavudine + lamivudine + efavirenz), genotypic analyses of isolates from patients with virologic failure through Week 144 showed development of efavirenz and lamivudine resistance-associated mutations to occur most frequently and with no difference between the treatment arms. The K65R mutation occurred in 8/47 (17%) analyzed patient isolates on the Tenofovir disoproxil fumarate arm and in 2/49 (4%) analyzed patient isolates on the stavudine arm. Of the 8 patients whose virus developed K65R in the tenofovir disoproxil fumarate arm through 144 weeks, 7 of these occurred in the first 48 weeks of treatment and one at Week 96. Other mutations resulting in resistance to Tenofovir disoproxil fumarate were not identified in this study.

In Study 934 of treatment-naïve patients (tenofovir disoproxil fumarate + EMTRIVA® + efavirenz versus zidovudine (AZT)/lamivudine (3TC) + efavirenz), genotypic analysis performed on HIV isolates from all patients with >400 copies/mL of HIV-1 RNA at Week 48 or early discontinuation showed development of efavirenz resistance-associated mutations occurred most frequently and was similar between the two treatment arms. The M184V mutation, associated with resistance to EMTRIVA and lamivudine, was observed in 2/12 (17%) analyzed patient

isolates in the tenofovir disoproxil fumarate tablets + EMTRIVA group and in 7/22 (32%) analyzed patient isolates in the zidovudine/lamivudine group. Through 48 weeks of Study 934, no patients have developed a detectable K65R mutation in their HIV as analyzed through standard genotypic analysis. Insufficient data are available to assess the development of the K65R mutation upon prolonged exposure to this regimen.

Cross-resistance: Cross-resistance among certain reverse transcriptase inhibitors has been recognized. The K65R mutation selected by tenofovir is also selected in some HIV-1 infected subjects treated with abacavir, didanosine, or zalcitabine. HIV isolates with this mutation also show reduced susceptibility to emtricitabine and lamivudine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors the K65R mutation. HIV-1 isolates from patients (N=20) whose HIV-1 expressed a mean of 3 zidovudine-associated reverse transcriptase mutations (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N), showed a 3.1-fold decrease in the susceptibility to tenofovir. Multinucleoside resistant HIV-1with a T69S double insertion mutation in the reverse transcriptase showed reduced susceptibility to tenofovir.

In Studies 902 and 907 conducted in treatment-experienced patients (tenofovir disoproxil fumarate tablet+ Standard Background Therapy (SBT) compared to Placebo + SBT), 14/304 (5%) of the tenofovir disoproxil fumarate-treated patients with virologic failure through Week 96 had >1.4-fold (median 2.7-fold) reduced susceptibility to tenofovir. Genotypic analysis of the baseline and failure isolates showed the development of the K65R mutation in the HIV-1 reverse transcriptase gene.

The virologic response to tenofovir disoproxil fumarate therapy has been evaluated with respect to baseline viral genotype (N=222) in treatment experienced patients participating in Studies 902 and 907.

In these clinical studies, 94% of the participants evaluated had baseline HIV-1 isolates expressing at least one NRTI mutation. These included resistance mutations associated with zidovudine

(M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E/N), the abacavir/emtricitabine/lamivudine resistance-associated mutation (M184V), and others. In addition the majority of participants evaluated had mutations associated with either PI or NNRTI use. Virologic responses for patients in the genotype substudy were similar to the overall study results.

Several exploratory analyses were conducted to evaluate the effect of specific mutations and mutational patterns on virologic outcome. Because of the large number of potential comparisons, statistical testing was not conducted. Varying degrees of cross-resistance of tenofovir disoproxil fumarate to pre-existing zidovudine resistance associated mutations were observed and appeared to depend on the number of specific mutations. Tenofovir disoproxil fumarate -treated patients whose HIV-1 expressed 3 or more zidovudine resistance-associated mutations that included either the M41L or L210W reverse transcriptase mutation showed reduced responses to tenofovir disoproxil fumarate therapy; however, these responses were still improved compared with placebo.

The presence of the D67N, K70R, T215Y/F, or K219Q/E/N mutation did not appear to affect responses to tenofovir disoproxil fumarate therapy.

In the protocol defined analyses, virologic response to Tenofovir disoproxil fumarate was not reduced in patients with HIV-1 that expressed the abacavir/emtricitabine/Lamivudine resistance-associated M184V mutation. In the presence of zidovudine resistance associated mutations, the M184V mutation did not affect the mean HIV-1 RNA responses to Tenofovir disoproxil fumarate treatment. HIV-1 RNA responses among these patients were durable through Week 48.

Studies 902 and 907 Phenotypic Analyses: The virologic response to Tenofovir disoproxil fumarate therapy has been evaluated with respect to baseline phenotype (N=100) in treatment-experienced patients participating in two controlled trials. Phenotypic analysis of baseline HIV-1 from patients in these studies demonstrated a correlation between baseline susceptibility to Tenofovir disoproxil fumarate and response to Tenofovir disoproxil fumarate therapy.

Following table summarizes the HIV-1 RNA response by baseline Tenofovir disoproxil fumarate susceptibility.

HIV-1 RNA Response at Week 24 by Baseline Tenofovir disoproxil fumarate Susceptibility (Intent-To-Treat)[1]

Baseline Tenofovir Disoproxil Fumarate Tablets Susceptibility[2]	**Change in HIV-1 RNA[3] (N)**
<1	0.74 (35)
>1 and ≤3	0.56 (49)
>3 and ≤4	0.3 (7)
>4	0.12 (9)

1. Tenofovir susceptibility was determined by recombinant phenotypic Antivirogram assay (Virco).
2. Fold change in susceptibility from wild-type.
3. Average HIV-1 RNA change from baseline through Week 24 ($DAVG_{24}$) in $\log_{10}$ copies/mL.

5.2 Pharmacokinetic properties

Pharmacokinetics

The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption: Tenofovir disoproxil fumarate is a water soluble diester prodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from tenofovir disoproxil fumarate tablets in fasted patients is approximately 25%. Following oral administration of a single dose of Tenofovir disoproxil fumarate Tablet 300 mg to HIV-1 infected patients in the fasted state, maximum serum concentrations (C_{max}) are achieved in 1.0 ± 0.4 hrs. C_{max} and AUC values are 296 ± 90 ng/mL and 2287 ± 685 ng·hr/mL, respectively.

The pharmacokinetics of tenofovir are dose proportional over a Tenofovir disoproxil fumarate

dose range of 75 to 600 mg and are not affected by repeated dosing.

Effects of Food on Oral Absorption: Administration of tenofovir disoproxil fumarate tablets following a high-fat meal (~700 to 1000 kcal containing 40 to 50% fat) increases the oral bioavailability, with an increase in tenofovir $AUC_{0-\infty}$ of approximately 40% and an increase in C_{max} of approximately 14%. However, administration of tenofovir disoproxil fumarate tablets with a light meal did not have a significant effect on the pharmacokinetics of tenofovir when compared to fasted administration of the drug. Food delays the time to tenofovir C_{max} by approximately 1 hour. C_{max} and AUC of tenofovir are 326 ±119 ng/mL and 3324 ± 1370 ng·hr/mL following multiple doses of tenofovir disoproxil fumarate tablets 300 mg once daily in the fed state, when meal content was not controlled.

Distribution: In vitro binding of tenofovir to human plasma or serum proteins is less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 mcg/mL. The volume of distribution at steady-state is 1.3 ± 0.6 L/kg and 1.2 ±0.4 L/kg, following intravenous administration of tenofovir 1.0 mg/kg and 3.0 mg/kg.

Metabolism and Elimination: In vitro studies indicate that neither tenofovir disoproxil nor tenofovir are substrates of CYP450 enzymes.

Following IV administration of tenofovir, approximately 70–80% of the dose is recovered in the urine as unchanged tenofovir within 72 hours of dosing. Following single dose, oral administration of tenofovir disoproxil fumarate tablets, the terminal elimination half-life of tenofovir is approximately 17 hours. After multiple oral doses of tenofovir disoproxil fumarate tablets 300 mg once daily (under fed conditions), 32 ± 10% of the administered dose is recovered in urine over 24 hours.

Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

Special Populations

There were insufficient numbers from racial and ethnic groups other than Caucasian to adequately determine potential pharmacokinetic differences among these populations.

Tenofovir pharmacokinetics are similar in male and female patients.

Pharmacokinetic studies have not been performed in children (<18 years) or in the elderly (>65 years).

The pharmacokinetics of tenofovir following a 300 mg single dose of tenofovir disoproxil fumarate tablets have been studied in non-HIV infected patients with moderate to severe hepatic impairment. There were no substantial alterations in tenofovir pharmacokinetics in patients with hepatic impairment compared with unimpaired patients. No change in tenofovir disoproxil fumarate dosing is required in patients with hepatic impairment.

The pharmacokinetics of tenofovir disoproxil fumarate are altered in patients with renal impairment. In patients with creatinine clearance <50 mL/min or with end-stage renal disease (ESRD) requiring dialysis, C_{max}, and $AUC_{0-\infty}$ of tenofovir were increased. It is recommended that the dosing interval for tenofovir disoproxil fumarate tablets be modified in patients with creatinine clearance <50 mL/min or in patients with ESRD who require dialysis.

Pharmacokinetic Parameters (Mean ± SD) of Tenofovir* in Patients with Varying Degrees of Renal Function

Baseline Creatinine Clearance (mL/min)	**>80 (N=3)**	**50–80 (N=10)**	**30–49 (N=8)**	**12–29 (N=11)**
C_{max} (ng/mL)	335.4 ± 31.8	330.4 ± 61.0	372.1 ± 156.1	601.6 ± 185.3
$AUC_{0-\infty}$ (ng·hr/mL)	2184.5 ± 257.4	3063.8 ± 927.0	6008.5 ± 2504.7	15984.7 ± 7223.0
CL/F (mL/min)	1043.7 ± 115.4	807.7 ± 279.2	444.4 ± 209.8	177.0 ± 97.1
CL_{renal} (mL/min)	243.5 ± 33.3	168.6 ± 27.5	100.6 ± 27.5	43.0 ± 31.2

*300 mg, single dose of tenofovir disoproxil fumarate

Tenofovir is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%. Following a single 300 mg dose of Tenofovir disoproxil fumarate Tablets, a four-hour hemodialysis session removed approximately 10% of the administered tenofovir dose.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal Toxicology

Tenofovir and tenofovir disoproxil fumarate administered in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) greater than or equal to 6 fold those observed in humans caused bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Evidence of renal toxicity was noted in 4 animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2 to 20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral carcinogenicity studies of tenofovir disoproxil fumarate in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in humans at the therapeutic dose for HIV infection. At the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.

Tenofovir disoproxil fumarate was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus

assay, tenofovir disoproxil fumarate was negative when administered to male mice.

There were no effects on fertility, mating performance or early embryonic development when

tenofovir disoproxil fumarate was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day seven of gestation. There was, however, an alteration of the estrous cycle in female rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tenofovir disoproxil fumarate tablets 300 mg contains the following excipients Croscarmellose Sodium, Lactose Monohydrate, Microcrystalline cellulose, Pregelatinised starch, Magnesium Stearate, Opadry White (Y-1-7000)

Composition of Opadry White (Y-1-7000)

i) Hydroxy propyl methyl cellulose 2910/Hypromellose 5Cp

ii) Titanium Dioxide

iii) Polyethylene glycol

6.2 Incompatibilites

None.

6.3 Shelf life

The product has a shelf life of 24 Months.

6.4 Special precautions for storage

Do not Store above 30ºC. Protect from light. Keep the medicines away from reach of children.

6.5 Nature and contents of container

Description	Unit count or fill size

(including materials of construction)	
HDPE Container – 60 CC of 38 mm neck finish Diameter- 46 x Height- 69.5 mm] [White Opaque HDPE Container] [38 mm] [HDPE Opaque Screw cap white opaque] [with induction seal liner] [“Sealed for your protection”]	30 tablets in HDPE container

6.6 Special precautions for disposal

No special requirements. Any unused product or waste material should be disposed of in accordance of with local requirement

7. MARKETING AUTHORISATION HOLDER

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Tel: 91-80-67840738/290

Fax: 91-80-67840700

8. REFERENCE NUMBER

Not Applicable

9. DATE OF REVISION OF THE TEXT

Not Applicable