Zolec®

Efavirenz 600 mg
Emtricitabine 200 mg
Tenofovir Disoproxil Fumarate 300 mg

Coated tablets

Made in Argentina
Sold under filed prescription

Fórmula

Each coated tablets of ***Zolec®*** contains: 600 mg of efavirenz, 200 mg of emtricitabine and Tenofovir Disoproxil Fumarate 300 mg (Equivalent to 245 mg of Tenofovir Disoproxil). Excipients: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, Opadry II white 85F28751(*), red iron oxide. (*) Composition of Opadry II white 85F28751: polyvinyl alcohol; polyethylene glycol; talc; titanium dioxide.

Therapeutic Action

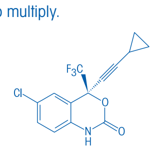
Antiretroviral therapy for the treatment of HIV-1 infection (human immunodeficiency virus type 1). Fixed combination of three antiretrovirals, two nucleoside reverse transcriptase inhibitors (tenofovir and emtricitabine) and one non-nucleoside (Efavirenz).
ATC code: J05AR06

Indications and use

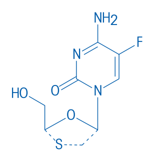
• HIV-1 infections in adults and pediatrics patients aged 12 years and over: ***Zolec®***, is indicated as a single therapy or in combination with other antiretroviral agents for the treatment of HIV-1 (human immunodeficiency virus type 1).

Pharmacological properties

Zolec® contains three antiretroviral (efavirenz, emtricitabina and Tenofovir Disoproxil Fumarate) fixed dose active substances in the same tablet to treat human immunodeficiency virus (HIV) infection.
Each of these active substances, work by interfering with an enzyme (reverse transcriptase) that is essential for the virus to multiply.
Efavirenz is an NNRTI Non-Nucleoside Reverse Transcriptase Inhibitor of HIV-1.
Emtricitabine is a synthetic nucleoside analogue of cytidine.
Tenofovir Disoproxil Fumarate (Tenofovir DF) is converted in vivo to Tenofovir, a nucleoside monophosphate (nucleotide) analogue of 5´-adenosine monophosphate.

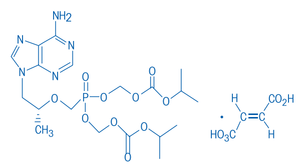


Efavirenz: the chemical name is (S)-6-chloro-4-(cyclopropylenthynyl)-1,4-dihydro-4(trifluoromethyl)-2H-3,1-benzoxazin-2-ona. Molecular formula is $C_{14}H_9ClF_3NO_2$. is an NNRTI Non-Nucleoside Reverse Transcriptase Inhibitor of HIV-1.
Its activity is mediated primarily by the non-competitive inhibition of HIV-1 reverse transcriptase. It does not inhibit HIV-2 RT or the α, β and γ (alpha, beta, or gamma) polymerases of human DNA.
Efavirenz is a white to slightly pinkish crystalline powder with a molecular mass of 315.62. It is practically non-water-soluble (less than 10mcg/ml).



Emtricitabine: the chemical name is 5-fluoro-1-(2R,5S)-[2-(hydroximethyl)-1,3-oxatiolano-5-il]cytosine. Emtricitabine is the (-) enantiomer of a cytidine analogue thio, which differs from other cytidine analogues in that it has fluorine in the 5-position.
Emtricitabine is a white to off-white crystalline powder with a solubility of approximately 112 mg/mL in water at 25°C. The partition coefficient (logarithm p) of emtricitabine is -0.43 and the pKa value is 2.65. The molecular formula is $C_8H_{10}FN_3O_3S$ and the molecular weight 247.24. Its structural formula is as follows:
Emtricitabine is phosphorylated by cellular enzymes to form 5′-triphosphate Emtricitabine. The latter competes with 5′-triphosphate deoxycytidine, the natural substrate of HIV-1 reverse transcriptase, inhibiting it and when it is incorporated into incipient viral DNA chain termination occurs. Emtricitabine 5′-triphosphate is a weak inhibitor of mammalian DNA, α, β and ε (alpha, beta and epsilon) polymerases and mitochondrial DNA (gamma) polymerase.

Tenofovir Disoproxil Fumarate: Tenofovir Disoproxil Fumarate is an acid salt Fumaric acid of bis-isopropoxycarbonyloxymethyl ester derived from Tenofovir. The chemical name of Tenofovir Disoproxil Fumarate is 9-[(R)-2-[[bis [[(isopropoxycarbonyl) oxy]-ethoxy]phosphinyl]methoxy]propyl] adenine fumarate (1:1). Its molecular formula is $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$ and its molecular weight is 635,52. Its structural formula is as follows:



Tenofovir Disoproxil Fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in water at 25°C. The partition coefficient (logarithm p) of Tenofovir Disoproxil Fumarate is 1.25 and the pKa value is 3.75. All doses are expressed in terms of Tenofovir Disoproxil Fumarate, unless otherwise noted.
Tenofovir Disoproxil Fumarate is an acyclic di esther nucleoside phosphonate analogue of adenosine monophosphate. Tenofovir Disoproxil Fumarate requires initial hydrolysis of the diester to become tenofovir and subsequent phosphorylation by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits HIV-1 reverse transcriptase activity by competing with the natural substrate deoxyadenosine 5′-triphosphate and, following its incorporation into DNA, by terminating the DNA strand.
Tenofovir diphosphate is a weak inhibitor of α and β polymerases of mammalian DNA and mitochondrial DNA γ polymerase.

Antiviral activity: *Efavirenz, Emtricitabine and Tenofovir Disoproxil Fumarate:* In association studies evaluating antiviral activity in cell cultures of Emtricitabine and Efavirenz together, efavirenz and tenofovir together and emtricitabine and tenofovir together, antiviral effects were observed between additives and synergists.

Efavirenz: Efavirenz at varying concentrations between 1.7 and 25nM inhibits the replication of non-mutant strains adapted in the laboratory and clinical strains in cell cultures between 90-95% (CE_{90-95}) in cultures of lymphoblastoid cell lines, mononuclear leukocytes in peripheral blood and macrophages or monocytes.
Has demonstrated additive activity when associated with delavirdine and nevirapine (non-nucleoside TR inhibitors), abacavir, didanosine, lamivudine, estavudine, zalcitabine, zidovidine (nucleoside TR inhibitors), amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir (protease inhibitors), and enfuvirtide (fusion inhibitor).
On the other hand, it demonstrated antiviral activity between additive and antagonist in culture of cells with atazanavir. Efavirenz demonstrated antiviral activity against isolated B clade strains and most isolated non-clade B strains (subtypes A, AE, AG, C, D, F, G, J and N) but had reduced antiviral activity against viruses of the O group. Efavirenz is not active against HIV-2.
Synergistic antiviral activity of Emtricitabine and Tenofovir Disoproxil Fumarate has been observed in studies in cell cultures in which it was evaluated the antiviral activity of both drugs in combination.

Emtricitabine: Its antiviral activity was evaluated against clinical and laboratory isolates of HIV-1, lymphoblastoid cell lines, MAGI-CCR5 cell line and peripheral blood mononuclear cells. The 50% effective concentration values (EC_{50}) were between 0.0013 and 0.64 μM (0.0003 to 0.158 μg/ml). Effects that varied between additives and synergists were observed in association studies with nucleoside inhibitors of retrotranscriptase such as abacavir, lamivudine, stavudine, zalcitabine, zidovudine; Non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine) and protease inhibitors such as amprenavir, nelfinavir, ritonavir, saquinavir. Emtricitabine displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G and O. (EC_{50} between 1.6 and 5.5 μM).

Tenofovir Disoproxil Fumarate: Its antiviral activity was evaluated against isolated laboratory and clinical strains of HIV, in lymphoblastoid cell lines, primary monocyte-macrophage cells, and peripheral blood lymphocytes. The 50% effective concentration values (EC_{50}) were between 0.04 and 8.5 μM. Effects that varied between additives and synergists were observed in association studies of Tenofovir with nucleoside reverse transcriptase inhibitor drugs (such as abacavir, didadosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (e.g. delavirdine, Efavirenz, nevirapine) and protease inhibitors (e.g. amprenavir, nelfinavir, ritonavir, saquinavir). Tenofovir displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, G and O. (EC50 between 0.5 to 2.2 μM) and specific activity of strains against HIV-2 (with EC_{50} values between 1.6 and 5.5 μM).

Resistance:

Emtricitabine and Tenofovir Disoproxil Fumarate: HIV-1 strains with reduced susceptibility to the combination of Emtricitabine and Tenofovir were selected.
Resistance to Emtricitabine or Tenofovir has been seen *in vitro* and in some HIV-1 infected patients due to the development of an M184V or M184I substitution in RT with Emtricitabine or a K65R substitution in RT with Tenofovir. Genotypic analysis of these strains identified M184V/I and/or K65R amino acid substitutions in viral reverse transcriptase. Also, Tenofovir has selected a K70E substitution in HIV-1 reverse transcriptase that produced a decrease in Tenofovir sensitivity.

Emtricitabine: Emtricitabine-resistant HIV strains have been selected both in vivo, in patients without pre-treatment, and in treatment failure, as well as *in vitro*. The most common mutation detected was at codon 184 of the reverse transcriptase gene, whereby methionine is substituted for valine or isoleucine (M184 V/I).

Tenofovir Disoproxil Fumarate: HIV-1 strains with reduced susceptibility to Tenofovir were found in cell cultures. These viruses manifested a K65R substitution in reverse transcriptase and reported a 2- to 4-fold reduction in Tenofovir sensitivity.
The same mutation was found in strains isolated from patients in clinical trials, either with low but variable prevalence. The most commonly observed amino acid substitution in clinical studies with Efavirenz is K103N (54%).
In a clinical study of patients without previous antiretroviral therapy, in the resistance analysis of all patients with confirmed virological failure (> 400 copies/ml of HIV-1 RNA at week 144) or who dropped out prematurely, it was observed that the most frequent form of resistance was genotype resistance to Efavirenz, predominantly the K103N substitution. Resistance to Efavirenz was found in 13/19 patients treated with Emtricitabine + Tenofovir Disoproxil Fumarate and in 21/29 patients in the fixed dose combination group of zidovudine and lamivudine. The M184V amino acid substitution associated with resistance to Emtricitabine and lamivudine was observed in 2/19 of isolates from the patients treated in the group treated with Emtricitabine + Tenofovir Disoproxil Fumarate and in 10/29 of strains isolated from patients in the zidovudine group and lamivudine in association. In the 144 weeks of the aforementioned study, no patient presented K65R substitution detectable in their HIV-1, according to the genotypic analyzes performed.
K103N is the most frequently observed amino acid substitution in clinical studies with Efavirenz (54%); one or more reverse transcriptase substitutions at amino acid positions 98, 100, 101, 103, 106, 108, 188, 190, 225, 227 and 230 were observed in patients who did not respond to Efavirenz treatment associated with other anti retrovirals. Other resistance substitutions that were frequently observed were L100I (87%), K101E/Q/R (14%), V108I (11%), G190S/T/A (7%), 225H (18%) and M230I/L (11%).
In a selection in cell culture HIV-1 isolated strains with rapidly decreased sensitivity to Efavirenz appeared (> 380-fold increase in CE_{90} value). The genotypic characterization of these viruses identified substitutions that produced substitutions of a single amino acid L100I or V179D, double substitutions L100I/V108I and triple substitutions L100I/V179D/Y181C of the reverse transcriptase.

Cross resistance:

Cross-resistance has been described between non-nucleoside inhibitors of TR, also between certain nucleoside inhibitors. Clinical strains isolated from the clinic that were characterized as resistant to efavirenz were also phenotypically resistant in cell culture to delavirdine and venirapine compared to baseline values. Clinical viral isolates, resistant to delavirdine, nevirapine, with substitutions associated with resistance to non-nucleoside reverse transcriptase inhibitors (A98G, L100I, K101I, K101E, K103N/S, V106A, Y181X, Y188X, G190X, P225H, F227L or M230L) showed decreased sensitivity to efavirenz in cell culture. More than 90% of INRT resistant isolates tested in cell culture retained sensitivity to efavirenz. Emtricitabine and Tenofovir Disoproxil Fumarate: Cross-resistance has been recognized between certain nucleoside reverse transcriptase inhibitors (INRTs). The M184V/I and/or K65R substitutions found in cell cultures treated with combination of Emtricitabine and Tenofovir were also observed in some strains isolated from HIV-1 in patients who failed treatment with tenofovir in combination with either lamivudine or emtricitabine, or abacavir or didanosine. Therefore, cross-resistance between these drugs can occur in patients whose virus contains one or both amino acid substitutions. Emtricitabine resistant strains (M184V/I) demonstrated cross-resistance to lamivudine and zalcitabine but did not tolerate didanosine, stavudine, tenofovir, zidovudine and non-nucleoside reverse transcriptase inhibitors (delavirdine, Efavirenz and nevirapine). HIV-1 strains containing the K65R mutation selected in vivo by abacavir, didanosine, tenofovir and zalcitabine, demonstrated reduced susceptibility to inhibition by Emtricitabine. Viruses with mutations conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to Emtricitabine.
HIV-1 containing the K103N substitution associated with resistance to non-nucleoside reverse transcriptase inhibitors was sensitive to Emtricitabine.
Tenofovir Disoproxil Fumarate: HIV-1 strains isolated from patients who had a mean of 3 zidovudine-associated reverse transcriptase amino acid substitutions (M41L, D67N, K70R, L210W, T215Y/F or K219Q/E/N) indicated a decrease in 3.1 times in susceptibility to Tenofovir.
Subjects whose viruses express a substitution in L74V without resistance associated with zidovudine, had reduced response to Tenofovir.
There are few data regarding patients with reduced response to Tenofovir whose viruses express Y115F or Q151M or T69 insertion.

Pharmacokinetic Properties

Efavirenz: in patients infected with HIV, after oral administration, the time to reach the maximum concentration (t_{max}) is 3 to 5 hours; its absorption is increased by foods rich in fat or hyper caloric. It has high binding to plasma proteins (99%), mostly albumin. It is metabolized in the liver by CYP3A and 2B6 to inactive metabolites; it can induce its own metabolism. The elimination half-life ranges from 52 to 76 hours after the administration of single doses and from 40 to 55 hours after the administration of several doses. Its excretion is fecal (16-60% mostly as unchanged drug) and urinary (14 to 34% as metabolites).
Tenofovir Disoproxil Fumarate: following an oral administration of Tenofovir Disoproxil Fumarate, peak concentrations of tenofovir in serum were achieved after 1.0 ± 0.4 hours. The oral bioavailability of tenofovir from Tenofovir Disoproxil Fumarate in fasting patients is approximately 25%. The *in vitro* binding of tenofovir to human plasma proteins is <0.7% and independent of the concentration in the range of 0.01-25 mg/mL. Approximately 70-80% of the intravenous dose of tenofovir is recovered as unmodified drug in the urine. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of Tenofovir, its elimination half-life is approximately 17 hours.
Emtricitabine: following after an oral administration of Emtricitabine, it is rapidly absorbed at peak plasma concentrations at or about 2 hours post dose. Its bioavailability is 92-93%. It has low binding to plasma proteins <4%, and its binding is independent of the concentration within the range of 0.02-200 mg/mL. After the administration of radio-labeled Emtricitabine, approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of emtricitabine include 3′-sulfoxide diastereomers and its glucuronic acid conjugate. Emtricitabine is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose, the plasma half-life of Emtricitabine is approximately 10 hours.
Effects of Feeding on Oral Absorption: ***Zolec®*** has not been evaluated in the presence of food. Administration of Efavirenz with a high fat meal increased the mean AUC and C_{max} of Efavirenz by 28% and 79%, respectively, compared to administration in a fasted state.
Compared to fasted administration, dosing of Tenofovir Disoproxil Fumarate and Emtricitabine in combination with either a high fat meal (784 kcal; 49 gs of fat) or a light meal (373 kcal; 8 gs of fat) delayed the C_{max} of Tenofovir in 0.75 hour approximately. Also, the mean AUC and C_{max} of Tenofovir were increased by 35% and 15%, administered with either a high fat meal or a light meal.

Special Populations:

Race: the administration of Efavirenz to HIV-1-infected patients of diverse racial groups had similar pharmacokinetic characteristics.
Emtricitabine: no pharmacokinetic differences due to race have been identified.
Tenofovir: no evaluation sufficient number of subjects to determine pharmacokinetic differences in race.
Gender: the pharmacokinetics of its active principles is similar in female as well as male patients.
Age: pharmacokinetic studies have not been performed with Efavirenz, Emtricitabine or Tenofovir in elderly patients (over 65 years of age).
Pediatric patients: there have been no pharmacokinetic studies of this combination in pediatric patients. ***Zolec®*** should not be administered to pediatric patients <12 years of age or in patients with body weight less than 40 kg.
In open pharmacokinetic studies in which Efavirenz was administered to pediatric patients aged 3-16 years, >40kg (who had received prior treatment with nucleoside reverse transcriptase inhibitor), their pharmacokinetics were similar to that of adults receiving 600mg doses of Efavirenz. When Emtricitabine at doses of 200 mg/day was administered to children 13 to 17 years, its pharmacokinetics was similar to that observed in adults at the same dose.
In patients aged 12 to <18 years who evaluated the pharmacokinetic profile of Tenofovir 300mg/day similar profiles were observed than those obtained in adult patients with similar treatment.
Renal Impairment: the pharmacokinetics of Efavirenz has not been studied in patients with renal impairment; however, less than 1% is excreted unchanged in the urine, changes in its pharmacokinetics may not be expected in the presence of renal dysfunction. The pharmacokinetics of both Emtricitabine and Tenofovir are altered in patients with renal impairment. In patients with a creatinine clearance less than 50 mL/min, the C_{max} and AUC_{0-inf} of Emtricitabine and tenofovir were increased.
Hepatic Impairment: the pharmacokinetics of ***Zolec®*** or other products with the same fixed association in hepatic impairment have not been evaluated. The pharmacokinetics of emtricitabine alone have not been evaluated in patients with this condition. However, emtricitabine is not metabolized significantly by liver enzymes; therefore the impact of hepatic impairment should be limited. Efavirenz did not show pharmacokinetic changes in patients with mild hepatic dysfunction (Child-Pugh class A) compared to the control group in a multiple dose study. Adequate data are available to determine whether moderate or severe hepatic dysfunction alter the pharmacokinetic characteristics of Efavirenz.
In patients not infected by HIV-1 with mild to moderate hepatic impairment the pharmacokinetics of a dose of 300mg tenofovir were evaluated. There were no substantial alterations in the pharmacokinetics of tenofovir in this group compared to the pharmacokinetics of patients without Tenofovir.

Drug Interaction: no drug interaction studies have been performed using either ***Zolec®*** tablets or other fixed combinations of Efavirenz, Emtricitabine and Tenofovir Disoproxil Fumarate.
This fixed combination, should not be co-administered with medicines containing efavirenz, unless required for dose adjustment, e.g. with rifampicin. Nor should it be given concomitantly with other cytidine analogs such as lamivudine due to similarities with Emtricitabine. It should not be administered concomitantly with adefovir dipivoxil.

Efavirenz: when Efavirenz and Tenofovir were given, their pharmacokinetic characteristics were unaffected with regard to the administration of both drugs separately. No pharmacological interaction studies were performed between efavirenz and other INRT, other than tenofovir, lamivudine and zidovudine. It is not expected that clinically significant interactions will occur.
Efavirenz has been shown to induce hepatic enzymes *in vivo*, thus enhancing the transformation of some drugs that are metabolized via CYP3A4. Also *in vitro*, efavirenz was shown to inhibit CYP 2C9, 2C19 and 3A4 isoenzymes, with Ki values (between 8.5 and 17μM) within the limits of plasma concentrations observed with Efavirenz. Also, at concentrations well above those clinically achieved, *in vitro* Efavirenz inhibited CYP2D6 and CYP1A2 (K_i between 82 and 160 μM), but did not inhibit CYP2E1. Concomitant administration of efavirenz with drugs metabolized primarily by isoenzymes 2C9, 2C19 and 3A4 may alter the concentrations of the drug administered concomitantly. CYP3A4-inducing drugs would be expected to increase clearance of Efavirenz, decreasing plasma concentrations. No clinically significant interactions were observed between Efavirenz, zidovudine, lamivudine, azithromycin, fluconazole, lorazepam, cetirizine or paroxetine. Single doses of famotidine, aluminum and magnesium antacids with simethicone had no effect on Efavirenz exposures.
Exposure to Efavirenz may be increased when administered with medicinal products (e.g. ritonavir) or foods (e.g. grapefruit juice) that inhibit CYP3A4 or CYP2B6 activity. Compounds or herbal medicines (e.g. extracts of Ginkgo Biloba and St John's wort), which induce these enzymes may cause a reduction in plasma concentrations of efavirenz. Concomitant use of St. John's wort is contraindicated. Concomitant use of Ginkgo biloba extracts is not recommended.

Table 1: Pharmacological interactions: changes in pharmacokinetics parameters of efavirenz administered concomitantly with other drugs

				Change % average - Pharmacokinetics parameters o FC de Efavirenz (90% CI)[a]		
Concomitant administered drug	**Dose**	**Efavirenz dose (mg)**	**N**	**Cmax**	**AUC**	**Cmin**
Indinavir	800 mg c/8h x 14 days	200 mg 1 q.d. x 14 days	11	↔	↔	↔
Lopinavir/ritonavir	400/100 mg b.i.d. x 9 days	600 mg 1 q.d. x 9 days	11,12[b]	↔	↓16 (↓38 to ↑15)	↓16 (↓42 to ↑20)
Nelfinavir	750 mg q8h x 7 days	600 mg q.d. x 7 days	10	↓12 (↓32 ↑13)[c]	↓12 (↓35 to ↑18)[c]	↓21 (↓53 to ↑33)
Ritonavir	500 mg b.i.d. x 8 days	600 mg q.d. x 10 days	9	↑14 (↑4 to ↑6)	↑21 (↑10 to ↑34)	↑25 (↑7 to ↑46)[c]
Saquinavir SGC[d]	1200 mg q8h x 10 days	600 1 q.d. x 10 days	13	↓13 (↓5 to ↓20)	↓12 (↓4 to ↓19)	↓14 (↓2 to ↓24)
Boceprevir	800 mg q8h x 6 days	600 q.d. x 16 days	NA	↑11 (↑2 to ↑20)	↑20 (↑15 to ↑26)	ND
Simeprevir	150 mg q.d. x 14 days	600 q.d. x 14 days	23	↔	↓10 (↓5 to ↓15)	↓13 (↓7 to ↓19)
Claritromicina	500 mg b.i.d. x 7 days	400 mg q.d. x 7 days	12	↑11 (↑3 to ↑19)	↔	↔
Itraconazole	200 mg b.i.d. x 14 days	600 mg q.d. x 28 days	16	↔	↔	↔
Rifabutin	300 mg q.d. x 14 days	600 mg q.d. x 14 days	11	↔	↔	↓12 (↓24 to ↑1)
Rifampicin	600 mg x 7 days	600 mg q.d. x 7 days	12	↓20 (↓11 to ↓28)	↓26 (↓15 to ↓36)	↓32 (↓15 to ↓46)
Artemeter/ Lumefantrin	Artemeter 20 mg/lumefantrin 120 mg tablets (6 doses de 4 tab x 3 days)	600 mg q.d. x 26 days	12	↔	↓17	NA
Atorvastatin	10 mg q.d. x 4 days	600 mg q.d. x 15 days	14	↔	↔	↔
Pravastatin	40 mg q.d. x 4 days	600 mg q.d. x 15 days	11	↔	↔	↔
Simvastatin	40 mg q.d. x 4 days	600 mg q.d. x 15 days	14	↓12 (↓28 to ↑8)	↔	↓12 (↓25 to ↑3)
Carbamazepine	200 mg q.d. x 3 days, 200 mg b.i.d. x 3 days, then 400 mg q.d. x 15 days	600 mg q.d. x 35 days	14	↓21 (↓15 to ↓26)	↓36 (↓32 to ↓40)	↓47 (↓41 to ↓53)
Diltiazem	240 mg x 14 days	600 mg q.d. x 28 days	12	↑16 (↑6 to ↑26)	↑11 (↑5 to ↑18)	↑13 (↑1 to ↑26)
Sertraline	50 mg q.d. x 14 days	600 mg q.d. x 14 days	13	↑11 (↑6 to ↑16)	↔	↔
Voriconazole	400 mg orally b.i.d. day 1, then 200 mg orally b.i.d. x 8 days	400 mg q.d. x 9 days	NA	↑38[e]	↑44[e]	NA
	300 mg orally b.i.d. days 2-7	300 mg q.d. x 7 days	NA	↓14[f] (↓7 to ↓21)	↔[f]	NA
	400 mg orally b.i.d. days 2-7	300 mg q.d. x 7 days	NA	↔[f]	↑17[f] (↑6 to ↑29)	NA

b.i.d.: twice daily, every 12hours
q.d.: once daily
q8h: every 8 hours
NA: no available
a: ↑: increase; ↓: decrease; ↔: no change
b: parallel groups design. N: correspond to Efavirenz + lopinavir/ritonavir. N: corresponde al Efavirenz solo
c: IC95%
d: soft capsules
e: IC95% no available
f: In relation to steady-state administration of Efavirenz (600 mg once daily for 9 days)

Table 2: Pharmacological interactions: changes in pharmacokinetics parameters of Efavirenz administered concomitantly with other drugs

				Change % average - Pharmacokinetics parameters of administered drug concomitantly with Efavirenz (90% CI)[a]		
Concomitant administered drug	**Dose**	**Efavirenz dose (mg)**	**N**	**Cmax**	**AUC**	**Cmin**
Atazanavir	400 mg q.d. with Light meal days 1–20	600 mg q.d. with light meal days 7–20	27	↓59 (↓49 to ↓67)	↓74 (↓68 to ↓78)	↓93 (↓90 to ↓95)
	400 mg q.d. days 1–6, then 300 mg q.d. days 7–20 with con ritonavir 100 mg q.d. and light meal	600 mg q.d. 2 hours after atazanavir and ritonavir days 7–20	13	↑14[b] (↓17 to ↑58)	↑39[b] (↑2 to ↑88)	↑48[b] (↑24 to ↑76)
	300 mg q.d. ritonavir 100 mg q.d. days 1-10 (pm), then 400 mg q.d. ritonavir 100 mg q.d. days 11-24 (pm) (simultaneous with Efavirenz)	600 mg q.d. with light meal days 11-24 (pm)	14	↑17 (↑8 to ↑27)	↔	↓42 (↓31 to ↓51)
Indinavir	1000 mg q8h x 10 days	600 mg q.d. x 10 days	20			
	After morning dose			↔[c]	↓33[c] (↓26 to ↓39)	↓39[c] (↓24 to ↓51)
	After afternoon dose			↔[c]	↓37[c] (↓26 to ↓46)	↓52[c] (↓47 to ↓57)
	After evening dose			↓29[c] (↓11 to ↓43)	↓46[c] (↓37 to ↓54)	↓57[c] (↓50 to ↓63)
Lopinavir/ ritonavir	400/100 mg b.i.d. x 9 days	600 mg q.d. x 9 days	11,7[d]	↔[e]	↓19[e] (↓36 a ↑3)	↓39[e] (↓3 to ↓62)
Nelfinavir Metabolite AG-1402	750 mg q8h x 7 days	600 mg q.d. x 7 days	10	↑21 (↑10 to ↑33) ↓40 (↓30 to ↓48)	↑20 (↑8 a ↑34) ↓37 (↓25 a ↓48)	↔ ↓43 (↓21 to ↓59)
Ritonavir	500 mg b.i.d. x 8 days	600 mg q.d. x 10 days	11			
	After morning dose			↑24 (↑12 to ↑38)	↑18 (↑6 to ↑33)	↑42 (↑9 to ↑86)[f]
	After afternoon dose			↔	↔	↑24 (↑3 to ↑50)
Saquinavir SGC[g]	1200 mg q8h x 10 days	600 mg q.d. x 10 days	12	↓50 (↓28 to ↓66)	↓62 (↓45 to ↓74)	↓56 (↓16 to ↓77)[f]
Maraviroc	100 mg b.i.d.	600 mg q.d.	12	↓51 (↓37 to ↓62)	↓45 (↓38 to ↓51)	↓45 (↓28 to ↓57)
Raltegravir	400 mg single dose	600 mg q.d.	9	↓36 (↓2 to ↓59)	↓36 (↓20 to ↓48)	↓21 (↓51 to ↑28)
Boceprevir	800 mg 3 times/day x 6 days	600 mg q.d. x 16 days	NA	↓8 (↓22 to ↑8)	↓19 (↓11 to ↓25)	↓44 (↓26 to ↓58)
Simeprevir	150 mg q.d. x 14 days	600 mg q.d. x 14 days	23	↓51 (↓46 to ↓56)	↓71 (↓67 to ↓74)	↓91 (↓88 to ↓92)
Clarithro 14-OH metabolito	500 mg b.i.d. x 7 days	400 mg q.d x 7 days	11	↓26 (↓15 to ↓35) ↑49 (↑32 to ↑69)	↓39 (↓30 to ↓46) ↑34 (↑18 to ↑53)	↓53 (↓42 to ↓63) ↑26 (↑9 to ↑45)
Itraconazol Hidroxi itraconazol	200 mg b.i.d. x 28 days	600 mg q.d. x 14 days	18	↓37 (↓20 to ↓51) ↓35 (↓12 to ↓52)	↓39 (↓21 to ↓53) ↓37 (↓14 to ↓55)	↓44 (↓27 to ↓58) ↓43 (↓18 to ↓60)
Posaconazole	400 mg (oral suspension) b.i.d. x 10-20 days	400 mg q.d. x 10-20 days	11	↓45 (↓34 to ↓53)	↓50 (↓40 to ↓57)	NA
Rifabutina	300 mg q.d. x 14 days	600 mg q.d. x 14 days	9	↓ 32 (↓ 15 to ↓46)	↓38 (↓28 to ↓47)	↓45 (↓31 to ↓56)
Artemeter/Lumefantrina Artemeter dihidroartemisinina lumefantrina	Artemether 20 mg/lumefantrine 120 mg tab (6 doses 4 tablets x 3 days)	600 mg q.d. x 26 days	12	↓21 ↓38 ↔	↓51 ↓46 ↓21	NA NA NA
Pravastatina	40 mg q.d. x 4 days	600 mg q.d. x 15 days	13	↓32 (↓59 to ↑12)	↓44 (↓26 to ↓57)	↓19 (↓0 to ↓35)
Atorvastatina	10 mg q.d. x 4 days	600 mg q.d. x 15 days	14	↓14 (↓1 to ↓26)	↓43 (↓34 to ↓50)	↓69 (↓49 to ↓81)
Incluyendo metabolitos				↓15 (↓2 to 26)	↓32 (↓21 to ↓41)	↓48 (↓23 to ↓64)
Simvastatina	40 mg x 4 days	600 mg q.d. x 15 days	14	↓72 (↓63 to ↓79)	↓68 (↓62 to ↓73)	↓45 (↓20 to ↓62)
Incluyendo metabolitos				↓68 (↓55 to 78)	↓60 (↓52 to ↓68)	NA
Carbamazepina Metabolito epóxido	200 mg q.d. x 3 days, 200 mg b.i.d. x 3 days, then 400 mg q.d. x 29 days	600 mg q.d. x 14 days	12	↓20 (↓15 to ↓24) ↔	↓27 (↓20 to ↓33) ↔	↓35 (↓24 to ↓44) ↓13 (↓30 to ↑7)
Diltiazem Desacetyl diltiazem N-monodesmethyl diltiazem	240 mg x 21 days	600 mg q.d. x 14 days	13	↓60 (↓50 to ↓68) ↓64 (↓57 to ↓69) ↓28 (↓7 to ↓44)	↓69 (↓55 to ↓79) ↓75 (↓59 to ↓84) ↓37 (↓17 to ↓52)	↓63 (↓44 to ↓75) ↓62 (↓44 to ↓75) ↓ 37 (↓17 to ↓52)
Etinilestradiol/Norgestimato						
Etinilestradiol/	0,035 mg/0,25 mg x 14 days	600 mg q.d. x 14 days	21	↔	↔	↔
Norelgestromina			21	↓46 (↓39 to ↓52)	↓64 (↓62 to ↓67)	↓82 (↓79 to ↓85)
Levonorgestrel			6	↓80 (↓77 to ↓83)	↓83 (↓79 to ↓87)	↓86 (↓80 to ↓90)
Metadona	Steady maintenance 35-100 mg q.d.	600 mg q.d. x 14 to 21 days	11	↓45 (↓25 to ↓59)	↓52 (↓33 to ↓66)	NA
Bupropion Hidroxi bupropion	150 mg (one dose extended release)	600 mg q.d. x 14 days	13	↓34 (↓21 to ↓47) ↑50 (↑20 to ↑80)	↓55 (↓48 to ↓62) ↔	NA NA
Sertralina	50 mg q.d. x 14 days	600 mg q.d. x 14 days	13	↓29 (↓ 5 to ↓40)	↓ 39 (↓27 to ↓50)	↓46 (↓31 to ↓58)
Voriconazole	400 mg orally, b.i.d. x 1 day then 200 mg orally b.i.d. x 8 days	400 mg q.d. x 9 days	ND	↓61[i]	↓77[i]	NA
	300 mg orally b.i.d.days 2-7	300 mg q.d. x 7 days	ND	↓36[j] (↓21 to ↓49)	↓ 55[j] (↓45 to ↓62)	NA
	400 mg orally b.i.d. days 2-7	300 mg q.d. x 7 days	ND	↑23[j] (↓1 to ↑53)	↓ 7[j] (↓23 to ↑13)	NA

b.i.d.: twice daily, every 12hours
q.d.: once daily
q8h: every 8 hours
NA: no available
a: ↑: increase; ↓: decrease; ↔: no change
b: regarding 400mg atazanavir once a day
c: the comparison dose was indinavir 800mg every 8 hours for 10 days.
d: parallel groups design. N: corresponds to Efavirenz + lopinavir/ritonavir. N: corresponds only to lopinavir/ritonavir.
e: values of lopinavir. The pharmocokinetics characteristics of 100mg ritonavir twice a day are not affected by the co-administration of Efavirenz.
f: IC 95%
g: soft capsules
h: No available, insufficient data
i: IC 90% no available
j: related with administration of voriconazol in steady maintenance (400mg over a day, then 200mg orally every 12 hours for 2 days)

Emtricitabina and Tenofovir Disoproxil Fumarato: The pharmacokinetic characteristics of Emtricitabine and Tenofovir at steady state were not affected when Emtricitabine and Tenofovir Disoproxil Fumarate were co-administered, compared to the administration of each drug separately.
In vitro pharmacological interaction studies and clinical pharmacokinetics, as well as pharmacokinetic properties, have demonstrated that the possibility of CYP-mediated interactions affecting Emtricitabine and Tenefovir with other medicinal products is low.
Emtricitabine and Tenofovir are excreted primarily by the kidneys, through glomerular filtration and acicular tubular secretion. No pharmacological interactions have been observed due to competition for renal excretion. However, the administration of these, concomitantly with other medicinal products that are eliminated by active tubular secretion, may increase the concentrations of Emtricitabine, Tenofovir and/or the drug administered concomitantly. Drugs that decrease renal function may also increase emtricitabine and/or Tenofovir concentrations.
There were no clinically significant pharmacological interactions between Emtricitabine, famciclovir, indinavir, stavudine, Tenofovir Disoproxil Fumarate and zidovudine. Similarly, in studies in healthy volunteers, no clinically significant pharmacological interactions were observed between Tenofovir Disoproxil Fumarate and abacavir, Efavirenz, Emtricitabine, entecavir, indinavir, lamivudine, the combination of lopinavir and ritonavir, methadone, Nelfinavir, oral contraceptives, ribavirin, the combination of saquinavir and ritonavir or tracolimus.
Following the administration of several doses of Emtricitabine/Tenofovir to HIV negative patients who were receiving chronic maintenance therapy with methadone, oral contraceptives, or single doses of ribavirin, steady-state pharmacokinetic characteristics were similar to those observed in previous studies, which would indicate the absence of clinically significant pharmacological interactions between these drugs and Tenofovir Disoproxil Fumarate. The effects of the drugs administrated concomitantly on C_{max}, AUC and C_{min} of Tenofovir are shown in Table 3. The effects of concomitant administration of Tenofovir Disoproxil Fumarate on C_{max}, AUC and C_{min} of the concomitantly administered drugs are shown in Table 4.

Table 3: Pharmacological interactions: changes in pharmacokinetics parameters of tenofovir administered concomitantly with other drugs[a,b]

Co-administered drug	Dose of co-administered drug	N	Change % average - Pharmacokinetics parameters of Tenofovir (90% CI)[c]		
			Cmax	**AUC**	**Cmin**
Atazanavir[d]	400 mg q.d. x 14 days	33	↑ 14 (↑ 8 a ↑ 20)	↑ 24 (↑ 21 to ↑ 28)	↑ 22 (↑ 15 to ↑ 30)
Atazanavir/ ritonavir[d]	300/100 q.d.	12	↑ 34 (↑ 20 a ↑ 51)	↑ 37 (↑ 30 to ↑ 45)	↑ 29 (↑ 21 to ↑ 36)
Darunavir/ ritonavir[e]	300/100 mg b.i.d.	12	↑ 24 (↑ 8 a ↑ 42)	↑ 22 (↑ 10 to ↑ 35)	↑ 37 (↑ 19 to ↑ 57)
Didanosin[f]	250 or 400 mg q.d. x 7 days	14	↔	↔	↔
Lopinavir/ ritonavir	400/100 mg b.i.d. x 14 days	24	↔	↑ 32 (↑ 25 to ↑ 38)	↑ 51 (↑ 37 to ↑ 66)
Tipranavir/ ritonavir[g]	500/100 mg b.i.d.	22	↓ 23 (↓ 32 a ↓ 13)	↓ 2 (↓ 9 to ↑ 5)	↑ 7 (↓ 2 to ↑ 17)
	750/200 mg b.i.d. (23 doses)	20	↓ 38 (↓ 46 a ↓ 29)	↑ 2 (↓ 6 to ↑ 10)	↑ 14 (↑ 1 to ↑ 27)

b.i.d.: twice daily, every 12hours
q.d.: once daily
q8h: every 8 hours
a: every study was performed on health volunteers
b: patients received 300 mg tenofovir once a day
c: ↑: increase; ↓: decrease; ↔: no change
d: Reyataz technical data
e: Prezista technical data
f: patients received didanosin buffered tablets
e: Aptivus technical data

Table 4: Pharmacological interactions: changes in pharmacokinetics parameters of the co-administered drugs with Tenofovir[a,b]

Co-administered drug	Dose of co-administered drug	N	Change % average - Pharmacokinetics parameters of Tenofovir (90% CI)[c]		
			Cmax	**AUC**	Cmin
Atazanavir[d]	400 q.d. x 14 days	34	↓ 21 (↓ 27 to ↓ 14)	↓ 25 (↓ 30 to ↓ 19)	↓ 40 (↓ 48 to ↓ 32)
	Atazanavir/ritonavir 300/100 mg q.d. x 42 days	10	↓ 28 (↓ 50 to ↑ 5)	↓ 25[e] (↓ 42 to ↓ 3)	↓ 23[e] (↓ 46 to ↑ 10)
Darunavir[f]	Darunavir/ritonavir 300/100 mg q.d.	12	↑ 16 (↓ 6 to ↑ 42)	↑ 21 (↓ 5 to ↑ 54)	↑ 24 (↓ 10 to ↑ 69)
Didanosin[g]	250 mg oce, concomitantly with Tenofovir and light meal[h]	33	↓ 20[i] (↓ 32 to ↓ 7)	↔[g]	NA
Lopinavir Ritonavir	Lopinavir/ritonavir 400/100 mg b.i.d. x 14 days	24	↔	↔	↔
	Lopinavir/ritonavir 400/100 mg b.i.d. x 14 days	24	↔	↔	↔
Tipranavir[j]	Tipranavir/ritonavir 500/100 mg b.i.d.	22	↓ 17 (↓ 26 to ↓ 6)	↓ 18 (↓ 25 to ↓ 9)	↓ 21 (↓ 30 to ↓ 10)
	Tipranavir/ritonavir 750/200 mg b.i.d. (23 dose)	20	↓ 11 (↓ 16 to ↓ 4)	↓ 9 (↓ 15 to ↓ 3)	↓ 12 (↓ 22 to 0)

b.i.d.: twice daily, every 12hours
q.d.: once daily
q8h: every 8 hours
a: every study was performed on health volunteers
b: patients received 300 mg tenofovir once a day
c: ↑: increase; ↓: decrease; ↔: no change
d: Reyataz technical data
e: in VIH positive patients, adittion of Tenofovir Disoproxil Fumarate to 300mg of atazanavir plus 100mg of ritonavir shown values of AUC and C_{min} of atazanavir 2, 3 and 4 times higher than the ones observed with 400mg of atazanavir administered alone.
f: Prezista technical data
e: Videz EC technical data. Patients received didanosin capsules with enteric cover
h: 373kcal, 8,2 g of fat
i: compared to 400mg of didanosin (enteric capsules) administered alone fasting.
j: Aptivus technical data
k: patients received didanosin buffered tablets

Concomitant administration of Tenofovir Disoproxil Fumarate with didanosine causes changes in the pharmacokinetic characteristics of didanosine, which may have clinical significance.
Administration of Tenofovir Disoproxil Fumarate with enteric coated capsules of didanosine significantly increases C_{max} and AUC of didanosine. When enteric coated capsules of 250 mg of didanosine were given with Tenofovir Disoproxil Fumarate, were observed exposures to didanosine similar to those observed with didanosine 400mg capsules alone administered fasting. The mechanism of this interaction is unknown. View interactions.

Posology and method of administration:

The usual dosage in adults and pediatric patients over 12 years of age, with a body weight higher than or equal to 40 kg is 1 tablet taken orally once daily.
If possible, it is recommended to be given on an empty stomach **(i.e., one hour before or 2 hours after a meal), at night before bedtime.**
Administration on an empty stomach is recommended, since food may increase exposure to efavirenz, which can produce an increase in the frequency of adverse reactions. In order to improve tolerance to efavirenz with respect to adverse reactions in the nervous system, it is recommended to take the dose at bedtime.
Renal impairment: ***Zolec®*** is not recommended for patients with moderate to severe renal impairment (creatinine clearance (CrCl) <50mL/min), as these patients require dose interval adjustment of emtricitabine and tenofovir disoproxil fumarate that cannot be achieved with the combination tablet.
Elderly: ***Zolec®*** should be administered with caution to elderly patients.
Dose adjustment: if ***Zolec®*** is given concomitantly with rifampicin to patients weighing 50 kg or more, it may be considered the additional administration of Efavirenz 200 mg/day (800 mg total).

Contraindications:

In patients with previous hypersensitivity, clinically significant to Efavirenz (Steven Johnson, erythema multiforme, toxic eruptions) ***Zolec®*** is contraindicated. It is also contraindicated in patients with a hypersensitivity to any of the components of the product that has previously been manifested. Concomitant use with voriconazole: the co-administration with voriconazole is contraindicated. Efavirenz significantly decreases voriconazole plasma concentrations, with a decrease of its efficacy, voriconazole also significantly increases Efavirenz plasma concentrations, increasing the risk of adverse reactions associated with Efavirenz.

Special warnings:

Lactic Acidosis/Severe Hepatomegaly with Steatosis: Lactic acidosis and severe hepatomegaly with steatosis have been observed, including fatal cases, by using nucleoside analogs such as Tenofovir, either alone or in combination with other antiretrovirals. Most of these cases occurred in women. Obesity and prolonged exposure to nucleosides may be risk factors.
Special care should be taken when administering nucleoside analogues to any patient with known risk factors for hepatic diseases. However, cases have also been reported in patients with no known risk factors. Treatment with ***Zolec®*** should be suspended in any patient or individual presenting clinical or laboratory findings suggesting lactic acidosis or hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations).
Patients with HIV and hepatitis B (HBV) virus co-infection: It is recommended that all HIV patients would be screened for the presence of hepatitis B virus (HBV) before initiating antiretroviral therapy with ***Zolec®***. ***Zolec®*** is not recommended for the treatment of chronic HBV infection, as the safety and efficacy in patients infected with HBV and HIV were not established. Severe acute exacerbations of hepatitis B have been observed in some patients co-infected with HBV and HIV after discontinuation of the combination of tenofovir and emtricitabine. In some patients treated with emtricitabine alone, exacerbations of hepatitis b were associated with hepatic decompensation and liver failure. In patients with HBV discontinuing treatment with ***Zolec®***, hepatic function should be closely monitored by clinical and laboratory monitoring for at least several months. If necessary, anti-hepatitis B therapy may be instituted.
Do not administer this drug together with adefovir Dipivoxil.
Immunization against hepatitis B should be offered to all patients not infected with this virus.
Psychiatric symptoms by Efavirenz: psychiatric adverse reactions have been reported in patients treated with efavirenz, including severe, such as depression. Patients with a prior history of psychiatric disorders appear to be at greater risk of these severe psychiatric adverse reactions. In particular, severe depression was more common in those with a history of depression. There have also been post-marketing reports of severe depression, death by suicide, delusions, and psychosis-like behavior. Patients should be advised that if they experience symptoms such as severe depression, psychosis or suicidal ideationthoughts, they should contact their doctor immediately to assess the possibility that the symptoms may be related to the use of efavirenz, and if so, to determine whether the risk of continuing therapy outweighs the benefits.
Nervous system symptoms: Symptoms including, but not limited to, dizziness, insomnia, somnolence, impaired concentration, and abnormal dreaming nightmares, have been reported in patients receiving Efavirenz 600 mg daily in clinical studies. Dizziness was also seen in clinical studies with emtricitabine and Tenofovir Disoproxil Fumarate. Headache has been reported in clinical studies with Emtricitabine. Nervous system symptoms associated with efavirenz usually begin during the first one or two days of therapy and generally resolve after the first two to four weeks. Patients should be informed that if they do occur, these common symptoms are likely to improve with continued therapy and are not predictive of subsequent onset of any of the less frequent psychiatric symptoms.
Seizures: Convulsions have been observed in patients receiving Efavirenz, generally in the presence of a known medical history of seizures. Patients who are receiving concomitant anticonvulsant medicinal products primarily metabolized by the liver, such as phenytoin, carbamazepine, and phenobarbital, may require periodic monitoring of plasma levels. In a drug interaction study, carbamazepine plasma concentrations were decreased when

carbamazepine was co-administered with Efavirenz. Caution must be taken in any patient with a history of seizures.
Renal Insufficiency: ***Zolec®*** is not recommended in patients with moderate or severe renal impairment (creatinine clearance <50 ml/min).
It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy with ***Zolec®***, and also monitored after 2 to 4 weeks of treatment, after 3 months of treatment and every 3 to 6 months thereafter for example).
In patients with a history of renal dysfunction, e.g. patients who have had renal events while receiving adefovir, it is recommended to evaluate creatinine clearance, phosphataemia, glucosuria, and proteinuria prior to initiating therapy with ***Zolec®*** and periodically.
Patients with moderate or severe renal impairment require a dose adjustment of emtricitabine and Tenofovir Disoproxil Fumarate that cannot be achieved with the combination tablet.
Use of ***Zolec®*** should be avoided with concurrent o recent use of a nephrotoxic medicinal product (e.g. NSAIDs at high doses, or multiples NSAIDs). If concomitant use of ***Zolec®*** and nephrotoxic agent (e.g. aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir, interleukin-2) is unavoidable, renal function must be monitored weekly.
In HIV+ patients treated with Tenofovir who had risk factors for renal dysfunction, acute renal failure was observed after initiating high doses or multiple NSAIDs. Some of these required hospitalization and renal replacement. In case of patients with renal risk, consider alternative NSAID replacement if necessary. Renal failure, renal insufficiency, increased creatinine, hypophosphatemia and proximal tubulopathy (including Fanconi's syndrome) have been reported with the use of Tenofovir Disoproxil Fumarate in clinical practice.
It is recommended that creatinine clearance is calculated in all patients prior to initiating therapy and afterwards when appropriate.
Persistent bone pain or worsening of bone pain, limb pain, muscle pain or fractures or weakness may be associated with proximal renal tubulopathy. If bone abnormalities are suspected then appropriate consultation should be obtained.

Bone effects of tenofovir: decreased bone mineral density has been observed in patients treated with tenofovir, as well as increases in the markers of bone metabolism, suggesting an increase in bone turnover. Likewise, the levels of Parathyroid hormones and 1.25 vit.D.
In children younger than 18 years of age and HIV+ treated with tenofovir, a lower gain of bone mineral density has been observed than in the untreated infected ones, but not affecting growth (height).
The effects on changes in bone mineral density related to tenofovir that produce long-term effects in bone-health and future risk of fractures are unknown.
Bone monitoring should be considered in HIV-infected patients who have a history of bone fractures or have risk of osteopenia. Although the effect of calcium and vitamin D supplementation has not been studied, such supplementation may be beneficial to all patients. If bone abnormalities are suspected, appropriate advice must be seeked.
Cases of osteomalacia associated with proximal renal tubulopathy has been reported with the treatment of Tenofovir, manifested as bone pain or pain of extremities and which can lead to fractures. In cases of proximal renal tubulopathy, arthralgia and muscle pain or weakness were also reported.
Hypophosphatemia and osteomalacia secondary to proximal tubulopathy should be considered in patients at risk of renal impairment who have muscle or bone symptoms while taking Tenofovir.

Immune Reactivation Syndrome: San immune reconstitution syndrome has been observed in patients receiving antiretroviral combined therapy, including Tenofovir. During the initial phase of combined antiretroviral therapy, patients whose immune system responds, an inflammatory reaction to asymptomatioc or residual opportunistic pathogens may arise (such as Mycobacterium infection Avium, cytomegalovirus, Pneumocystis jirovecii pneumonia or tuberculosis), which may require more extensive evaluation and treatment.
Autoimmune disorders (such as Grave's disease, polymyositis and Guillén Barre syndrome) have also been reported to occur in the setting of inmune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of tretament.

Warnings:

Concomitant administration of related products: In the treatment of HIV-1 infection in adult and pediatric patients ≥12 years, weighing more than 40kg: ***Zolec®*** should not be administered concomitantly with other medicinal products containing the components: Tenofovir, Emtricitabine, fixed combinations of Emtricitabine + Tenofovir such as Remivir®, nor did fixed-dose associations of elvitegravir/cobistat/Emtricitabine/Tenofovir Disoproxil Fumarate neither Emtricitabine/rilpivirine/Tenofovir.
It should not be co-administered with products containing efavirenz, unless needed for dose adjustment, e.g. cases of co-administration with rifampicin.
It should not be administered concomitantly with other cytidine analogs such as lamivudine, due to its similarity to Emtricitabine.
Also remember to take with lamivudine associated (neither to zidovudine nor to abacavir). ***Zolec®*** should not be administered concomitantly with adefovir or didanosine. See Interactions section.

Change from protease inhibitor regimen: patients who have previously received antiretroviral therapy, with an inhibitor of protease, could have a decrease of the response to the treatment, when changing to ***Zolec®***.

Opportunistic Infections: Patients receiving ***Zolec®***, or any other antiretroviral therapy may continue to develop opportunistic infections as other complications of HIV infection and should therefore, be under strict clinical observation of medical experts in the treatment of patients with HIV-associated diseases.

HIV transmission: Although viral suppression with effective antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions should be taken, in accordance with national guidelines, to prevent transmission.

Skin reactions: Mild to moderate rash has been reported with the individual components of ***Zolec®***. The rash associated with the efavirenz component usually resolves with continued therapy. Appropriate antihistamines and/or corticosteroids may improve tolerability and hasten the resolution of rash. Severe rash associated with blistering, moist desquamation or ulceration has been reported in less than 1% of patients treated with efavirenz. The incidence of erythema multiforme or Stevens-Johnson syndrome was approximately 0.1%. ***Zolec®*** must be discontinued in patients developing severe rash associated with blistering, desquamation, mucosal involvement or fever. Experience with Efavirenz in patients who discontinued other antiretroviral agents of the NNRTI class is limited. ***Zolec®*** is not recommended in patients who have had experienced a life-threatening cutaneous reaction (e.g. Stevens-Johnson syndrome) while taking an NNRTI.

Hepatotoxicity: it is recommended the monitoring of hepatic enzymes before and during treatment in patients with liver disease, including Hepatitis B or C infection, in patients with high levels of transaminases and in patients treated with other medicinal products associated with hepatic toxicity. Evaluate the risk-benefits of continuing the treatment in patients with persistent increases of serum transaminases higher than 5 times the normal upper limit, assessing the unknown risk of hepatic toxicity vs. benefit of treatment.

Redistribution of Fat/Lipodystrophy: Redistribution or accumulation of body fat, including central obesity, increase of dorsocervical fat ("buffalo hump"), loss of peripheral and facial fat, increased bust size and "cushingoid" appearance in patients receiving antiretroviral therapy have been observed. Currently, the mechanism and long-term consequences of these events are unknown. A causal relationship cannot be established yet.

Mitochondrial dysfunction: Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, demonstrated *In Vitro* and *In Vivo*.
There have been reports of mitochondrial dysfunction in HIV negative infants exposed in utero and/or postnatally to nucleoside analogues. The main adverse reactions reports are haematological disorders (anemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hyperlonia, convulsion, abnormal behavior). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed in utero to nucleos(T)ide analogues, who present with severe clinical findings of unknown etiology and should undergo clinical and laboratory follow-up, and, in case of relevant signs or symptoms a possible mitochondrial dysfunction should be thoroughly investigated. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

• Interactions with other drugs
As ***Zolec®*** contains Efavirenz, Emtricitabine and Tenofovir, any interaction that have been identified with these agents individually may occur with the fixed combination.
Interactions have been reported separately with emtricitabine and tenofovir, evaluating their interaction with other drugs.
The interactions of greater clinical relevance are given with:

- *Didanosine:* Administer with caution. Tenofovir increases the maximum concentration of didanosine and the area under the curve, and may develop adverse events related to didanosine including pancreatitis, lactic acidosis and neuropathy. Deletion of CD4+ lymphocyte counts has also been observed in patients receiving Tenofovir Disoproxil Fumarate with 400mg of didanosine daily. Therefore the co-administration of ***Zolec®*** and didanosine in patients receiving this combination should be closely monitored for events associated with didanosine. It is recommended to reduce the dose of didanosine when administered concomitantly with Tenofovir Disoproxil Fumarate. The use of didanosine should be discontinued in patients who develop associated adverse events.
- **Protease inhibitors: co-administration with atazanavir may decrease its concentration and increase tenofovir concentration.** Atazanavir and lopinavir/ritonavir have been shown to increase Tenofovir concentrations. The mechanism of this interaction is unknown. Co-administration of atazanavir/ritonavir and ***Zolec®*** is not recommended.
  Atazanavir, lopinavir or darunavir together with ritonavir and ***Zolec®***, may increase the concentration of Tenofovir. Therefore the adverse events must be controlled and ***Zolec®*** discontinuated in case of adverse events related to Tenofovir.
  Co-administration of atazanavir with ***Zolec®*** is not recommended since co-administration of atazanavir with Efavirenz or Tenofovir Diproxil Fumarate (two of the components of ***Zolec®***) decrease plasma concentrations of atazanavir; and on the other hand, atazanavir increases concentrations of Tenofovir. There is insufficient information to support the dosing recommendations combined with ***Zolec®***.
  As the Tenofovir Disoproxil Fumarate is a substrate of glycoprotein P (Pgp) transporters and of breast cancer resistance protein (BCRP), when Tenofovir is given together with an inhibitor of the above, an increase in its concentration could be observed. On the other hand, this triple combination with darunavir/ritonavir could generate a suboptimal C_{min} of darunavir. In that case, use Darunavir/ritonavir 600/100 mg twice daily. Use with caution. Indicate monitoring of renal function, particularly in patients with underlying systemic or renal disease, or in those taking nephrotoxic drugs.
- Fosamprenvir: Adequate doses of fosamprenavir and the fixed combination of Efavirenz, Emtricitabine and Tenofovir have not been established. If fosamprevir/ritonavir is administered once daily with ***Zolec®***, an additional 100 mg/day of ritonavir (300 mg total) is recommended. Or adjust ritonavir if fosamprenavir/ritonavir is given twice a day.
- Indinavir: Indinavir decreases its concentration in the presence of Efavirenz. The optimal dose of indinavir is unknown. Increasing the dose of indinavir to 1000 mg every 8 hours does not compensate for the increased metabolism of indinavir due to Efavirenz. The magnitude of the observed pharmacokinetic interaction should be taken into consideration when choosing a regimen containing both indinavir and ***Zolec®***.
- Ritonavir/Efavirenz: the association of 500 mg of ritonavir every 12 hours simultaneously with 600 mg of Efavirenz once daily, was related to a higher frequency of clinical adverse reactions (dizziness, nausea, paresthesia) and laboratory abnormalities (increased liver enzymes). Monitoring of liver enzymes is recommended if ***Zolec®*** is co-administered with efavirenz.
- Saquinavir/ritonavir: Insufficient data are available to make a dosing recommendation for saquinavir/ritonavir when dosed with ***Zolec®***. Co-administration of saquinavir/ritonavir and ***Zolec®*** is not recommended. Use of ***Zolec®*** in combination with saquinavir as the sole protease inhibitor (IP) is not recommended.
- Maraviroc: its concentrations are modified according to the presence of Efavirenz (decreases AUC and C_{max}), but not with Tenofovir. Refer to the technical data of Maraviroc.
- Raltegravir: el Efavirenz disminuye las concentraciones plasmáticas de raltegravir. No se ha evaluado la significancia clínica, por lo que puede administrarse junto a la presente combinación, sin ajuste de dosis.
- Inhibidores no nucleosídicos de transcriptasa reversa (INNTR): podría alterar la concentración de Efavirenz. La combinación de dos INNTR no demostró ser beneficiosa.
- Raltegravir: Efavirenz decreases plasma concentrations of raltegravir. The clinical significance has not been evaluated, so they could be co-administered without dose adjustement.
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs): could alter the concentration of Efavirenz. Since use of two NNRTIs proved no beneficial in terms of efficacy and safety, co-administration is not recommended.
- Medicines that affect renal function: keep in mind that Emtricitabine and Tenofovir are mainly excreted in the urine through glomerular filtration and active tubular secretion. Therefore drugs which are eliminated by tubular secretion (such as acyclovir, adefovir, dipivoxil, cidofovir, ganciclovir, valaciclovir, valganciclovir, aminoglycosides and high doses of NSAIDs) may alter their excretion or the components of ***Zolec®***. Also, drugs that decrease renal function may increase emtricitabine and tenofovir concentrations.
- Do not co-administer ***Zolec®*** with any other HIV treatment containing any of its active ingredients alone or in fixed combinations.
- Because of the similarities between emtricitabine and lamivudine, co-administration of ***Zolec®*** with other medicines containing lamivudine alone or with fixed combinations is not recommended.
- Do not administer ***Zolec®*** with adefovir.
- Hepatitis C antivirals:
  - Boceprevir/efavirenz: plasma trough concentrations of boceprevir were decreased when administered with efavirenz, which decreases the therapeutic effect. The association should be avoided.
  - Simeprevir/Efavirenz: It is NOT recommended its use with ***Zolec®*** as it decreases the effect of simeprevir.
- Anticoagulants: dose adjustement of warfarin or acenocuumarol may be requiered when co-administered with ***Zolec®*** for potential interaction with Efavirenz.
- Anticonvulsants:
  - Carbamazepine: Efavirenz decreases carbamazepine concentrations and vice versa. An alternative anticonvulsant should be considered. Carbamazepina plasma levels should be monitpred periodically.
  - Phenoltoin, Phenobarbital and other CYP isoenzyme substrates: when ***Zolec®*** is co-administered with an anticonvulsant that is a substrate of CYP isoenzymes, periodic monitoring of anticonvulsant levels should be conducted. An alternative anticonvulsant should be considered.
- Antidepressants:
  - Sertraline: when co-administered with ***Zolec®*** may decrease sertraline concentrations. Dosage adjustment should be considered according to clinical response.
  - Bupropion: when co-administered with Efavirenz may decrease the concentrations of the norepinephrine and dopamine reuptake inhibitor, increasing its metabolite. The dose of bupropion should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded.
- Antibiotics: clarithromycin co-administered with Efavirenz demonstrated changes in plasma levels and onset of rash. Alternatives to clarithromycin (e.g. azithromycin) may be considered.
- Antimycobacterials:
  - Rifabutin decreases its concentrations when given with Efavirenz. The daily dose of rifabutin should be increased when given with ***Zolec®***. Individual tolerability and virological response should be considered when making the dose adjustment.
  - Rifampicin: may decrease efavirenz concentrations, therefore, when co-administered with ***Zolec®***, an aditional 200 mg/day of Efavirenz (800mg total) may be provided. Individual tolerability and virological response should be considered when making the dose adjustment.
- Antifungal:
  - Itraconazole: it decreases its concentrations, it induces CYP3A4 when co-administered with Efavirenz. An alternative antifungal treatment should be considered.
  - Ketoconazole: plasma ketoconazole concentration may decrease, although no interaction studies have been performed.
  - Posaconazole/Efavirenz: plasma concentrations are decreased. Concomitant use of posaconazole and ***Zolec®*** should be avoided.
  - Voriconazole/Efavirenz: decreases concentrations of voriconazole and increases efavirenz. Since ***Zolec®*** is a fixed-dose combination product, the dose of Efavirenz cannot be altered; therefore, voriconazole and ***Zolec®*** must not be co-administered.
- Antimalarials: artemether/lumefantrine/Efavirenz: since decreased concentrations of artemether or lumefantrine may result in a decreased of antimalarial efficacy, caution is recommended when ***Zolec®*** and artemether/lumefantrine tablets are co-administered.
- Hormonal contraceptives: A reliable method of barrier contraception must be used in addition to hormonal contraceptives. Efavirenz had no effect on ethinylestradiol concentrations; however, progestagen concentrations (norelgestromin and levonorgestrel) were markedly decreased. There was no EE/Norgestimate effect on efavirenz concentrations. Although, interaction between etonogestrel (implant) and efavirenz has not beed studied, cases of contraceptive failure have been reported in women exposed to Efavirenz.
- Cardiovascular agents:
  - Diltiazem: el Efavirenz puede disminuir sus concentraciones y las de sus metabolitos. Ajustar dosis a respuesta clínica.
  - Verapamil, felodipine, nifedipine, nicardipine: as they are CYP3A4 substrates, their plasma concentrations could decrease when co-administered with efavirenz. Dose adjustments of calcium channel bloquers when co-administered with ***Zolec®*** should be guided by clinical response.
- Immunosupressants: Interactions with cyclosporine, tacrolimus and sirolimus co-administered with Efavirenz have not been studied. Dose adjustment of the immunosuppressant agent may be required. Close monitoring of immunosuppressant concentrations for at least two weeks (until stable concentrations are reached) is recommended when starting or stopping treatment with ***Zolec®***.
- Opiods: patients receiving methadone and ***Zolec®*** concomitantly should be monitored for signs of withdrawal and their methadone dose increased as required to alleviate withdrawal symptoms.

Carcinogénesis, Mutagénesis y Trastornos de la Fertilidad:

Efavirenz: Long-term carcinogenicity studies with efavirenz were performed in mice and rats. Doses of 0, 25, 75, 150 or 300 mg/kg daily for two years were given to mice. The incidence of hepatocellular adenomas and carcinomas and alveolar or bronchiolar adenomas of the lung were increased with respect to the reference values in females. There was no increase in the incidence of tumors regarding to reference values in male mice.
In the studies in which rats received Efavirenz doses of 0, 25, 50, 100 mg/kg daily for two years no increase in incidence of tumors was observed with respect to reference values. Systemic exposure (according to AUC) in mice was approximately 1.7 times higher than in humans receiving doses of 600 mg/day. The exposure in rats was less than humans. The mechanism of carcinogenic potential is unknown. However, Efavirenz was not mutagenic or clastogenic in conventional genotoxicity assays. These results were consisted with the analysis of bacterial mutation of S. typhimurium and E. coli, mutation analysis in Chinese mammalian hamster ovary cells, chromosomal aberration analysis in human lymphocytes of peripheral blood or ovary cell of Chinese hamster and analysis in vivo of micronucleus in bone marrow of mice. Due to the absence of genotoxic activity of efavirenz, the relevance in humans of neoplasm in mice treated with Efavirenz is unknown.
Efavirenz did not alter the mating or fertility of male or female rats and did not affect the spermatozoa of treated male rats. The reproductive performance of offspring born of female rats was unaffected after were given Efavirenz. Due to the faster clearance of efavirenz in rats, the systemic exposures reached on these studies were equivalent or less than the exposures reached in humans at therapeutically doses of Efavirenz.

Emtricitabine:
In studies of long-term carcinogenesis, there were no increases in the incidence of tumors in mice exposed to doses of up to 750 mg/kg/day of Emtricitabine (26 times the human dose of 200 mg/day) or in rats exposed to doses up to 600 mg/Kg/day (31 times the therapeutic dose of humans).
Emtricitabine was not genotoxic in the bacterial reversal test (Ames test), mouse lymphoma, or mouse micronucleus test.
The fertility of male rats given doses 140 times higher than those corresponding to the human dose or in female rats exposed to doses 60 times higher than those recommended in humans were not altered. Fertility was not affected either in the offspring of rats that were exposed intra uterus and until sexual maturity at doses up to 60 times those corresponding to the recommended human dose of 200mg/day. The incidence of fetal variations and malformations was not increased in embryo-fetal toxicity studies carried out with emtricitabine at exposures (AUC) higher than 60-fold in mice and approximately 120-fold in rabbits with respect to human exposures according to the recommended daily dose.

Tenofovir Disoproxil Fumarate:
In long-term carcinogenesis studies, increases in the incidence of hepatic adenomas were observed in mice exposed to doses comparable to approx. 16 times the human dose for HIV-1 treatment. No other carcinogenic effect was observed in rats
females exposed to doses up to 5 times the human dose. Tenofovir was mutagenic in the mouse lymphoma test and negative in the In vitro mutagenicity Test of Ames. It was negative when the mouse micronucleus test, was performed in vivo.
Fertility, mating behavior and early embryonic development were not altered in male rats given doses equivalent to 10 times the human dose, during the 28 days prior to mating, or in female rats exposed to such doses during the 15 days prior to mating and until the seventh day of gestation.
Reproduction studies were carried out on rats and rabbits at doses up to 14 and 19 times the ones for humans, taking as comparative the body surface area and there were no evidence of impaired fertility or damage to the fetus due to Tenofovir.

Combination of emtricitabine and Tenofovir Disoproxil Fumarate: Genotoxicity and repeated-dose toxicity studies of one month or less with the combination of these two components found no exacerbation of toxicological effects compared to studies with the separate components.

Preclinical data:
Efavirenz: Unsustained seizures were observed in 6 of 20 monkeys receiving efavirenz at doses that produced plasma AUC 4 to 13 times higher than those of the humans who received the recommended dose.
Tenofovir Disoproxil Fumarate: Tenofovir and Tenofovir Disoproxil Fumarate administered to rats, dogs and monkeys in toxicological studies with exposures levels (according to AUC) greater or equal than 6 times to those observed in humans caused bone toxicity. Bone toxicity was diagnosed as osteomalacia (monkeys) and reduced bone mineral density (BMD) (rats and dogs). Osteomalacia observed in monkeys appeared to be reversible by reducing doses or discontinuing the use of Tenofovir.
Signs of renal toxicity were observed in four animal species receiving tenofovir and Tenofovir Disoproxil Fumarate. In these animals, increases in serum creatinine BUN (blood urea nitrogen), glycosuria, proteinuria, phosphaturia and/or calciuria and decreases of serum phosphate in different degrees, were observed. These toxicities were observed in exposures (according to AUC) 2 to 20 times higher than those observed in humans. The relationship between renal abnormalities, especially phosphaturia, with bone toxicity is unknown.

Pregnancy: Category D. Fetal damage from Efavirenz may occur if administered during the first trimester of pregnancy. Do not administer ***Zolec®*** in pregnant women. Pregnancy must be avoided in women receiving ***Zolec®***. Barrier contraception should always be used in combination with other methods of contraception (combination of barrier method and another method e.g. hormonal is recommended). Moreover, and because of the long half-life of efavirenz, use adequate contraceptives measures for 12 weeks after discontinuation of ***Zolec®*** is recommended.

Breast-feeding: Efavirenz, Emtricitabine and Tenofovir have been shown to be excreted in human milk. There is insufficient information on the effects of Efavirenz, Emtricitabine and Tenofovir in newborns/infants. A risk to the infants cannot be excluded. Therefore ***Zolec®*** should not be used during breast-feeding. As a general rule, it is recommended that HIV infected women do not breast-feed infants in order to avoid transmission of HIV to the infant.

Pediatric population: ***Zolec®*** should only be given to pediatric patients aged 12 years or older with a body weight greater than 40 kg, since it is not possible to make dose adjustments for smaller patients with each individual component.

Elderly: In clinical studies with Efavirenz, emtricitabine or Tenofovir Disoproxil Fumarate, a number of patients greater than or equal to 65 years were not included to determine if the response of patients in this age group is different from the younger ones. Special care must be taken since it is a fixed association, with no dose adjustment possible, possible concomitant cardiac pathologies, possible decreased renal or hepatic function and concomitant treatments.

Hepatic impairment: ***Zolec®*** is not recommended in patients with severe or moderate hepatic impairment since there are no sufficient studies needed to dose determination. Patients with mild liver disease may be treated with the normal recommended dose. Patient should be monitored carefully for adverse reactions, as Efavirenz metabolizes by CYP3A4.

Renal impairment: ***Zolec®*** is not recommended for patients with moderate or severe renal impairment (creatinine clearance (CrCl) <50 ml/min). Patients with moderate or severe renal impairment require dose interval adjustement of emtricitabine and Tenofovir Disoproxil Fumarate that cannot be achieved with the combination tablet.

Adverse reactions:
A combination of efavirenz, emtricitabine and Tenofovir Disoproxil Fumarate has been studied in clinical trials. Adverse reactions were generally consistent with those seen in previous studies of the individual components.
The following adverse reactions are reported as the most common (≥10%) of a clinical study in which patients with HIV-1 without previous treatment, received the combination of efavirenz/tenofovir disoproxil fumarate/emtricitabine (***Zolec®***) vs another combination therapy (zidovudine/lamivudine + Efavirenz): diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams and rashes. They were generally consistent with those seen in previous studies of the individual components.
Another study conducted with patients with stable virological suppression who changed their current treatment to a fixed-dose combination as ***Zolec®*** showed profile of events similar to the previously described, and consistent with those seen in previous studies of the individual components.
In other sections (warnings and precautions) you can find information on the following selected adverse reactions:

- *Lactic acidosis and severe hepatomegaly with steatosis, even fatal: have been reported with the use of nucleoside analogues, including Tenofovir Disoproxil Fumarate (one of the components of* ***Zolec®****), in combination with other antiretrovirals. Obesity and prolonged exposure may be risk factors.*
- *Hepatic failure with Efavirenz:* hepatic failure, including cases of patients without pre-existing liver disease or other risk factors such as those indicated in the post-marketing notifications, were sometimes characterized by a fatal ending, which in some cases progressed to transplantation or death.
- *HBV infection:* Severe acute exacerbations of Hepatitis B have been observed in patients with concomitant Hepatitis B and HIV-1 who discontinued treatment with the combination of Tenofovir 300 mg + Emtricitabine 200 mg.
- *Psychiatric symptoms:* Patients with a history of psychiatric disorders appear to be at increased risk for psychiatric severe adverse reactions. Severe depression, suicide ideation, non-fatal suicide attempts, aggressive behavior, paranoid reactions and manic reactions, were notified in clinical studies with Efavirenz. In patients with a history of injecting drug use, psychiatric and those taking psychiatric medication have more frequent onset of these symptoms. In the post-marketing experience, suicides, delusions, and psychotic behavior were reported, although they cannot be established a causal relationship.
- *Nervous system symptoms:* Nervous system symptoms are common with Efavirenz, one of the components of this medicine. In clinical trials, about half of the patients had these events: dizziness, insomnia, impaired concentration, drowsiness, abnormal dreams, hallucinations. Other: euphoria, confusion, agitation, amnesia, stupor, abnormal thoughts and depersonalization. Most of them with mild to moderate intensity, only 2% severe and only 2% of patients discontinued treatment because of these symptoms. They usually start during the first day or the first two days of treatment with efavirenz and usually resolve after the first two to four weeks. When administering along with meals, symptoms may appear more frequently due to an increase in plasma levels of Efavirenz. Bedtime administration seems to improve tolerance to these symptoms.
- *New onset or worsening of renal dysfunction:* ***Zolec®*** may cause kidney damage, it is recommended to monitor renal function. Acute renal impairment and Fanconi syndrome associated to Tenofovir have been reported. Emtricitabine is also excreted by kidney. The proximal renal tubulopathy was generally resolved or improved upon discontinuation of Tenofovir Disoproxil Fumarate. However, in some patients, the decrease in creatinine clearance was not resolved completely despite discontinuation of Tenofovir Disoproxil Fumarate. Patients at risk for renal failure (such as patients with baseline renal risk factors, advanced treatment with concomitant nephrotoxic medicinal products) present an increased risk of renal function despite discontinuation of Tenofovir Disoproxil Fumarate.
- *Bone effects of Tenofovir Disoproxil Fumarate:* Reduction of bone mineral density. In clinical studies conducted with Tenofovir (one of the components of ***Zolec®***), BMD reduction was observed in the lumbar and hip spine. Clinically relevant fractures were also reported, but not in incidence higher than in the control group. Moreover, significant increases were reported in both, biochemical markers of bone metabolism (FAL of bone tissue, serum osteocalcin, serum C-telopeptide and urinary N-telopeptide), and parathyroid hormone and 1.25 vitamin D.
- *Rash:* in clinical trials with Efavirenz the rashes consisted generally of maculopapular rashes mild to moderate occurring during the first two weeks after initiation of favirenz treatment. In most of the patients the rash was resolved by continuing with Efavirenz treatment over the course of a month. If you decide to restart treatment with ***Zolec®*** is suggested to use appropriate antihistamines and/or corticosteroids.
- *Immune reactivation syndrome:* In patients treated with the fixed combination of Emtricitabine 200 mg + Tenofovir 300 mg inflammatory response to residual or indolent opportunistic infections were reported. In the context of immune reactivation, cases of autoimmune disorders (such as Graves syndrome, polymyositis, Guillain-Barré syndrome) were reported, at variable onset time, even many months after starting treatment.
  In addition to the adverse reactions mentioned, the following adverse reactions were observed in clinical studies conducted with Efavirenz, Emtricitabine and Tenofovir.

• Efavirenz: the most frequently reported adverse reactions were psychiatric disorders, and nervous system disorders. Selected moderate to severe adverse events observed in ≥2% of patients treated with Efavirenz were: pain, concentration disorders, abnormal dreams, drowsiness, anorexia, dyspepsia, abdominal pain, nervousness and pruritus. Pancreatitis was also reported, although no causal relationship could be established. Asym-ptomatic increases in serum amylase were observed in a greater number of subjects treated with Efavirenz 600 mg. vs. control group. In clinical studies in pediatric patients (3 months to 21 years), similar to adults adverse reactions were shown, with a greater incidence of eruptions and severe eruptions.
• Emtricitabine and Tenofovir Disoproxil Fumarate: in clinical trials at least 5% of patients (with or without antiretroviral therapy) treated with Emtricitabine/Tenofovir Disorpoxil Fumarate with other antiretrovirals shown: arthralgia, increased cough, dyspepsia, fever, myalgia, abdominal pain, low back pain and rashes (rash, pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash and allergic reaction). Changes in skin color, hyperpigmentation of palms or plants, mild to asymtomtic, were generally reported in patients treated with Emtricitabine. Its mechanism and clinical importance are unknown. Anemia (7%) and hyperpigmenation (32%) were present in the pediatric patients. Patients 12 to 18 years of age treated with tenofovir had adverse reactions consistent with those observed in clinical trials in adults.
Laboratory abnormalities.- laboratory abnormalities presented in clinical trials in patients receiving Efavirenz + Emtricitabine + Tenofovir in more than 1% of the patients were:
Any laboratory abnormality ≥ grade 3: 30% vs 26%;
Fasting Cholesterol (>240 mg/dL): 22%;
Creatine kinase (male:>990 U/L) (female:>845 U/L): 9%;
Serum amylase (>175 U/L): 8%;
Alkaline phosphatase (>550 U/L): 1%
AST (men:>180 U/L) (Fem:>170 U/L): 3%;
ALT (men:>215 U/L) (fem:>170 U/L): 2%;
Hemoglobin (<8.0 mg/dL): 0%;
Hyperglycemia (>250 mg/dL): 2%;
Hematuria (>75 hematies/CAR): 3%;
Glucosuria (≥ 3+): <1%
Neutrophils (<750/mm3): 3%;
Fasting Triglycerides (>750 mg/dl): 4%
Other studies have described some grade 3, 4 abnormalities such as: increases in bilirubin (>2.5xULN), increases in pancreatic amylase (>2xULN), increases or decreases in serum glucose (>250 mg/dl or <40 mg/dl), increases in serum lipase (>2xULN), in up to 3% of patients treated with Emtricitabine or Tenofovir Disoproxil Fumarate with other antiretroviral agents. Increased transaminases of more than 5 times ULN were reported in clinical trials of patients co-infected with Hepatitis B and C, with no needed of discontinuation of treatment for hepatobiliary disorders.

Post-marketing experience:
During the post-approval use of Efavirenz, Emtricitabine and Tenofovir Disoproxil Fumarate the following adverse reactions have been identified.
As this type of reactions are from voluntary notification, from a population of an indeterminate size, it is not always possible to reliably or establish a causal relationship with drug exposure.
Efavirenz: Cardiac disorders: Palpitations; **Ear and labyrinth disorders:** Tinnitus, vertigo; **Reproductive system and breast disorders:** Gynecomastia; **Eye disorders:** Vision abnormalities; **Digestive disorders:** Constipation, malabsorption; **General disorders and place of administration abnormalities:** Asthenia; **Hepatobiliary disorders:** Increases in liver enzymes, hepatic insufficiency, and hepatitis. Some of the post-marketing hepatic impairment studies, included cases in patients who did not have nor pre-existing liver disease neither other factors, also were characterized by a sudden fatal evolution, which in some cases progressed until it required a transplant or caused the death. **Immune system disorders:** Allergic reactions; **Metabolism and nutrition disorders:** Redistribution or accumulation of body fat, hypercholesterolemia, hypertriglyceridemia; **Musculoskeletal and connective tissue disorders:** Arthralgia, myalgia, myopathy. **Disorders of nervous system:** abnormalities of coordination, ataxia, cerebellar disorders of balance and coordination, seizures, hypoesthesia, paresthesia, neuropathy, tremors; **Psychiatric disorders:** Aggressive reactions, agitation, delusional ideas, emotional lability, mania, neurosis, paranoia, psychosis, suicide; Respiratory, **thoracic and mediastinal disorders:** Dyspnea; **Skin and subcutaneous tissue disorders:** Flushing, erythema multiforme, photoallergic dermatitis, Stevens-Johnson syndrome.
Emtricitabine: no post-marketing adverse reactions have been identified for inclusion in this section.
Tenofovir Disoproxil Fumarate: Immune system disorders: Allergic reactions, including angioedema; **Metabolism and nutrition disorders:** Lactic acidosis, hypokalemia, hypophosphatemia; **Respiratory, thoracic and mediastinal disorders:** Dyspnea; **Digestive disorders:** Pancreatitis, increased amylase, abdominal pain; **Hepatobiliary disorders:** Hepatic steatosis, hepatitis, increased liver enzymes (More frequently, increase of AST, ALT and γGT); **Skin and subcutaneous tissue disorders:** Rash; **Musculoskeletal and connective tissue disorders:** Rhabdomyolysis, osteomalacia (manifested by bone pain and may contribute to fractures), muscle weakness, myopathy; **Renal and urinary disorders:** Acute renal failure, renal insufficiency, acute tubular necrosis, Fanconi's syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenic diabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria; **General disorders and place of administration abnormalities:** Asthenia.

Overdose
If overdose occurs, the patient must be monitored for evidence of toxicity, including monitoring of the vital constants and observation of the patient's clinical condition; supportive treatment should be applied when necessary.
Administration of activated charcoal may be used to aid rmoval of unabsorved Efavirenz. There is no specific antidote for overdose with Efavirenz. Since Efavirenz is highly protein bound, dialysis is unlikely to remove significant quantities of it from blood. Haemodialysis may eliminate Emtricitabine and Tenofovir, but if is unlikely to significantly eliminate Efavirenz.

Efavirenz: some patients accidentally taking 600 mg Efavirenz twice daily have reported increased nervous system symptoms. One patient experienced involuntary muscle contractions.

Emtricitabine: The clinical experience available at doses superior to that of Emtricitabine is limited. In a clinical pharmacology study, single doses of Emtricitabine from 1200 mg to 11 patients were given and no serious adverse reactions were reported.

Tenofovir Disoproxil Fumarate: The clinical experience available at doses above the therapeutic dose of 300mg of Tenofovir Disoproxil Fumarate is limited. In one study, 600mg to 8 patients were given orally for 28 days and no serious adverse reactions were reported. The effects of higher doses are unknown.
Up to 30% of the Emtricitabine dose and approximately 10% of the Tenofovir dose can be remove by haemodialysis. It is not known whether Emtricitabine or Tenofovir can be removed by peritoneal dialysis.

In the event of an overdose, go to the nearest Hospital or contact the Toxicology Centers.

How to store:
Keep the bottle tightly closed, in dry place, between 15°C and 30°C.
Do not use this medicine after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

How supplied:
1 bottle with 30 coated tablets, with silica gel desiccant.
1 bottle with 60 coated tablets, with silica gel desiccant.

KEEP THIS AND ALL MEDICINES IN THE ORIGINAL PACKAGE AND OUT OF THE REACH OF CHILDREN
THIS MEDICINE MUST BE USED EXCLUSIVELY UNDER PRESCRIPTION AND MEDICAL SURVEILLANCE AND CAN NOT BE REPEATED WITHOUT NEW MEDICAL PRESCRIPTION

Medicinal product authorized by the Ministry of Health.
Certificate N° 58.277.
Technical Director: Alfredo Boccardo - Pharmacist.
Manufactured by Laboratorio Elea Phoenix S.A.,
Av. Gral. Lemos N° 2809, Los Polvorines, Buenos Aires, Argentina.

000000-00 1-pm-g

Laboratorio ELEA PHOENIX